Ir-catalyzed diastereoselective isomerization of primary allylic alcohols

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UNIVERSITÉ DE GENÈVE FACULTÉ DES SCIENCES

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Ir-Catalyzed Diastereoselective Isomerization of Primary Allylic Alcohols

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par

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After endless mountains and rivers that leave doubt whether there is a path out, suddenly one encounters the shade of a willow, bright flowers and a lovely village

You LU (1125-1210)
A poet of the southern Song dynasty, China

Publication List

Part of work decribed in this thesis has already been published:

1. Steric Parameters in the Ir-Catalyzed Regio- and Diastereoselective Isomerization of Primary Allylic Alcohols
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2. Well-Defined Transition Metal Hydrides in Catalytic Isomerizations
E. Larionov, **H. Li**, C. Mazet,* *Chem. Commun.* **2014**, *50*, 9816−9826 (review).

3. Catalyst−Directed Diastereoselective Isomerization of Allylic Alcohols for the Stereoselective Construction of C(20) in Steroid Side Chains: Scope and Topological Diversification
H. Li, C. Mazet,* *J. Am. Chem. Soc.* **2015**, *137*, 10720−10727.

4. Organometallic Complexes of Iridium (Update 2015)
H. Li, C. Mazet,* *SOS Science of Synthesis*, R. A. Aitken, M. B. Nielsen, J. Drabowicz, J. J. Li, B. J. Plietker, T. Wirth, Eds., Thieme: Stuttgart−New York, **2016**, Knowledge Updates 2015/2, pp. 21−58 (book chapter).

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5. Modulation of Active Sites in Supported $Au_{38}(SC_2H_4Ph)_{24}$ Cluster Catalysts: Effect of Atmosphere and Support Material
B. Zhang, S. Kaziz, **H. Li**, M. G. Hevia, D. Wodka, C. Mazet, T. Bürgi,* N. Barrabés,* *J. Phys. Chem. C* **2015**, *119*, 11193−11199.

6. $Pd_2Au_{36}(SR)_{24}$ Cluster: Structure Studies
B. Zhang, S. Kaziz, **H. Li**, D. Wodka, S. Malola, O. Safonova, M. Nachtegaal, C. Mazet, I. Dolamic, J. Llorca, E. Kalenius, L. M. L. Daku, H. Hakkinen, T. Bürgi,* N. Barrabés,* *Nanoscale* **2015**, *7*, 17012−17019

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Abbreviation

Å: angstrom

Ac: acetyl

1-Ad: 1-adamantyl

AIBN: azobisisobutyronitrile

aq.: aqueous

atm: atmosphere

BAr_F: tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate

$BF_3 \bullet Et_2O$: boron trifluoride diethyl etherate

BF_4: tetrafluoroborate

BINAP: [2,2‘-bis(diphenylphosphino)-1,1‘-binaphthyl]

n-BuLi: *normal*-butyllithium

t-Bu: *tert*-butyl

Bz: benzoyl

cat.: catalyst

CDI: carbonyl diimidazole

CH_2Cl_2: dichloromethane

ClO_4: perchlorate

cod: 1,5-cyclooctadiene

Cs_2CO_3: cesium carbonate

CsF: cesium fluoride

CsOPiv: cesium pivalate

Cy: cyclohexyl

DBH: 1,3-dibromo-5,5-dimethylhydantoin

1,2-DCE: 1,2-dichloroethane

DEAD: diethyl azodicarboxylate

DIBAL: diisobutylalluminium hydride

DMAP: 4-(dimethylamino)pyridine

dr: diastereomeric ratio

DTBMP: 2,6-di-*tert*-butyl-4-methylpyridine

ee: enantiomeric excess

equiv.: equivalent

Et: ethyl

Et_2O: diethyl ether

EtOAc: ethylacetate

g: gram

h: hour

Hz: Hertz

J: coupling constant

Ir: iridium

L: ligand

LFER: linear free energy relantionship

$LiAlH_4$: lithium aluminum hydride

Me: methyl

mg: milligram

min: minute

mol: mole

MOM: methoxymethyl

mmol: millimole

m.p.: melting point

MS: molecular sieves

MsCl: methanesulfonyl chloride

ν: wave number

nbd: norbornadiene

n-Bu: *normal*-butyl

NCS: *N*-chlorosuccinimide

n.d.: not determined

NFSI: *N*-fluorobenzenesulfonimide

NHC: *N*-heterocyclic carbene

NMI: *N*-methylimidazole

NOESY: nuclear Overhauser effect spectroscopy

n.r.: no reaction

OTf: trifluoromethanesulfonate

PCC: pyridinium chlorochromate

$Pd(acac)_2$: palladium(II) diacetylacetonate

PF_6: hexafluorophosphate

Ph: phenyl

PHOX: Phosphinooxazoline

ppm: part per million

PPTS: pyridinium *p*-toluenesulfonate

i-Pr: *iso*-propyl

quant.: quantitative

q: quartet

s: singlet

t: triplet

TBAF: tetrabutylammonium fluoride

TBS: *tert*-butyldimethylsilyl

TEMPO: 2,2,6,6-Tetramethylpiperidine 1-oxyl

Tf_2O: trifluoromethanesulfonic anhydride

THF: tetrahydrofuran

TIPS: tri-*iso*-propylsilyl

TLC: thin layer chromatography

TMS: trimethylsilyl

$TMSN_3$: trimethylsilyl azide

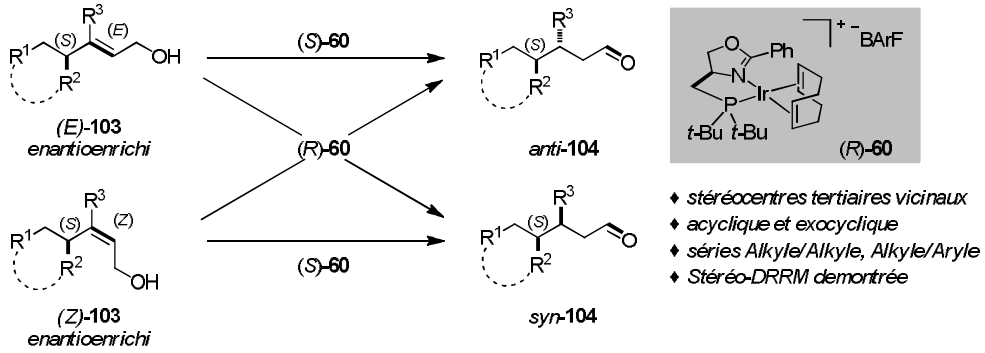
TON: turn over number

p-TsOH•H_2O: *p*-toluenesulfonic acid monohydrate

TsCl: *p*-toluenesulfonyl chloride

Résumé

Au cours des dernières années, des méthodes efficaces d'isomérisations énantiosélectives d'alcools allyliques prochiraux ont été rapportées indépendamment par notre groupe et d'autres. Cependant, l'isomérisation diastéréosélective avec des substrats chiraux a été peu étudiée à ce jour. Dans cette thèse, trois différentes séries d'alcools allyliques ont été utilisés en réaction d'isomérisation catalysée par un complexe d'iridium et les différents résultats obtenus y sont présentés.

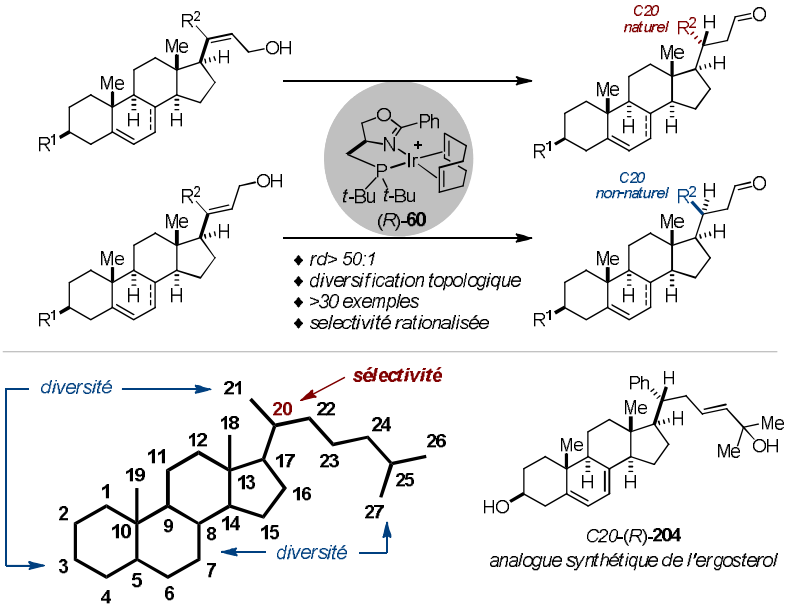


Scheme 5.1. *Isomérisation diastéréosélective orientée par le catalyseur avec les substrats énantioenrichis **103**.*

Dans le chapitre 2, nous avons mené l'isomérisation diastéréosélective dirigée par le catalyseur avec les **alcools allyliques énantioenrichis 103** utilisant les deux énantiomères du catalyseur **60** (Schéma 5.1). Alors que de bons rendements, de parfaits *rd* et d'excellents *ee* ont été couramment obtenus avec les substrats *acycliques*, nous avons aussi démontré la faisabilité de réactions stéréodivergentes sur les mélanges racémiques (stéréo-DRRM) avec deux substrats *acycliques* représentatifs. Le prolongement de cette étude aux substrats exocycliques a finalement abouti à la synthèse formelle d'insecticides d'origines naturelles, les sesquiterpènes (−)-juvabione (**87**) et (−)-epijuvabione (**88**).

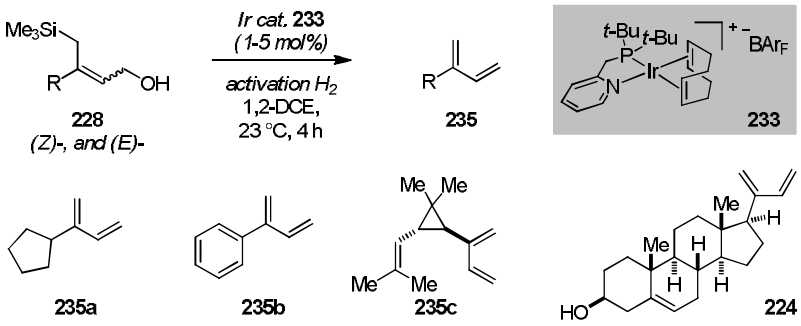
Dans le chapitre 3, nous avons ensuite évalué les **alcools allyliques stéroïdiens** dans l'isomérisation diastéréosélective dirigée par le catalyseur pour le stéréocontrôle de C20, le premier stéréocentre tertiaire du domaine acyclique dans les dérivés stéroïdiens (Schéma 5.2). Suivant une voie de synthèse modulaire uniforme, nous avons preparé une variété d'alcools allyliques stéroïdiens. Ces alcools ont ensuite été utilisés en isomérisation diastéréosélective avec (*R*)-**60** permettant d'accéder indifféremment à la configuration naturel C20-(*R*) et non naturel C20-(*S*), malgré la forte tendance naturellement imposée par le squelette stéroïdien. La portée de notre procédé a été davantage mise en évidence par la diversification topologique de la chaîne latérale, ainsi que dans le corps polycyclique avancé et complexe de l'architecture stéroïdienne. Une fonctionnalisation post-isomérisation a

également été démontrée via l'obtention de **204** comme analogue synthétique de l'ergostérol.



Scheme 5.2. *Construction stéréosélective de C20 dans la chaine lateral de steroides via l'utilisation de d'alcools allyliques stéroidiens.*

Dans le chapitre 4, nous avons décrit la découverte d'une réaction d'élimination vinylogue de Peterson catalysée par un complex d'iridium à partir **d'alcools allyliques silanes 228** via l'utilisation de l'analogue **223** du catalyseur de Crabtree (Scheme 5.3). Des études approfondies ont permis de mettre en évidence un mécanisme distinct impliquant des hydrures d'iridium. De bons rendements ont été généralement obtenus avec les deux isomères géométriques. L'application de cette méthode à une fonctionnalisation tardive a également été démontrée.



Scheme 5.3. *Elimination vinylogue de Peterson d'alcools allylques silane catalysé par l'iridium.*

Pris ensemble, les résultats présentés dans cette thèse peuvent façonner notre compréhension et finalement inspirer de nouvelles découvertes dans le domaine de l'isomérisation stéréosélective.

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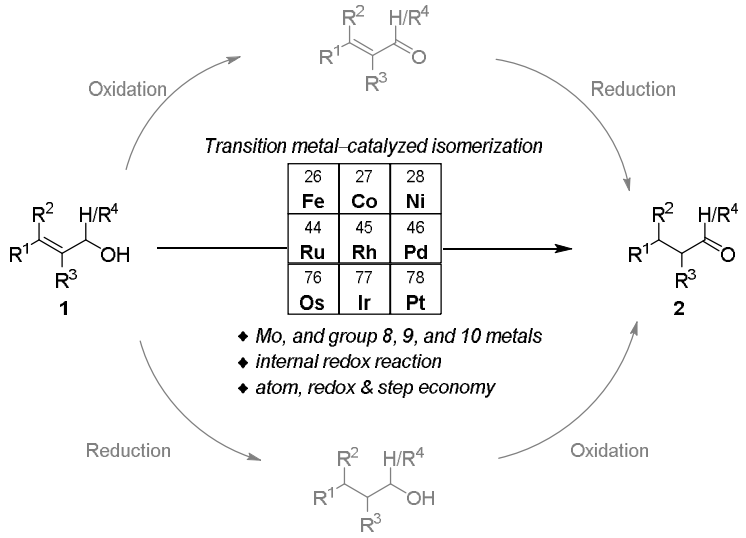
Chapter 1. General Introduction

1.1 Transition Metal-Catalyzed Isomerizations of Allylic Alcohols into Carbonyl Compounds

Carbonyl compounds are among the most versatile building blocks widely used in pharmacy, agrochemicals as well as material science.[1] Therefore, developing powerful methods to form carbonyl compounds (**2**) using the corresponding allylic alcohols (**1**) is of great interest. Traditional approaches always require oxidation/reduction sequences or *vice versa*. On the other hand, transition metal–catalyzed isomerization of allylic alcohols into the corresponding carbonyl compounds, known as an internal redox reaction, is much more appealing owing to the economic and environmentally benign process (Scheme 1.1).[2,3]



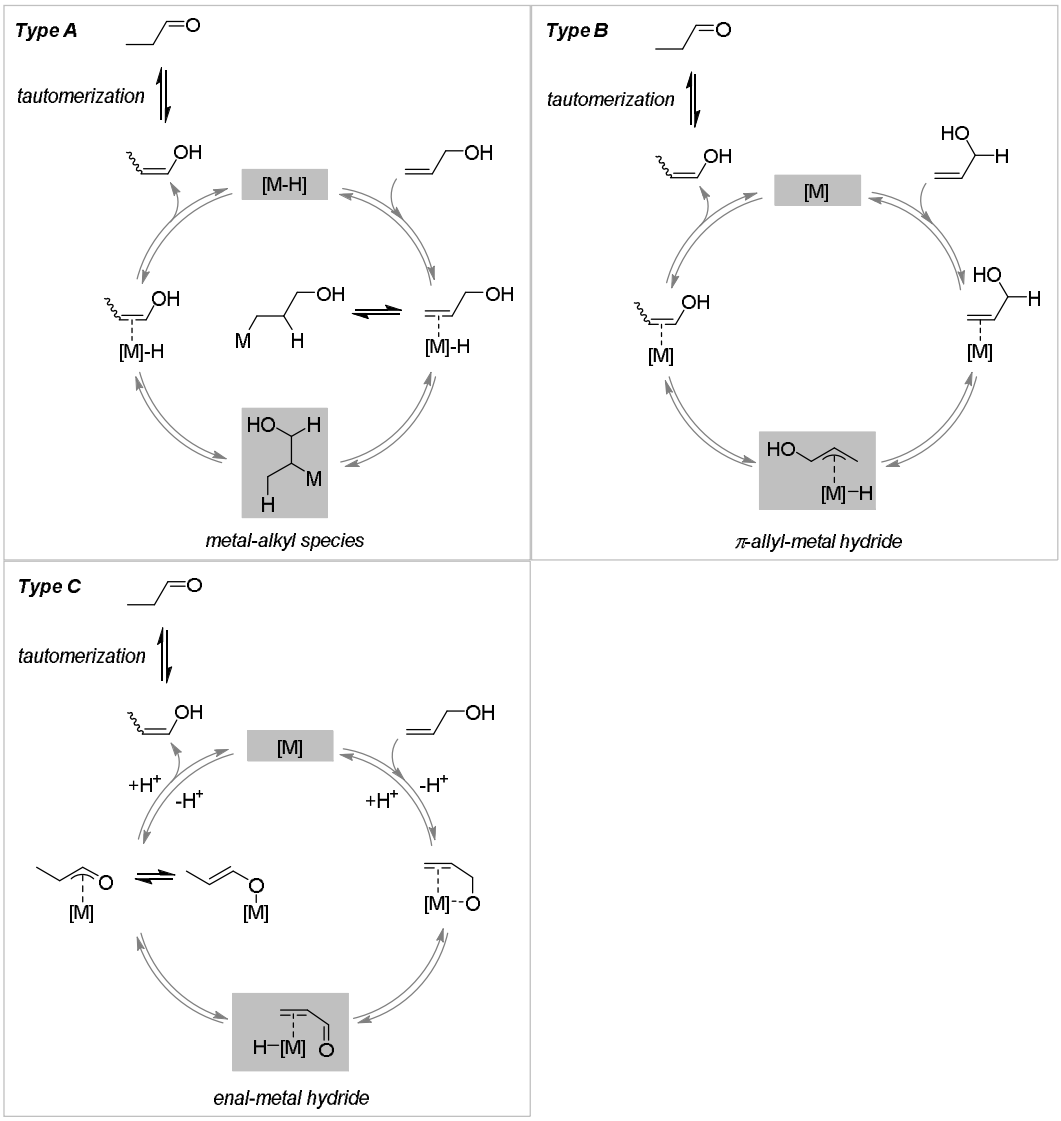
Scheme 1.1. *General strategy to access carbonyl compounds starting from the corresponding allylic alcohols.*

To date, the transition metal-catalyzed isomerization of allylic alcohols into carbonyl compounds has been reported using many transition metal complexes especially platinum metals (Scheme 1.1).[4] In the following discussion, we will mainly focus on the general

[1] *Modern Carbonyl Chemistry*, J. Otera, Ed., Wiley−VCH: Weinheim, **2000**.
[2] (a) B. M. Trost, *Science* **1991**, *254*, 1471−1477; (b) B. M. Trost, *Angew.Chem. Int. Ed.* **1995**, 34, 259−281; (c) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res*. **2008**, *41*, 40−49; (d) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854−2867.
[3] (a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press: New York, **1998**; (b) R. A. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH: Weinheim, **1997**.
[4] For recent reviews, see: (a) R. C. van der Drift, E. Bouwman, E. Drent, *J. Organomet. Chem.* **2002**, *650*, 1−24; (b) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27−52; (c) G. C. Fu, *Modern Rhodium−Catalyzed Organic Reactions*, P. A. Evans, Ed., Wiley−VCH: Weinheim, **2005**, Chapter 4; (d) V. Cadierno, P. Crochet, J. Gimeno, *Synlett* **2008**, 1105−1124; (e) L. Mantilli, C. Mazet, *Chem. Lett*. **2011**, *40*, 341−344; (f) N. Ahlsten, A. Bartoszewicz, B. Martin-Matute, *Dalton Trans*. **2012**, *41*, 1660−1670.

mechanisms of this process. At the end of the chapter some recent advances including the contributions from our lab will also be discussed.

1.1.1 General mechanisms



Scheme 1.2. *General mechanisms for transition metal-catalyzed isomerization of allylic alcohols into the carbonyl compounds.*

Three types of mechanisms are generally accepted to rationalize this isomerization reaction (Scheme 1.2).[4,5]

(i) **The metal hydride mechanism** (Scheme 1.2, type A). The allylic alcohol first π-coordinates with a metal hydride complex which is generated *in-situ* or *ex-situ*. Subsequent migratory insertion of the metal hydride into the alkene moiety generates the key metal-alkyl

[5] E. Larionov, H. Li, C. Mazet, *Chem. Commun.* **2014**, *50*, 9816−9826.

species. While further β-hydride elimination furnishes a η^2-enol metal hydride complex, final decomplexation releases the free enol and regenerates the metal hydride catalyst which will reengage into the catalytic cycle. Final tautomerization of the enol yields the corresponding carbonyl compound.

(ii) **The π-allyl mechanism** (Scheme 1.2, type B). The catalytic cycle starts again with π-coordination of the alkene moiety to the metal complex. Formal oxidative addition of the C−H single bond of the allylic alcohol forms a π-allyl−metal hydride intermediate. Reductive elimination generates a η^2-enol metal complex. Final decoordination provides the metal catalyst as well as the free enol which further tautomerizes into the corresponding carbonyl compound.

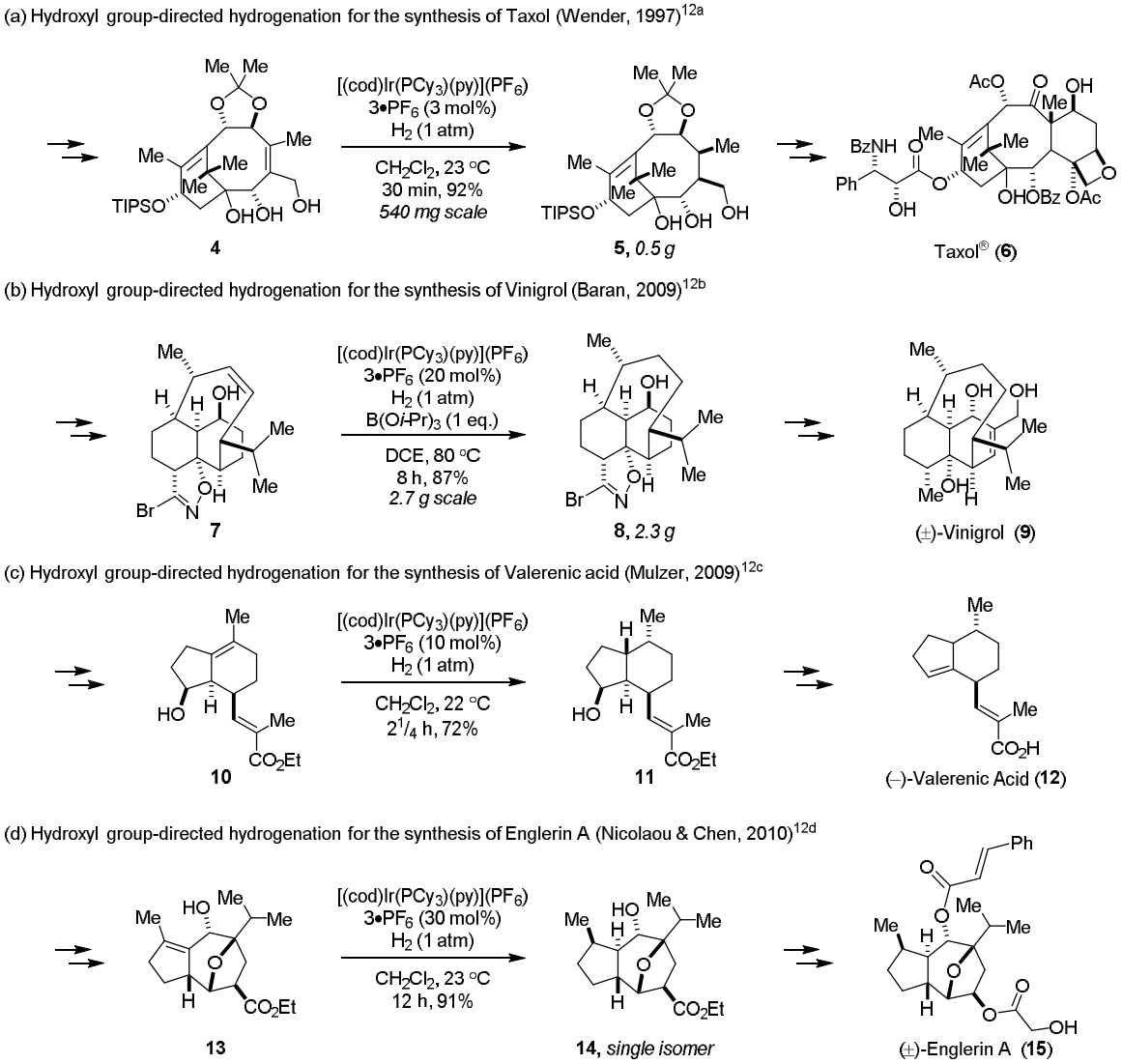
(iii) **The intramolecular 1,3-hydrogen shift mechanism** (Scheme 1.2, type C).[6] Normally under basic conditions, deprotonation of the allylic alcohol results in the initial formation of a transition metal alkoxide complex. Subsequent β-hydride elimination furnishes an enal−metal hydride intermediate. Further intramolecular conjugate addition to the enal generates a π-oxa-allyl−metal complex. Final protonation releases the metal catalyst as well as the free enol which forms the corresponding carbonyl compound after the tautomerization.

The mechanisms aforementioned have been proposed mainly based on labelling experiments and DFT calculations.[7] Experimental evidences have been rarely provided in the literature. With rare exceptions, all previous attempts to isolate and identify the catalytic intermediates have been unsuccessful.[8]

1.1.2 Recent examples of non-asymmetric isomerization reactions

In the early 1980s, Crabtree[9] and Stork[10] independently reported the directed homogeneous hydrogenation of a series of allylic and homoallylic alcohols using Crabtree catalyst **3**•PF_6. This hydroxyl group−directed hydrogenation has been widely applied in organic synthesis since its discovery, owing to the broad compatibility with various substrates and the predictability of the stereochemical outcome (Scheme 1.3).[11,12]

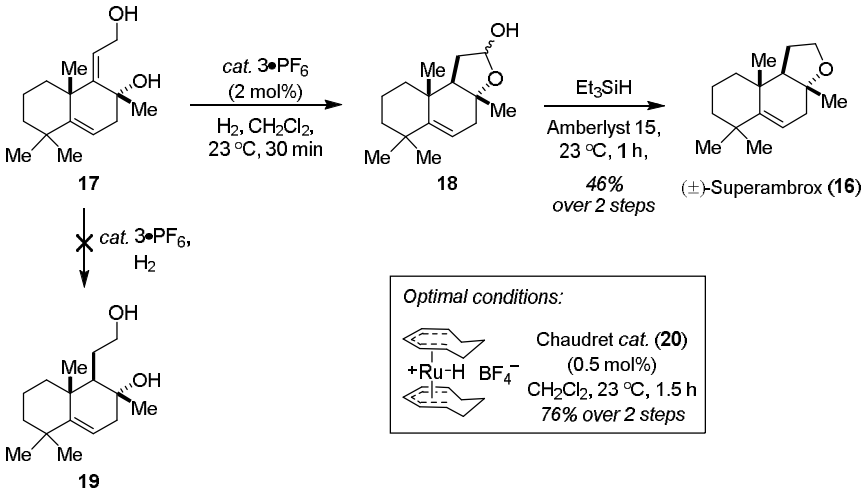
[6] B. M. Trost, R. J. Kulawiec, *J. Am. Chem. Soc.* **1993**, *115*, 2027−2036.
[7] For selected recent examples using DFT caclulations, see: (a) V. Branchadell, C. Crévisy, R. Grée, *Chem. −Eur. J.* **2003**, *9*, 2062−2067; (b) V. Cadierno, S. E. García-Garrido, J. Gimeno, A. Varela-Álvarez, J. A. Sordo, *J. Am. Chem. Soc.* **2006**, *128*, 1360−1370; (c) A. Varela-Álvarez, J. A. Sordo, E. Piedra, N. Nebra, V. Cadierno, J. Gimeno, *Chem. −Eur. J.* **2011**, *17*, 10583−10599; (d) S. Manzini, A. Poater, D. J. Nelson, L. Cavallo, S. P. Nolan, *Chem. Soc.* **2014**, *5*, 180−188; (e) E. Larionov, L. Lin, L. Guénée, C. Mazet, *J. Am. Chem. Soc.* **2014**, *136*, 16882−16894.
[8] (a) M. Batuecas, M. A. Esteruelas, C. García-Yebra, E. Oñate, *Organometallics* **2010**, *29*, 2166−2175; (b) L. Mantilli, C. Mazet, *Tetrahedron Lett.* **2009**, *50*, 4141−4144; (c) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, 48, 5143−5147.
[9] (a) R. H. Crabtree, M. W. Davis, *Organometallics* **1983**, *2*, 681−682; (b) R. H. Crabtree, M. W. Davis, *J. Org. Chem.* **1986**, *51*, 2655−2661.
[10] G. Stork, D. Kahne, *J. Am. Chem. Soc.* **1983**, *105*, 1072−1073.
[11] J. M. Browm, *Angew. Chem. Int. Ed.* **1987**, *26*, 190−203.



Scheme 1.3. *Selected examples of directed hydrogenation using Crabtree catalyst in organic synthesis.*

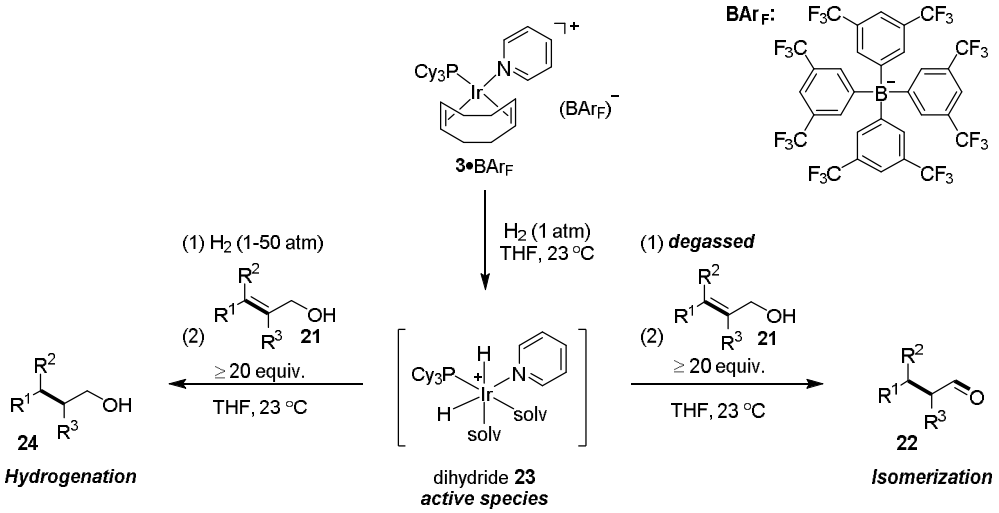
In 2006, *en route* to Superambrox (**16**) which is a valuable fragrance chemical with a strong ambery odor (Scheme 1.4),[13] Fehr and Farris treated diol **17** with Crabtree catalyst **3**•PF_6 under hydrogenation conditions. Surprisingly, the corresponding lactol **18** was obtained through hydroxyl group-directed isomerization of allylic alcohol, rather than the corresponding diol **19** which they initially expected by directed hydrogenation. Later under optimal conditions, superior results were obtained (76% over 2 steps) in the presence of 0.5 mol% of Chaudret's ruthenium hydride catalyst **20**. Labelling and crossover experiments with catalyst **20** supported the intramolecular 1,3-hydrogen shift mechanism.[13b]

[12] (a) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Gränicher, J. B. Houze, J. Jänichen, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, T. P. Mucciaro, M. Mühlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor, K. Tomooka, *J. Am. Chem. Soc.* **1997**, *119*, 2755−2756; (b) T. J. Maimone, J. Shi, S. Ashida, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 17066−17067; (c) J. Ramharter, J. Mulzer, *Org. Lett.* **2009**, *11*, 1151−1153; (d) K. C. Nicolaou, Q. Kang, S. Y. Ng, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 8219−8222.
[13] (a) C. Fehr, I. Farris, *Angew. Chem. Int. Ed.* **2006**, *45*, 6904–6907; (b) C. Fehr, I. Magpantay, L. Saudan, H. Sommer, *Eur. J. Org. Chem.* **2010**, 6153−6156.



Scheme 1.4. *Hydroxyl group-directed diastereoselective isomerization (Fehr)*.

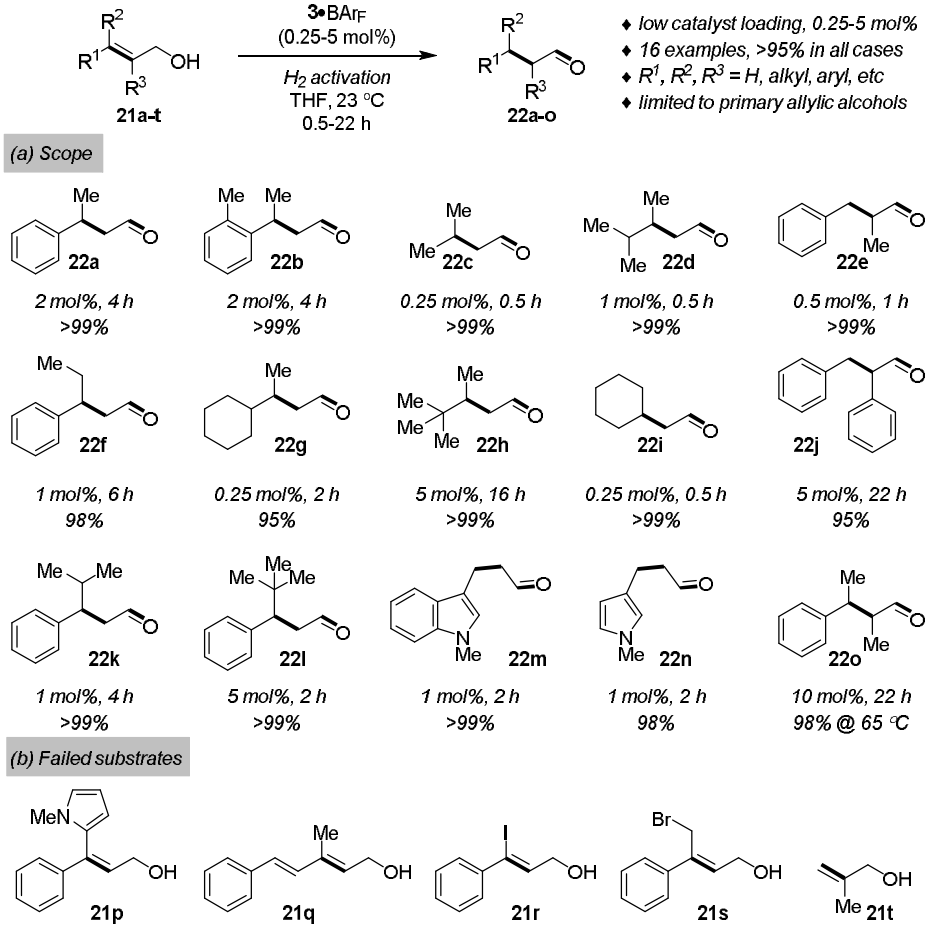
In 2009, the Mazet group reported an iridium-catalyzed isomerization of primary allylic alcohols **21** into the corresponding aldehydes **22** under very mild reaction conditions using achiral Crabtree catalyst **3**•BAr_F (Schemes 1.5 and 1.6).[8b,14] By simply modifying the original experimental procedure of hydrogenation (Scheme 1.5), isomerization occurred exclusively without any competing hydrogenation of the double bond. Specifically, upon the treatment of **3**•BAr_F with molecular hydrogen in anhydrous THF for 1 min, dihydride **23** is generated. Two freeze-pump-thaw cycles are then applied to the solution mixture in order to remove the excess of molecular hydrogen. The isomerization reaction is performed at ambient temperature after subsequent addition of a primary allylic alcohol into the cold solution and delivers exclusively the desired aldehyde **22** after the reaction.



Scheme 1.5. *Hydrogenation versus isomerization using Crabtree catalyst* ***3•BAr$_F$***.

[14] L. Mantilli, D. Gérard, C. Besnard, C. Mazet, *Eur. J. Inorg. Chem*. **2012**, 20, 3320–3330.

The reaction scope was generally broad (Scheme 1.6). Isomerization with 2,3-disubsituted, 3,3-disubstituted, and tertasubstituted primary allylic alcohols **21a**-**o** all delivered good results. Aryl, alkyl, and heterocyclic substituents were also tolerated under the reaction conditions. However, 3,3-diaryl substrate **21p**, cinnamyl conjugated substrate **21q**, and halogenated allylic alcohols **21r-s** failed to give the isomerization products.

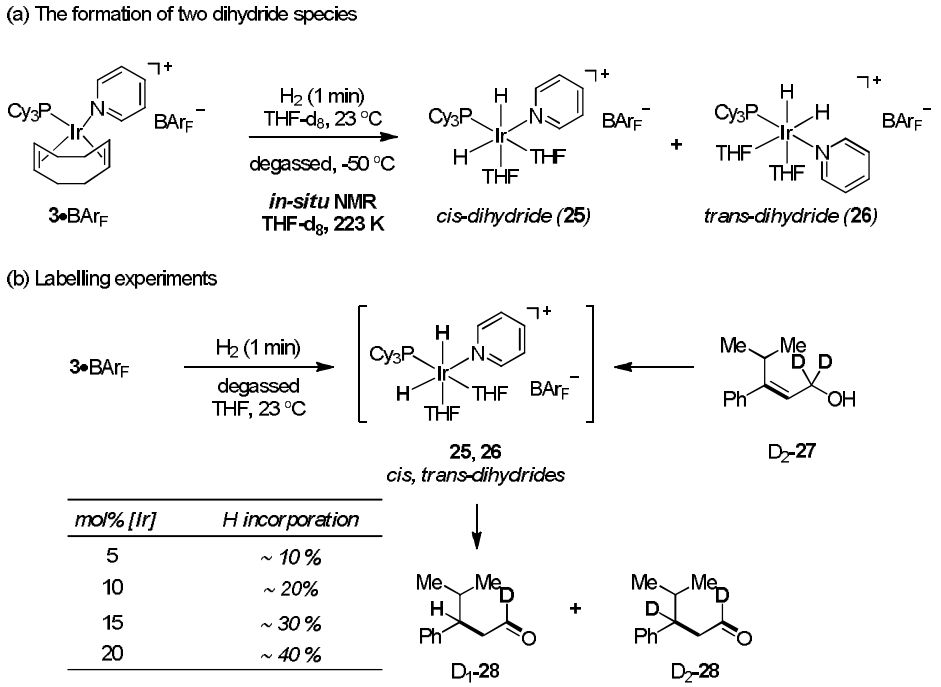


Scheme 1.6. *Isomerization of primary allylic alcohols into the corresponding aldehydes catalyzed by* ***3•BAr$_F$*** *(Mazet)*.

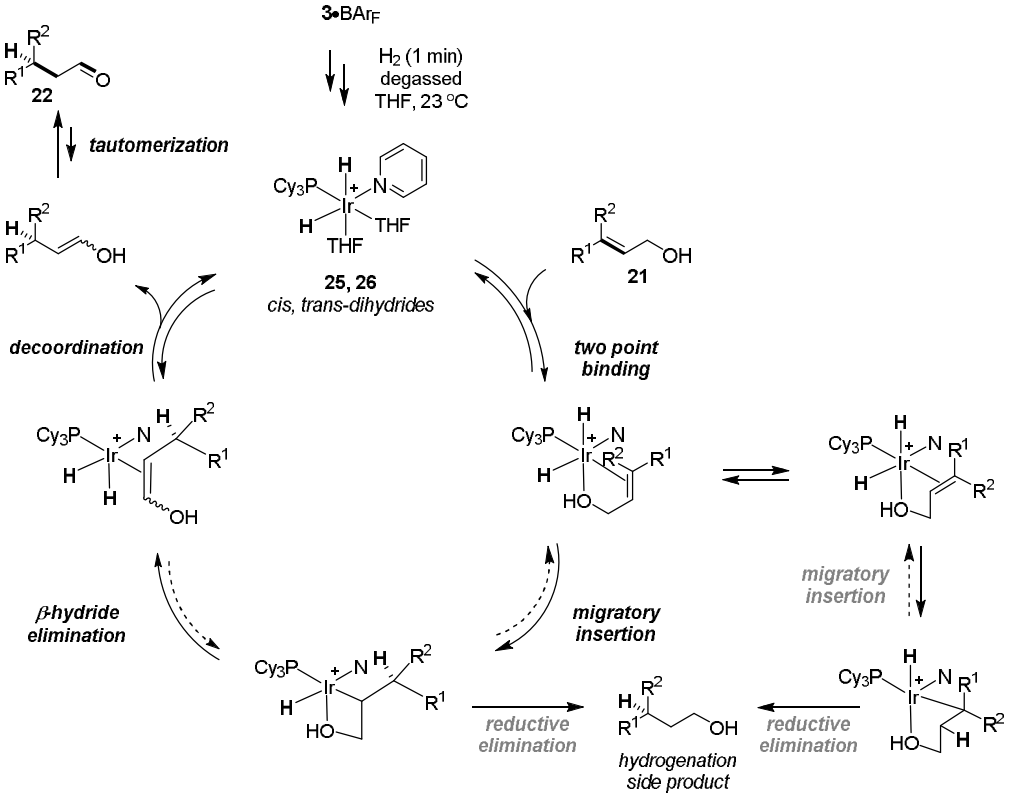
Mechanistic studies revealed that two distinct dihydride species (*cis*-dihydride **25** and *trans*-isomer **26**) were formed in-situ in THF-d_8 solution after activation with molecular hydrogen (Scheme 1.7a), as confirmed by multidimensional NMR experiments. Subsequent labelling and crossover experiments supported an intermolecular iridium hydride mechanism (Scheme 1.7b).

Finally, a catalytic cycle has been proposed based on detailed mechanistic studies (Scheme 1.8). A mixture of *cis*- and *trans*-dihydride species (**25** and **26**) is formed upon initial activation of **3**•BAr$_F$ with molecular hydrogen. The two-point binding of substrate **21** with iridium dihydrides followed by migratory insertion provides iridium-alkyl complex. Subsequent β-hydride elimination generates an enol-iridium dihydride intermediate. Final

decoordination regenerates the iridium dihydride species and releases the free enol. The tautomerization of enol delivers the desired aldehyde **22**.

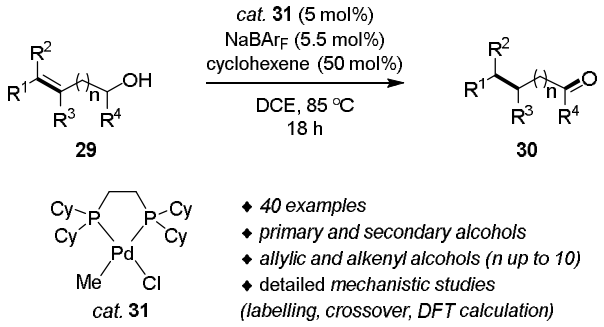


Scheme 1.7. *Detailed mechanistic studies.*



Scheme 1.8. *Proposed catalytic cycle.*

In 2014, as a continuation of the research on isomerization reactions using well-defined palladium hydride complex,[15] the Mazet group disclosed a general palladium precatalyst **31** for the isomerization of highly substituted allylic, homoallylic and alkenyl alcohols (Scheme 1.9).[16] Notable functional group tolerance has been demonstrated with more than 40 examples of primary and secondary allylic and alkenyl alcohols **29**. Detailed mechanistic studies including labelling, crossover experiments, as well as computational studies supported a chain-walking process involving iterative migratory insertion/β-H elimination sequences.



Scheme 1.9. *Palladium-catalyzed isomerization of allylic and alkenyl alcohols (Mazet).*

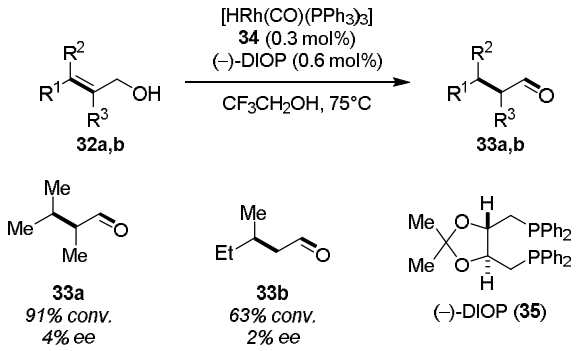
To summarize, in this chapter we introduced the transition metal-catalyzed isomerization of allylic alcohols into carbonyl compounds. Three general types of mechanism have been discussed, followed by the recent advances including the contributions from our group. Enantioselective isomerizations catalyzed by transition metal catalyst will be discussed in detail in the following section.

1.2 Transition Metal-Catalyzed Enantioselective Isomerization of Primary and Secondary Allylic Alcohols[4]

1.2.1 Early examples

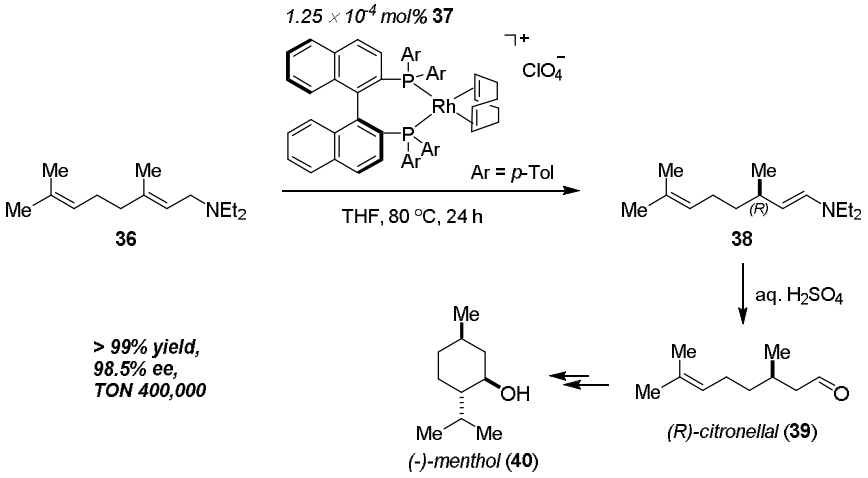
In 1976, Botteghi and Giacomelli reported the very first example of the asymmetric isomerization of primary allylic alcohols **32** into the corresponding aldehydes **33** (Scheme 1.10)[17]. Using $[HRh(CO)(PPh_3)_3]$ (**34**) as a precatalyst combined with (–)-DIOP (**35**) as the ligand, 2-4% *ee* were measured by the optical rotation.

[15] D. J. Vyas, E. Larionov, C. Besnard, L. Guénée, C. Mazet, *J. Am. Chem. Soc*. **2013**, *135*, 6177−6183.
[16] E. Larionov, L. Lin, L. Guénée, C. Mazet, *J. Am. Chem. Soc*. **2014**, *136*, 16882−16894.
[17] C. Botteghi, G. Giacomelli, *Gazz. Chim. Ital.* **1976**, *106*, 1131–1134.



Scheme 1.10. *The first asymmetric isomerization of allylic alcohols into the corresponding aldehydes*.

In the 1980s, a notable asymmetric isomerization of allylic amine **36** catalyzed by [(BINAP)Rh] cationic complex (**37**) has been developed (Scheme 1.11).[18] Further optimization and collaboration between academia and industry led to its final application into the ton-scale synthesis of (–)-menthol **40**, which still represents one of the milestone achievements in asymmetric homogeneous catalysis to date.[19]



Scheme 1.11. *[(BINAP)Rh]-catalyzed isomerization of allylic amines in 1980s*.

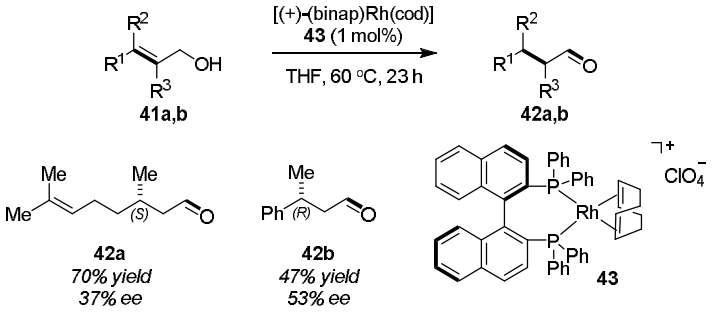
The same protocol has later been applied to the isomerization of allylic alcohols (Scheme 1.12).[20] Whereas both primary and secondary allylic alcohols **41** showed excellent reactivity during the isomerization reaction, only inferior enantioinduction was observed as shown by two examples. After systematic screening of numerous privileged chiral ligands for the $[Rh(cod)_2](OTf)$-catalyzed asymmetric isomerization of geometrically pure geraniol and nerol, Chapuis and co-workers at Firmenich drew a similar conclusion that BINAP again

[18] (a) H. Kumobayashi, S. Akutagawa, S. Otsuka, C. Botteghi, G. Giacomelli, *J. Am. Chem. Soc*. **1978**, *100*, 3949−3950; (b) K. Tani, T. Yamagata, S. Otsuka, A Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, *J. Chem. Soc., Chem. Commun*. **1982**, 600−601; (c) K. Tani, T. Yamagata, A Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, S. Otsuka, *J. Am. Chem. Soc*. **1984**, *106*, 5208−5217; (d) S.-i. Inoue, H. Takaya, K. Tani, S. Otsuka, T. Sato, R. Noyori, *J. Am. Chem. Soc*. **1990**, *112*, 4897−4905.

[19] (a) S. Akutagawa, *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Eds., Springer: Berlin, **1999**, Chapter 23, vol. 2, pp. 813–832; (b) S. Akutagawa, *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Eds., Springer: Berlin, **1999**, Chapter 41.1, vol. 3, pp. 1461–1472.

[20] K. Tani, *Pure Appl. Chem*. **1985**, 57, 1845–1854.

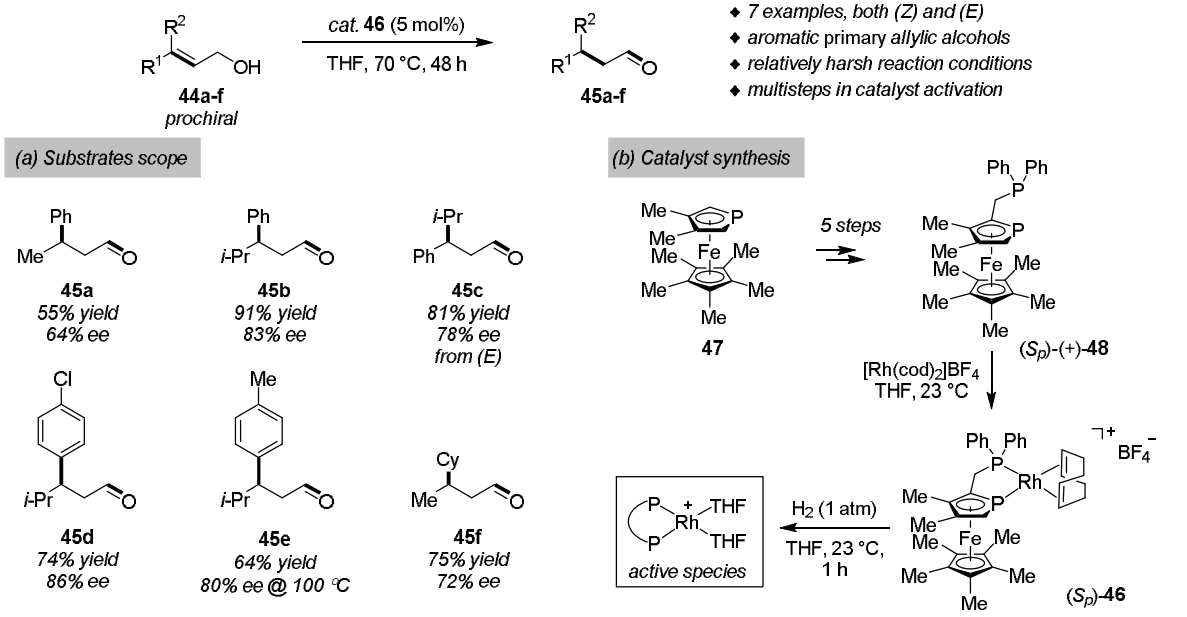
gave the optimal results.[21] Up to 60% *ee* and 51% *ee* were obtained for geraniol and nerol respectively.[22]



Scheme 1.12. *[(BINAP)Rh]-catalyzed isomerization of primary allylic alcohols*.

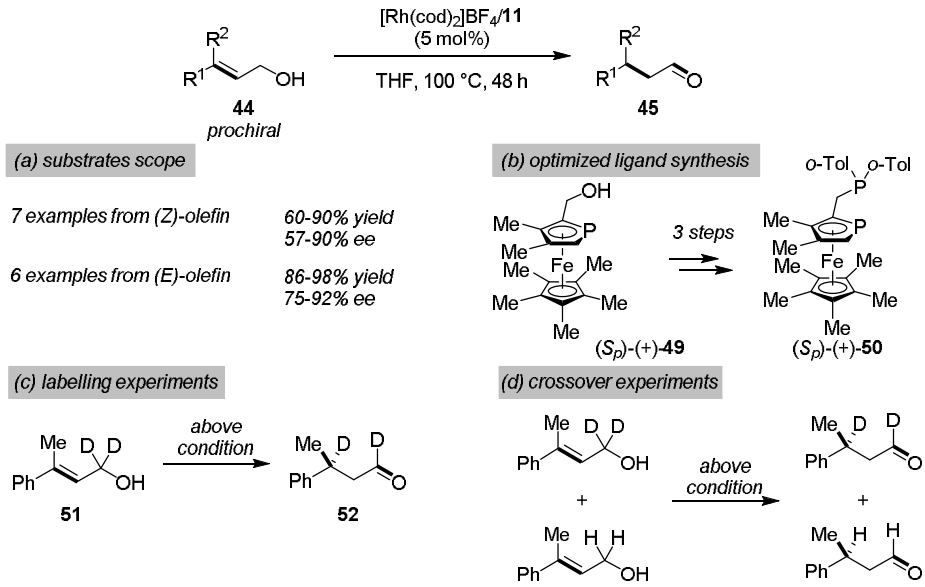
1.2.2 Recent advances

In 2000, the real breakthrough in the enantioselective isomerization of primary allylic alcohols has been reported by Fu and co-workers (Scheme 1.13).[23a] Using Rh/chiral planar phosphaferrocene complex (**46**), they were able to establish the enantioselective isomerization with good levels of enantioselectivity. A relatively narrow susbtrate scope was reported using mainly aromatic primary allylic alcohols **44** (7 examples)



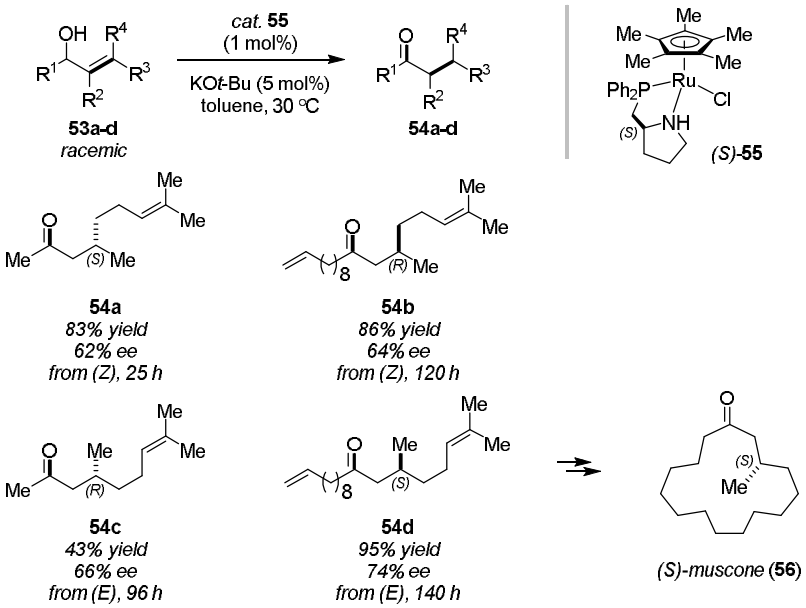
Scheme 1.13. *Enantioselective isomerization of primary allylic alcohols into the corresponding aldehydes (Fu)*.

[21] (a) T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693; (b) *Privileged Chiral Ligands and Catalysts*, Q.-L. Zhou, Ed., Wiley-VCH: Weinheim, **2011**.
[22] C. Chapuis, M. Barthe, J.-Y. Saint Laumer, *Helv. Chim. Acta* 2001, 84, 230–239.
[23] (a) K. Tanaka, S. Qiao, M. Tobisu, M. M. C. Lo, G. C. Fu, *J. Am. Chem. Soc*. **2000**, *122*, 9870–9871; (b) K. Tanaka, G. C. Fu, *J. Org. Chem*. **2001**, *66*, 8177–8186.



Scheme 1.14. *Scope and mechanistic studies of enantioselective isomerization of primary allylic alcohols (Fu).*

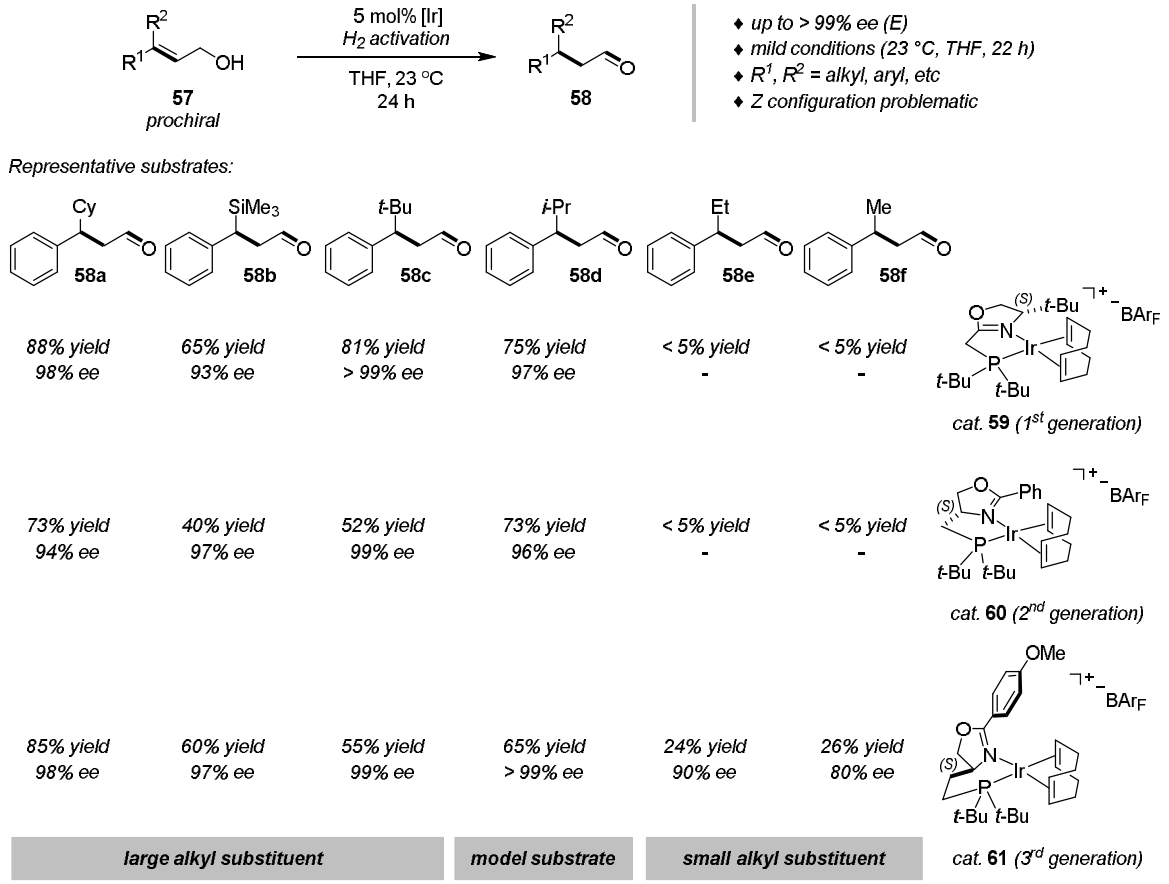
In 2001, after a further optimization by introducing a new chiral planar phosphaferrocene ligand **50** (Scheme 1.14),[23b] the Fu group obtained improved substrate scope, enantioselectivity and yield after the isomerization reaction. Extensive mechanistic studies (labelling and crossover experiments) supported an intramolecular 1,3-hydrogen shift mechanism. However, the harsh reaction conditions and the limited accessibility of the chiral ligands prevented its further application.



Scheme 1.15. *Enantioselective isomerization of racemic secondary allylic alcohols (Ikariya).*

The number of successful examples in enantioselective isomerization of racemic secondary allylic alcohols is rather limited compared to the steady progress using prochiral

primary allylic alcohols.[24] In 2005, using chiral ruthenium complex (*S*)-**55**, the Ikariya group reported the enantioselective isomerization of secondary allylic alcohols **53** into the corresponding ketones **54** (Scheme 1.15).[25] Labelling experiments supported an intramolecular 1,3-hydrogen shift mechanism. Good levels of enantioselectivity (62-74% *ee*) were obtained with limited examples. Starting from **54d**, they also reported the synthesis of (*S*)-muscone (**56**).

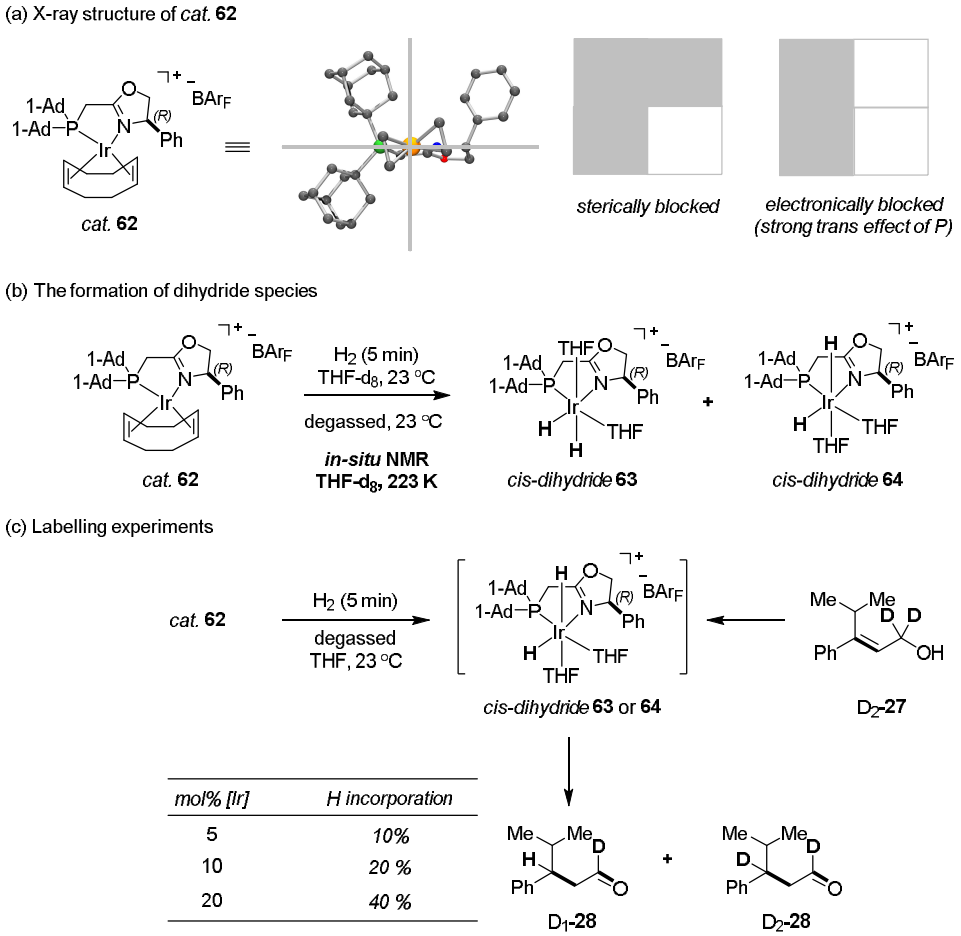


Scheme 1.16. *Enantioselective isomerization of primary allylic alcohols into the corresponding aldehydes (Mazet).*

After establishing the isomerization protocol using the achiral catalyst **3**•BAr_F, the Mazet group subsequently explored an asymmetric isomerization using various chiral analogues of **3**•BAr_F. Three generations of different iridium (P,N) complexes **59**-**61** have been synthesized in pratical yields starting from commercially available amino acids. The high modularity and accessibility of these chiral iridium (P,N) complexes allowed a subsequent screening of the reaction conditions (Scheme 1.16). The aldehydes were obtained in good yields under the

[24] (a) M. Kitamura, K. Manabe, R. Noyori, *Tetrahedron Lett.* **1987**, *40*, 4719–4720; (b) K. Hiroya, Y. Kurihara, K. Ogasawara, *Angew. Chem. Int. Ed.* **1995**, *34*, 2287–2289.
[25] M. Ito, S. Kitahara, T. Ikariya, *J. Am. Chem. Soc.* **2005**, *127*, 6172–6173.

optimal conditions with up to >99% *ee*.[8c,26]. However, substrates containing either small alkyl susbtitutents or two alkyl substitutents at C3 showed low reactivity and poor enantioselectivity during the isomerization, which was concurrently concomitant with the competing *E/Z* isomerization of the starting material. The allylic alcohols with (*Z*)-configuration were also less reactive and problematic in this isomerization.

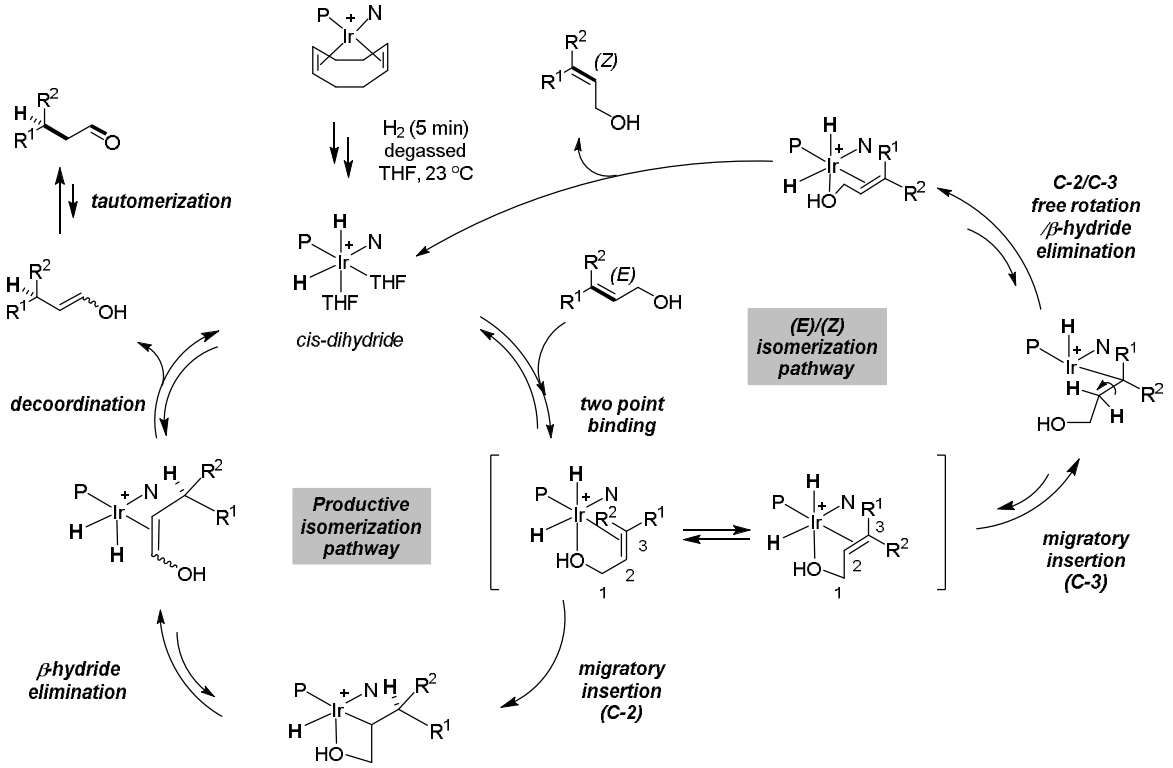


Scheme 1.17. *Mechanistic studies for the enantioselective isomerization of primary allylic alcohols*.

Detailed mechanistic studies have also been conducted using one of the first generation catalyst **62** (Scheme 1.17).[8c] Specifically, X-ray crystallographic analysis of catalyst **62** showed that three of the four quadrants are spatially occupied from a steric point of view (Scheme 1.17a),[27,28] two by the bulky adamantyl susbtituents on the phosphorus atom and one by the phenyl ring of the oxazoline ring. Multidimensional NMR experiments proved the existence of *cis*-dihydride species **63** or **64** after activation with molecular hydrogen ($^2J_{HP}$ = 20 Hz), albeit the position of the apical hydride could not be unambiguously assigned (Scheme 1.17b). Finally, labelling experiments supported the intermolecular metal hydride

[26] (a) L. Mantilli, C. Mazet, *Chem. Commun.* **2010**, *46*, 445−447; (b) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem.−Eur. J.* **2010**, *16*, 12736−12745.
[27] The representations of all X-ray structures reported in this manuscript were generated using CYLview (Legault, C. Y.: CYLview, version 1.0.561b; Université de Sherbrooke: Sherbrooke, QC, 2009, http://www.cylview.org.).
[28] (a) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106−112; (b) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998−2007.

mechanism, where both hydrides have been transferred from the active species of the catalyst to the final product (Scheme 1.17c).

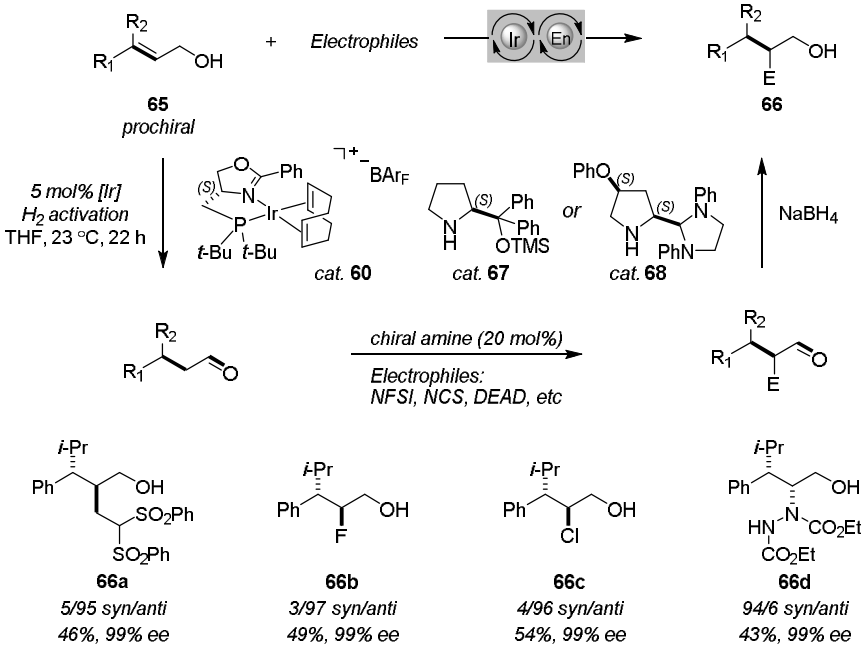


Scheme 1.18. *Proposed catalytic cycle*.

Based on the experimental results and the mechanistic studies, a catalytic cycle has been proposed accordingly (Scheme 1.18). Activation of precatalyst with molecular hydrogen in THF solution leads to the formation of a *cis*-dihydride species. The conformational binding of the substrate with the iridium dihydride is crucial because the stereochemistry of the final product is installed at this stage. Subsequent migratory insertion of the first hydride can potentially occur at the C2 or C3 position of the allylic alcohol. Migratory insertion at C2 followed by β-hydride elimination and decoordination regenerates the *cis*-iridium species as well as the enol, which further tautomerizes into the corresponding enantioenriched aldehyde. On the other hand, migratory insertion at C3 would result in free rotation of C2–C3 bond followed by β-hydride elimination to yield (*Z*)-allylic alcohol.

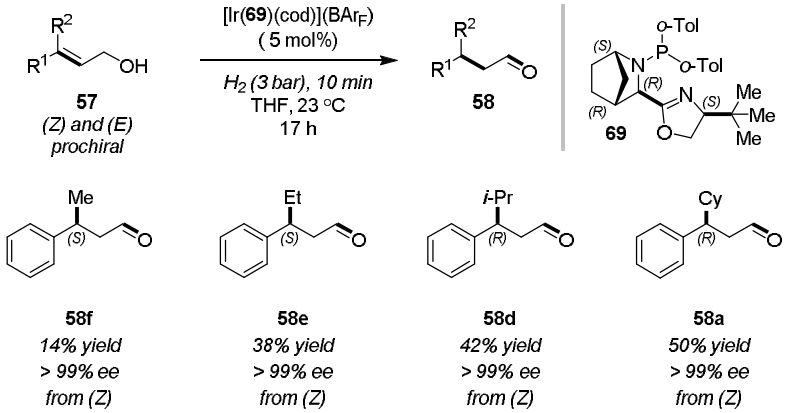
In 2011, in collaboration with the Alexakis group, the Mazet group reported a one-pot asymmetric reaction to access acyclic α,β-chiral aldehydes (Scheme 1.19).[29] While the initial isomerization reaction proceeded smoothly in the presence of iridium catalyst **60**, various organocatalyzed α-functionalizations of aldehydes were found to be compatible. Thus, acyclic α,β-chiral aldehydes can be obtained in good yields, *dr* and excellent enantioselectivity using this sequential strategy.

[29] A. Quintard, A. Alexakis, C. Mazet, *Angew. Chem. Int. Ed.* **2011**, *50*, 2354–2358.



Scheme 1.19. *Sequential isomerization/enantioselective α-functionalization of aldehydes*.

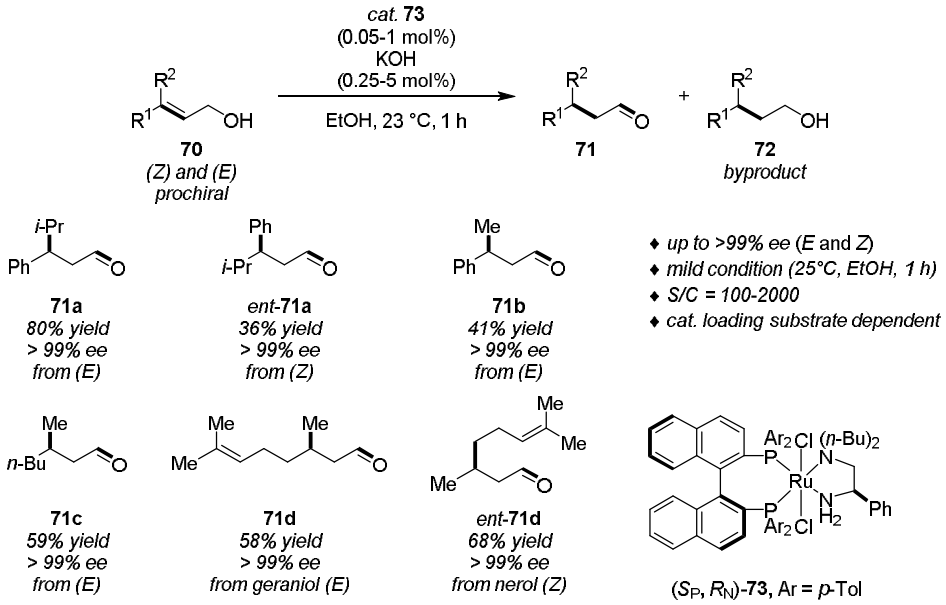
In 2011, using their own iridium (P,N) complexes which have been previously applied to the asymmetric hydrogenation of olefins,[30] the Andersson group reported another example of enantioselective isomerization of primary allylic alcohols **57** into aldehydes **58** (Scheme 1.20).[31] Similarly to the previous results from the Mazet group,[8c,26] high yields and excellent levels of enantioselectivity were generally obtained using (*E*)-substituted aromatic primary allylic alcohols. As for (*Z*)-substituted allylic alcohols, the aldehydes could also be obtained with up to >99% *ee* albeit with low to moderate yields.



Scheme 1.20. *Enantioselective isomerization of primary allylic alcohols into the corresponding aldehydes (Andersson).*

[30] For recent reviews on asymmetric hydrogenation with Ir-P,N catalysts, see: (a) K. Källström, I. Munslow, P. G. Andersson, *Chem.−Eur. J*. **2006**, *12*, 3194–3200; (b) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res*. **2007**, *40*, 1402–1411; (c) T. L. Church, P. G. Andersson, *Coord. Chem. Rev*. **2008**, *252*, 513–531.
[31] J.-Q. Li, B. Peters, P. G. Andersson, *Chem.−Eur. J*. **2011**, *17*, 11143–11145.

Recently, the Ohkuma group reported an efficient enantioselective isomerization of primary allylic alcohols into the corresponding aldehydes catalyzed by the [$RuCl_2$(*tol*-binap)-(dbapen)]/KOH system in ethanol (Scheme 1.21).[32] The Ohkuma protocol is exceptional due to the very low catalyst loading (0.05-1 mol%). The isomerization is effective at ambient temperature with a wide variety of primary allylic alcohols. Perfect enantioselectivity is generally obtained. Labelling experiments also supported an intramolecular 1,3-hydrogen shift mechanism. However, the contamination with fully reduced alcohol **72** and the lack of uniform reaction conditions may prevent further application of this prominent method.



Scheme 1.21. *Enantioselective isomerization of primary allylic alcohols into the corresponding aldehydes (Ohkuma)*.

To conclude, in this chapter we discussed the recent developments in the enantioselective isomerization of allylic alcohols into the corresponding carbonyl compounds. Several groups reported the highly efficient enantioselective isomerization reactions of primary allylic alcohols in recent years, including three generations of iridium (P,N) catalysts established in our group. On the other hand, the lack of efficient methods for the enantioselective isomerization of secondary allylic alcohols to date still calls for the continuous endeavor in this field in the near future.

[32] N. Arai, K. Sato, K. Azuma, T. Ohkuma, *Angew. Chem. Int. Ed.* **2013**, *52*, 7500−7504.

1.3 Objectives

Efficient enantioselective isomerization methods have been independently reported by our group and others in recent years. However, the application of this highly economic process has barely been documented to date. In this thesis we evaluate multi-functionalized allylic alcohols to establish a novel and synthetically useful selective isomerization method.

At the outset of our investigations, the main goals of this thesis were as follows:

a) To explore the isomerization reactions using allylic alcohols with a pre-installed adjacent carbon stereocenter, we initially planned to investigate the effect of steric variations from both substrates and catalysts on the stereoselective outcome of the reaction. Subsequently using both enantiomers of chiral iridium catalysts, we aimed to develop catalyst-directed diastereoselective isomerizations by employing both acyclic and cyclic substrates. This work will be described in Chapter 2.
b) In Chapter 3, we disclosed the continuation of the approach followed in Chapter 2. The interest of developing catalyst-controlled diastereoselective methods is to later apply them in advanced and stereochemically complex molecular architectures. We anticipated that the knowledge gained on simple acyclic and cyclic substrates could be translated to complex steroidal derivatives. Not only would we be able to tackle the so-called 'C20 challenge' (the first *exocyclic* tertiary stereocenter of the steroid side chains) by stereocontrolled installation of the stereochemistry at C20, but we could also provide an efficient access to a collection of both C20-(*R*) ('*natural*') and C20-(*S*) ('*unnatural*') isomers. These might be of biological relevance due to the distinct biological activity measured for the very rare examples reported in the literature.
c) In Chapter 4, we describe the optimization of a vinylogous Peterson elimination reaction that was discovered serendipitously during the optimization of the catalyst controlled isomerization of steroidal derivatives described in Chapter 3. Reaction optimization, preliminary mechanistic studies, and substrate scope will be disclosed.

1.4 References

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Chapter 2. Catalyst-Directed Diastereoselective Isomerization of Allylic Alcohols for the Construction of Vicinal Tertiary Stereocenters

2.1 Principle of Catalyst-Directed Diastereoselective Reactions and Our Strategy

2.1.1 General introduction

The development of catalytic enantioselective reactions starting from prochiral substrates is an essential task in contemporary synthetic chemistry.[1] However, substantially more difficult is the development of diastereoselective methods from advanced intermediates possessing multiple stereogenic centers, where a chiral catalyst must control the stereochemical outcome of new stereocenters regardless of a highly complex environment.[2] Multianalysis of the influence from both substrate and catalyst is generally required to design efficient catalyst-directed diastereoselective reactions.[3]

During a reaction employing a chiral catalyst **Cat*** and a chiral substrate **A***, diastereomeric products **C*** and **C*′** are formed. The stereochemical control elements from the substrate (internal diastereocontrol) and from the catalyst (external diastereocontrol) can behave either constructively (match effect) or destructively (mismatch effect). Thus, these internal or external diastereocontrols may predominate and account for the final product ratio observed.

As shown in Schemes 2.1 and 2.2, when a reaction displays a 10:1 diastereomeric ratio at ambient temperature using a chiral substrate **A*** and an achiral catalyst **Cat**, the energy difference between the two reaction pathways is 1.4 kcal/mol. For analogous reactions which give the product in a 10:1 enantiomeric ratio with an achiral substrate **A** and either enantiomer of a chiral catalyst (**Cat*** or ***ent*-Cat***), the energy difference between the two reaction pathways is again 1.4 kcal/mol (Schemes 2.1b and 2.2b, c).

After combining the chiral substrate **A*** with the chiral catalyst **Cat***, one can expect two distinct stereochemical outcomes.

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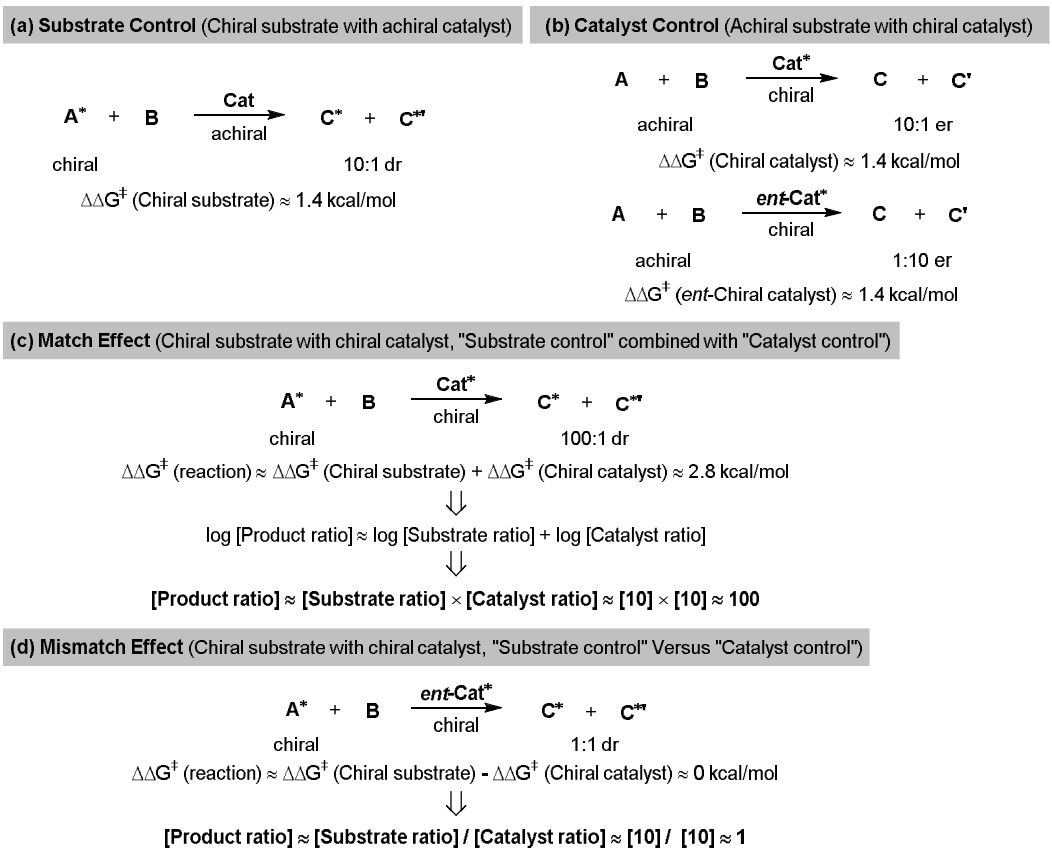
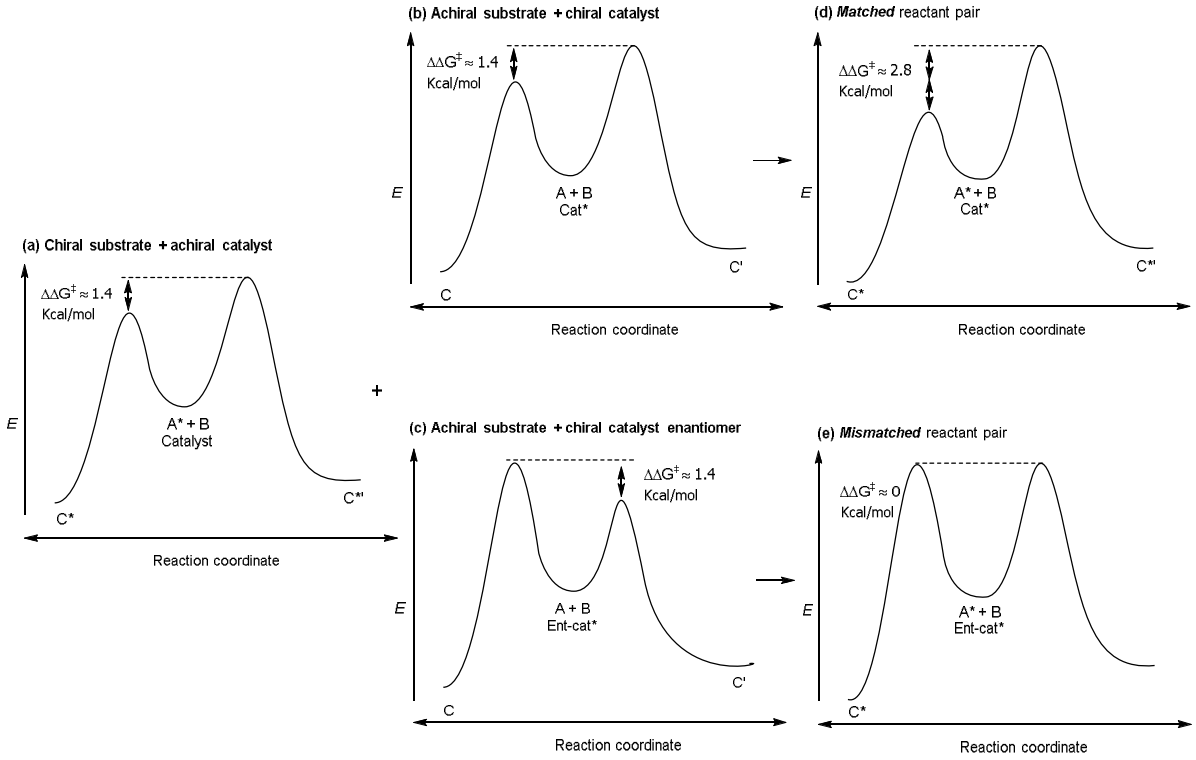


Scheme 2.1. *Match-mismatch effect in catalyst-directed diastereoselective reactions*.



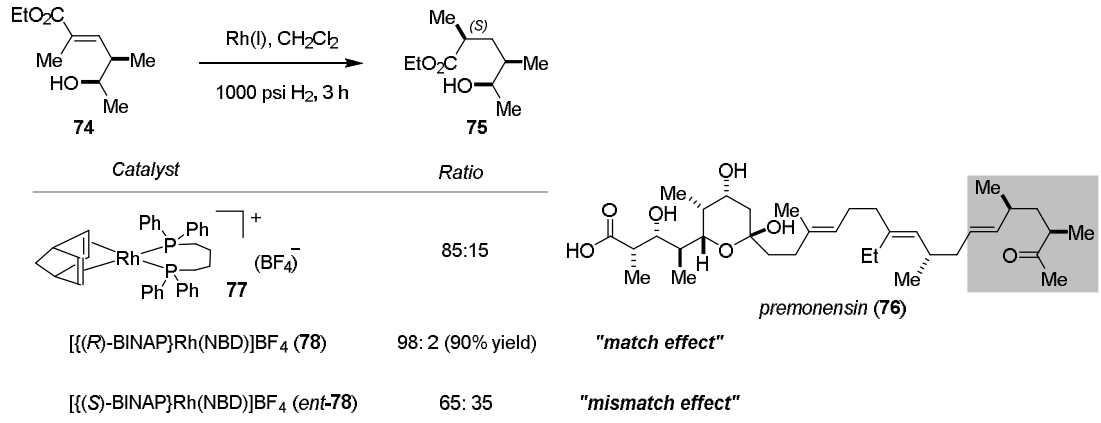
Scheme 2.2. *Match-mismatch effect illustrated by reaction coordinate diagrams.*

(1) A match effect occurs when substrate control and catalyst control both favor the formation of the same configuration (see Schemes 2.1c, 2.2d). The energy difference between the two reaction pathways raises to 2.8 kcal/mol, and the diastereomeric ratio measured is 100:1.
(2) A mismatch effect takes place when substrate control and catalyst control act oppositely and generate products of opposite absolute configurations (Schemes 2.1d and 2.2e). In such a case the energy difference is 0 kcal/mol and the diastereomeric ratio measured is 1:1.

In the following paragraph, we discuss only two representative examples to illustrate these principles.

2.1.2 Selected examples

In 1986, *en route* to premonensin (**76**),[4] the Evans group conducted a catalytic hydrogenation of enoate **74** (Scheme 2.3). While the achiral catalyst [(dppb)Rh(NBD)](BF_4) (**77**) gave a 85:15 ratio with (*S*)-**75** as the major isomer. Further optimization of this hydrogenation showed that reduced product (*S*)-**75** was obtained in a 98:2 ratio with catalyst **78** due to a match situation. A 65:35 ratio was obsereved in the presence of *ent*-**78**, indicative of mismatch effects.



Scheme 2.3. *Catalyst-directed diastereoselective hydrogenation reactions (Evans)*.

In 2002, the Jacobsen group reported a remarkable example of catalyst-directed diastereoselective hetero-Diels-Alder (Scheme 2.4).[5] With a broad range of enantioenriched aldehydes **80**, excellent diastereocontrol was observed in both match and mismatch situations, using the chiral Cr catalyst **83**.

[4] D. A. Evans, M. DiMare, *J. Am. Chem. Soc.* **1986**, *108*, 2476–2478.
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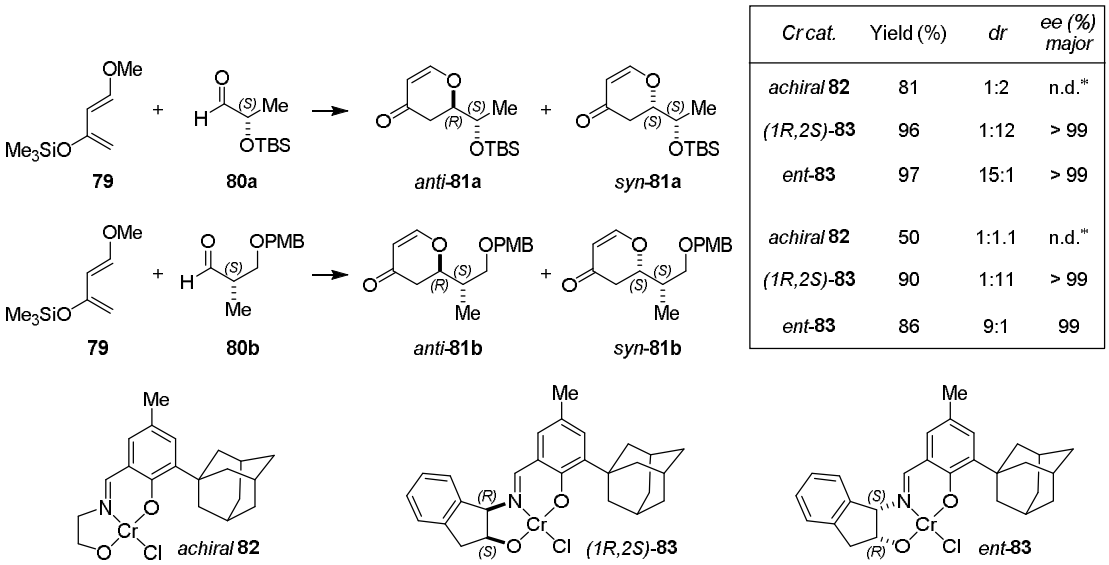
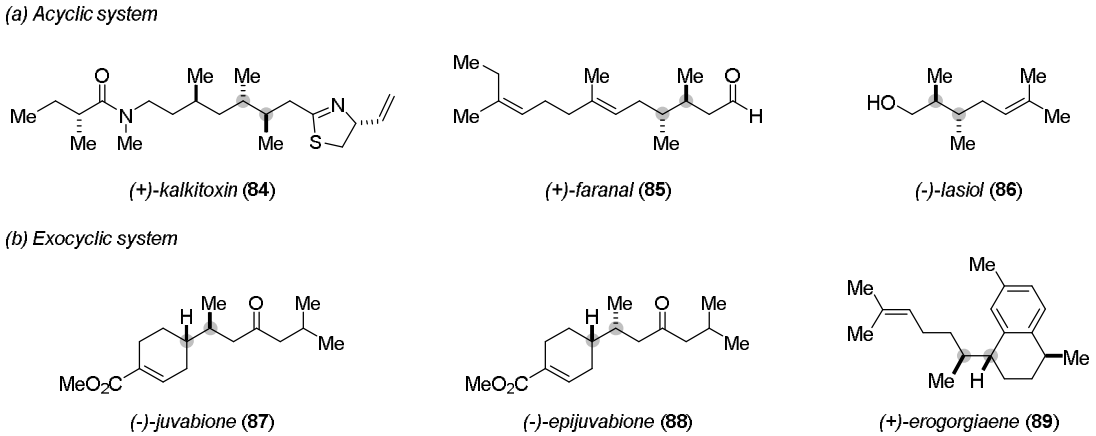


Cr cat.	Yield (%)	dr	ee (%) major
achiral **82**	81	1:2	n.d.*
(1R,2S)-**83**	96	1:12	> 99
ent-**83**	97	15:1	> 99
achiral **82**	50	1:1.1	n.d.*
(1R,2S)-**83**	90	1:11	> 99
ent-**83**	86	9:1	99

Scheme 2.4. *Catalyst-directed diastereoselective hetero-Diels-Alder reactions (Jacobsen). *n.d. = not determined.*

2.1.3 Our strategy to access vicinal tertiary stereogenic carbon centers

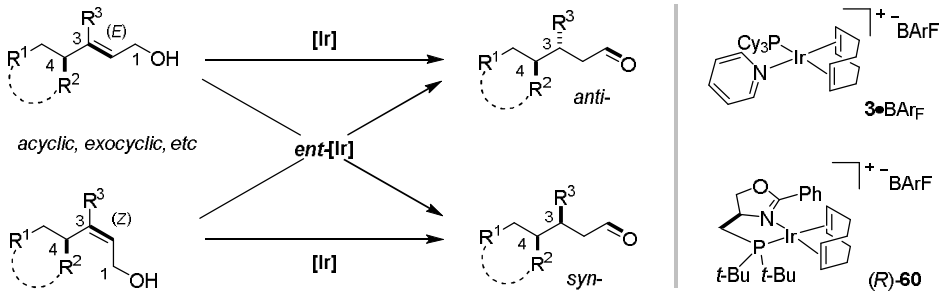


Scheme 2.5. *Representative biological active natural products **84-89** bearing vicinal tertiary stereogenic carbon centers.*

Natural products continuously serve as an inspiration for the development of new methodologies, which in turn facilitate the synthesis of natural products as well as their structural analogues for subsequent biological validation. Complex molecules bearing vicinal tertiary stereogenic carbon centers are commonly found in nature (Scheme 2.5). For example, the insect pheromones (+)-faranal (**85**), and (−)-lasiol **86** all contain *acyclic* vicinal tertiary carbon centers. On the other hand, (−)-juvabione (**87**), and (+)-erogorgiaene (**89**) are representative sesquiterpenes with *exocyclic* vicinal tertiary stereocenters. Numerous synthetic efforts have been engaged for the synthesis of individual natural products during

the last decades. From a strategic point of view, a unified method which could provide access to both *acyclic* and *exocyclic* vicinal tertiary carbon centers in a stereocontrolled manner would streamline access to this recurrent motif.

Based on the enantioselective isomerization of achiral allylic alcohols recently developed in our laboratory,[6] we envisaged the possibility to employ a chiral substrate with an adjacent tertiary carbon center at C4 (Scheme 2.6). If successful, such a strategy would provide direct access to the corresponding aldehyde bearing vicinal tertiary carbon centers at C3 and C4. Catalyst-directed diastereoselective isomerization with either enantiomer of a chiral iridium catalyst could ideally furnish *anti* and *syn*-aldehydes at will.



Scheme 2.6. *Catalyst-directed diastereoselective isomerization to access vicinal tertiary carbon centers*.

Our previous observations revealed that the stereoselective outcome in the Ir-catalyzed isomerization of allylic alcohols depends on the olefin geometry.[6] Our initial strategy was built upon the well-established selectivity principle for prochiral olefinic substrates in stereospecific transformations (Scheme 2.6).[1,3] Such a strategy has rarely been practiced for elaborated structures possessing stereocenters at close proximity of the reactive olefin. It is also worth mentioning that the lower reactivity and selectivity typically observed in the enantioselective isomerization of (Z)-allylic alcohols in our previous studies were additional source of uncertainty to the success of this approach.[6]

2.2 Diastereoselective Isomerization of Racemic *Acyclic* Primary Allylic Alcohols

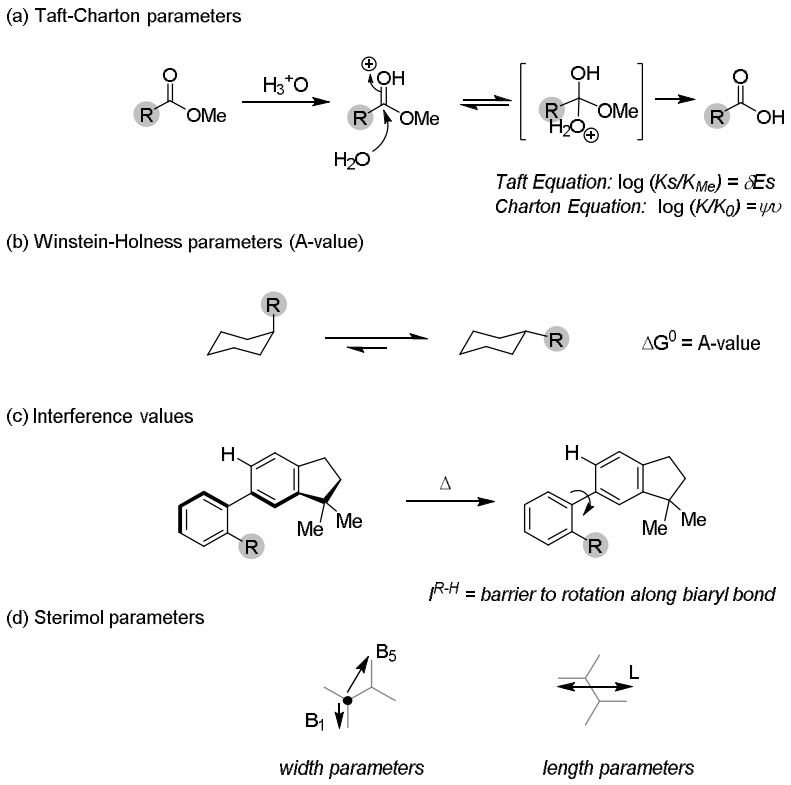
We commenced our study with diastereoselective isomerization of racemic *acyclic* primary allylic alcohols. During our previous inverstigations on the iridium-catalyzed enantioselective isomerization of prochiral primary allylic alcohols, we have shown that excellent Linear Free Energy Relationships (LFER) could be obtained by correlating log(*er*) with the steric parameters of the substrate substituent. This eventually led to the design of a

[6] (a) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, 48, 5143−5147; (b) L. Mantilli, C. Mazet, *Chem. Commun.* **2010**, *46*, 445−447; (c) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem.−Eur. J.* **2010**, *16*, 12736−12745.

third generation of catalysts (*cat.* **61**, see Scheme 1.16).[6c] As a direct continuation of this work, we questioned whether LFER could also be elaborated for the diastereoselective isomerization of racemic primary allylic alcohols with a vicinal stereocenter using achiral iridium catalysts. Of important note, examples of such analysis for diastereoselective transformation are much less common.[7]

2.2.1 General introduction to the steric descriptors

One of the challenges associated with our study was the identification of appropriate reference steric parameters for the linear free-energy relationship analysis. As shown in Scheme 2.7a, Taft steric parameters were first developed in the 1950s based on the relative rate of acid-catalyzed hydrolysis of methyl esters.[8] Later, by taking inductive and resonance factors into account, Charton modified Taft's original experimental results and introduced Charton values (ν).[9]



Scheme 2.7. *Most common steric parameters.*

[7] (a) W. Adam, C. M. Mitchell, C. R. Saha-Möller, *Eur. J. Org. Chem.* **1999**, 785−790; (b) B. Meynhardt, U. Lüning, C. Wolff, C. Näther, *Eur. J. Org. Chem*. **1999**, 2327−2335; (c) L. You, J. S. Berman, A. Lucknasawichien, E. V. Anslyn, *J. Am. Chem. Soc.* **2012**, *134*, 7126−7134.
[8] (a) R. W. Taft Jr., *J. Am. Chem. Soc*. **1952**, *74*, 3120–3128; (b) R. W. Taft Jr., *J. Am. Chem. Soc*. **1953**, *75*, 4538–4539.
[9] (a) M. Charton, *J. Am. Chem. Soc*. **1975**, *97*, 1552–1556; (b) M. Charton, *J. Am. Chem. Soc*. **1975**, *97*, 3691–3693; (c) M. Charton, *J. Org. Chem*. **1976**, *41*, 2217–2220.

The Winstein-Holness values (A-value, Scheme 2.7b),[10] another typical widely recognized steric parameters, arise from the conformational study of mono-substituted cyclohexane rings. A-values are based on the observed equilibrium of conformers caused by 1,3-diaxial steric repulsions. Interefence values are another example of an experimentally determined steric parameter (Scheme 2.7c).[11] These values are normally based on the heat-induced half-life of racemization in 2,2'-substituted biphenyl systems.

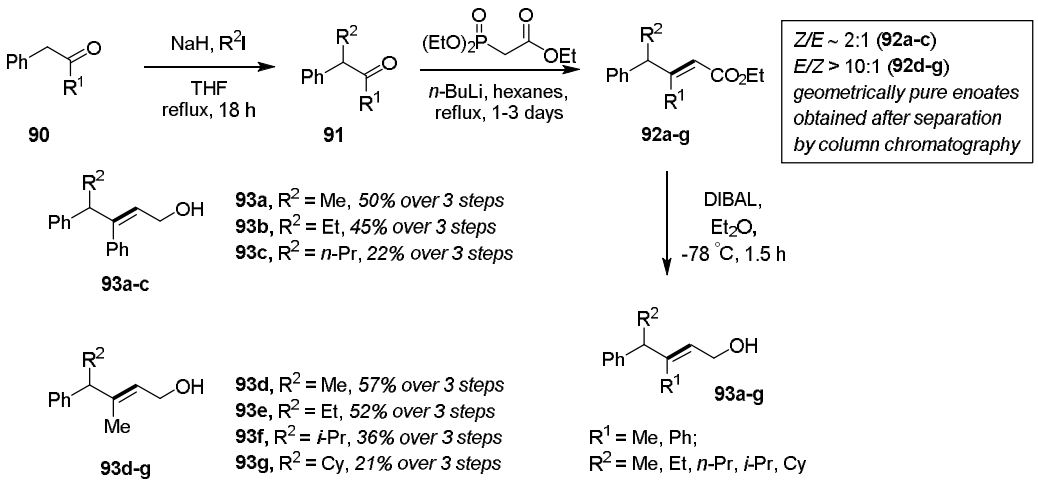
Finally, introduced by Verloop and co-workers in 1970s (Scheme 2.7d),[12] Sterimol parameters are distinguishable from the other steric parameters. To describe different dimensional properties for a single substituent, three subparameters are created: two width parameters (minimum width B_1, and maximum width B_5) and a length parameter (*L*). Additionally, values reported in dimensional units (Å) also provide more detailed information about the nature of a steric effect.

Recently, Sigman and co-workers have demonstrated that Charton and Sterimol parameters can be appropriately used in the context of enantioselective catalysis.[13] They convincingly established that the log of the enantiomeric ratio (*er*) of various enantioselective transformations can be correlated with descriptors of the size of the substituents of either the chiral ligands or of the substrates.

*2.2.2 Preparation of racemic acyclic primary allylic alcohols **93a-g***

Since the aryl/alkyl and alkyl/alkyl primary allylic alcohols behave differently in the Ir-catalyzed enantioselective isomerization,[6,14] racemic substrates belonging to these two categories were synthesized (Scheme 2.8). Starting from commercially available ketones using a 3-step procedure, the geometrically pure allylic alcohols **93a-g** were obtained in practical yields following a Horner-Wadsworth-Emmons reaction/DIBAL reduction sequence.

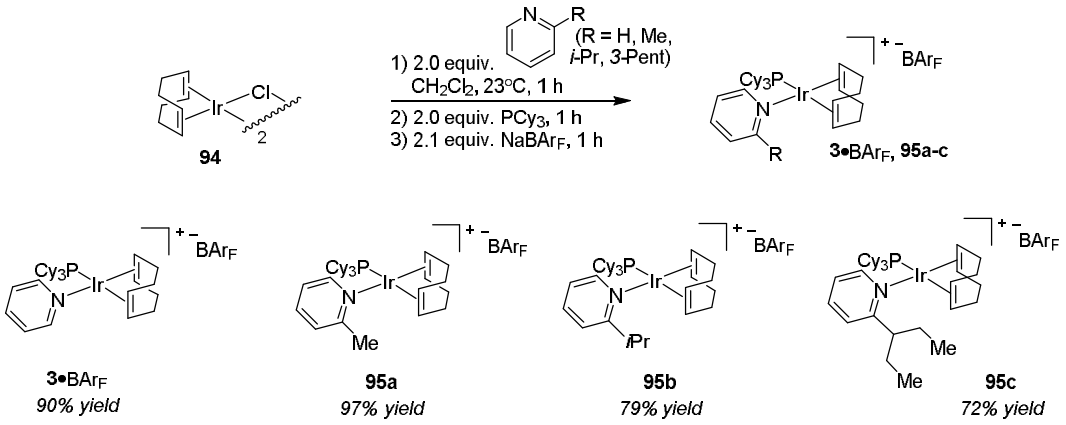
[10] S. Winstein, N. J. Holness, *J. Am. Chem. Soc.* **1955**, *77*, 5562–5578.
[11] (a) R. Adams, H. C. Yuan, *Chem. Rev*. **1933**, *12*, 261–338; (b) G. Bott, L. D. Field, S. Sternhell, *J. Am. Chem. Soc*. **1980**, *102*, 5618–5626.
[12] (a) A. Verloop, *Drug Design*, E. J., Ariens, Ed., Academic Press: New York, **1976**, Vol. III, p 133; (b) A. Verloop, J. Tipker, *Biological Activity and Chemical Structure*, J. A. Buisman, Ed., Elsevier: Amsterdam, **1977**, p 63; (c) A. Verloop, J. Tipker, *QSAR in Drug Design and Toxicology*, D. Hadzi, B. Jerman-Blazic, Eds., Elsevier: Amsterdam, **1987**, p 97; (d) A. Verloop, *IUPAC Pesticide Chemistry*, J. Miyamoto, Ed., Pergamon: Oxford, **1983**, Vol. 1, p 339.
[13] (a) J. J. Miller, M. S. Sigman, *Angew. Chem. Int. Ed.* **2008**, *47*, 771–774; (b) M. S. Sigman, J. J. Miller, *J. Org. Chem*. **2009**, *74*, 7633–7643; (c) K. C. Harper, M. S. Sigman, *Proc. Natl. Acad. Sci. U. S. A*. **2011**, *108*, 2179–2183; (d) K. C. Harper, M. S. Sigman, *Science* **2011**, *333*, 1875–1878; (e) K. C. Harper, E. N. Bess, M. S. Sigman, *Nat. Chem*. **2012**, *4*, 366–374; (f) K. C. Harper, S. C. Vilardi, M. S. Sigman, *J. Am. Chem. Soc*. **2013**, *135*, 2482–2485; (g) K. C. Harper, M. S. Sigman, *J. Org. Chem*. **2013**, *78*, 2813–2818.
[14] For details see Chaper 1.2.2.



Scheme 2.8. *General procedure for the synthesis of racemic substrates **93a-g**.*

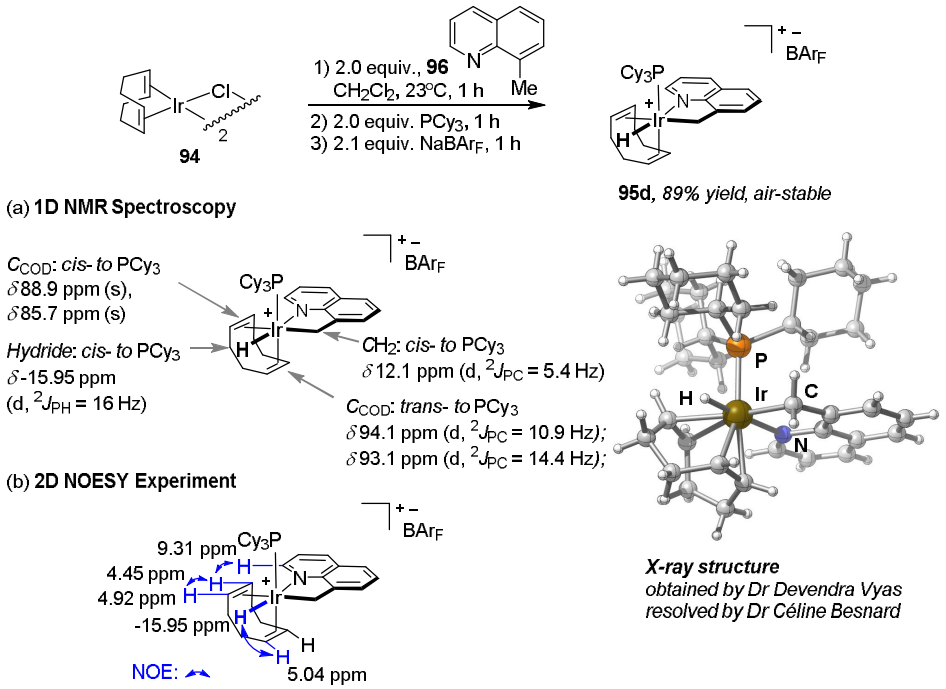
2.2.3 One-pot synthesis of Crabtree catalyst analogs

To evaluate the potential influence of the ligand substitution on the diastereoselectivity of the isomerization reaction, we prepared a series of Crabtree catalyst analogs **95a**-**c** (Scheme 2.9). Starting from $[Ir(cod)Cl]_2$ (**94**), a one-pot protocol which was recently developed in our laboratory allowed us to prepare Crabtree catalyst **3**•BAr_F in 90% yield.[15,16] Three *ortho*-substituted pyridine derivatives were then subjected to the same one-pot protocol and gave complexes **95a-c** after purification by chromatography as air-stable orange solids.



Scheme 2.9. *Syntheses of the Crabtree catalyst **3**•BAr_F and its analogs **95a-c**.*

[15] L. Mantilli, D. Gérard, C. Besnard, C. Mazet, *Eur. J. Inorg. Chem*. **2012**, 3320–3330.
[16] (a) R. H. Crabtree, *Acc. Chem. Res*. **1979**, *12*, 331–337; (b) R. H. Crabtree, A. Gautier, G. Giordano, T. Kahn, *J. Organomet. Chem.* **1977**, *141*, 113–121; (c) B. Wüstenberg, A. Pfaltz, *Adv. Synth. Catal*. **2008**, *350*, 174–178.



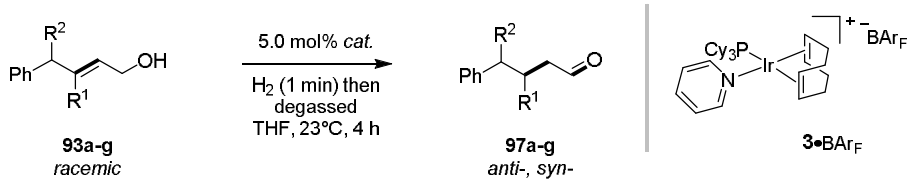
Scheme 2.10. *Synthesis and spectroscopic features of **95d**.*

When 8-methylquinoline (**96**) was employed, iridium monohydride complex **95d** was isolated as an air-stable solid in 89% yield. The structure was initially determined by multinuclear and bidimensional NMR spectroscopy, and later unambiguously confirmed by single crystal X-ray diffraction analysis.[17] It is noteworthy that cyclometalation occurred by C(sp^3)-H bond activation at ambient temperature.[18] Subsequent studies in our group revealed that this iridium monohydride complex **95d** is a competent precatalyst for the isomerization of epoxides.[19]

2.2.4 Diastereoselective isomerization of racemic acyclic primary allylic alcohols

With seven representative substrates **93a**-**g** (Table 2.1), we next investigated the diastereoselective isomerization reaction using the standard activation protocol previously developed in our group for the achiral catalyst **3**•BAr_F (5 mol% cat., 1 min. activation with molecular hydrogen followed by degassing). After 4 h, the products were systematically isolated in excellent yields after reduction to the corresponding alcohols (78-96%). The diastereomeric ratio were determined by ^{1}H NMR spectroscopy at the aldehyde stage.

[17] The X-ray structure of **95d** was obtained by Dr Devendra Vyas and later resolved by Dr Céline Besnard.
[18] Cyclometallated cationic iridium hydride complexes are not common and are usually the result of a C(sp^2)–H bond activation. For relevant examples, see: (a) R. H. Crabtree, M. Lavin, L. Bonneviot, *J. Am. Chem. Soc.* **1986**, *108*, 4032–4037; (b) B. P. Patel, R. H. Crabtree, *J. Am. Chem. Soc.* **1996**, *118*, 13105–13106; (c) X. Li, C. D. Incarvito, R. H. Crabtree, *J. Am. Chem. Soc.* **2003**, *125*, 3698–3699; (d) M. A. Esteruelas, F. J. Fernandez-Alvarez, M. Olivan, E. Onate, *Organometallics* **2009**, *28*, 2276–2284; (e) G. Song, Y. Su, R. A. Periana, R. H. Crabtree, K. Han, H. Zhang, X. Li, *Angew. Chem. Int. Ed.* **2010**, *49*, 912–917.
[19] N. Humbert, D. J. Vyas, C. Besnard, C. Mazet, *Chem. Commun*. **2014**, *50*, 10592–10595.



entry[a]	substrate	R^1	R^2 (Charton value, ν)	R^2 (Sterimol B_1)	yield[b] (%)	*dr*[c,d] (*syn/anti*)
1	**93a**	Ph	Me (0.52)	Me (1.52)	78	1/2.6
2	**93b**	Ph	Et (0.56)	Et (1.52)	89	1/2.3
3	**93c**	Ph	*n*-Pr (0.68)	*n.r.*[e]	81	1/2.1
4	**93d**	Me	Me (0.52)	Me (1.52)	94	1/2.4
5	**93e**	Me	Et (0.56)	Et (1.52)	96	1/1.1
6	**93f**	Me	*i*-Pr (0.76)	*i*-Pr (1.9)	92	22/1
7	**93g**	Me	Cy (0.87)	Cy (1.91)	94	30/1

*[a] Average of two runs (0.1 mmol of **93a-g**). [b] Isolated yields of the corresponding alcohol after reduction. [c] Determined by ^{1}H NMR. [d] Relative configuration assigned by chemical correlation or by analogy. [e] n.r. = Not reported.*

Table 2.1. *Diastereoselective isomerization of racemic primary allylic alcohols **93a-g**.*

As shown in Table 2.1 and Figure 2.1, for the aryl/alkyl series (Table 2.1, entries 1-3 and Figure 2.1a), the LFER between log(*dr*) and the Charton values were satisfactory. As for the alkyl/alkyl series (Table 2.1, entries 4-7), the *syn*/*anti* ratio varied from 1/2.4 (**97d**) to 30/1 (**97g**) in favor of the *syn* isomer. Excellent correlations between log(*dr*) and the corresponding steric descriptors were observed (Figure 2.1b for Charton values, Figure 2.1c for Sterimol minium width B_1).

We further evaluated the influence of the catalyst substituents on the diastereoselectivity by engaging **3**•BAr_F and its analogs **95a-d** into the isomerization reaction of *rac*-**93a** (Table 2.2). Whereas **95d** was inactive using the standard isomerization procedure, the other catalysts delivered the corresponding aldehyde **97a** quantitatively after 4 h at ambient temperature. The *syn*/*anti* ratio decreased gradually from 1/2.6 to 1/1.7 with the size of the catalyst substituents increasing. Further LFER analyses showed that again, excellent correlations between log(*dr*) and either steric descriptors were obtained (Figures 2.2a,b for Charton values, Figure 2.2c for Sterimol minium width B_1).

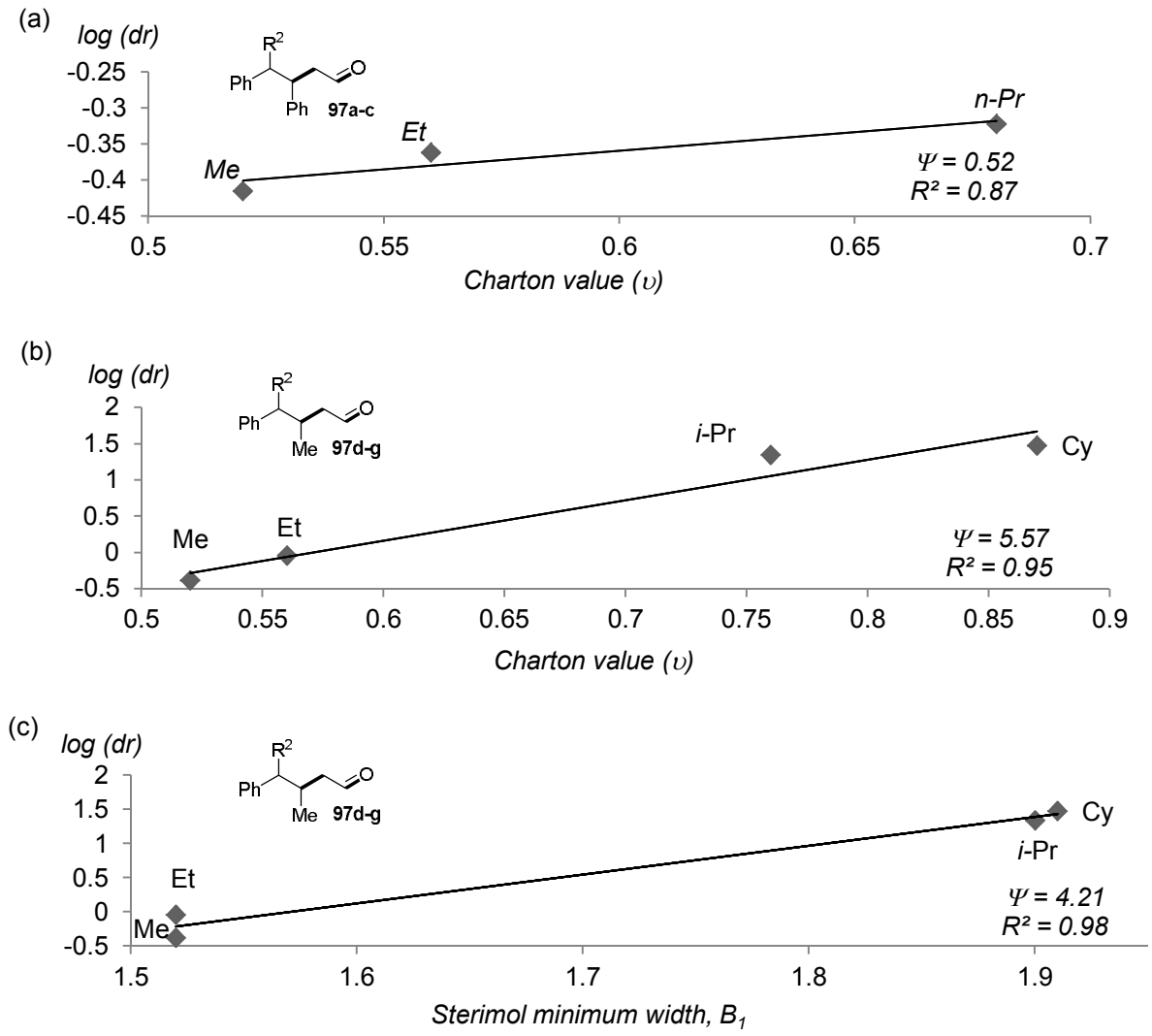
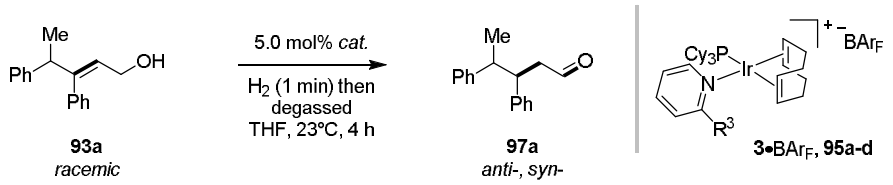


Figure 2.1. *Linear free energy relationships analysis of diastereoselective isomerization of **93a-g**.*



entry[a]	catalyst	loading (mol%)	R^2 (Charton valure, ν)	R^2 (Sterimol B_1)	yield[b] (%)	*dr*[b] (*syn/anti*)
1	**3**•BAr_F	5.0	H (0)	H (1.0)	> 99	1/2.6
2	**95a**	7.5	Me (0.52)	Me (1.52)	> 99	1/2.3
3	**95b**	7.5	*i*-Pr (0.76)	*i*-Pr (1.90)	> 99	1/1.9
4	**95c**	10	$CHEt_2$ (1.28, 1.51)	$CHEt_2$ (2.13)	> 99	1/1.7
5	**95d**	7.5	-	-	*n.r.*[c]	*n.d.*[d]

*[a] Average of two runs (0.1 mmol of **93a**). [b] Determined by ^1H NMR. [c] n.r. = No reaction. [d] n.d. = Not determined.*

Table 2.2. *Diastereoselective isomerization of **93a** using Crabtree catalyst analogs.*

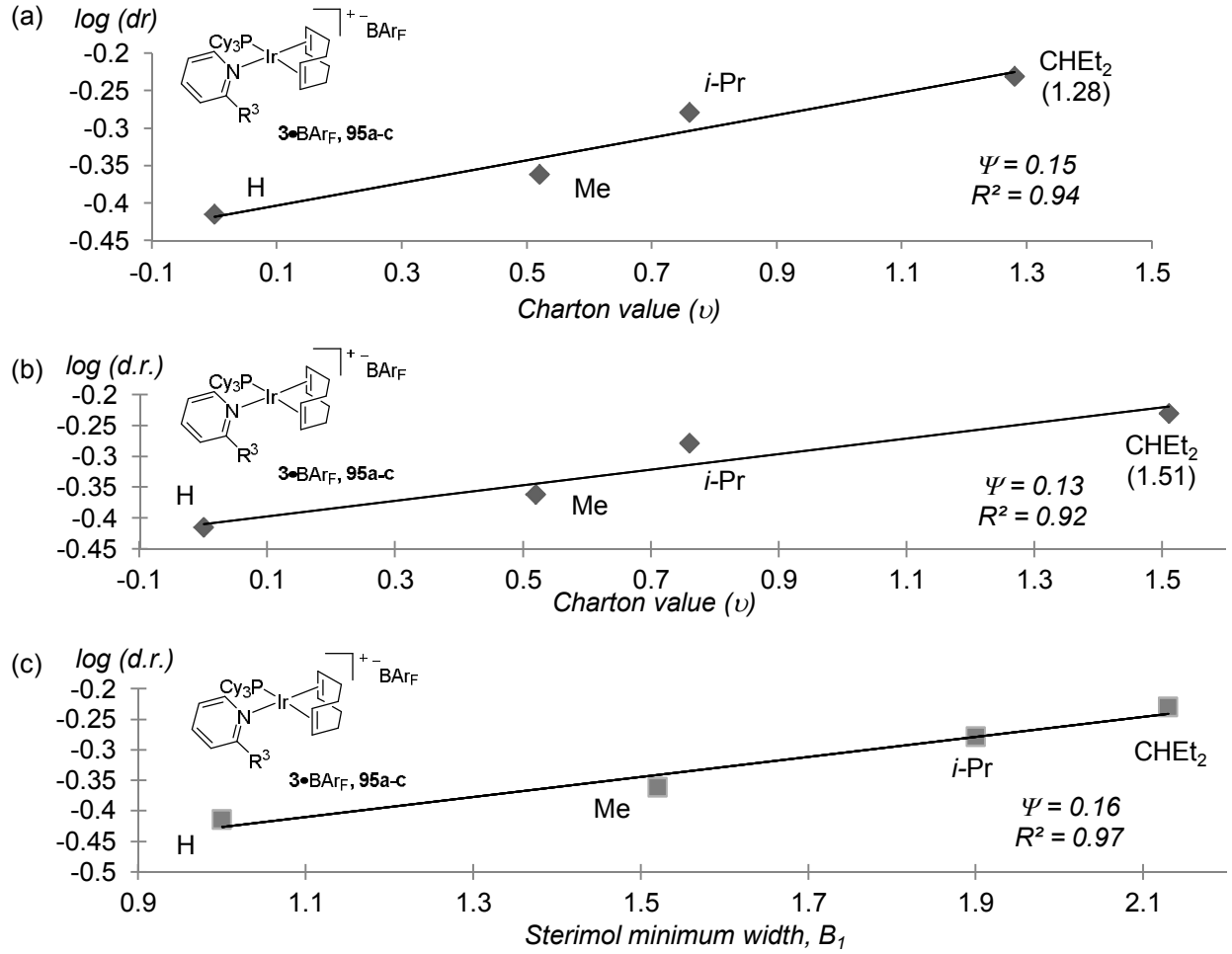
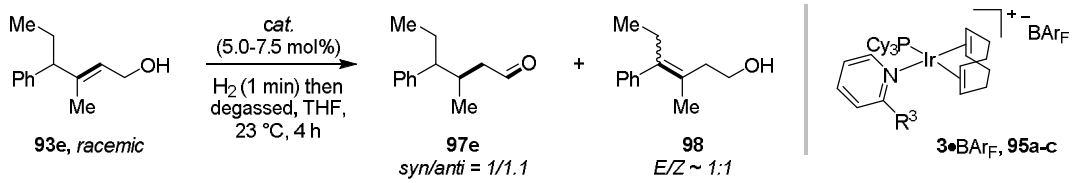


Figure 2.2. *Linear free energy relationships analysis of diastereoselective isomerization using Crabtree catalyst analogs*.

2.2.5 Regioselective isomerization of racemic acyclic primary allylic alcohols

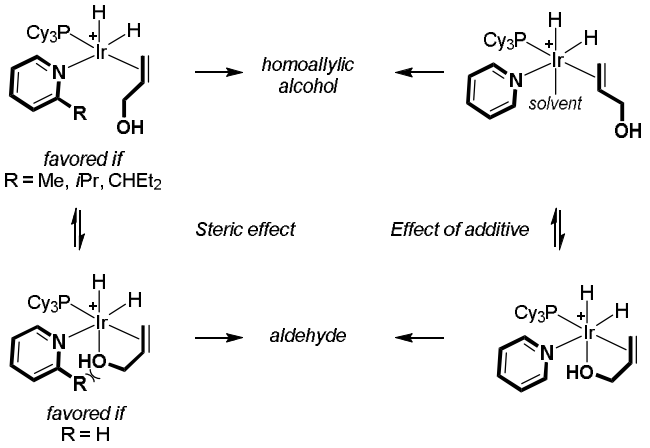
In the isomerization of the alkyl/alkyl substrate **93e**, whereas **3**•BAr_F delivered aldehyde **97e** exclusively after 4 h at ambient temperature (Table 2.3, entry 1), a mixture of aldehyde **97e** and homoallylic alcohol **98** was obtained with the sterically more demanding catalysts **95a-c** (Table 2.3, entries 2-4). Homoallylic alcohol **98** was always formed as the major product, with the best regioselectivity obtained using **95b** (entry 3). Preliminary investigations showed that other alkyl/alkyl substrates **93d** and **93f-g** all behave similarly.



entry[a]	catalyst	loading (mol%)	additive	yield[b] (%)	**97e/98**[b]
1	**3**•BAr_F	5.0	-	> 99	**100/0**
2	**95a**	7.5	-	> 99	38/62
3	**95b**	7.5	-	> 99	**15/85 (58)**[c]
4	**95c**	7.5	-	> 99	21/79
5	**3**•BAr_F	5.0	H_2O (5 mol%)	> 99	81/19
6	**3**•BAr_F	5.0	H_2O (100 mol%)	> 99	78/22
7	**3**•BAr_F	5.0	MeCN (5 mol%)	97	69/31

*[a] Average of two runs (0.1 mmol of **93e**). [b] Determined by ^1H NMR. [c] Isolated yield of **98**.*

Table 2.3. *Regioselective isomerization of **93e** into aldehyde **97e** and homoallylic alcohol **98**.*



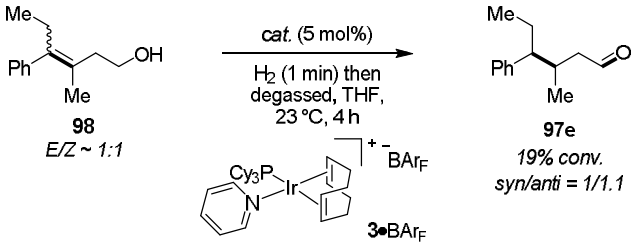
Scheme 2.11. *Proposed rationale for the regioselectivity switch during the isomerization reaction.*

To rationalize this observation (Scheme 2.11), we propose that the sterically demanding *ortho*-substituents of the pyridine ligand in catalysts **95a-c** may prevent 2-point binding of the allylic alcohol to the iridium center. Since 2-point binding is a necessary requirement for the productive isomerization to aldehydes, perturbing chelation of the substrate may result in unproductive isomerization to the homoallylic alcohol. In line with this hypothesis, the isomerization of **93e** using **3**•BAr_F in the presence of controlled amount of polar coordinating sovents (H_2O, MeCN, see Table 2.3, entries 5-7) generated again a mixture of **97e** and **98**,[20]

[20] Similar results were obtained if H_2O or MeCN were added prior or after activation of the iridium catalyst by molecular hydrogen.

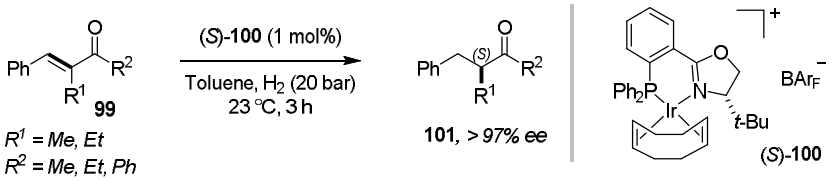
further suggesting that 2-point binding of the allylic alcohol is in competition with coordination of polar solvents (Scheme 2.11).

Finally, homoallylic alcohol **98** was isolated in 58% yield as a 1:1 *E/Z* mixture. Re-engagment of **98** under the conditions for catalytic isomerization provided **97e** in only 19% yield (Scheme 2.12). This clearly indicated that **98** was derived from an independent regioselective isomerization rather than acting as an intermediate formed during the isomerization of **93e** to **97e**. Despite the relatively low yield, this reaction still represents the first example for the isomerization of a tetrasubstituted homoallylic alcohol using Crabtree catalyst.



Scheme 2.12. *Isomerization of homoallylic alcohol **98** into aldehyde **97e**.*

2.3 Preparation of Enantioenriched Primary Allylic Alcohols

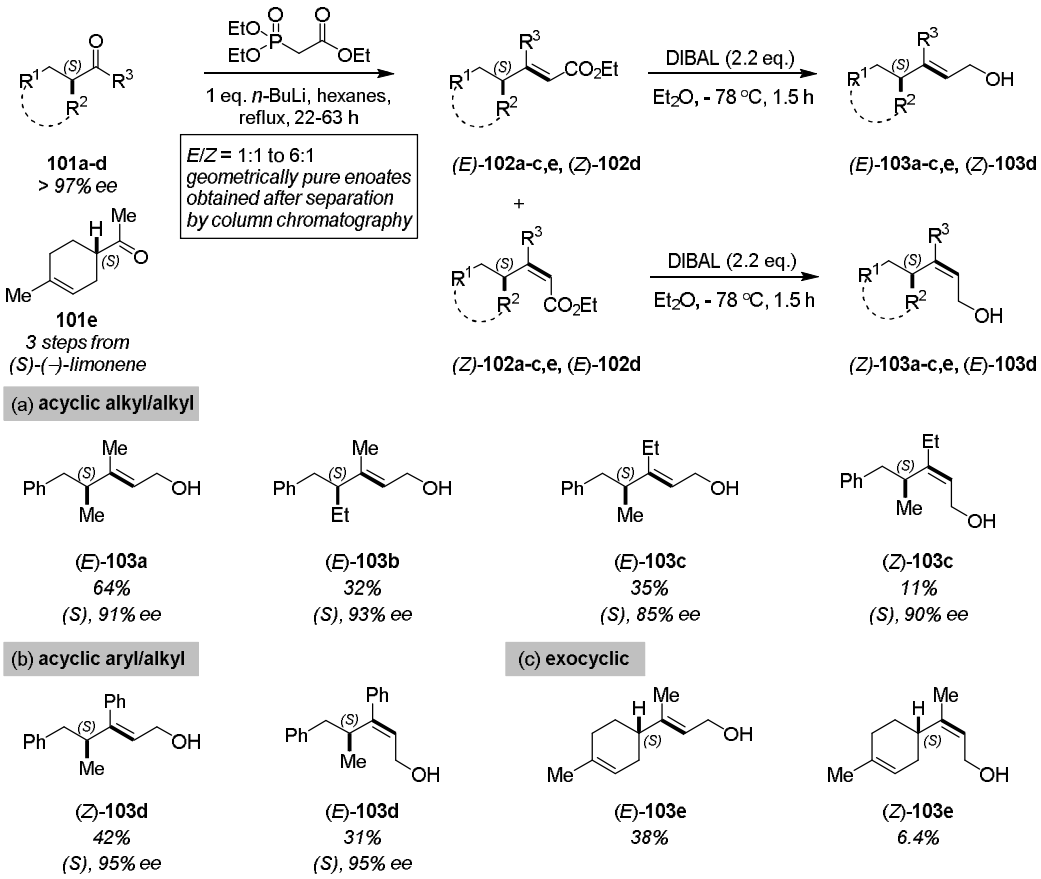


Scheme 2.13. *Syntheses of enantioenriched acyclic ketones **101** via enantioselective hydrogenation*.

Based on the fact that aryl/alkyl and alkyl/alkyl primary allylic alcohols behave differently during the isomerization,[6] and to access both *acyclic* and *exocyclic* vicinal tertiary carbon centers after isomerization, we synthesized three series of enantioenriched primary allylic alcohols (*acyclic* alkyl/alkyl, *acyclic* aryl/alkyl, and *exocyclic*, (*Z*) and (*E*)).

The Ir-catalyzed enantioselective hydrogenation developed by Lu and Bolm in 2008 was employed to access enantioenriched *acyclic* ketones **101** (Scheme 2.13).[21] Upon treatment of enones **99** with 1 mol% of (*S*)-**100**, we were pleased to get *acyclic* ketones (*S*)-**101** in excellent yields and >97% *ee* in all cases. The racemic *acyclic* ketones *rac*-**101** were prepared in parallel using standard conditions for heterogeneous hydrogenation.[22]

[21] S.-M. Lu, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 8920–8923.
[22] Typical heterogeneous hydrogenation reaction conditions: 5 wt% Pd/C, H_2 (3 bar), THF, 23 °C, 2.5 h, quantitative yield.



Scheme 2.14. *Preparation of enantioenriched acyclic and exocyclic primary allylic alcohols **103a**-**e**.*

With both racemic and enantioenriched *acyclic* ketones **101** in hand, a subsequent Horner-Wadsworth-Emmons reaction afforded enoates **102** as a mixture of (*Z*) and (*E*) isomers (Scheme 2.14). After purification and separation by chromatography the geometrically pure (*Z*) and (*E*)-enoates **102a**-**d** were isolated and independently subjected to chemoselective reduction with DIBAL. Both (*Z*) and (*E*)-allylic alcohols **103a**-**d** were obtained quasi-quantitatively in geometrically pure form.

Finally, *exocyclic* ketone **101e** obtained from (*S*)-(–)-limonene in 3 steps was also engaged in an identical synthetic route and furnished geometrically pure (*Z*) and (*E*)-*exocyclic* allylic alcohols **103e**.[23]

[23] 2.3 g of **101e** was prepared in 3 steps based on the known procedure starting from (*S*)-(–)-limonene, see: V. J. Davissont, C. D. Poulter, *J. Am. Chem. Soc*. **1993**, *115*, 1245–1260.

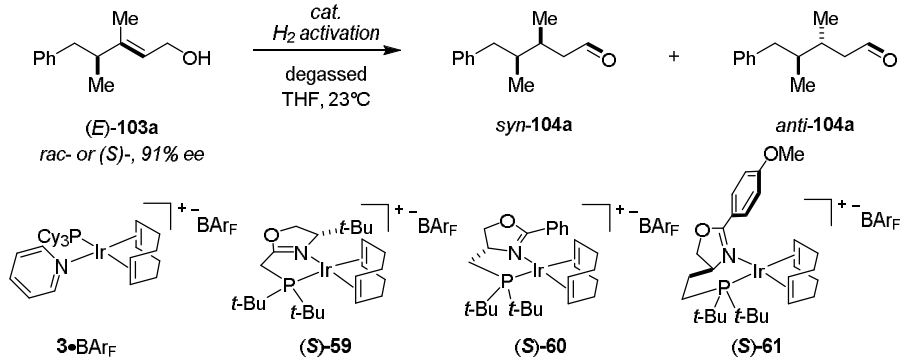
2.4 Catalyst-Directed Diastereoselective Isomerization of *Acyclic* Allylic Alcohols

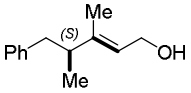
*2.4.1 Catalyst-directed diastereoselective isomerization of model substrate (E)-**103a***

To examine the catalyst-directed diastereoselective isomerization of *acyclic* allylic alcohols, model susbtrate (*E*)-**103a** was initially subjected to the standard isomerization procedure (5 mol% *cat*., 1 min. H_2 activation/degassing with **3**•BAr_F or 5 min. H_2 activation/degassing with **59**-**61**).[6,24] Whereas Crabtree catalyst gave quantitative yields for both racemic and enantioenriched substrates (Table 2.4, entries 1, 2), the *syn*/*anti* ratios were moderate, and slightly in favor of *anti*-**104a**. The erosion of enantiomeric ratio of the product observed after reduction revealed that a partial racemization occurred during the isomerization with **3**•BAr_F. This partial racemization can be due to the in-situ generation of transient tetrasubstituted homoallylic alcohol via regioselective isomerization.[25]

We continued by evaluating a series of chiral iridium complexes for the isomerization of (*E*)-**103a** (Table 2.4, entries 3-5). Catalyst (*S*)-**60** was found to be optimal as it offered the best balance in terms of reactivity and diastereoselectivity. Increasing the catalyst loading led to *anti*-**104a** in 77% isolated yield with a similarly high diastereoselectivity in favor of the *anti* product (*syn*/*anti* = 1/12) (Table 2.4, entry 6). By using the catalyst enantiomer (*R*)-**60** (Table 2.4, entry 7), *syn*-**104a** was obtained in 63% isolated yield along with a satisfactory diastereoselectivity (*syn*/*anti* = 5.4/1) due to mismatch effects. Excellent enantiomeric ratios were also observed (> 99% *ee*).

[24] L. Mantilli, C. Mazet, *Tetrahedron Lett.* **2009**, *50*, 4141−4144.
[25] See Chapter 2.2.5 for details.



entry[a]	substrate	catalyst	loading (mol%)	conversion to aldehyde (%)[b]	*dr*[b,c] (*syn/anti*)	*%ee major*[d]
1	*rac*-(*E*)-**103a**	**3**•BAr_F	5.0	> 99	1/1.4	0
2		**3**•BAr_F	5.0	> 99	1/1.6	81
3		(*S*)-**59**	5.0	41	1/8	99
4	(*S*)-(*E*)-**103a**, *91% ee*	(*S*)-**60**	5.0	75	1/12	> 99
5		(*S*)-**61**	5.0	53	5.5/1	> 99
6	*(S)*-(*E*)-**103a**	(*S*)-**60**	7.5	97(77)[e]	1/12	> 99
7		(*R*)-**60**	7.5	63[e]	5.4/1	> 99

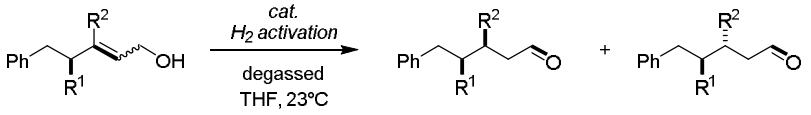
*[a] Average of two runs (0.1 mmol of (E)-**103a**). [b] Determined by ^{1}H NMR. [c] Relative configuration assigned by analogy. [d] Determined by chiral HPLC of the corresponding alcohol after reduction. [e] Isolated yield of **104a**.*

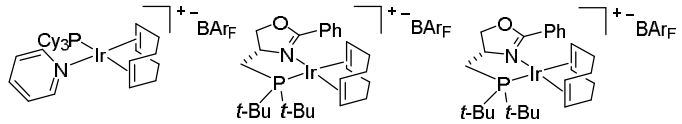
Table 2.4. *Optimization of model isomerization reaction with (E)-**103a**.*

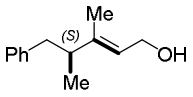
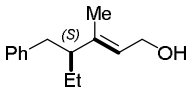
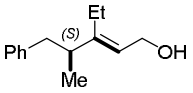
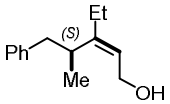
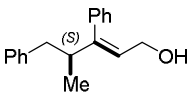
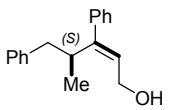
2.4.2 Substrate scope

Applying the optimal conditions to our collection of *acyclic* substrates led to similarly good results (Table 2.5). The corresponding products were systematically isolated in good yields using both alkyl/alkyl and aryl/alkyl substrates. *Syn*- and *anti*-isomers were always obtained in high diastereomeric ratio after isomerization. Despite the regular occurrence of partial racemization using **3**•BAr_F (Table 2.5, entries 2, 6, and 14), excellent enantiomeric ratios were again observed with the chiral catalyst **60**. Overall, we have developed a catalyst-directed diastereoselective isomerization of *acyclic* allylic alcohols. Good yields, perfect *dr* and excellent *ee* were generally obtained.

In contrast to the lower reactivity and selectivity detected in the previous enantioselective isomerization of (*Z*)-allylic alcohols,[6] catalyst-directed diastereoselective isomerization proceeded equally well with both (*Z*) and (*E*) geometries for these substrates. In line with the selectivity model proposed for the stereospecific isomerization of prochiral allylic alcohols (Scheme 2.6), reverse diastereoselectivity were obtained between the isomerization of (*Z*) and (*E*)-substrates.





entry[a]	substrate	catalyst	loading (mol%)	yield of aldehyde (%)	*dr*[b,c] (*syn/anti*)	*%ee major*[d]
1	*rac*-(*E*)-**103a**	**3**•BAr$_F$	5.0	> 99	1/1.4	-
2		**3**•BAr$_F$	5.0	> 99	1/1.6	81
3		(*S*)-**60**	7.5	77	1/12	> 99
4	(*S*)-(*E*)-**103a**, *91% ee*	(*R*)-**60**	7.5	63	5.4/1	> 99
5	*rac*-(*E*)-**103b**	**3**•BAr$_F$	5.0	> 99	1/1.1	-
6		**3**•BAr$_F$	5.0	> 99	1/1.1	51
7		(*S*)-**60**	7.5	69	1/10	> 99
8	(*S*)-(*E*)-**103b**, *93% ee*	(*R*)-**60**	7.5	59	13/1	96
9	*rac*-(*E*)-**103c**	**3**•BAr$_F$	7.5	> 99	1/1.6	-
10		**3**•BAr$_F$	7.5	> 99	1/1.7	85
11		(*S*)-**60**	7.5	52	1/9.4	94
12	(*S*)-(*E*)-**103c**, *85% ee*	(*R*)-**60**	7.5	30	4.5/1	> 99
13	*rac*-(*Z*)-**103c**	**3**•BAr$_F$	5.0	> 99	1/1.1	-
14		**3**•BAr$_F$	5.0	> 99	1/1.1	86
15		(*S*)-**60**	7.5	74	5.7/1	> 99
16	(*S*)-(*Z*)-**103c**, *90% ee*	(*R*)-**60**	7.5	79	1/12	> 99
17	*rac*-(*Z*)-**103d**	**3**•BAr$_F$	5.0	> 99	1.7/1	-
18		**3**•BAr$_F$	5.0	> 99	1.7/1	95
19		(*S*)-**60**	7.5	56	16/1	> 99
20	(*S*)-(*Z*)-**103d**, *95% ee*	(*R*)-**60**	7.5	37	1/10	> 99
21	*rac*-(*E*)-**103d**	**3**•BAr$_F$	5.0	> 99	1/1	-
22		**3**•BAr$_F$	5.0	> 99	1/1	81
23		(*S*)-**60**	7.5	62	1/21	> 99
24	(*S*)-(*E*)-**103d**, *95% ee*	(*R*)-**60**	7.5	80	23/1	> 99

*[a] Average of two runs (0.1 mmol of **103**). [b] Determined by ^{1}H NMR. [c] Relative configuration assigned by analogy. [d] Determined by chiral HPLC of the corresponding alcohol after reduction.*

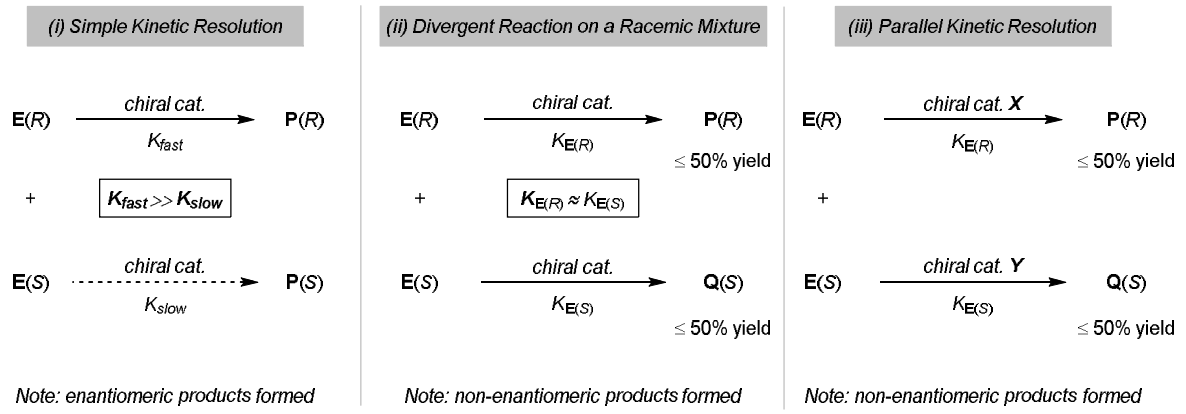
Table 2.5. *Catalyst-directed diastereoselective isomerization of acyclic substrates **103a-d**.*

2.5 Stereodivergent Reaction on a Racemic Mixture

Catalytic asymmetric methods that furnish enantioenriched products are of prime importance in modern organic synthesis.[1,26] In addition to enantioselective catalysis and catalyst-directed diastereoselective reaction, an underutilized strategy to prepare enantioenriched products is to perform divergent reactions on racemic mixtures (DRRM). A DRRM takes place when each enantiomer of a racemic starting material reacts with a single chiral catalyst and furnishes two enantioenriched non-enantiomeric products.[27]

Encouraged by the satisfactory results obtained during the catalyst-directed diastereoselective isomerization using enantioenriched *acyclic* substrates, we explored the possibility to develop a divergent reaction on a racemic mixture starting from racemic *acyclic* substrates.

2.5.1 Divergent reaction on a racemic mixture (DRRM)



Scheme 2.15. *Reactions using racemic starting material with chiral catalyst.*

In principle, when a racemic starting material is treated with a chiral catalyst, three scenarios can be envisaged (Scheme 2.15).[26]

(i) A simple kinetic resolution (KR) occurs when one enantiomer of starting material **E**(*R*) reacts much faster with the chiral catalyst than with its enantiomer **E**(*S*). In an ideal scenario, one can obtain enantiopure product in 50% yield, as well as recovered enantiopure starting material in 50% yield.

(ii) A divergent reaction on a racemic mixture (DRRM) takes place when both enantiomers of starting material react with a single chiral catalyst at similar rates and furnishes non-

[26] *Fundamentals of Asymmetric Catalysis*, P. J. Walsh, M. C. Kozlowski, Eds., University Science Books: Sausalito, CA, **2009**.
[27] L. C. Millera, R. Sarpong, *Chem. Soc. Rev*. **2011**, *40*, 4550–4562.

enantiomeric products (**P**(*R*), and **Q**(*S*), Scheme 2.15). With excellent catalyst control, both products can be formed in high yields (up to 50%) and with high enantioselectivity.
(iii) Based on the initial convention of Kagan and Vedejs, [28,29] parallel kinetic resolutions (PKR) constitute a special case of divergent reactions on racemic mixtures, where both enantiomers of the starting material react with two different chiral catalysts and deliver non-enantiomeric products.

Of the reactions that do employ divergent reactions on racemic mixtures, there are three general categories: *chemodivergent*, *regiodivergent*, and *stereodivergent*.[27,30] In the following chapter we illustrate the principle of divergent reactions on racemic mixtures with some relevant examples from the literature.

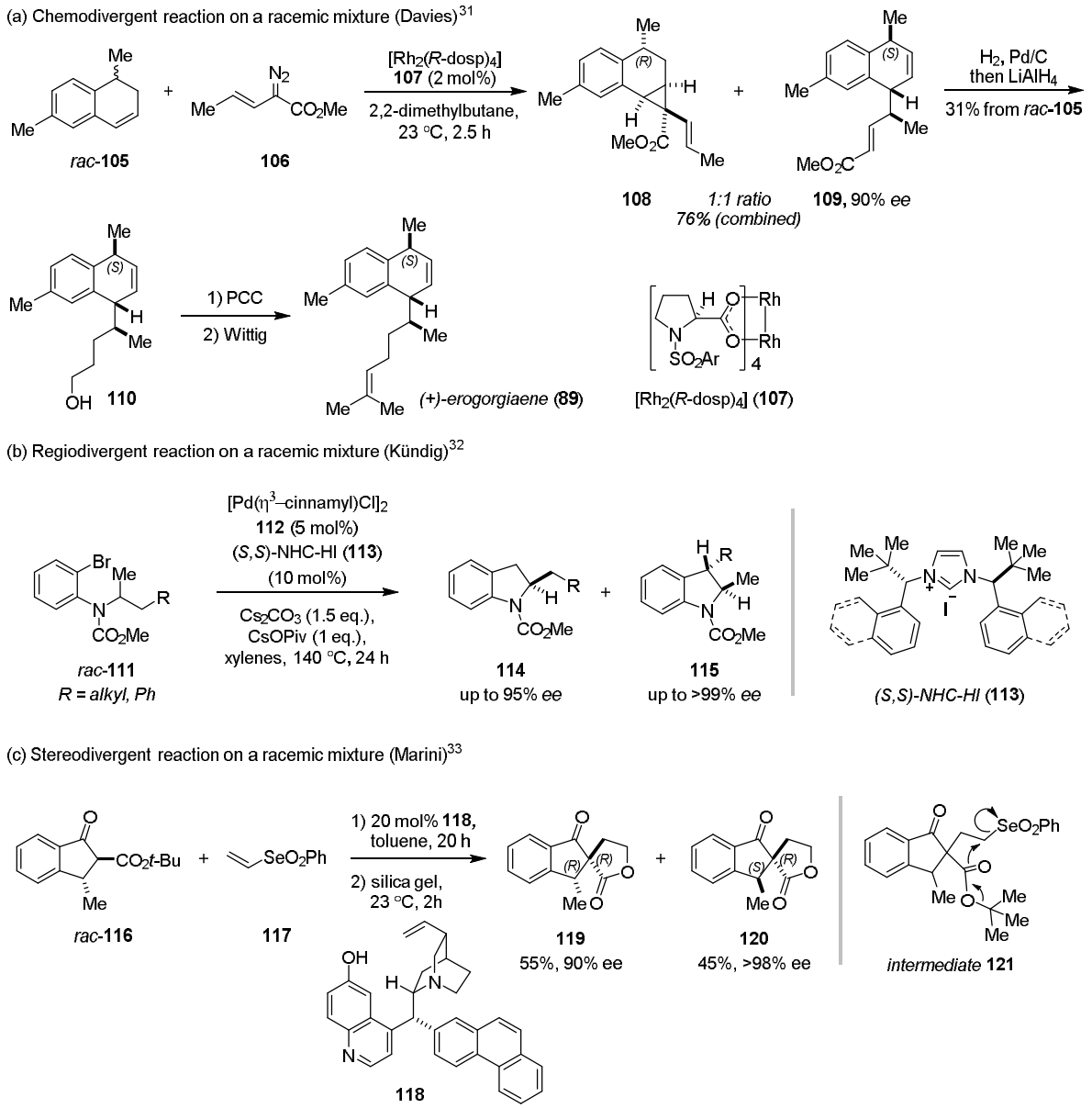
2.5.2 Selected examples

In 2005, *en route* to (+)-erogorgiaene (**89**),[31] Davies and Walji developed a remarkable *chemodivergent* reaction on a racemic mixture (Scheme 2.16a). Starting from *rac*-**105**, cyclopropane **108** and enoate **109** were obtained in 76% overall yields (1:1 ratio) after coupling with diazo **106**. Whereas direct cyclopropanation of (*R*)-**105** afforded **108**, sequential C-H insertion/Cope rearrangement of (*S*)-**105** provided **109** in 90% *ee*. Subsequent 3-step functional group manipulation enabled the synthesis of natural product (+)-erogorgiaene (**89**).

A notable *regiodivergent* example was reported by the Kündig group in 2012 (Scheme 2.16b).[32] Starting from carbamate *rac*-**111**, C(sp^3)-H insertion catalyzed by a chiral [(NHC)Pd] complex resulted in a regiodivergent reaction. Due to the competition between C_{methyl}-H and $C_{methylene}$-H activation, **114** and **115** were obtained from (*S*)- and (*R*)-**111** respectively.

Finally, through an organocatalyzed Michael addition/cyclization sequence (Scheme 2.16c),[33] Marini and co-workers reported a *stereodivergent* reaction on a racemic mixture. Racemic β-keto ester **116** reacted with vinyl selenone **117** and delivered two diastereoisomers **119** and **120** both with excellent enantiomeric excess.

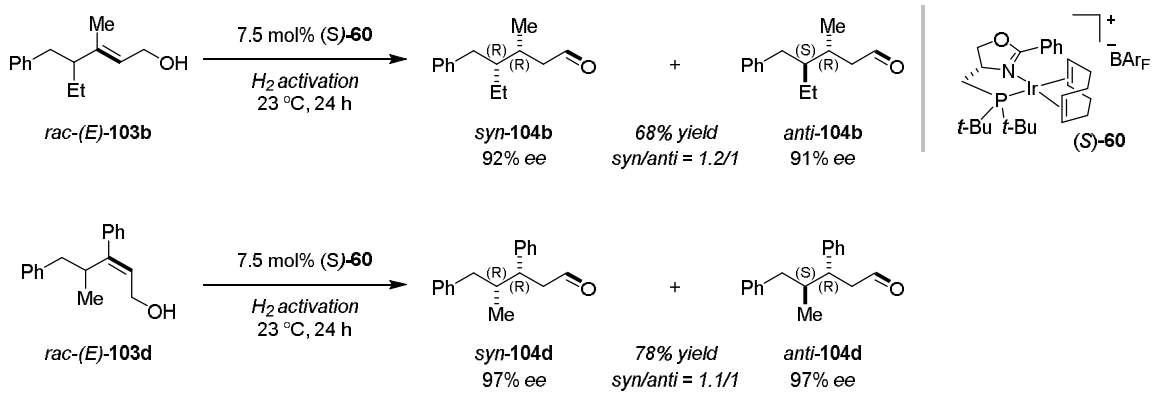
[28] (a) H. B. Kagan, *Tetrahedron* **2001**, *57*, 2449–2459; (b) R. R. Kumar, H. B. Kagan, *Adv. Synth. Catal*. **2010**, *352*, 231–242.
[29] E. Vedejs, M. Jure, *Angew. Chem. Int. Ed*. **2005**, *44*, 3974–4001.
[30] *Fundamentals of Asymmetric Catalysis*, P. J. Walsh, M. C. Kozlowski, Eds., University Science Books: Sausalito, CA, **2009**, Chapter 8, pp. 225–270.
[31] H. M. L. Davies, A. M. Walji, *Angew. Chem. Int. Ed.* **2005**, *44*, 1733–1735.
[32] D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, *Chem. Sci.,* **2012**, *3*, 1422–1425.
[33] S. Sternativo, A. Calandriello, F. Costantino, L. Testaferri, M. Tiecco, F. Marini, *Angew. Chem. Int. Ed.* **2011**, *50*, 9382–9385.



Scheme 2.16. *Divergent reactions on racemic mixtures.*

2.5.3 Our preliminary results

At the outset of our investigations, *rac*-(*E*)-**103b** was subjected to the optimal isomerization conditions. The aldehydes *syn*-**104b** and *anti*-**104b** were isolated in 68% as an inseparable mixture (*syn*/*anti* = 1.2/1). To our delight, high enantiomeric excess (91-92% *ee*) were also obtained. Upon treatment of another racemic substrate *rac*-(*E*)-**104d** with (*S*)-**60**, the corresponding *syn*-**104d** and *anti*-**104d** were obtained as an inseparable mixture (*syn*/*anti* = 1.1/1), with again excellent enantioselectivity (97% *ee* in both cases).



Scheme 2.17. *Stereodivergent reactions on racemic mixtures with acyclic substrates*.

These two representative examples demonstrated the feasibility of stereodivergent reactions on racemic mixtures for the isomerization of racemic *acyclic* substrates using chiral catalyst **60**. Further extension of the scope of this reaction is still needed by employing different series of *acyclic* substrates (alkyl/alkyl, aryl/alkyl, (*Z*) and (*E*)).

2.6 Catalyst-Directed Diastereoselective Isomerization of *Exocyclic* Allylic Alcohols

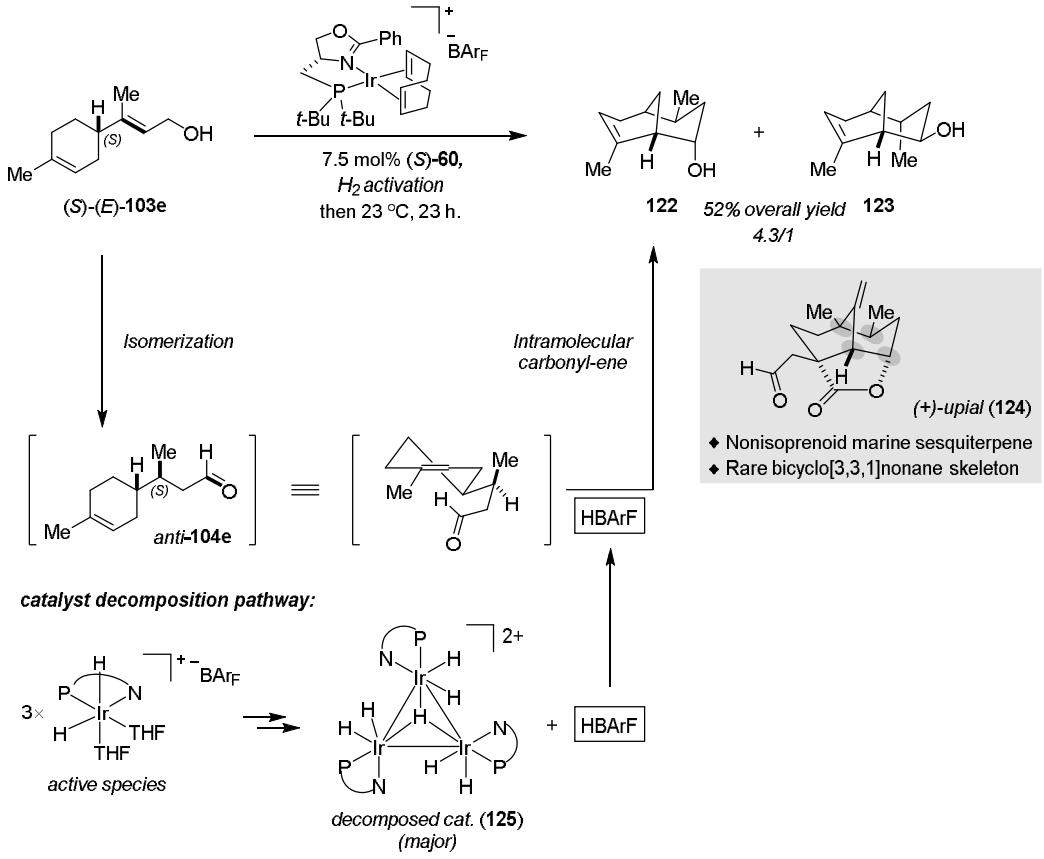
2.6.1 Tandem isomerization/intramolecular carbonyl-ene reaction

Based on the satisfactory results obtained using *acyclic* substrates, we next decided to evaluate *exocyclic* allylic alcohols **103e** in the catalyst-directed diastereoselective isomerization. Both *rac*-(*E*)-**103e** and *rac*-(*Z*)-**103e** were initially engaged using the optimal conditions for **3**•BAr_F and delivered aldehydes **104e** in quantitative yields (*syn*/*anti* = 1/1). Upon treatment of (*S*)-(*E*)-**103a** with (*S*)-**60** (Scheme 2.18), diastereomeric alcohols **122** and **123** were obtained in a 4.3/1 mixture in 52% overall yield. The expected aldehyde **104e** was not formed. The structure of **122** was unambiguously determined by NMR spectroscopy and was found to be consistent with the data reported previously.[34] Of note, **122** possesses an unique bicyclic [3,3,1]nonane skeleton with four pre-installed stereogenic carbon centers. It can be viewed as a synthetic structural analog of the marine sesquiterpene (+)-upial (**124**).[35]

A tandem isomerization/intramolecular carbonyl-ene reaction is proposed to account for the reaction outcome (Scheme 2.18). Specifically, initial isomerization of (*S*)-(*E*)-**103a** with (*S*)-**60** delivers *anti*-**104e** as the major isomer. Aldehyde *anti*-**104e** undergoes further intramolecular carbonyl-ene reaction to yield the final product **122** in the presence of trace amount of acid. Such acid can be generated in-situ upon decomposition of the iridium

[34] (a) A. de O. Dias, R. Augusti, E. N. dos Santos, E. V. Gusevskaya, *Tetrahedron Lett.* **1997**, *38*, 41–44; (b) C. G. Vieira, M. C. de Freitas, E. N. dos Santos, E. V. Gusevskaya, *ChemCatChem* **2012**, *4*, 795–801.
[35] G. Schulte, P. J. Scheuer, O. J. McConnell, *J. Org. Chem.* **1980**, *45*, 552–554.

dihydride species during the isomerization.[36,37] We propose that the absence of intramolecular carbonyl-ene reaction of **104e** to **122** and **123** when **3**•BAr_F is employed might be due to a neutralizing effect of the decoordinated pyridine ligand released from **3**•BAr_F upon decomposition.



Scheme 2.18. *Catalyst-directed diastereoselective isomerization reaction of (S)-(E)-**103e**.*

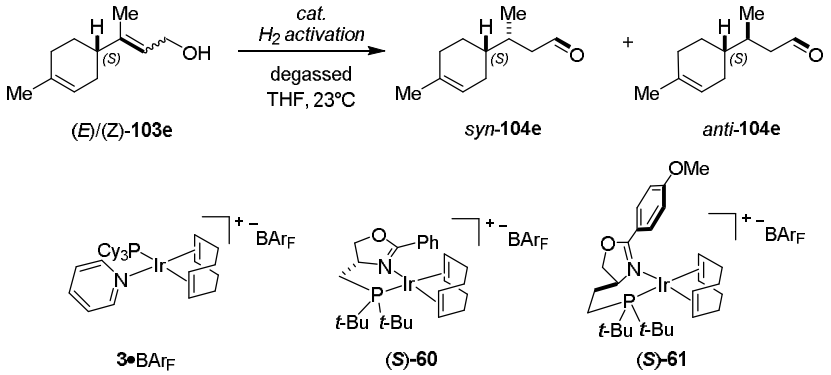
2.6.2 Catalyst-directed diastereoselective isomerization of exocyclic allylic alcohols

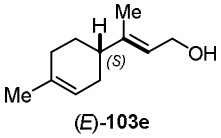
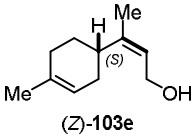
To avoid the intramolecular carbonyl-ene reaction with chiral catalyst **60**, the isomerization reaction was performed in the presence of 2,6-di-*t*-Bu-4-methylpyridine (DTBMP), a non-coordinating base with a similar pK_a to pyridine.[38] Finally, (*Z*) and (*E*)-**103e** were subjected to the reaction conditions for isomerization (Table 2.6). In the presence of 15 mol% of DTBMP, both *syn*-**104e** and *anti*-**104e** were obtained in good yields using chiral catalyst **60**, albeit in a moderate diastereomeric ratio (up to 3.7/1). Catalyst (*S*)-**61** did not provide superior results so far (Table 2.6, entries 4, 8).

[36] Upon decomposition of iridium dihydride species a trinuclear cluster is formed as the major product along with other dimers and tetramers. For details see: (a) D. F. Chodosh, R. H. Crabtree, H. Felkin, G. E. Morris, *J. Organomet. Chem.* **1978**, *161*, C67–C70; (b) D. F. Chodosh, R. H. Crabtree, H. Felkin, S. Morehouse, G. E. Morris, *Inorg. Chem.* **1982**, *21*, 1307–1311; (c) Y. Xu, M. A. Celik, A. L. Thompson, H. Cai, M. Yurtsever, B. Odell, J. C. Green, D. M. P. Mingos, J. M. Brown, *Angew. Chem. Int. Ed.* **2009**, *48*, 582–585.

[37] For the acidity of relevant iridium dihydride species, see: (a) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249−6253; (b) R. H. Morris, *J. Am. Chem. Soc*. **2014**, *136*, 1948−1959.

[38] In the presence of an inorganic base (such as Na_2CO_3), poor conversion to **104e** was observed.



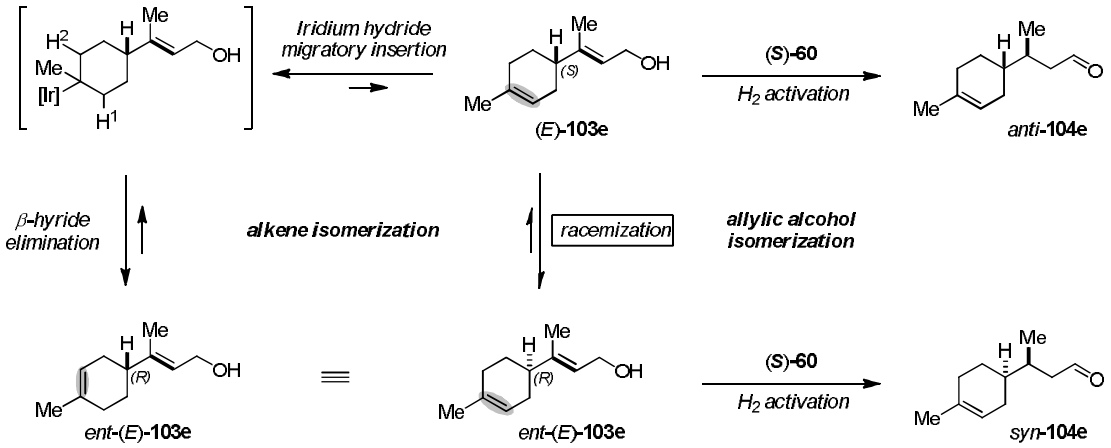
entry[a]	substrate	catalyst	loading (mol%)	yield of aldehyde (%)	*dr*[b,c] (*syn/anti*)
1	 (*E*)-**103e**	**3**•BAr$_F$	5.0	98	1/1
2		(*S*)-**60**[d]	7.5	90	1/3.4
3		(*R*)-**60**[d]	7.5	90	3.1/1
4		(*S*)-**61**[d]	7.5	45	2.4/1
5	 (*Z*)-**103e**	**3**•BAr$_F$	5.0	75	1/1
6		(*S*)-**60**[d]	7.5	83	3.7/1
7		(*R*)-**60**[d]	7.5	82	1/3.7
8		(*S*)-**61**[d]	7.5	41	1/5.0

[a] *Average of two runs (0.1 mmol of **103e**).* [b] *Determined by ^{1}H NMR.* [c] *Relative configuration assigned by chemical correlation.* [d] *In the presence of 15 mol% of DTBMP.*

Table 2.6. *Catalyst-directed diastereoselective isomerization of exocyclic allylic alcohols **103e**.*

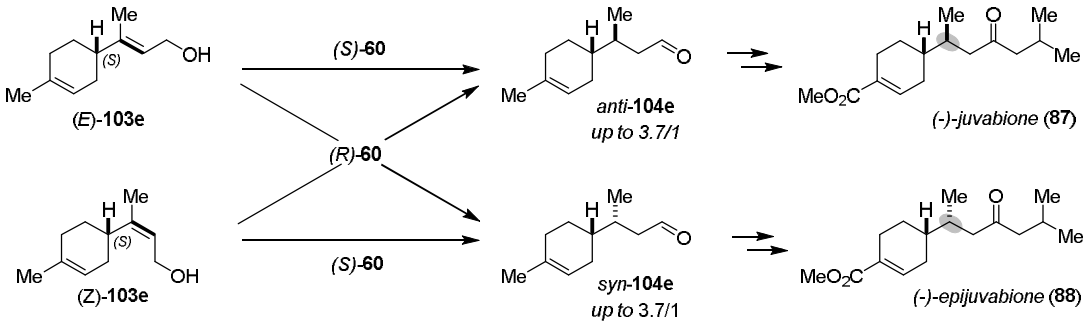
The moderate *dr* (up to 3.7/1) obtained after the isomerization might be due in part to the lack of stereocontrol during the migratory insertion of the active iridium dihydride. An alternative racemization mechanism may also account for the stereoselective outcome (Scheme 2.19). Specifically, in parallel to the productive isomerization of allylic alcohol (*E*)-**103e** into aldehyde *anti*-**104e** using (*S*)-**60**, racemization of substrate (*E*)-**103e** into *ent*-(*E*)-**103e** might also occur concurrently by isomerization of the endocyclic C=C bond.[39] In such a situation isomerization of *ent*-(*E*)-**103e** would deliver *syn*-**104e**.

[39] For a relevant review, see: E. Larionov, H. Li, C. Mazet, *Chem. Commun.* **2014**, *50*, 9816−9826.



Scheme 2.19. *Potential racemization of (E)-**103e** based on alkene isomerization mechanism.*

Nonetheless, catalyst permutation restored satisfactory reactivity for the isomerization. We were able to access both *syn*-**104e** and *anti*-**104e** starting from (*Z*)-**103e** and (*E*)-**103e** by using either enantiomer of the chiral catalyst (Scheme 2.20). Getting access to aldehydes *syn*-**104e** and *anti*-**104e**, we provides a formal synthesis of two sesquiterpenes (–)-juvabione (**87**) and (–)-epijuvabione (**88**) as subsequent derivatizations have been reported in the literature.[40,41]



Scheme 2.20. *Formal synthesis of sesquiterpenes (–)-juvabione (**87**) and (–)-epijuvabione (**88**).*

2.7 Conclusion

In conclusion, we have shown that the diastereoselective isomerization of primary allylic alcohols can be quantified using steric descriptors for both the substrate substituents and the catalyst substituents. We also conducted catalyst-directed diastereoselective isomerization using enantioenriched substrates and chiral catalysts. Both enantioenriched *acyclic* and *exocyclic* allylic alcohols performed well under the optimal isomerization conditions. Good yields, perfect *dr* and excellent *ee* were generally obtained using *acyclic* substrates. The

[40] C. Fuganti, S. Serra, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 97−101.
[41] *Organic Synthesis via Examination Selected Natural Products,* D. J. Hart, Ed., World Scientific: Hackensack, NJ, **2011**, Chapter 5, pp. 155–202.

feasibility of a divergent reaction on a racemic mixture (DRRM) has also been demonstrated on 2 different substrates. Finally, we extended our current study to *exocyclic* substrates and underscored its potential synthetic utility by the formal synthesis of the naturally occurring insecticidal sesquiterpenes (−)-juvabione (**87**) and (−)-epijuvabione (**88**).

2.8 References

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(2) (a) S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem. Int. Ed.* **1985**, *24*, 1−30; (b) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev*. **1993**, *93*, 1307−1370; (c) J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed*. **2012**, *51*, 10954−10990.
(3) *Fundamentals of Asymmetric Catalysis*, P. J. Walsh, M. C. Kozlowski, Eds., University Science Books: Sausalito, CA, **2009**, Chapter 13, pp. 427–454.
(4) D. A. Evans, M. DiMare, *J. Am. Chem. Soc.* **1986**, *108*, 2476–2478.
(5) G. D. Joly, E. N. Jacobsen, *Org. Lett.* **2002**, *4*, 1795–1798.
(6) (a) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, 48, 5143−5147; (b) L. Mantilli, C. Mazet, *Chem. Commun.* **2010**, *46*, 445−447; (c) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem.−Eur. J*. **2010**, *16*, 12736−12745.
(7) (a) W. Adam, C. M. Mitchell, C. R. Saha-Möller, *Eur. J. Org. Chem.* **1999**, 785−790; (b) B. Meynhardt, U. Lüning, C. Wolff, C. Näther, *Eur. J. Org. Chem*. **1999**, 2327−2335; (c) L. You, J. S. Berman, A. Lucknasawichien, E. V. Anslyn, *J. Am. Chem. Soc.* **2012**, *134*, 7126−7134.
(8) (a) R. W. Taft Jr., *J. Am. Chem. Soc*. **1952**, *74*, 3120–3128; (b) R. W. Taft Jr., *J. Am. Chem. Soc.* **1953**, *75*, 4538–4539.
(9) (a) M. Charton, *J. Am. Chem. Soc*. **1975**, *97*, 1552–1556; (b) M. Charton, *J. Am. Chem. Soc*. **1975**, *97*, 3691–3693; (c) M. Charton, *J. Org. Chem*. **1976**, *41*, 2217–2220.
(10) S. Winstein, N. J. Holness, *J. Am. Chem. Soc.* **1955**, *77*, 5562–5578.
(11) (a) R. Adams, H. C. Yuan, *Chem. Rev*. **1933**, *12*, 261–338; (b) G. Bott, L. D. Field, S. Sternhell, *J. Am. Chem. Soc*. **1980**, *102*, 5618–5626.
(12) (a) A. Verloop, *Drug Design*, E. J., Ariens, Ed., Academic Press: New York, **1976**, Vol. III, p 133; (b) A. Verloop, J. Tipker, *Biological Activity and Chemical Structure*, J. A. Buisman, Ed., Elsevier: Amsterdam, **1977**, p 63; (c) A. Verloop, J. Tipker, *QSAR in Drug Design and Toxicology*, D. Hadzi, B. Jerman-Blazic, Eds., Elsevier: Amsterdam, **1987**, p 97; (d) A. Verloop, *IUPAC Pesticide Chemistry*, J. Miyamoto, Ed., Pergamon: Oxford, **1983**, Vol. 1, p 339.

(13) (a) J. J. Miller, M. S. Sigman, *Angew. Chem. Int. Ed.* **2008**, *47*, 771–774; (b) M. S. Sigman, J. J. Miller, *J. Org. Chem*. **2009**, *74*, 7633–7643; (c) K. C. Harper, M. S. Sigman, *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 2179–2183; (d) K. C. Harper, M. S. Sigman, *Science* **2011**, *333*, 1875–1878; (e) K. C. Harper, E. N. Bess, M. S. Sigman, *Nat. Chem*. **2012**, *4*, 366–374; (f) K. C. Harper, S. C. Vilardi, M. S. Sigman, *J. Am. Chem. Soc*. **2013**, *135*, 2482–2485; (g) K. C. Harper, M. S. Sigman, *J. Org. Chem*. **2013**, *78*, 2813–2818.

(14) For details see Chaper 1.2.2.

(15) L. Mantilli, D. Gérard, C. Besnard, C. Mazet, *Eur. J. Inorg. Chem*. **2012**, 3320–3330.

(16) (a) R. H. Crabtree, *Acc. Chem. Res*. **1979**, *12*, 331–337; (b) R. H. Crabtree, A. Gautier, G. Giordano, T. Kahn, *J. Organomet. Chem.* **1977**, *141*, 113–121; (c) B. Wüstenberg, A. Pfaltz, *Adv. Synth. Catal*. **2008**, *350*, 174–178.

(17) The X-ray structure of **95d** was obtained by Dr Devendra Vyas and later resolved by Dr Céline Besnard.

(18) Cyclometallated cationic iridium hydride complexes are not common and are usually the result of a C(sp^2)–H bond activation. For relevant examples, see: (a) R. H. Crabtree, M. Lavin, L. Bonneviot, *J. Am. Chem. Soc*. **1986**, *108*, 4032–4037; (b) B. P. Patel, R. H. Crabtree, *J. Am. Chem. Soc*. **1996**, *118*, 13105–13106; (c) X. Li, C. D. Incarvito, R. H. Crabtree, *J. Am. Chem. Soc*. **2003**, *125*, 3698–3699; (d) M. A. Esteruelas, F. J. Fernandez-Alvarez, M. Olivan, E. Onate, *Organometallics* **2009**, *28*, 2276–2284; (e) G. Song, Y. Su, R. A. Periana, R. H. Crabtree, K. Han, H. Zhang, X. Li, *Angew. Chem. Int. Ed.* **2010**, *49*, 912–917.

(19) N. Humbert, D. J. Vyas, C. Besnard, C. Mazet, *Chem. Commun*. **2014**, *50*, 10592–10595.

(20) Similar results were obtained if H_2O or MeCN were added prior or after activation of the iridium catalyst by molecular hydrogen.

(21) S.-M. Lu, C. Bolm, *Angew. Chem. Int. Ed*. **2008**, *47*, 8920–8923.

(22) Typical heterogeneous hydrogenation reaction conditions: 5 wt% Pd/C, H_2 (3 bar), THF, 23 °C, 2.5 h, quantitative yield.

(23) 2.3 g of **101e** was prepared in 3 steps based on the known procedure starting from (*S*)-(−)-limonene, see: V. J. Davissont, C. D. Poulter, *J. Am. Chem. Soc*. **1993**, *115*, 1245–1260.

(24) L. Mantilli, C. Mazet, *Tetrahedron Lett.* **2009**, *50*, 4141−4144.

(25) See Chapter 2.2.5 for details.

(26) *Fundamentals of Asymmetric Catalysis*, P. J. Walsh, M. C. Kozlowski, Eds., University Science Books: Sausalito, CA, **2009**.

(27) L. C. Millera, R. Sarpong, *Chem. Soc. Rev.* **2011**, *40*, 4550−4562.

(28) (a) H. B. Kagan, *Tetrahedron* **2001**, *57*, 2449–2459; (b) R. R. Kumar, H. B. Kagan, *Adv. Synth. Catal*. **2010**, *352*, 231–242.

(29) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed*. **2005**, *44*, 3974–4001.

(30) *Fundamentals of Asymmetric Catalysis*, P. J. Walsh, M. C. Kozlowski, Eds., University Science Books: Sausalito, CA, **2009**, Chapter 8, pp. 225–270.

(31) H. M. L. Davies, A. M. Walji, *Angew. Chem. Int. Ed.* **2005**, *44*, 1733–1735.

(32) D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, *Chem. Sci.,* **2012**, *3*, 1422–1425.

(33) S. Sternativo, A. Calandriello, F. Costantino, L. Testaferri, M. Tiecco, F. Marini, *Angew. Chem. Int. Ed.* **2011**, *50*, 9382–9385.

(34) (a) A. de O. Dias, R. Augusti, E. N. dos Santos, E. V. Gusevskaya, *Tetrahedron Lett.* **1997**, *38*, 41–44; (b) C. G. Vieira, M. C. de Freitas, E. N. dos Santos, E. V. Gusevskaya, *ChemCatChem* **2012**, *4*, 795–801.

(35) G. Schulte, P. J. Scheuer, O. J. McConnell, *J. Org. Chem*. **1980**, *45*, 552–554.

(36) Upon decomposition of iridium dihydride species a trinuclear cluster is formed as the major product along with other dimers and tetramers. For details see: (a) D. F. Chodosh, R. H. Crabtree, H. Felkin, G. E. Morris, *J. Organomet. Chem.* **1978**, *161*, C67–C70; (b) D. F. Chodosh, R. H. Crabtree, H. Felkin, S. Morehouse, G. E. Morris, *Inorg. Chem.* **1982**, *21*, 1307–1311; (c) Y. Xu, M. A. Celik, A. L. Thompson, H. Cai, M. Yurtsever, B. Odell, J. C. Green, D. M. P. Mingos, J. M. Brown, *Angew. Chem. Int. Ed*. **2009**, *48*, 582–585.

(37) For the acidity of relevant iridium dihydride species, see: (a) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249−6253; (b) R. H. Morris, *J. Am. Chem. Soc*. **2014**, *136*, 1948−1959.

(38) In the presence of an inorganic base (such as Na_2CO_3), poor conversion to **104e** was observed.

(39) For a relevant review, see: E. Larionov, H. Li, C. Mazet, *Chem. Commun.* **2014**, *50*, 9816−9826.

(40) C. Fuganti, S. Serra, *J. Chem. Soc., Perkin Trans*. *1*, **2000**, 97−101.

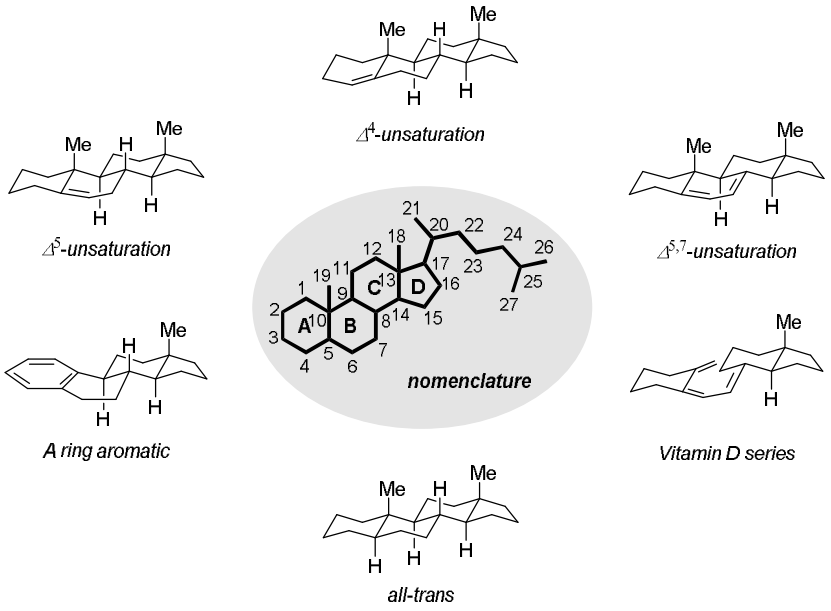
(41) *Organic Synthesis via Examination Selected Natural Products,* D. J. Hart, Ed., World Scientific: Hackensack, NJ, **2011**, Chapter 5, pp. 155–202.

3. Stereoselective Construction of C20 in Steroid Side Chain and Topological Diversification

3.1 The C20 Challenge and Our Strategy

3.1.1 General introduction to steroid C20

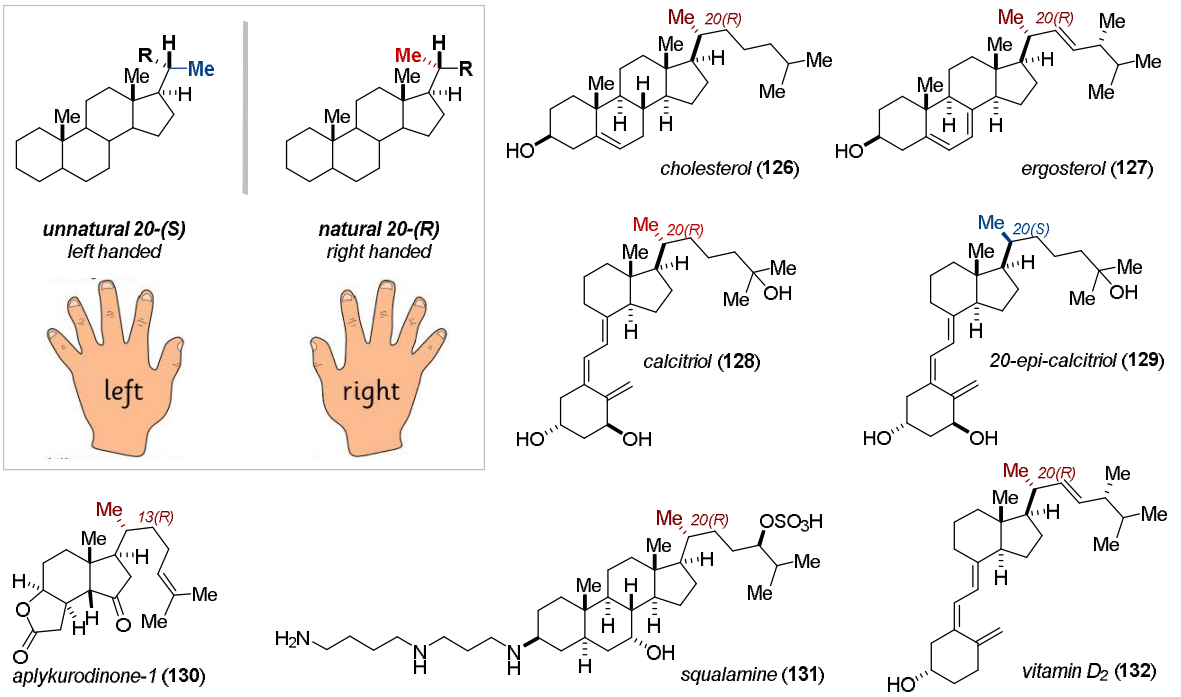
Steroids are a wide variety of naturally occurring compounds found in all the corners of the living world.[1] The discovery and investigation of steroids have not only left a lasting impact on many aspects of chemistry, biology, medicine but also on our society.[2] The challenges associated with their synthesis have raised fundamental questions and have repeatedly served as a fertile ground to advance knowledge in synthetic chemistry over the last century.[3] Their concomitant applications in biological, pharmaceutical and medical sciences have also led to essential discoveries which have profoundly impacted our society.[1,4]



Scheme 3.1. *Nomenclature and common skeletons of steroids*.

[1] *Steroid Chemistry at a Glance,* D. Lednicer, Ed., Wiley-VCH: Hoboken, NJ, **2010**.
[2] (a) P. Wallimann, T. Marti, A. Fürer, F. Diederich, *Chem. Rev*. **1997**, *97*, 1567−1608; (b) *Molecules That Changed the World*, K. C. Nicolaou, T. Montagnon, Eds., Wiley-VCH: Weinheim, **2008**; (c) *Molecules and Medicine*, E. J. Corey, B. Czakó, L. Kürti, Eds., Wiley: New York, **2008**; (d) M. Eggersdorfer, D. Laudert, U. Létinois, T. McClymont, J. Medlock, T. Netscher, W. Bonrath, *Angew. Chem. Int. Ed*. **2012**, *51*, 12960−12990.
[3] (a) R. Skoda-Földes, L. Kollár, *Chem. Rev*. **2003**, *103*, 4095−4129; (b) A.-S. Chapelon, D. Moraléda, R. Rodriguez, C. Ollivier, M. Santelli, *Tetrahedron* **2007**, *63*, 11511−11616; (c) D. T. Hog, R. Webster, D. Trauner, *Nat. Prod. Rep*. **2012**, *29*, 752−779; (d) E. G. Mackay, M. S. Sherburn, *Synthesis* **2015**, *47*, 1–21; (e) D. Urabe, T. Asaba, M. Inoue, *Chem. Rev*. **2015**, *115*, DOI: 10.1021/cr500716f. For selected recent examples, see: (f) K. S. Halskov, B. S. Donslund, S. Barfüsser, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2014**, *53*, 4137−4141; (g) S. Prévost, N. Dupré, M. Leutzsch, Q. Wang, V. Wakchaure, B. List, *Angew. Chem. Int. Ed*. **2014**, *53*, 8770−8773; (h) K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang, W. Tang, *Angew. Chem. Int. Ed*. **2015**, *54*, 3033−3037.
[4] J. A. R. Salvador, J. F. S. Carvalho, M. A. C. Neves, S. M. Silvestre, A. J. Leitão, M. M. C. Silva, M. L. Sá e Melo, *Nat. Prod. Rep*. **2013**, *30*, 324−374.

With some variations, steroids are generally characterized by a prototypical cyclopentenophenanthrene ring system and a side chain attached to this polycyclic framework at C-17 (Scheme 3.1).[1] Decades of investigations have revealed that every single position in the cyclopentanophenanthrene ring system certainly plays a key role in biological applications. Stereogenic centers are particularly sensitive points of mutation.[1]



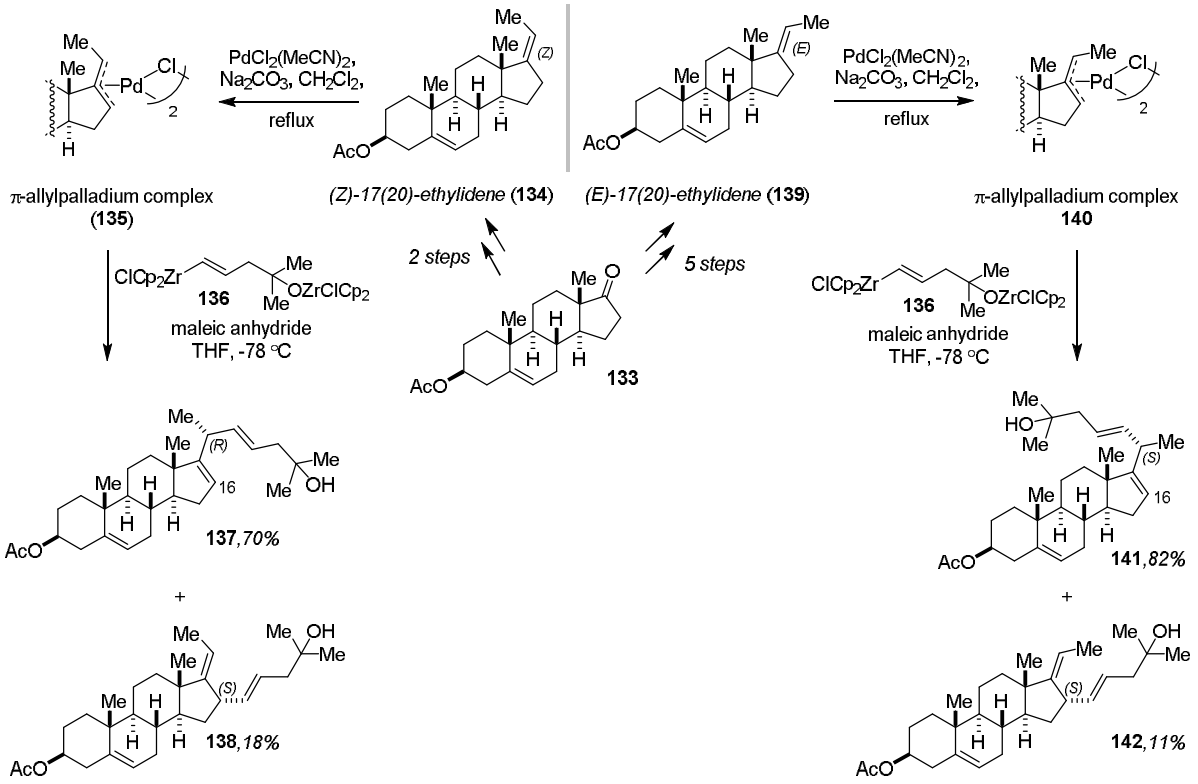
Scheme 3.2. *Representative steroids and steroids C20.*

Of note, C20–the first *exocyclic* stereocenter of the side chain directly adjacent to the polycyclic framework is of particular interest.[5,6] A majority of the biologically active steroids possess the so-called natural C20-(*R*) configuration (Scheme 3.2). These naturally occurring molecules or their synthetic analogues display an immense spectrum of biological activities ranging from *anti*-inflammatory properties to various antitumor activities, while some derivatives have been found to act as reversing substances for multidrug resistance in human carcinogenic cell lines. Steroids with the epimeric unnatural C20-(*S*) configuration are much rarer but distinguish themselves by significantly superior biological activities. For example, the *seco*-steroid 20-*epi*-calcitriol (**129**) is more potent than its natural epimer calcitriol (**128**) in regulating cell growth and cell differentiation. It also possesses immunosuppressive properties.[7]

[5] For the biosynthesis of steroid side chains, see: (a) J.-L. Giner, *Chem. Rev.* **1993**, *93*, 1735−1752; (b) W. D. Nes, *Chem. Rev.* **2011**, *111*, 6423−6451.
[6] (a) D. M. Piatak, J. Wicha, *Chem. Rev.* **1978**, *78*, 199−241; (b) J. Redpath, F. J. Zeelen, *Chem. Soc. Rev.* **1983**, 75−98; (c) B. B. Shingate, B. G. Hazra, *Chem. Rev.* **2014**, *114*, 6349−6382.
[7] (a) L. Binderup, S. Latini, E. Binderup, C. Bretting, M. Calverley, K. Hansen, *Biochem. Pharmacol.* **1991**, *42*, 1569−1575; (b) T. Fujishima, K. Konno, K. Nakagawa, M. Kurobe, T. Okano, H. Takayama, *Bioorg. Med. Chem.* **2000**, *8*, 123−134.

Driven by the distinct biological activity differences between C20-(*R*) and C20-(*S*) isomers, the stereocontrolled construction of this *exocyclic* stereocenter attracted much attention during the last century.[6] From a synthetic point of view, the stereoselective installation of C20 in steroid side chains also represents a formidable academic challenge.[6,8] As commented by Prof. Danishefsky in 2010: *One of the vexing problems in steroid total synthesis is that of exercising control of the configuration at C20. The challenge is that correlating the configuration of the presumably "freely rotating" C20 with the resident stereochemistry of the polycyclic domain.*[8g] In the following section we illustrate the C20 challenge with several representative examples from the literature.

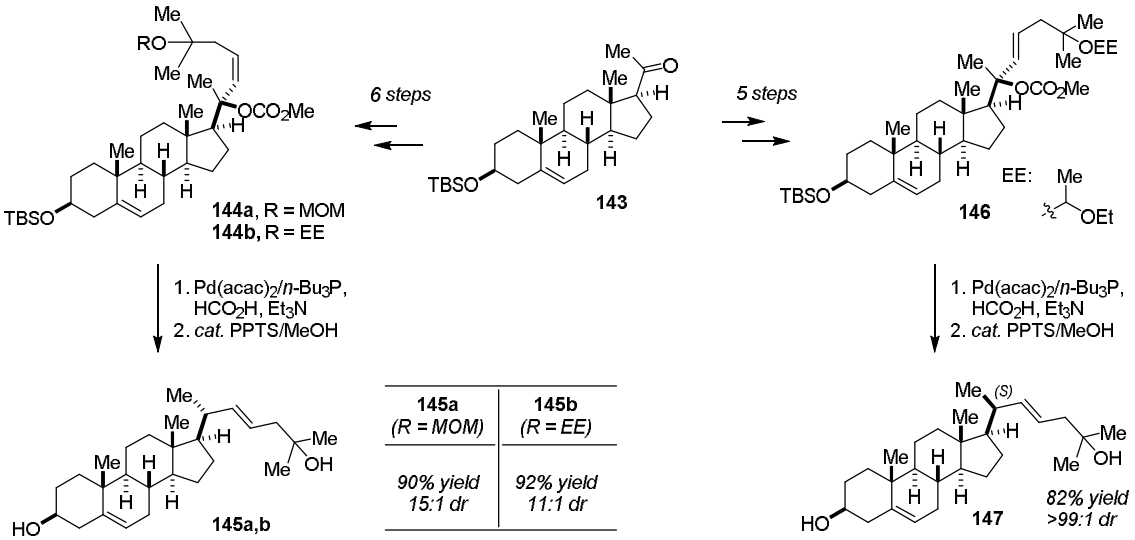
3.1.2 Selected examples for the stereoselective construction of steroid C20



Scheme 3.3. *Pd-mediated allylic alkenylation of alkenyl-zirconocene to install steroid C20 (Schwartz).*

[8] For selected recent examples, see: (a) T. Mandai, T. Mataumoto, M. Kawada, J. Tsuji, *J. Org. Chem.* **1992**, *57*, 6090−6092; (b) S. Harada, H. Kiyono, T. Taguchi, Y. Hanzawa, *Tetrahedron Lett.* **1995**, *36*, 9489−9492; (c) S. Harada, H. Kiyono, R. Nishio, T. Taguchi, Y. Hanzawa, *J. Org. Chem.* **1997**, *62*, 3994−4001; (d) M. de los Angeles Rey, J. A. Martínez-Pérez, A. Fernández-Gacio, K. Halkes, Y. Fall, J. Granja, A. Mouriño, *J. Org. Chem.* **1999**, *64*, 3196−3206; (e) Z. He, C. S. Yi, W. A. Donaldson, *Org. Lett.* **2003**, *5*, 1567−1569; (f) B. Saha, C. R. Smith, T. V. RajanBabu, *J. Am. Chem. Soc.* **2008**, *130*, 9000−9005; (g) Y. Zhang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 9567−9569.

In early 1980s, the Schwartz group conducted extensive investigations to install both C20-(*R*) and (*S*) stereocenters (Scheme 3.3).[9] (*Z*)-**134** and (*E*)-**139** were first prepared in 2 and 5 steps respectively from ketone **133** via two distinct approaches. The Pd-mediated allylic alkenylation of alkenyl-zirconocene **136** provided the desired C20-(*R*)-**137** and C20-(*S*)-**138** in good yields. However, this method suffers from the concomitant formation of the undesired C17 regioisomer (**138** or **142**) and the necessary ablation of the vicinal C17 stereocenter in **137** and **141**.

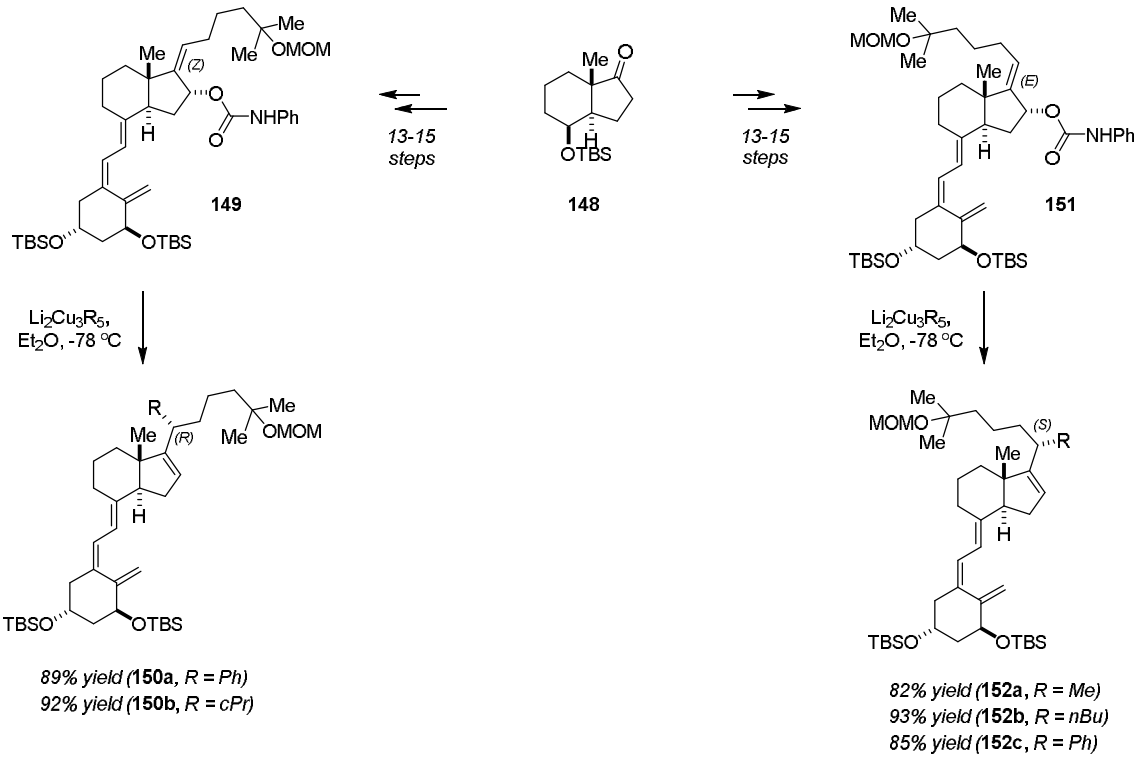


Scheme 3.4. *Pd-catalyzed hydrogenolysis of (Z) and (E) C20-allylic carbonates to install steroid C20 (Tsuji).*

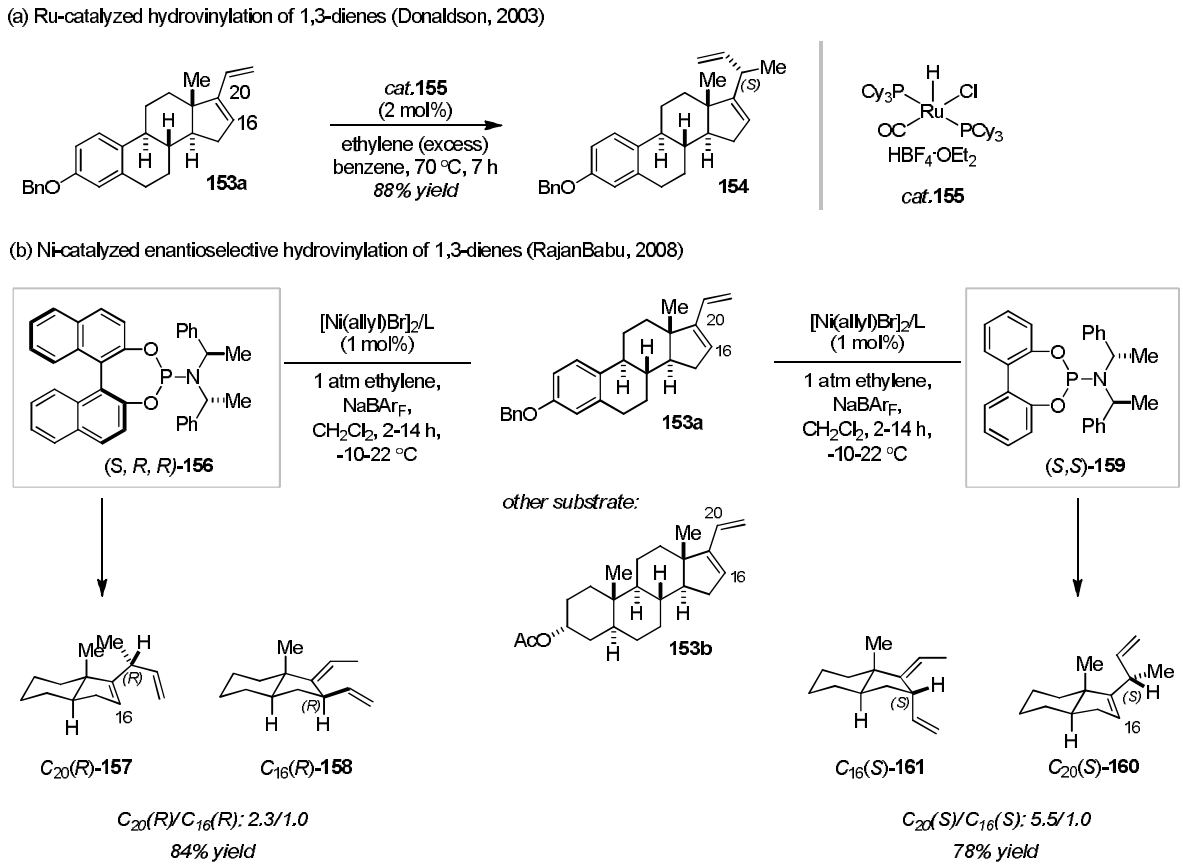
In 1992, the Tsuji group reported the stereospecific generation of both C20 epimers using a Pd-catalyzed hydrogenolysis of (*Z*) and (*E*)-allylic carbonates (Scheme 3.4).[8a] Both (*Z*)-**144** and (*E*)-**146** were first prepared via identical synthetic routes in 5-6 steps. A subsequent Pd-catalyzed hydrogenolysis followed by deprotection afforded **145** and **147** in high yields with high diastereoselectivity. However, this method is restricted to C20 analogs with only methyl substituent at C21.

In 1999, the Mouriño group synthesized various *seco*-steroid vitamin D C20 analogues using a S_N2' alkylation of (*Z*) and (*E*)-allylic carbamates (Scheme 3.5).[8d] Although multistep manipulations were required to prepare either (*Z*)-**149** or (*E*)-**151** from ketone **148**, the subsequent S_N2' alkylation proceeded smoothly and generated several C20-(*R*) and (*S*) vitamin D analogues for subsequent biological screening. The removal of the vicinal C17 stereocenter is an apparent drawback in this approach.

[9] (a) J. S. Temple, J. Schwartz, *J. Am. Chem. Soc*. **1980**, *102*, 7381–7382; (b) Y. Hayasi, M. Riediker, J. S. Temple, J. Schwartz, *Tetrahedron Lett.* **1981**, 22, 2629–2631; (c) J. S. Temple, M. Riediker, J. Schwartz, *J. Am. Chem. Soc*. **1982**, *104*, 1310–1315.

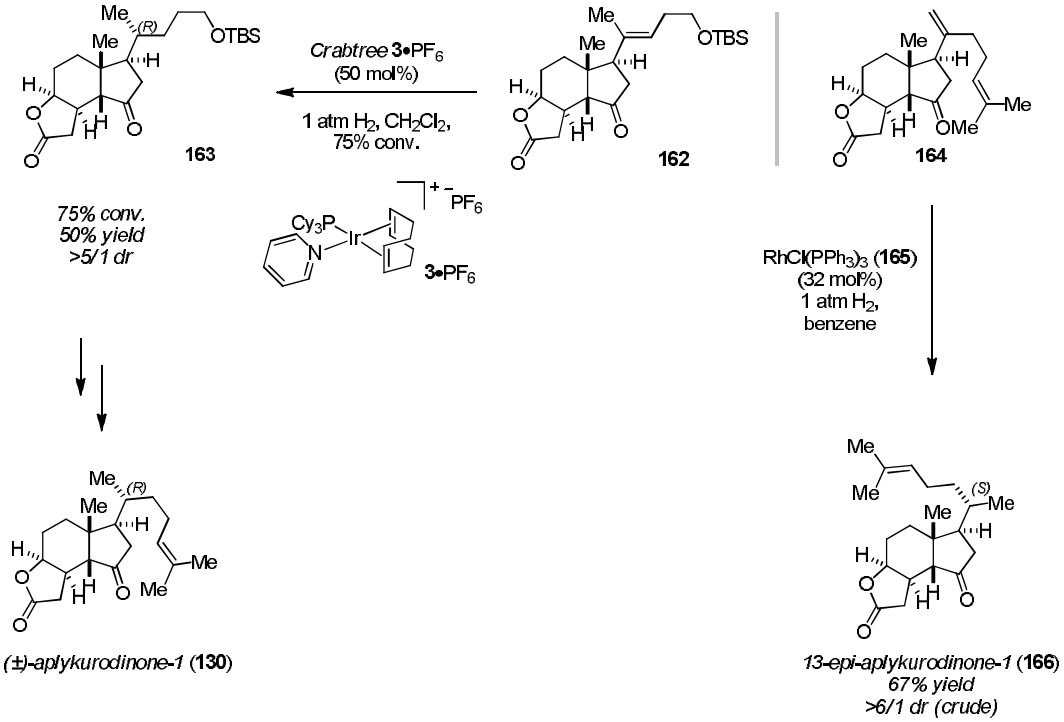


Scheme 3.5. *Preparation of vitamin D C20 analogues* via *S_N2' alkylation of (Z) and (E)-allylic carbamates (Mouriño).*



Scheme 3.6. *Transition metal-catalyzed hydrovinylation of 1,3-diene to install steroid C20.*

Recently, a transition metal-catalyzed hydrovinylation has also been applied to control the stereochemistry at C20 (Scheme 3.6). Upon treatment of 1,3-diene **153a** with a ruthenium catalyst **155**, the Donaldson group was able to obtain exclusively **154** as a C20-(*S*) analog (Scheme 3.6a).[8e] In 2008, en route to the installation of the stereochemistry at C20, the Rajanbabu group reported the first catalyst-directed hydrovinylation of steroidal 1,3-diene substrates (Scheme 3.6b).[8f] By examination of various chiral phosphoramidite ligands for the Ni-catalyzed asymmetric hydrovinylation, they were able to access both C20-(*R*) and (*S*) epimers starting from the same substrate **153a**. Another 1,3-diene **153b** was also evaluated and showed a similar stereochemical outcome. However, this method again suffers from poor regioselectivity and the necessary ablation of the vicinal C17 stereocenter.



Scheme 3.7. *Crabtree-catalyzed hydrogenation to synthesize degraded steroid **130** (Danishefsky).*

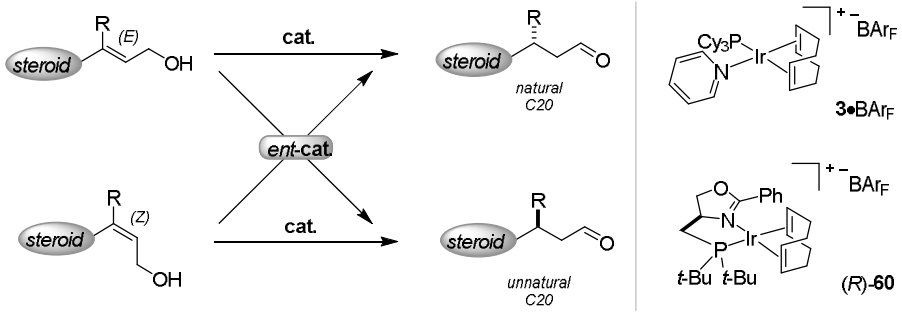
In 2010, *en route* to the degraded marine steroid aplykurodinone-1 (**130**) (Scheme 3.7),[8g] the Danishefsky group noticed that the desired C13-(*R*) isomer **163** can only be obtained through a Crabtree-catalyzed hydrogenation of **162**. In the presence of Wilkinson catalyst (**165**), the undesired C13-(*S*) epimer was formed exclusively using substrate **164**.

To summarize, although numerous methods have been introduced for the stereoselective installation of C20, they all come with deleterious impediments.[6,8,9] With rare exceptions (Scheme 3.6),[8f] two distinct synthetic routes are normally necessary to individually access each C20 epimer of a specific target. A majority of previous approaches follows long linear sequences employing stoichiometric rather than catalytic procedures and require repeated functional group manipulations. Of note, ablation of the vicinal C17 stereocenter has been

regularly practiced to facilitate stereocontrolled construction of C20.[6,8e,f,9] Finally, nominal modularity has been disclosed and almost invariably the steroidal derivatives possess only a methyl substituent at C21.[6,8d] Consequently, these synthetic constrains have precluded exploration of a topological diversification that would match the contemporary standards for wide therapeutic investigations.[10]

3.1.3 Our strategy

During our previous studies in the catalyst-directed diastereoselective isomerization, we obtained satisfactory results using *acyclic* substrates and moderate *dr* with *exocyclic* substrates. Encouraged by the aforementioned results, we envisaged the possibility to develop a catalyst-directed diastereoselective isomerization using steroidal allylic alcohols (Scheme 3.8). If successful, either enantiomer of a chiral iridium catalyst could ideally furnish the C20-(*R*) and C20-(*S*) epimers at will.



Scheme 3.8. *Our initial strategy for the stereoselective installation of steroid C20.*

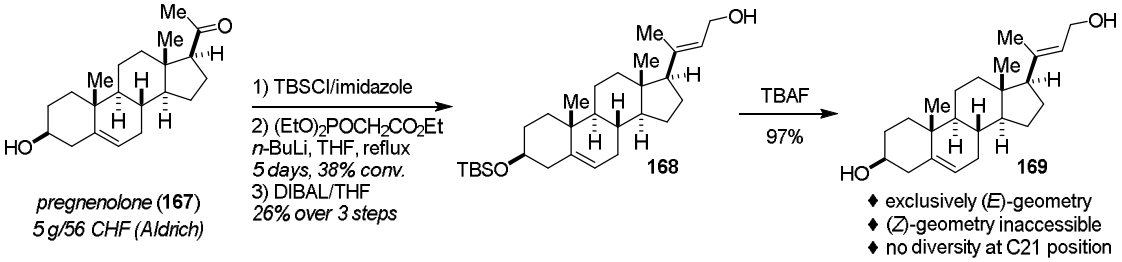
Based on the previous observation that the stereoselective outcome in the Ir-catalyzed isomerization of allylic alcohols depends on olefin geometry, our initial strategy again relied on the selectivity model proposed for the stereospecific transformations of prochiral allylic alcohols (Scheme 3.8). Aside from potential reactivity issues, we were concerned whether enantiomeric chiral catalysts (*R*)-**60** and (*S*)-**60** would be able to overcome the inherent stereochemical bias imposed by the steroid scaffold and impart high level of selectivity at C20 in both matched and mismatched situations. The moderate selectivity observed during the isomerization of *exocyclic* substrates in our previous studies were additional sources of uncertainty.[11]

[10] (a) O. Robles, D. Romo, *Nat. Prod. Rep.* **2014**, *31*, 318−334. For selected recent examples, see: (b) B. Czakó, L. Kürti, A. Mammoto, D. E. Ingber, E. J. Corey, *J. Am. Chem. Soc.* **2009**, *131*, 9014−9019; (c) J. Shi, H. Shigehisa, C. A. Guerrero, R. A. Shenvi, C.-C. Li, P. S. Baran, *Angew. Chem. Int. Ed.* **2009**, *48*, 4328−4331; (d) H. Renata, Q. Zhou, P. S. Baran, *Science* **2013**, *339*, 59−63.
[11] See Chapter 2.6.2 for details.

3.2 Modular Syntheses of Steroidal Allylic Alcohols

3.2.1 Scalable synthesis of model substrates

At the outset of our investigations, we focused on the devise of a short synthetic route that would give access to geometrically pure (*E*) and (*Z*) allylic alcohols. Initial attempts using the previous sequential Horner-Wadsworth-Emmons reaction/DIBAL reduction process was met with failure (Scheme 3.9). Both (*E*)-**168** and **169** were obtained exclusively after the reaction sequence starting from commercially available pregnenolone (**167**).

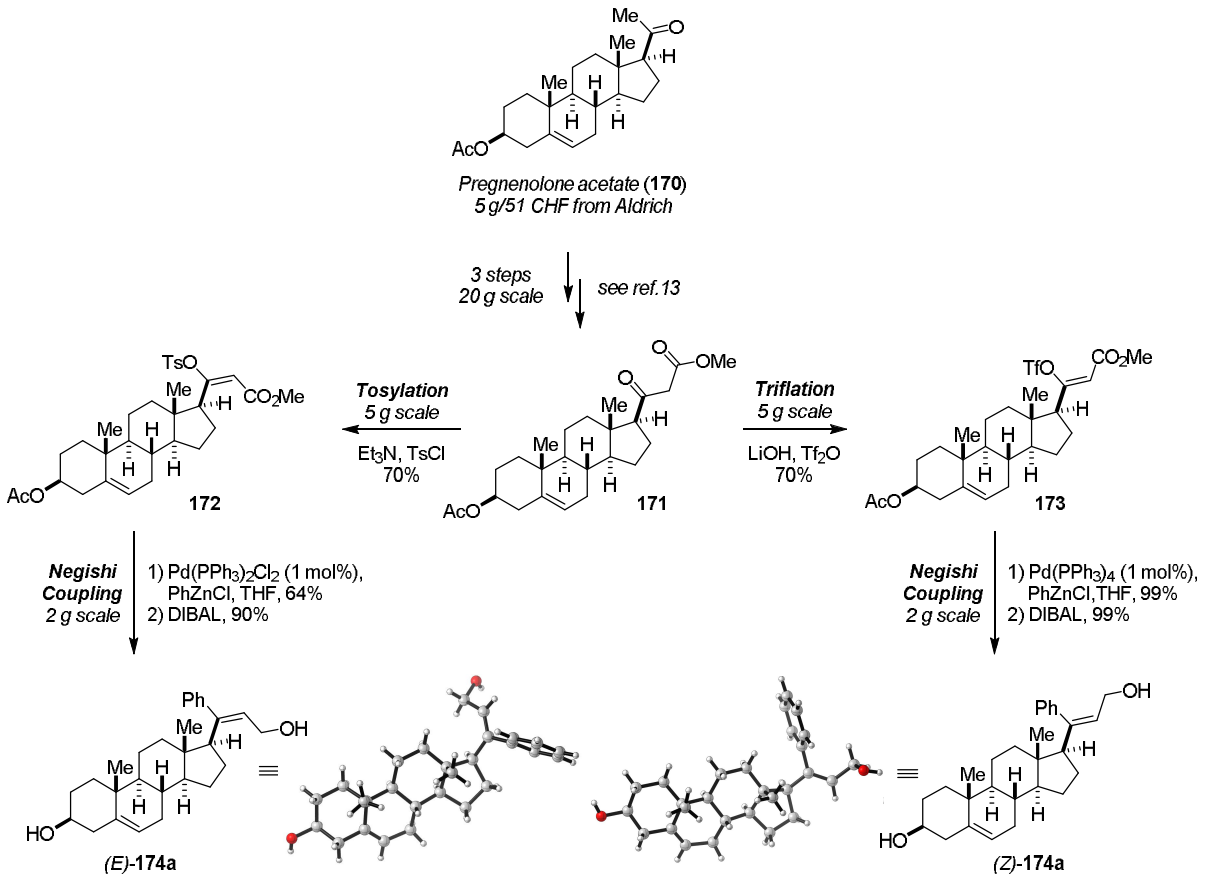


Scheme 3.9. *Initial attempts to synthesize steroidal allylic alcohol.*

To facilitate structural diversification, we envisioned that our approach should be articulated around a common synthetic precursor and rely on the orthogonality provided by transition metal-catalyzed cross-coupling methods.[12] Commercially available pregnenolone acetate **170** was considered as an ideal departing point because it possesses many of the representative attributes of a typical steroid skeleton (a cyclopentanophenanthrene ring system with multiple stereocenters, a Δ^5-unsaturation, an anchoring point at C3, a keto functionality at C20) (Scheme 3.10).

The corresponding 1,3-keto ester **171** was first prepared according to a literature procedure in up to 20 g.[13] Upon treatment of this pivotal intermediate **171** with Et_3N, *N*-methylimidazole and TsCl (3.0 equiv.), (*E*)-enol tosylate **172** was formed exclusively in 70% yield. Geometrically pure (*Z*)-enol triflate **173** was obtained in a similar yield after reaction of **171** with aqueous LiOH and triflic anhydride. In contrast to the original protocols independently developed by Tanabe and Frantz,[14,15] the stereocomplementary (*Z*)-enol tosylate and (*E*)-enol triflate derived from **171** were not accessible by changing the nature of the base.

[12] *Metal−Catalyzed Cross−Coupling Reactions and More*, A. de Meijere, S. Bräse, M. Oestreich, Eds., Wiley-VCH: Weinheim, **2014**.
[13] K. M. Allan, B. D. Hong, B. M. Stoltz, *Org. Biomol. Chem.* **2009**, *7*, 4960−4964.
[14] (a) H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe, *Org. Lett.* **2008**, *10*, 2131−2134; (b) A. Manabe, Y. Ohfune, T. Shinada, *Synlett* **2012**, *23*, 1213−1216.
[15] D. Babinski, O. Soltani, D. E. Frantz, *Org. Lett.* **2008**, *10*, 2901−2904.



Scheme 3.10. *Scalable synthesis of model (Z) and (E)-steroidal allylic alcohols.*

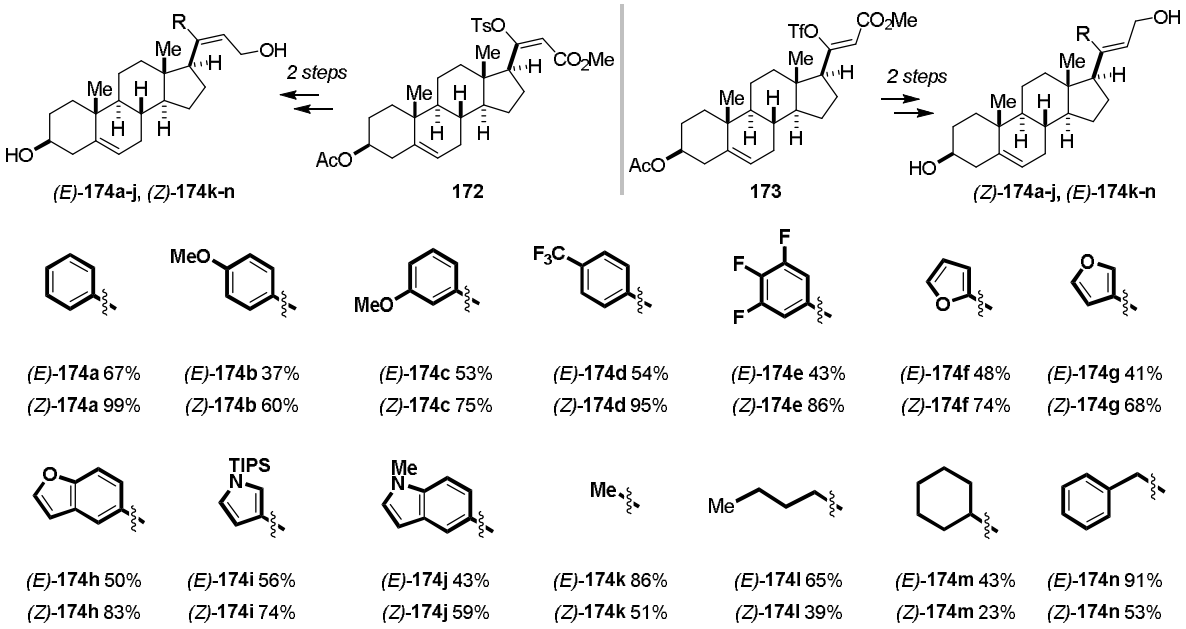
Both (*E*)-**172** and (*Z*)-**173** were subsequently subjected to stereoretentive Pd-catalyzed Negishi cross-coupling reactions with PhZnCl and afforded the corresponding enoates in excellent yields and perfect control of the olefin geometry.[14,16] Reduction of the enoates and simultaneous deprotection of the 3-hydroxyl moiety with an excess of di-isobutyl aluminum hydride (6.0 equiv.) delivered quasi-quantitatively the steroidal allylic alcohols (*E*)-**174a** and (*Z*)-**174a** as white crystalline materials. Both structures were later unambiguously confirmed by single crystal X-ray diffraction analyses. The robustness of our approach was also demonstrated by conducting all steps of the synthesis of (*E*)-**174a** and (*Z*)-**174a** on multi-gram quantity (2−5 g).

3.2.2 General approach to prepare both geometrical isomers of steroidal allylic alcohols

Following this unified route, a collection of 28 derivatives **174a**-**n** was prepared (Scheme 3.11). The mild reactivity associated with the organozinc reagent in the Negishi cross-coupling reactions enabled to introduce a wide variety of aryl, perfluorinated aryl, heteroaryl

[16] Y. Yang, N. J. Oldenhuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 615−619.

and alkyl groups with consistently perfect control of the olefin geometry. The yields were normally very high for the (*Z*)-allylic alcohols and moderate for the (*E*) isomers.



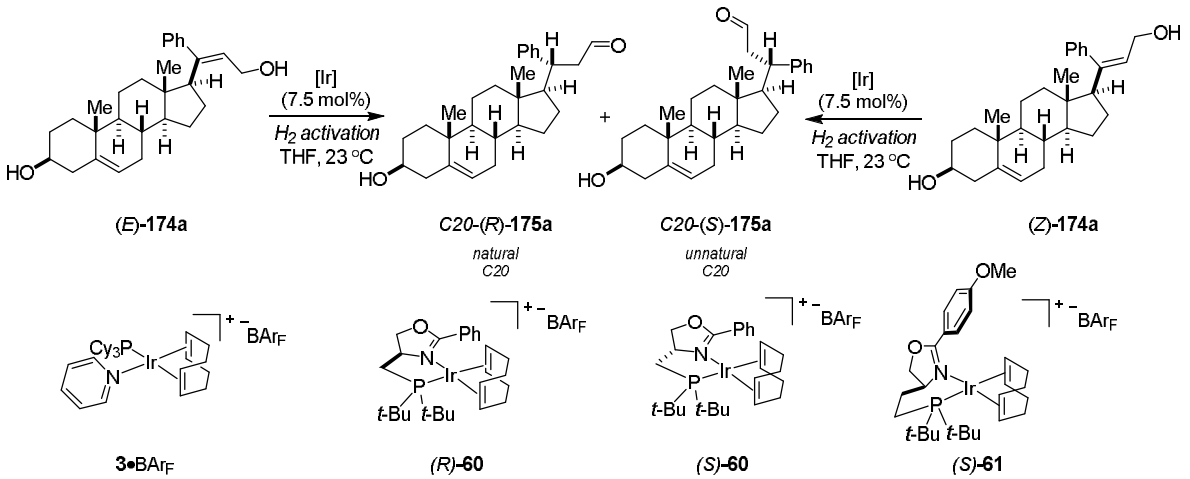
Scheme 3.11. *Scope of (Z) and (E)-steroidal allylic alcohols*

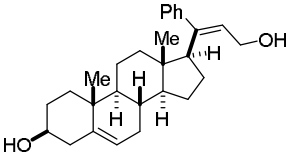
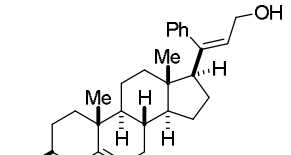
3.3 Stereospecific Isomerization of Model Allylic Alcohols

3.3.1 The optimization of model isomerization reaction

To evaluate the feasibility of our approach and to probe the innate selectivity imposed by steroidal allylic alcohols, we commenced our exploratory experiments with diastereoselective isomerization of two model substrates using the achiral catalyst **3**•BAr_F (Table 3.1). Isomerization of (*E*)-**174a** delivered aldehyde **175a** in 76% yield and 29:1 *dr* in favor of the natural C20-(*R*) (Table 3.1, entry 1). Isomerization of (*Z*)-**174a** afforded **175a** in 72% but in only 1.4:1 *dr* (Table 3.1, entry 4), indicating that the steroid domain imparts a very strong bias on the reaction outcome. Besides the successful application of our isomerization with a complex molecule, the compatibility of the iridium catalyst **3**•BAr_F with the endocyclic homoallylic alcohol is noteworthy as this is a common motif for Crabtree-catalyzed directed hydrogenations.[17]

[17] J. W. Suggs, S. D. Cox, R. H. Crabtree, J. M. Quirk, *Tetrahedron Lett.* **1981**, *22*, 303−306.



Entry	Substrate	Catalyst	Reaction Time (h)	Conversion to **175a**[a] (isolated yield)	Ratio of C20-(*R*)/(*S*)[a]
1	 (*E*)-**174a**	**3**•BAr_F	4	>99% (76%)	29:1
2		(*S*)-**60**	24	8%	1/8
3		(*R*)-**60**	24	94% (70%)	>50:1
4	 (*Z*)-**174a**	**3**•BAr_F	4	94% (72%)	1.4:1
5		(*S*)-**60**	24	9%	2.3:1
6		(*R*)-**60**	24	28%	1:50
7		(*R*)-**60**[b]	24	58% (49%)	1:50
8		(*S*)-**61**	24	<5%	*n.d.*[c]

[a] *Determined by ^{1}H NMR analysis of crude residue (400 MHz);* [b] *Using 15 mol% of catalyst;* [c] *n.d. = Not determined.*

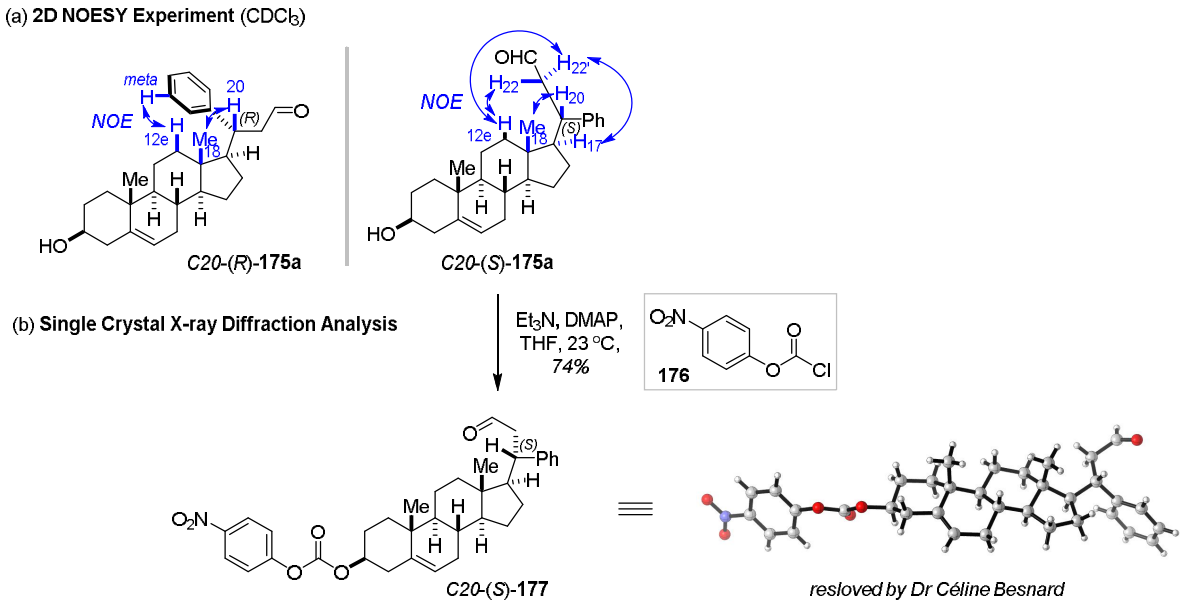
Table 3.1. *Optimization table for the isomerization of (E) and (Z)-allylic alcohols **174a**.*

We next evaluated the catalyst-directed diastereoselective isomerization reactions with both enantiomers of the chiral iridium catalyst. Although only nominal amounts of aldehyde **175a** were detected when (*S*)-**60** was used for the isomerization of (*E*)-**174a** and (*Z*)-**174a** (Table 3.1, entries 2, and 5), catalyst permutation restored satisfactory reactivity. Due to match effects between the chiral catalyst and the chiral substrate, isomerization of (*E*)-**174a** with (*R*)-**60** provided **175a** in 70% yield, essentially as a single C20-(*R*) diastereoisomer (>50:1 *dr*, see Table 3.1, entry 3).

More remarkably, isomerization of (*Z*)-**174a** gave **175a** in 28% yield and 1:50 *dr* in favor of the unnatural C20-(*S*) epimer (Table 3.1, entry 6). Despite the low yield, the ability of the chiral catalyst (*R*)-**60** to overcome the natural bias imposed by the substrate to such an extent is simply exceptional. Increasing the catalyst loading for the isomerization of (*Z*)-**174a**

led to **175a** in 49% yield with a similarly high diastereoselectivity (Table 3.1, entry 7). Of note, the remainder of these reactions consisted essentially of unreacted starting material. In contrast, the isomerization reaction did not proceed in the presence of chiral catalyst (S)-**61** (Table 3.1, entry 8).

3.3.2 The assignment of the stereochemistry

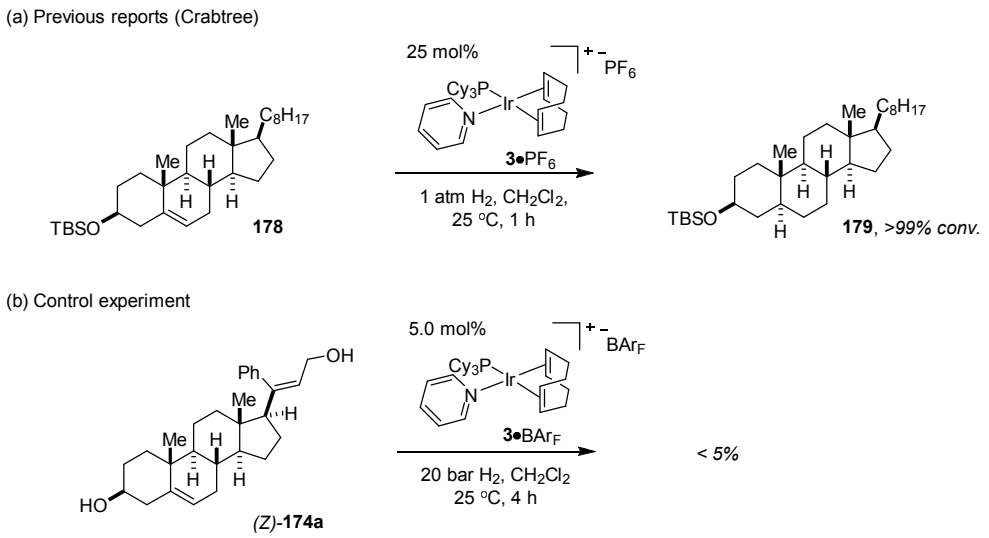


Scheme 3.12. *The structural assignment of isomerization products **175a**.*

The stereochemistry of both C20-(*R*) and C20-(*S*)-**175a** obtained after the isomerization were initially determined by multinuclear and bidimensional NMR experiments (Scheme 3.12a). Further derivatization of C20-(*S*)-**175a** with 4-nitrophenyl chloroformate (**176**) afforded carbonate C20-(*S*)-**177**, the structure of which was unambiguously confirmed by single crystal X-ray diffraction analysis.

3.3.3 Control experiments

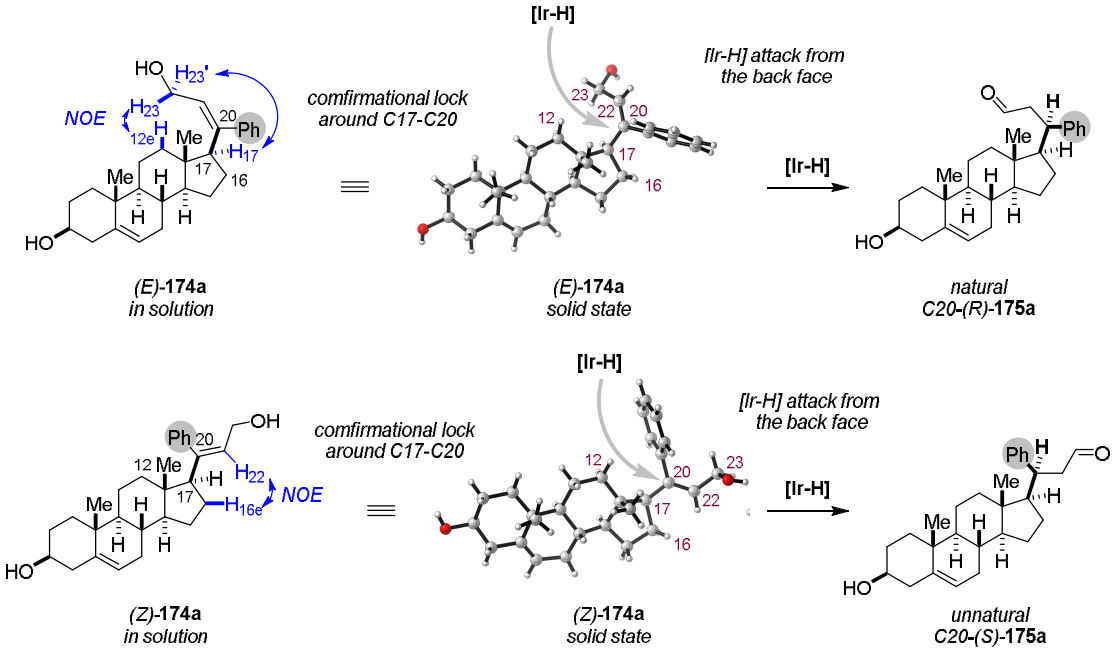
According to the previous studies by Crabtree and co-workers, product **179** was obtained quantitatively upon treatment of **178** with **3**•PF_6 under hydrogenation conditions (Scheme 3.13a).[17] Applying the similar reaction conditions using **3**•BAr_F to our model substrate (*Z*)-**174a** led to different reaction outcomes (Scheme 3.13b). No reactivity was observed after 4 h under 20 bar H_2 pressure, other attempts (15 mol% catalyst loading, 24 h reaction time, etc) did not provide any superior results.



Scheme 3.13. *Crabtree-catalyzed hydrogenation reactions.*

3.4 Selectivity Rationale

To rationalize the stereoselective outcome of the isomerization reactions, we conducted the comparative analyses of the structures of (*E*)-**174a** and (*Z*)-**174a** both in solid state and in solution (Scheme 3.14). Specifically, the orientation of the C=C bond of the allylic alcohols constitutes a determining parameter for substrate binding. The crystal structures of (*E*)-**174a** and (*Z*)-**174a** reveal that the phenyl substituent points to the C12 region of the steroid scaffold in (*Z*)-**174a** and is directed toward C16 in (*E*)-**174a**.



Scheme 3.14. *Proposed origin of the high diastereoselectivity obtained with (R)-**60**.*

Bidimensional NMR analyses of these two substrates are consistent with the solid state analyses and indicate that these orientations persist in solution (Scheme 3.14). Strong NOE contacts were detected between the diastereotopic protons H23/H23' and H12 and H17 in (*E*)-**174a**. A characteristic NOE interaction between H22 and H16 was clearly visible for (*Z*)-**174a**.

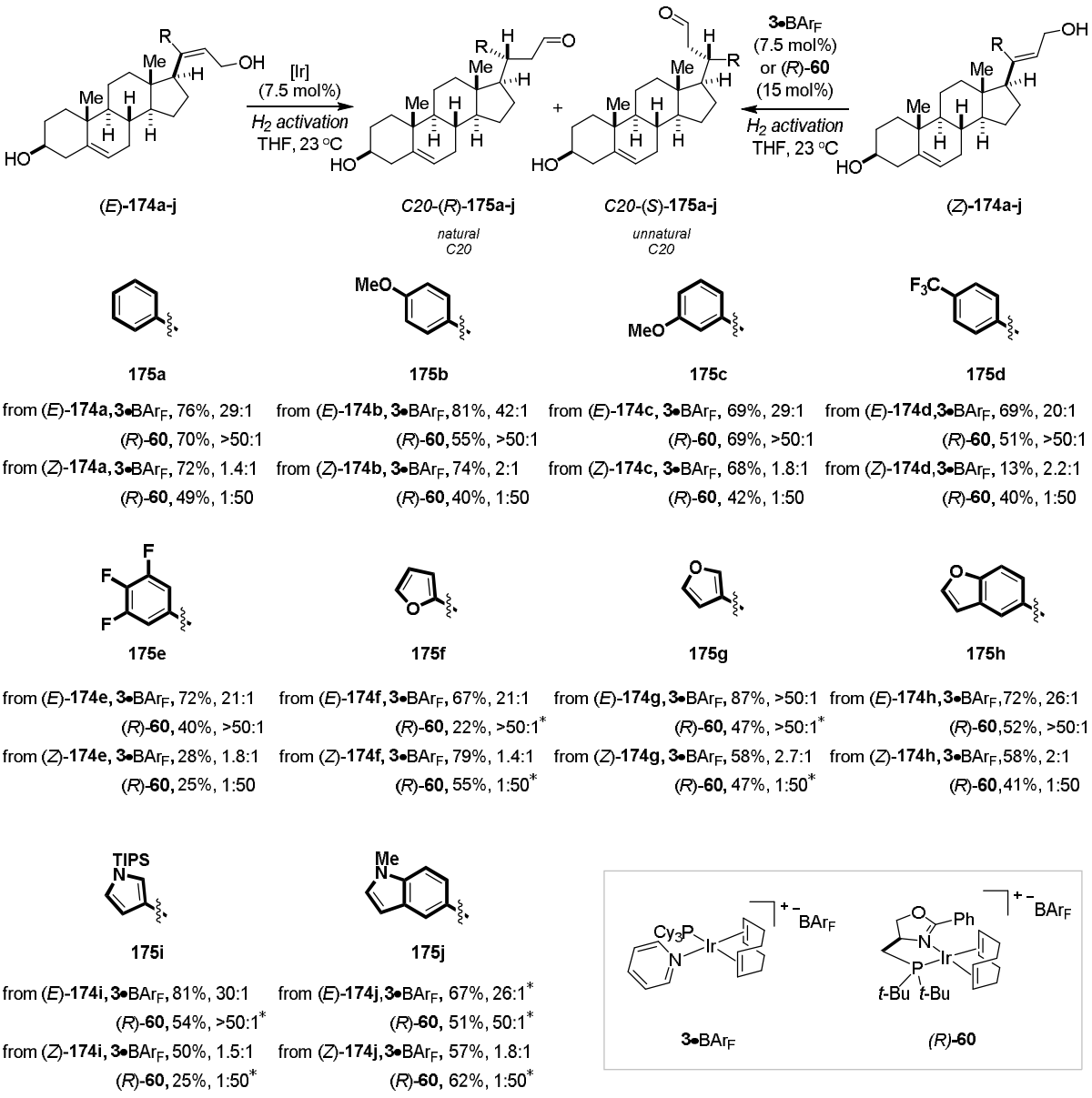
Collectively, these observations support the existence of a locked conformation around C17-C20 for both olefin geometries (Scheme 3.14). Regarding the high steric prominence of the steroid scaffold, it seems reasonable to assume that the catalyst can only approach the allylic alcohol from the back face. Finally, the results obtained in the isomerizations with (*R*)-**60** suggest that the binding orientation of the olefin to the active iridium-hydride intermediate is identical for both substrates and that the C20 substituents are simply permuted. The much reduced reactivity of (*S*)-**60** is presumably due to the lack of efficient coordination of the catalyst to the substrate. A detrimental steric clash might occur between the ligand substituents and the allylic alcohols substituents during back-face attack.[18]

3.5 Reaction Scope

*3.5.1 Scope for the isomerization of aromatic steroidal allylic alcohols **174a-j***

With 20 representative *aromatic* derivatives **174a**-**j**, we next investigated the synthetic versatility of the catalyst-directed diastereoselective isomerization of our steroidal allylic alcohols (Scheme 3.15). All the aromatic and heteroaromatic steroid derivatives of our collection were found to be suitable candidates. Catalyst **3**•BAr_F provided already the corresponding aldehydes C20-(*R*)-**175a**-**j** in excellent yield and high diastereoselectivity with (*E*)-**174a-j** (typically 20:1). The match effect obtained with the chiral catalyst (*R*)-**60** enabled to reach selectivity >50:1 in all cases. For (*Z*)-**174a-j**, innate selectivities ranging from 1.4:1 to 2.7:1 were measured. When the chiral catalyst (*R*)-**60** was employed the yields in aldehyde were lower than for the (*E*)-isomers. Nevertheless, diastereoselectivities remained exceptionally high and the C20-(*S*) epimer was formally obtained as a single isomer in all cases.

[18] Current studies are aiming at gaining a better understanding on the origin of the high diastereoselectivities obtained. It is likely that allylic strain (steric and electronic) may play a key role. For a relevant discussion on this phenomenon in the directed iridium-catalyzed hydrogenation of allylic alcohols, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev*. **1993**, *93*, 1307−1370.



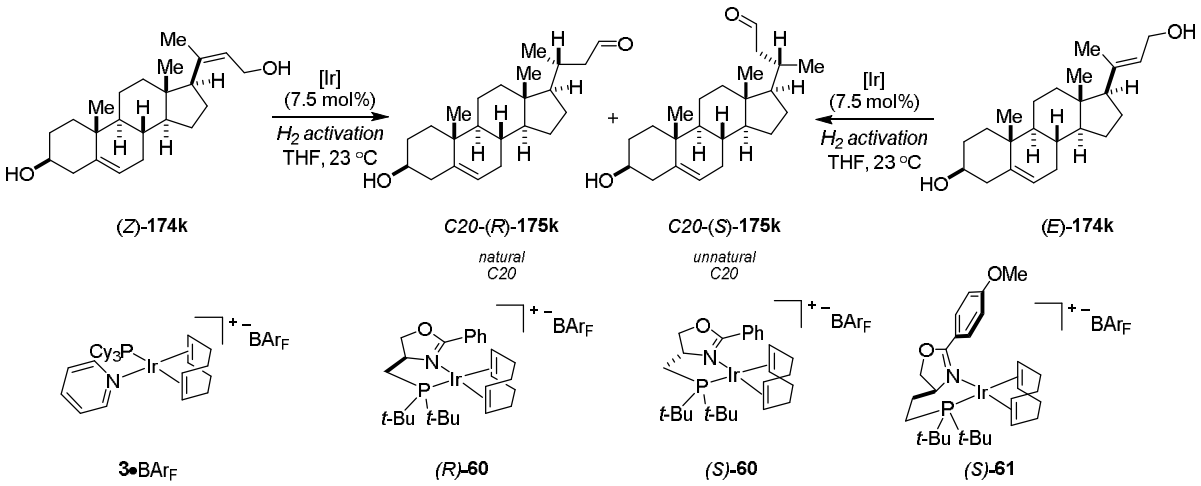
Scheme 3.15. *Scope in the isomerization of aromatic steroidal allylic alcohols. All ratios are indicated as C20-(R)/(S). *A catalytic amount of DTBMP is required.*

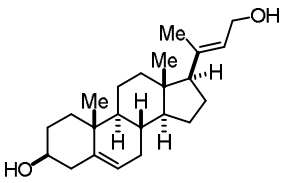
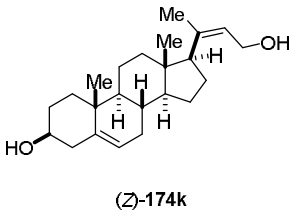
For the most sensitive derivatives (Scheme 3.15), we found that the use of catalytic amounts of DTBMP was beneficial to the reaction, supposedly because of its aptitude to quench traces of acid that may be generated upon iridium hydride decomposition.[19] Overall, the results obtained on 20 different aryl- or heteroaryl-containing substrates clearly demonstrate the remarkable ability of the chiral catalyst to overcome the innate bias imposed by the chiral steroidal scaffold. The compatibility of the method with electron-rich, electron-neutral, perfluorinated electron-deficient aryls as well as nitrogen or oxygen

[19] For the acidity of relevant iridium dihydride species, see: (a) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249−6253; (b) R. H. Morris, *J. Am. Chem. Soc*. **2014**, *136*, 1948−1959. For a similar observation see Chapter 2.6.1.

containing heterocycles must be particularly emphasized for potential applications in biological studies.[10c,d,20,21]

*3.5.2 The optimization of isomerization reaction of aliphatic steroidal allylic alcohol **174k***



Entry	Substrate	Catalyst	Reaction Time (h)	Consumption of **174k**[a] (isolated yield)	Ratio of C20-(*R*)/(*S*)[a]
1	 (*E*)-**174k**	**3**•BAr_F	4	>99% (40%)	10:1
2		(*S*)-**60**[b]	24	69% (23%)	10:1
3		(*R*)-**60**[b]	24	62% (12%)	1/1.6
4		(*S*)-**61**[b]	24	42% (<5%)	nd[c]
5	 (*Z*)-**174k**	**3**•BAr_F	4	>99% (23%)	16:1
6		(*S*)-**60**[b]	24	76% (<5%)	*n.d.*[d]
7		(*R*)-**60**[b]	24	80% (29%)	>50:1
8		(*S*)-**61**[b]	24	48% (<5%)	*n.d.*[c]

[a] *Determined by ^{1}H NMR analysis of crude residue (400 MHz);* [b] *Using 15 mol% of catalyst;* [c] *n.d. = Not determined.*

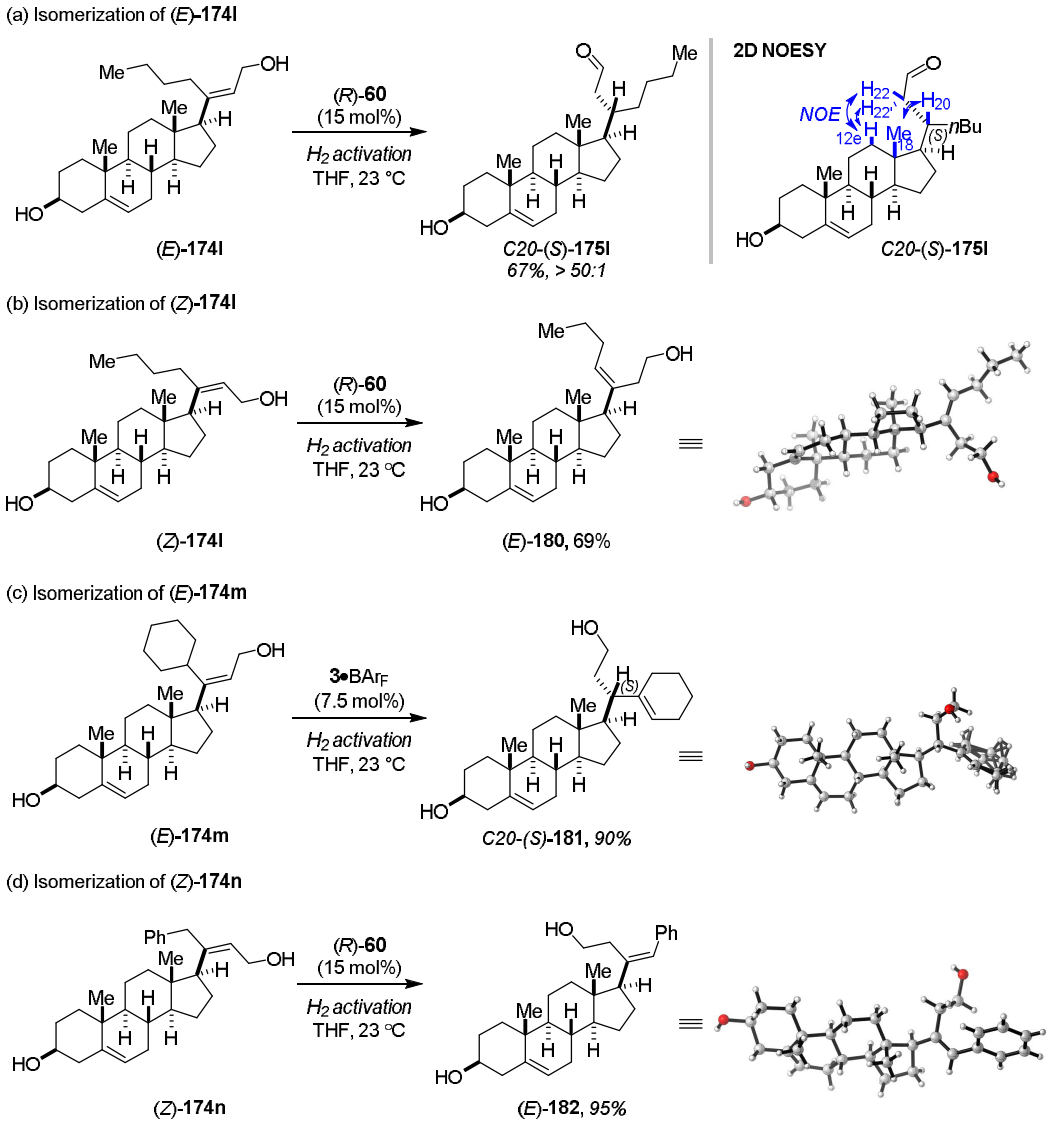
Table 3.2. *Optimization table for the isomerization of (E) and (Z)-allylic alcohols **174k**.*

Based on the satisfactory results obtained with *aromatic* steroidal allylic alcohols, we next decided to evaluate *aliphatic* steroidal allylic alcohols. The isomerization of (*E*)-**174k** and (*Z*)-**174k** with catalyst **3**•BAr_F proved more difficult as the resulting aldehydes were isolated in 40% and 23% yield (Table 3.2, entries 1, and 5). In both cases the natural C20-(*R*) isomer

[20] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432−2506.
[21] *Bioactive Heterocyclic Compound Classes: Pharmaceuticals*, J. Dinges, C. Lamberth, Eds., Wiley-VCH: Weinheim, **2012**.

was obtained preferentially (in 10:1 and 16:1 *dr* respectively). To our delight, isomerization of (*Z*)-**174k** with (*R*)-**60** allowed to reach an excellent selectivity level (>50:1 *dr*, see Table 3.2, entry 7). In the isomerization of (*E*)-**174k**, both the yield and selectivity dropped significantly (Table 3.2, entry 3). Neither (*S*)-**60** nor (*S*)-**61** displayed any marked reactivity for these substrates (Table 3.2, entries 2, 4, 6, and 8).

*3.5.3 The isomerization of aliphatic steroidal allylic alcohols **174l-n***

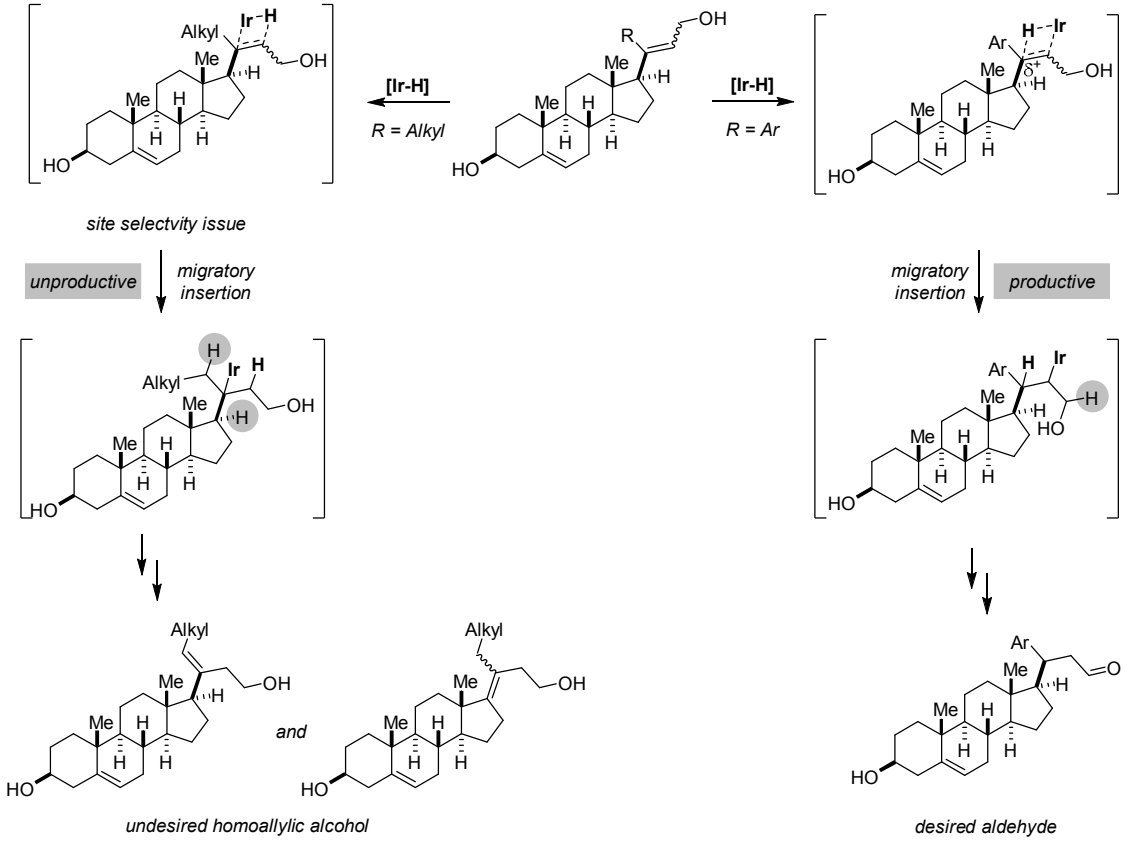


Scheme 3.16. *The isomerization of aliphatic steroidal allylic alcohols **174l-n**.*

Applying the optimal isomerization conditions to the rest of the *aliphatic* steroidal allylic alcohols **174l-n** did not provide superior results (Scheme 3.16). Specifically, allylic alcohols (*E*)-**174l** and (*Z*)-**174l** were evaluated to examine the effect of the length of the alkyl substituent. Whereas no aldehyde was obtained during the isomerization with **3**•BAr_F,

isomerization of (*E*)-**174l** by (*R*)-**60** provided C20-(*S*)-**175l** in 67% yield and >50:1 *dr*, as established on the basis of multidimensional NMR experiments (Scheme 3.16a).

Isomerization of (*Z*)-**174l** led only to the exclusive formation of homoallylic alcohol (*E*)-**180** (Scheme 3.16b). Examination of allylic alcohols (*E*)-**174m** afforded homoallylic alcohol C20-(*S*)-**181** upon isomerization with **3**•BAr_F (Scheme 3.16c). Finally, isomerization of (*Z*)-**174n** by (*R*)-**60** generated another homoallylic alcohol (*E*)-**180** (Scheme 3.16c). All the structures were unambiguously confirmed by single crystal X-ray diffraction analyses.



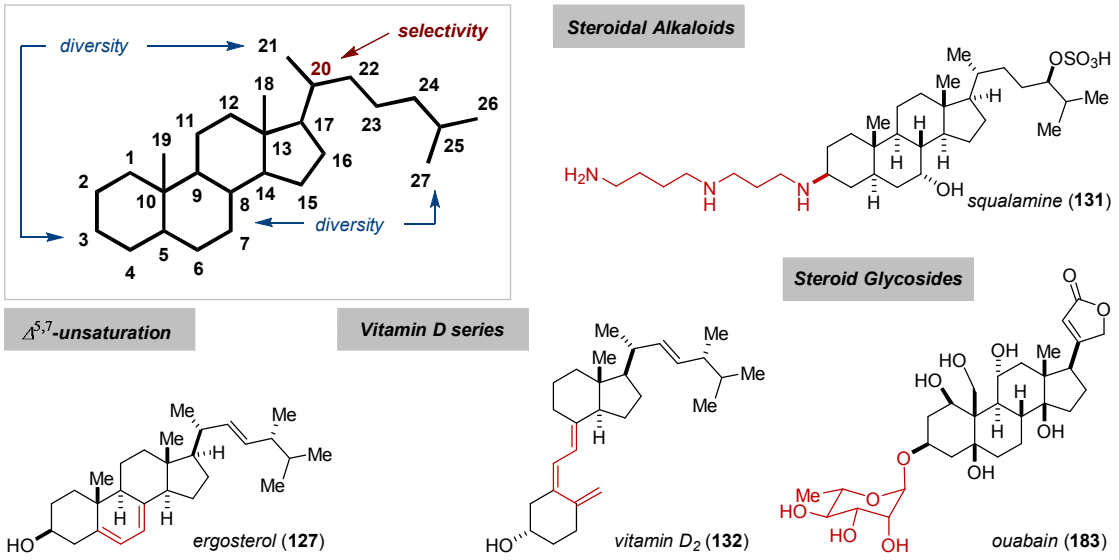
Scheme 3.17. *Electronic difference between aromatic and aliphatic steroidal allylic alcohols.*

Taken together, these results indicate that the electronic nature of the alkene substituent (aryl, heteroaryl *vs* alkyl) certainly influences site selectivity for migratory insertion of the iridium dihydride (Scheme 3.17). For aliphatic steroidal allylic alcohols, this may lead to unproductive isomerization or competing *E/Z* isomerization of the substrate and significantly obscure analysis of the stereoselective outcome of the reactions.[22] In the case of small alkyl substituents, the absence of a fixed orientation of the alkene around C17-C20 cannot be excluded. Therefore, it seems premature to elaborate a solid selectivity model for aliphatic steroidal allylic alcohols at this stage of investigations.

[22] (a) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, *48*, 5143−5147; (b) H. Li, C. Mazet, *Org. Lett.* **2013**, *15*, 6170−6173.

3.6 Topological Diversification

3.6.1 Topological diversification inspired by naturally occurring steroids



Scheme 3.18. *Potential topological diversifications inspired by naturally occurring steroids.*

Aside from the diversification in C21, the strategic use of the pregnenolone scaffold allows additional variations at crucial positions of the polycyclic domain and extension of the exocyclic side chain (Scheme 3.18). Such synthetic flexibility is of particular importance for potential applications in pharmaceutical and medical sciences. For instance, steroid glycosides bearing a sugar moiety at C3 (*i.e.,* ouagabin **183**) have been regularly employed in the treatment of congestive heart failure or as antitumor agents.[4,23] Steroidal alkaloids with an amino group at C3 (*i.e.,* squalamine **131**) often display significant anti-angiogenic properties.[4,24] Finally, steroids with a $\Delta^{5,7}$-unsaturation (*i.e.,* ergoserol **127**) not only constitute pivotal biosynthetic precursors of cholesterol derivatives and vitamin D analogues,[2d] but they are also targets for the treatment of fungal infections.[25,26]

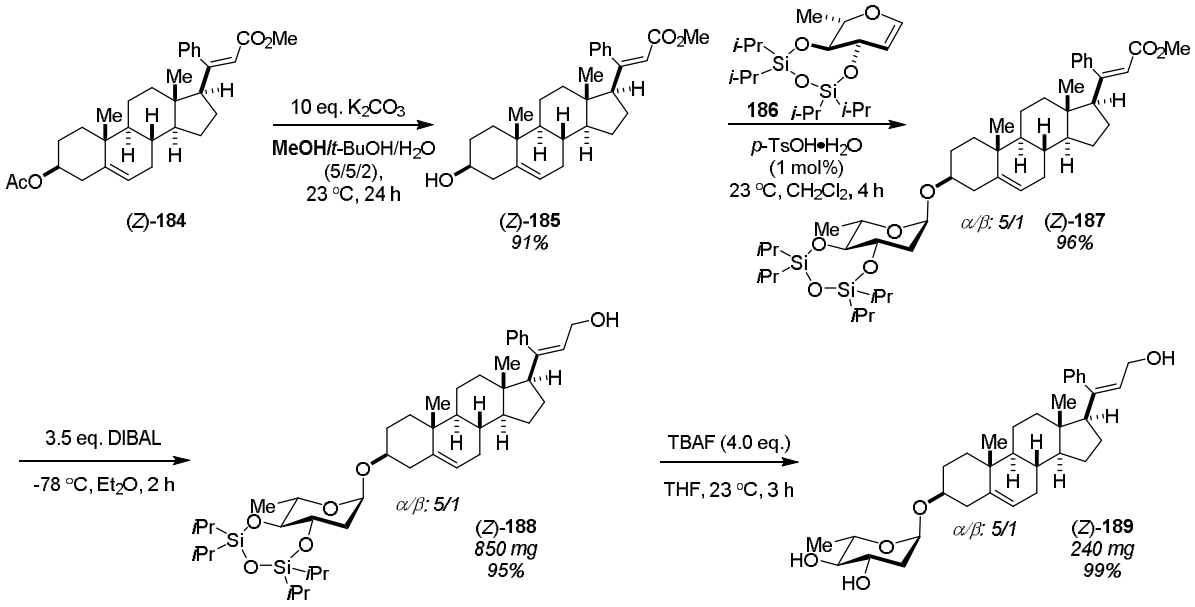
[23] (a) B. Heasley, *Chem.−Eur. J.* **2012**, *18*, 3092−3120. For recent synthetic efforts, see: (b) H. Zhang, M. S. Reddy, S. Phoenix, P. Deslongchamps. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272−1275; (c) M. S. Reddy, H. Zhang, S. Phoenix, P. Deslongchamps. *Chem. Asian J.* **2009**, *4*, 725–741; (d) K. Mukai, D. Urabe, S. Kasuya, N. Aoki, M. Inoue, *Angew. Chem. Int. Ed.* **2013**, *52*, 5300–5304; (e) K. Mukai, S. Kasuya, Y. Nakagawa, D. Urabe, M. Inoue, *Chem. Sci.* **2015**, *6*, 3383−3387; (f) H. Renata, Q. Zhou, G. Dünstl, J. Felding, R. R. Merchant, C.-H.Yeh, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 1330–1340, and ref. 10d.

[24] (a) K. S. Moore, S. Wehrli, H. Roder, M. Rogers, J. N. Forrest, D. McCrimmon, M. Zasloff, *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 1354–1358; (b) A. K. Sills, J. I. Williams, B. M. Tyler, D. S. Epstein, E. P. Sipos, J. D. Davis, M. P. McLane, S. Pitchford, K. Cheshire, F. H. Gannon, W. A. Kinney, T. L. Chao, M. Donowitz, J. Laterra, M. Zasloff, H. Brem, *Cancer Res.* **1998**, *58*, 2784–2792; (c) M. Zasloff, A. P. Adams, B. Beckerman, A. Campbell, Z. Han, E. Luijten, I. Meza, J. Julander, A. Mishra, W. Qu, J. M. Taylor, S. C. Weaver, G. C. L. Wong, *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 15978–15983.

[25] N. B. Javitt, *Steroids* **2008**, *73*, 149–157.

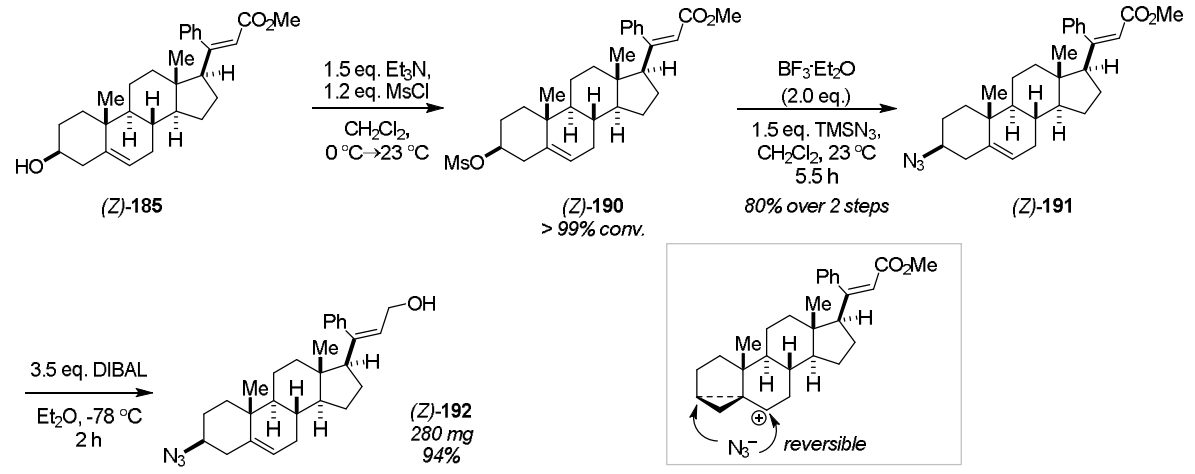
[26] (a) K. C. Gray, D. S. Palacios, I. Dailey, M. M. Endo, B. E. Uno, B. C. Wilcock, M. D. Burke, *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 2234–2239; (b) T. M. Anderson, M. C. Clay, A. G. Cioffi, K. A. Diaz, G. S. Hisao, M. D. Tuttle, A. J. Nieuwkoop, G. Comellas, N. Maryum, S. Wang, B. E. Uno, E. L. Wildeman, T. Gonen, C. M. Rienstra, M. D. Burke, *Nat. Chem. Biol.* **2014**, *10*, 400–406.

3.6.2 Scalable synthesis of advanced steroidal allylic alcohols



Scheme 3.19. *Preparation of polyhydroxylated (Z)-steroidal allylic alcohols.*

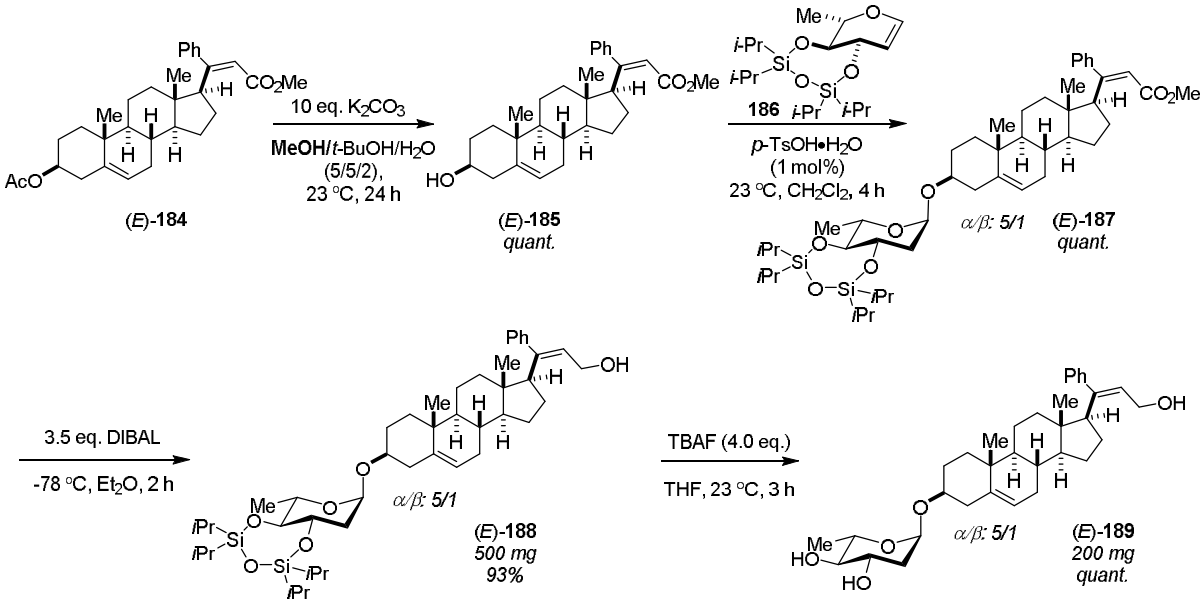
As shown in Scheme 3.19, we commenced our synthesis with enoate (*Z*)-**184**. A sequential acetate deprotection/acid-catalyzed glycosylation using glucal **186** followed by DIBAL reduction provided allylic alcohol (*Z*)-**188** bearing a disiloxane-protected glycosyl moiety at C3 with preferential α-selectivity (*α/β*: 5/1) in 83% overall yield.[27] Subsequent TBAF desilylation quantitatively delivered the corresponding polyhydroxylated allylic alcohol (*Z*)-**189**.



Scheme 3.20. *Preparation of azidated (Z)-steroidal allylic alcohol.*

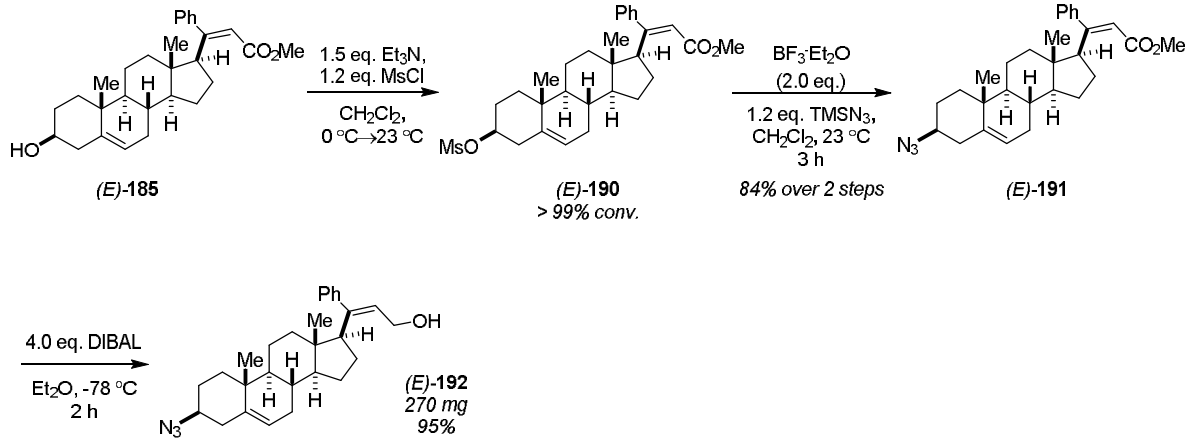
[27] E. I. Balmond, D. Benito-Alifonso, D. M. Coe, R. W. Alder, E. M. McGarrigle, M. C. Galan, *Angew. Chem. Int. Ed.* **2014**, *53*, 8190–8194.

Stereoretentive C3 azidation was performed by in situ treatment of the C3-mesylate derived from (*Z*)-**185** with $TMSN_3$ (1.5 equiv.) in the presence of $BF_3 \bullet OEt_2$ (2 equiv.) (Scheme 3.20).[28] Azidated allylic alcohol (*Z*)-**192** was obtained quasi-quantitatively by reduction with di-isobutyl aluminum hydride (DIBAL).



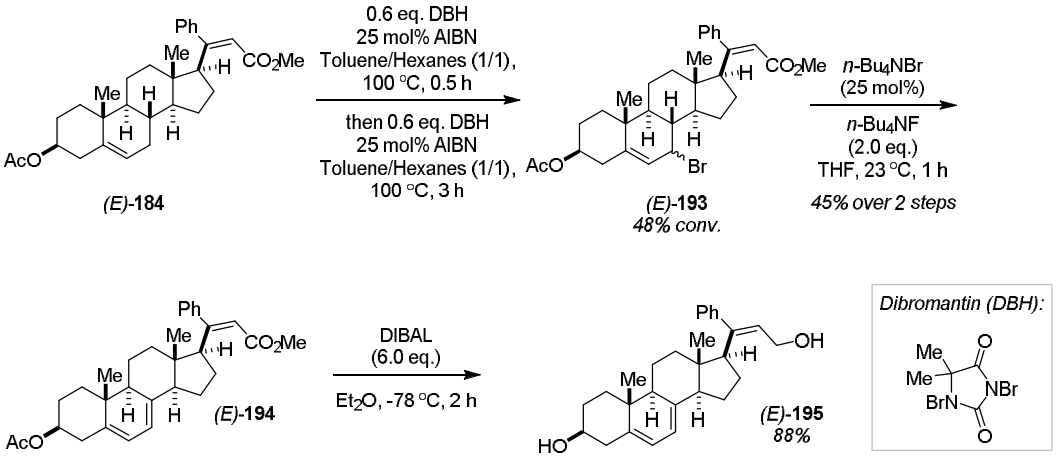
Scheme 3.21. *Preparation of polyhydroxylated (E)-steroidal allylic alcohols.*

After following identical synthetic routes to enoate (*E*)-**184** (Schemes 3.21 and 3.22), the complementary geometrical isomers of these allylic alcohols were obtained in uniformly high overall yields ((*E*)-**188** (α/β: 5/1), (*E*)-**189**, and (*E*)-**192**). All these reactions were conducted on scales ranging from 200 to 850 mg, exemplifying the synthetic potential of the overall approach.[29]



Scheme 3.22. *Preparation of azidated (E)-steroidal allylic alcohol.*

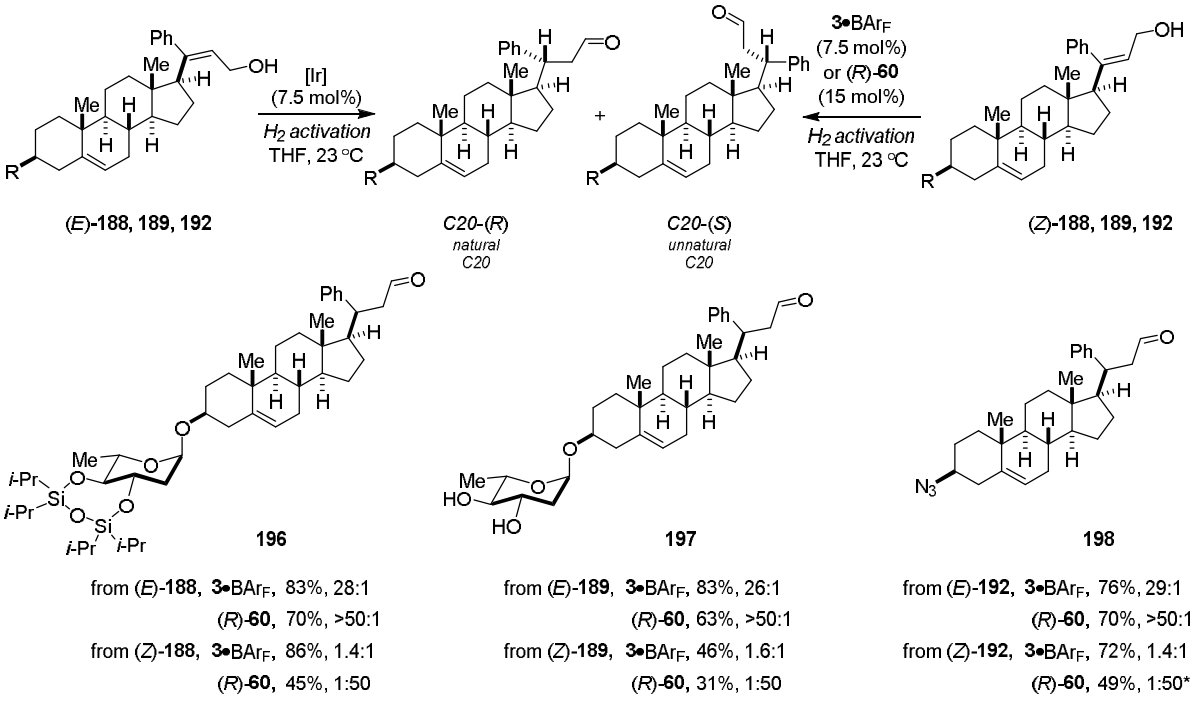
[28] Q. Sun, S. Cai, B. R. Peterson, *Org. Lett*. **2009**, *11*, 567–570.
[29] C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep*. **2014**, *31*, 419–432.



Scheme 3.23. *Preparation of $\Delta^{5,7}$-unsaturated (E)-steroidal allylic alcohol.*

Finally, installation of the $\Delta^{5,7}$-unsaturation was accomplished by C7 radical bromination of enoate (*E*)-**184** followed by dehydrobromination using *n*-Bu_4NBr and *n*-Bu_4NF in THF (Scheme 3.23).[30] Simultaneous C3 deprotection and enoate reduction with excess DIBAL afforded the allylic alcohol (*E*)-**195**.

3.6.3 Isomerization of advanced steroidal allylic alcohols



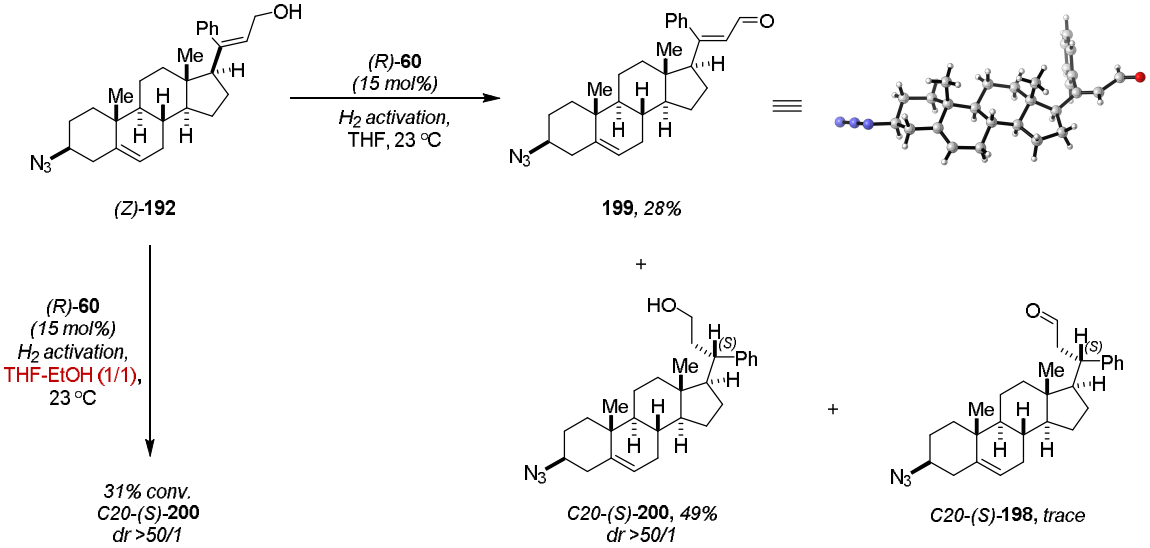
Scheme 3.24. *Isomerization of synthetically advanced steroidal allylic alcohols. All ratios are indicated as C20-(R)/(S). *Isolated as the corresponding saturated alcohol.*

[30] W. Li, J. Chen, Z. Janjetovic, T. Kim, T. Sweatman, Y. Lu, J. Zjawiony, R. C. Tuckey, D. Miller, A. Slominski, *Steroids* **2010**, *75*, 926–935.

At the outset of our inverstigations (Scheme 3.24), both geometrical isomers of these synthetically advanced steroidal allylic alcohols were evaluated in the iridium-catalyzed isomerization with (*R*)-**60** and delivered the desired aldehydes with excellent levels of C20 stereocontrol (>50:1 C20-(*R*), 63-70% yield from (*E*)-configuration; 50:1 C20-(*S*), 31-49% yield from (*Z*)-configuration).

Even though the suitability of the silyl-protected glycosyl fragment in (*E*)-**188** and (*Z*)-**188** was expected (Scheme 3.24), the tolerance of the iridium catalyst with regard to their polyhydroxylated analogues (*E*)-**189** and (*Z*)-**189** was more surprising as catalyst inhibition by the vicinal diols may have occurred.

Similarly, the azide-containing substrates (*E*)-**192** and (*Z*)-**192** underwent highly selective isomerization affording the C20-(*S*) and C20-(*R*) epimers in acceptable and good yields respectively (Scheme 3.24). Of note, isomerization of (*Z*)-**192** with (*R*)-**60** afforded the corresponding saturated alcohol C20-(*S*)-**200** rather than desired aldehyde C20-(*S*)-**198** (Scheme 3.25). The concurrent formation of **199** suggests that a transfer hydrogenation of C20-(*S*)-**198** might occur in the presence of remained starting material (*Z*)-**192**. To test our hypothesis, we conducted control experiments with protic solvent EtOH. The alcohol C20-(*S*)-**200** was formed exclusively after the isomerization presumably through tandem isomerization/transfer hydrogenation sequence. Nonetheless, these results clearly open the possibility to access a variety of *N*-containing functional groups as well as to perform bioconjugation reactions by Staudinger ligations or Huisgen-type cycloadditions.[31]

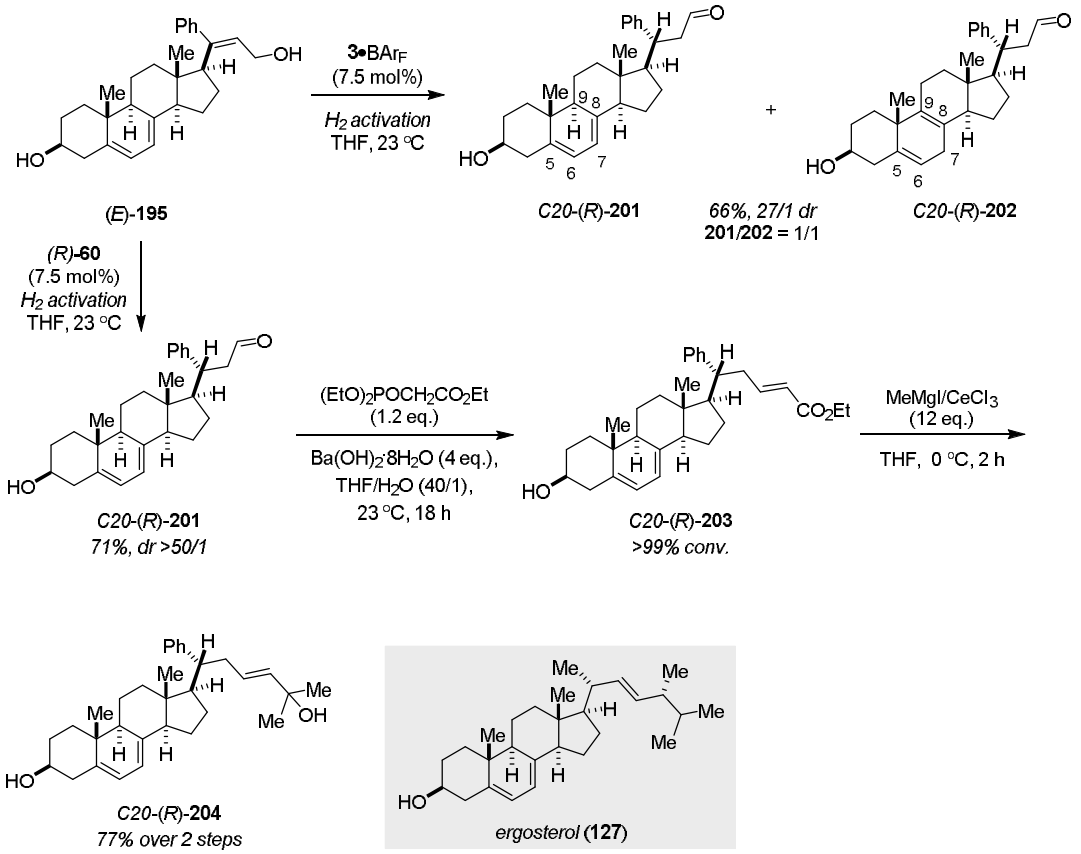


Scheme 3.25. *Tandem isomerization/transfer hydrogenation reaction of (Z)-**192** with (R)-**60**.*

Isomerization of the $\Delta^{5,7}$-unstaturated derivative (*E*)-**195** with (*R*)-**60** proceeded equally well (>50:1 C20-(*R*), 71% yield, see Scheme 3.26), despite our initial concerns regarding the

[31] M. Grammel, H. C. Hang, *Nat. Chem. Biol.* **2013**, *9*, 475–484.

compatibility of the *cis*-*cis*-1,3-diene moiety with the active iridium hydride intermediates.[32,33] Indeed, when (*E*)-**195** was tentatively isomerized with **3**•BAr_F, a 1:1 mixture of the $\Delta^{5,7}$- and $\Delta^{5,8}$-unstaturated aldehydes was obtained.



Scheme 3.26. *Isomerization of (E)-**195** and post-isomerization diversification.*

Finally, post-isomerization diversification was demonstrated starting from C20-(*R*)-**201** by exploiting the orthogonality offered by the different oxidation levels at C3 and C23. Following a Horner–Wadsworth–Emmons olefination/double addition to the carbonyl sequence, we were able to install the complete skeleton of the steroid side chain and obtained a C20-(*R*) ergosterol analogue C20-(*R*)-**204** (77% yield).[34,35]

[32] (a) X. Cui, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 14212–14213; (b) X. Cui, J. W. Ogle, K. Burgess, *Chem. Commun.* **2005**, 672–674.
[33] For ruthenium hydride-promoted isomerization of 1,3-dienes, see: J. R. Clark, J. R. Griffiths, S. T. Diver, *J. Am. Chem. Soc.* **2013**, *135*, 3327–3330.
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3.7 Conclusion

In summary, we have developed a stereospecific catalytic strategy for the perfectly stereocontrolled installation of C20, the first tertiary stereocenter of the acyclic domain in steroid derivatives. The catalytic isomerization reaction is remarkable for its mildness and high level of stereochemical predictability. The design of a uniform yet modular synthetic route to access a variety of steroidal primary allylic alcohols is another notable feature of our study. A range of allylic alcohols participates in the diastereoselective isomerization. Electron-rich and electron-poor aryl or heteroaryl substituents are particularly well-tolerated and the stereospecific nature of the reaction provides indifferently access to the natural C20-(*R*) and unnatural C20-(*S*) configurations – despite the strong innate bias imposed by the steroid scaffold. Alkyl containing substrates are more challenging as they affect regioselectivity of iridium-hydride insertion. Opportunity for post-isomerization topological diversification was also demonstrated. Given the central role played by steroids in biological, pharmaceutical and medical sciences, we expect our approach to become broadly applicable.

3.8 References

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(11) See Chapter 2.6.2 for details.
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(28) Q. Sun, S. Cai, B. R. Peterson, *Org. Lett*. **2009**, *11*, 567–570.

(29) C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep*. **2014**, *31*, 419–432.

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(31) M. Grammel, H. C. Hang, *Nat. Chem. Biol.* **2013**, *9*, 475–484.

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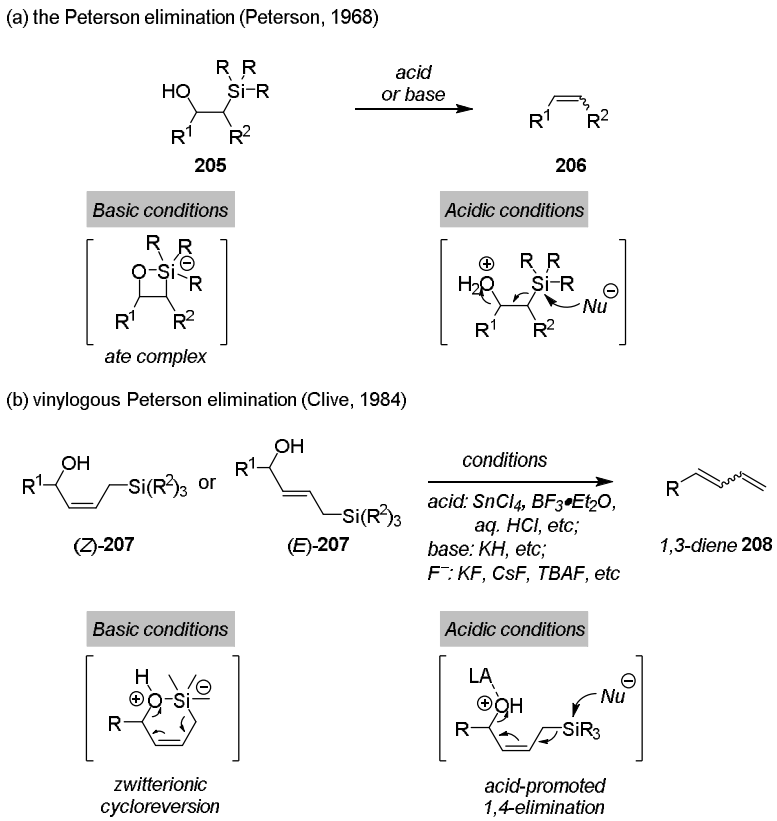
4. Ir-Catalyzed Vinylogous Peterson Elimination of Allylic Alcohols

4.1 Peterson and Vinylogous Peterson Eliminations

4.1.1 General introduction

The generation of alkenes starting from alcohols is a versatile transformation widely used in organic synthesis. The Peterson elimination, first described in 1968, is an elimination of β-hydroxysilane **205** to form alkene **206** (Scheme 4.1a).[1] Different reaction pathways have been generally accepted for the acid and base-promoted elimination reactions. Whereas the four-membered-ring ate complex is an essential intermediate under basic conditions, a 1,2-elimination process (nucleophilic attack to silane and simultaneous elimination of water) is believed to occur under acidic conditions.



Scheme 4.1. The *Peterson elimination and vinylogous Peterson elimination.*

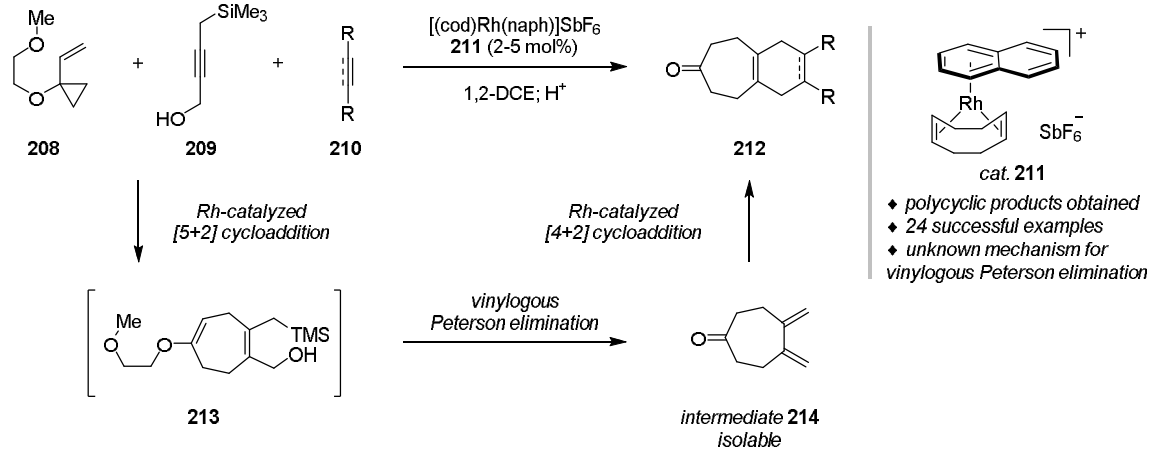
Many synthetic variants of the Peterson elimination have been disclosed since its discovery. In 1984, the Clive group first reported the formation of 1,3-diene **208** using γ-

[1] (a) D. J. Peterson, *J. Org. Chem.* **1968**, 33, 780–784; (b) T.-H. Chan, *Acc. Chem. Res*. **1977**, 10, 442–448.

hydroxy allylsilane **207** in the presence of potassium hydride (Scheme 4.1b).[2] To date, three different types of reaction conditions have been found to be effective for the vinylogous Peterson elimination (Lewis or Brønsted acids, strong bases, and fluoride reagents). In terms of reaction mechanism,[3] the Fleming group proposed a six-membered zwitterionic cycloreversion process under basic or fluoride conditions.[3c,d,4] A 1,4-elimination process is also proposed to occur under acidic conditions in analogy to the Peterson elimination.

The 1,3-dienes are important structural motifs which have been witnessed by their versatile applications in cycloadditions as well as in transition metal-catalyzed transformations.[5] Surprisingly, the vinylogous Peterson elimination, which provides a direct access to 1,3-dienes, still remains underexplored.[3] In the following chapter we illustrate the synthetic potential of the vinylogous Peterson elimination with two recent relevant examples from the literature.

4.1.2 Recent examples

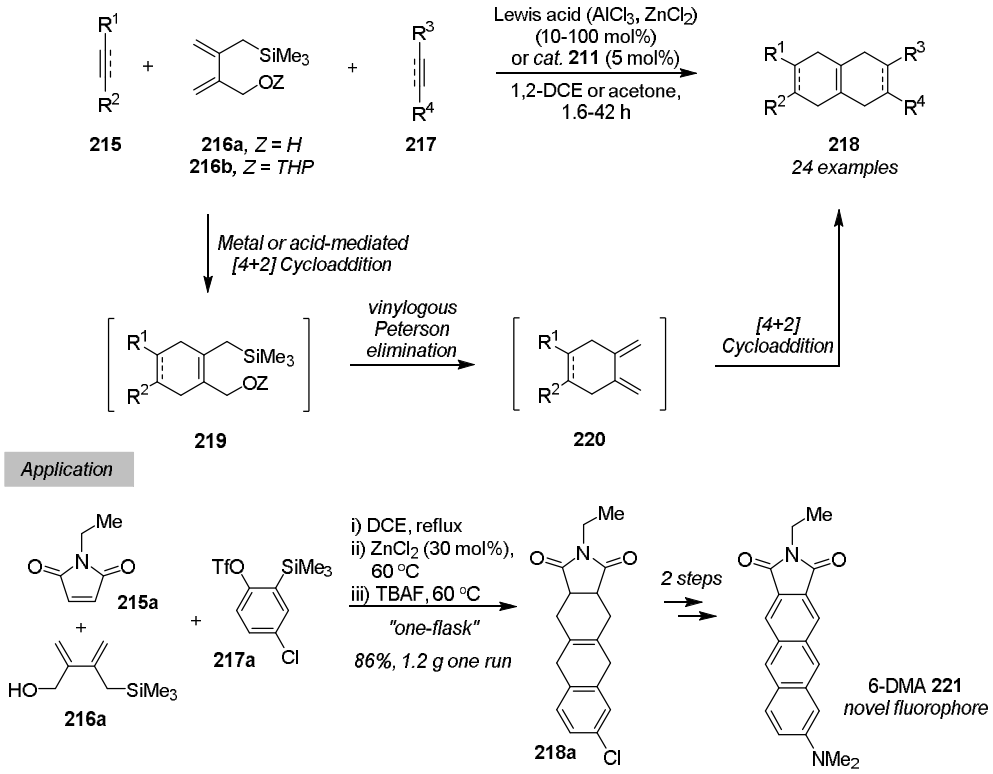


Scheme 4.2. *Rh-catalyzed multicomponent cycloaddtion (Wender).*

In 2014, the Wender group described a multicomponent process to access polycyclic products **212** (Scheme 4.2).[3h] Starting from simple commercially available building blocks

[2] A. G. Angoh, D. L. Clive, *J. Chem. Soc. Chem. Commun*. **1984**, 534–536.
[3] For relevant examples, see: (a) R. Angell, P. J. Parsons, A. Naylor, E. Tyrrell, *Synlett* **1992**, 599–600; (b) H. Maeta, K. Suzuki, *Tetrahedron Lett*. **1992**, *33*, 5969–5972; (c) I. Fleming, I. T. Morgan, A. K. Sarkar, *J. Chem. Soc., Chem. Commun*. **1990**, 1575–1577; (d) I. Fleming, I. T. Morgan, A. K. Sarkar, *J. Chem. Soc., Perkin Trans. 1*, **1998**, *17*, 2749−2764; (e) M. Harmata, G. J. Bohnert, *Org. Lett.* **2003**, *5*, 59–61; (f) M. Ahmed, C. E. Atkinson, A. G. M. Barrett, K. Malagu, A. P. Procopiou, *Org. Lett.* **2003**, *5*, 669–672; (g) T. Borg, P. Tuzina, P. Somfai, *J. Org. Chem.* **2011**, *76*, 8070–8075; (h) P. A. Wender, D. N. Fournogerakis, M. S. Jeffreys, R. V. Quiroz, F. Inagaki, M. Pfaffenbach, *Nat. Chem*. **2014**, *6*, 448−452; (i) P. A. Wender, M. S. Jeffreys, A. G. Raub, *J. Am. Chem. Soc*. **2015**, *137*, 9088−9093.
[4] I. Fleming, A. Barbero, D. Walter, *Chem. Rev*. **1997**, *97*, 2063−2192.
[5] For selected examples using 1,3-dienes in transition metal-catalyzed transformations, see: (a) F. Shibahara, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc*. **2008**, *130*, 14120–14122; (b) J. Y. Wu; B. Moreau; T. Ritter, *J. Am. Chem. Soc*. **2009**, *131*, 12915–12917; (c) L. Liao, M. S. Sigman, *J. Am. Chem. Soc*. **2010**, *132*, 10209−10211; (d) J. Y. Wu, B. N. Stanzl, T. Ritter, *J. Am. Chem. Soc*. **2010**, *132*, 13214–13216; (e) J. Raynaud, J. Y. Wu, T. Ritter, *Angew. Chem. Int. Ed.* **2012**, *51*, 11805–11808; (f) S. Parker, J. Boergel, T. Ritter, *J. Am. Chem. Soc*. **2014**, *136*, 4857–4860; (g) V. Saini, M. O'Dair, M. S. Sigman, *J. Am. Chem. Soc*. **2015**, *137*, 608−611; (h) T.-Y. Chen, R. Tsutsumi, T. P. Montgomery, I. Volchkov, M. J. Krische, *J. Am. Chem. Soc*. **2015**, *137*, 1798–1801.

208-**210**, a Rh-catalyzed multicomponent cycloaddtion cascades enabled flexible access to diverse polycycles **212** in a step-economy manner. Preliminary investigations revealed that a stable and isolable 1,3-diene intermediate **214** was formed from the in-situ generated alcohol **213**, presumably through a vinylogous Peterson elimination. However, the mechanism of this elimination remains unclear.



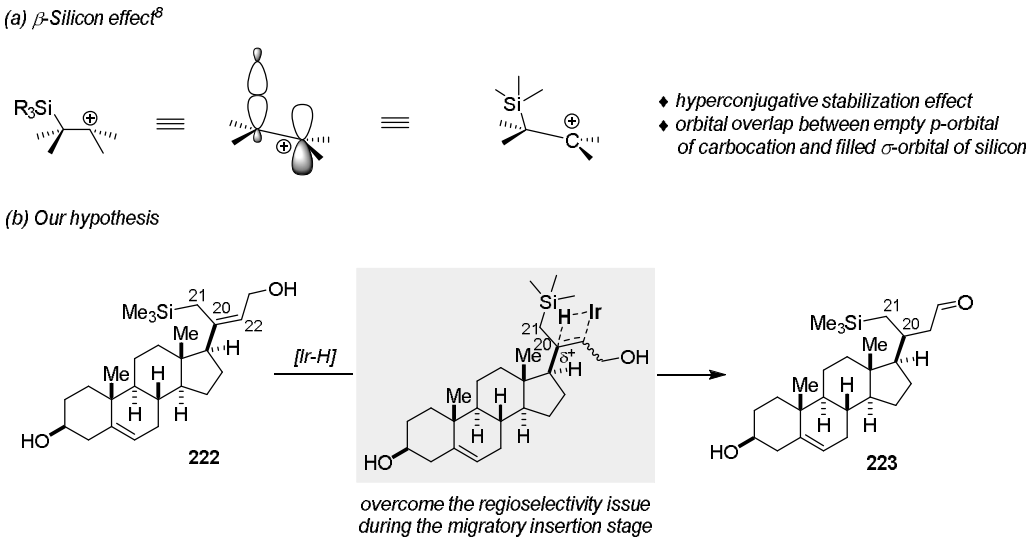
Scheme 4.3. *Successive cycloadditions using **216** (Wender).*

In 2015, the Wender group reported successive cycloadditions starting from versatile tetraethyleneethane (TME) equivalents **216** (Scheme 4.3).[3i] Through a one-flask [4+2]/elimination/[4+2] reaction sequence, common building blocks **215**-**217** were successively mixed to generate at the end polycycles **218** with high efficiency and diversity. The vinylogous Peterson elimination was suggested to be involved in this multicomponent cyclization cascade. Both Lewis acids ($AlCl_3$, $ZnCl_3$) and rhodium catalyst **211** were employed to promote the elimination. Finally, the authors highlighted the synthetic potential of their strategy with a 3-step synthesis of a new solvatochromic fluorophore **221**.

4.1.3 Our initial discovery

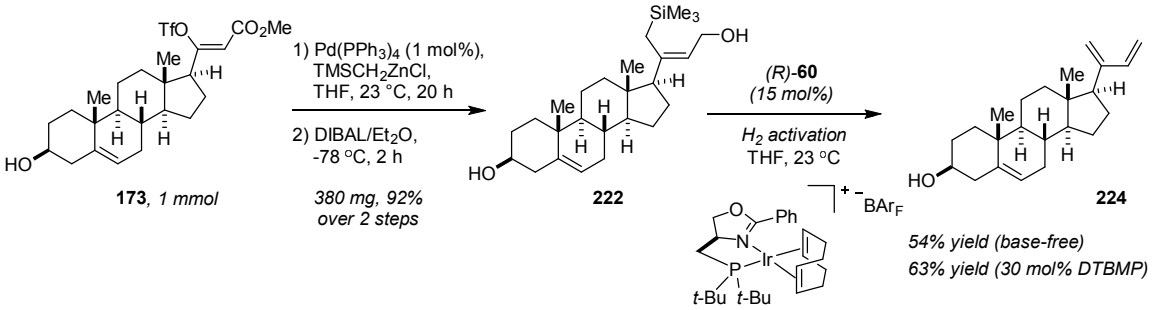
During our studies in the isomerization of steroidal allylic alcohols **174a**-**n**, distinct reaction outcomes have been observed between the isomerization of aromatic allylic alcohols **174a**-**j** and aliphatic allylic alcohols **174l-n**, presumably due to different site

selectivity during the migratory insertion of the transient iridium dihydride.[6] We hypothesized that such site selectivity difference can be influenced by the electronic nature of the alkene substituent (aryl, heteroaryl *vs* alkyl).[7]



Scheme 4.4. *Initial design for the isomerization of aliphatic steroidal allylic alcohol* ***222****.*

We envisaged that the installation of silane substituent at C21 could steer the productive isomerization. Previously known as β-silicon effect (Scheme 4.4a),[8] the hyperconjugative stabilization effect of silane substituent would change the electronic property of the β-carbon, which becomes more *electron deficient.* In our case, in the presence of silane substituent at C21 position (Scheme 4.4b), migratory insertion of the iridium hydride could preferentially occur at more *electron deficient* C20 position and would thus facilitate the formation of desired aldehyde **223** through the productive isomerization pathway.



Scheme 4.5. *Ir-catalyzed vinylogous Peterson elimination*.

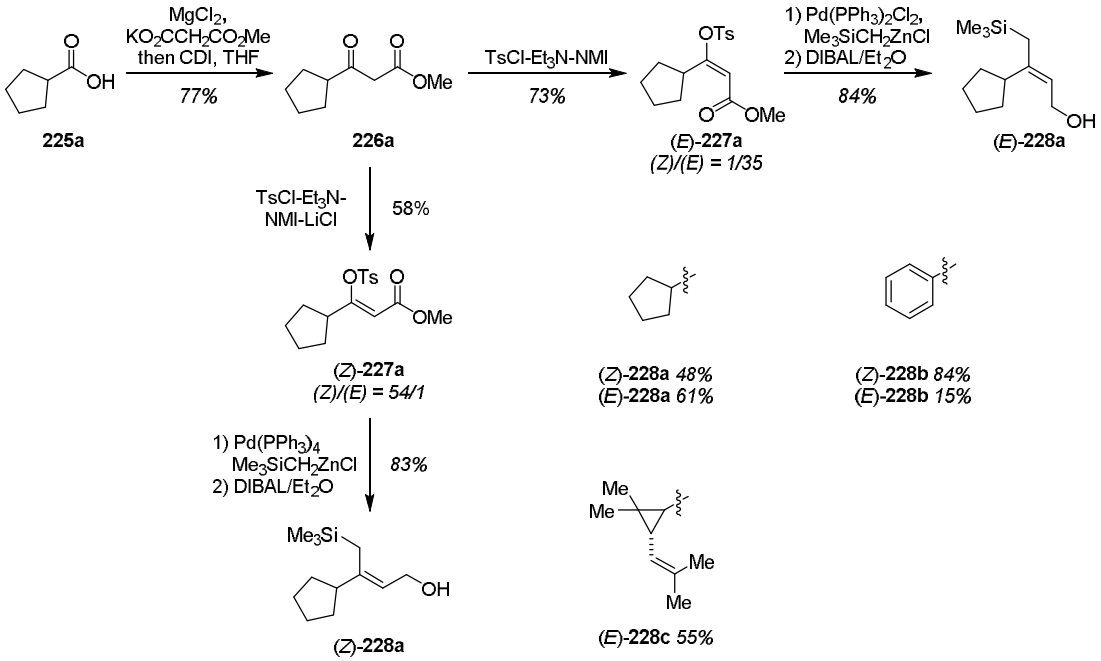
[6] For details see Chapter 3.5.
[7] For details see Scheme 3.17.
[8] J. B. Lambert, *Tetrahedron* **1990**, *46*, 2677–2689.

Following our previous procedure starting from vinyl triflate **173**,[9] the preparation of allylic silane **222** proceeded smoothly and afforded 380 mg of **222** in pratical yields over 2 steps (Scheme 4.5). We next evaluated the isomerization of **222**. Whereas the isomerization with **3**•BAr_F did not proceed, we obtained exclusively 1,3-diene **224** upon treatment with (*R*)-**60** *in the absence or presence of* DTBMP rather than the desired aldehyde **223**.

We concluded that the 1,3-diene **224** should be derived from a vinylogous Peterson elimination catalyzed by (*R*)-**60**. Encouraged by this result, we decided to explore the possibility to develop an Ir-catalyzed vinylogous Peterson elimination of allylic alcohols.

4.2 Preparation of Substrates and Iridium catalyst

*4.2.1 Modular syntheses of primary allylic alcohols **228a-c***



Scheme 4.6. *Modular approach to synthesize substrates **228a-c**. Yields refer to overall 3 steps from known β-keto ester **226**.*

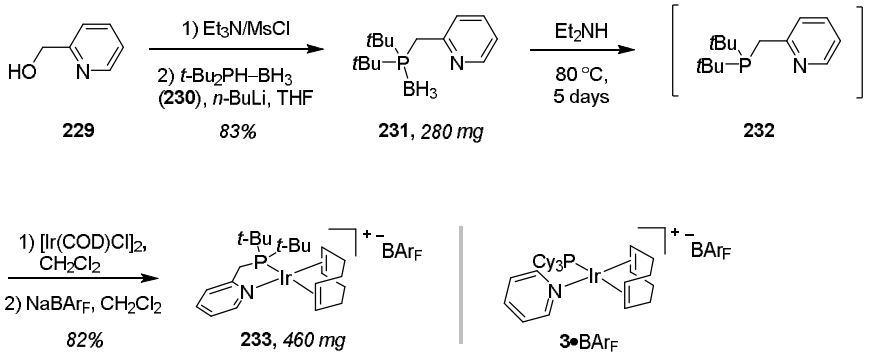
At the outset of our investigations, we envisaged that a uniform approach to access both geometrical isomers of substrates **228** would be preferable (Scheme 4.6). Similar to the protocol established previously for the synthesis of steroidal allylic alcohols, our approach relied again on the stereoselective (*Z*) and (*E*)-tosylation followed by stereoretentive Pd-catalyzed Negishi cross-coupling reactions.[9,10] Both aliphatic and aromatic substituents were

[9] H. Li, C. Mazet, *J. Am. Chem. Soc*. **2015**, *137*, 10720–10727. See also Chapter 3.2.
[10] (a) H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe, *Org. Lett.* **2008**, *10*, 2131−2134; (b) A. Manabe, Y. Ohfune, T. Shinada, *Synlett* **2012**, *23*, 1213−1216.

well tolerated during the process. Of note, cyclopropyl substituted alcohol (*E*)-**228c** was also prepared in practical yields starting from *rac*-chrysanthemic acid **225c**.

*4.2.2 Preparation of Crabtree catalyst analogue **233***

We also prepared a chelating version of Crabtree catalyst **233** (Scheme 4.7). Starting from commercially available 2-pyridinemethanol **229**, the 3-step protocol (mesylation,[11] the formation of phosphine-borane adduct **231**,[12] and one-pot iridium complex synthesis) which was recently developed in our laboratory allowed us to prepare 460 mg of Crabtree catalyst derivative **233**.[13]



Scheme 4.7. *Synthesis of iridium catalyst **233**.*

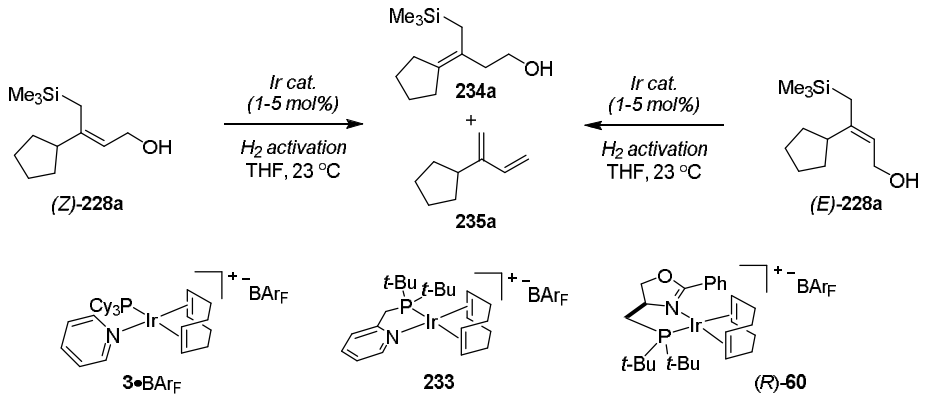
4.3 Catalytic Vinylogous Peterson Elimination of Model Primary Allylic Alcohols

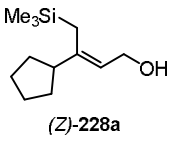
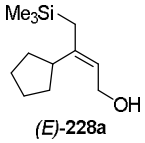
To examine the feasibility of a vinylogous Peterson elimination and evaluate the geometrical effect of the allylic alcohols (Table 4.1), model substrates (*Z*) and (*E*)-**228a** were initially subjected to the standard isomerization procedure (5 mol% *cat*., 1 min. H_2 activation/degassing with **3**•BAr_F and **233**, or 5 min. H_2 activation/degassing with **60**). In the presence of Crabtree catalyst **3**•BAr_F, we observed exclusively the formation of homoallylic alcohol **234a** in both cases (Table 4.1, entries 1 and 6). Similarly to our previous reaction outcome with aliphatic allylic alcohols **174l-n**,[6] such unproductive isomerization might be again due to different site selectivity during migratory insertion of the iridium hydride.

Using 1 mol% of **233** (Table 4.1, entries 2 and 7), we were delighted to obtain the desired 1,3-diene **235a** in quantitative yield from (*E*)-**228a** and 43% yield from (*Z*)-**228a**. Increasing the catalyst loading for the reaction of (*Z*)-**228a** afforded **235a** in quantitative yield (Table 4.1, entry 3). Switching to non-polar solvent (1,2-dichloroethane) resulted in a similar reaction

[11] J. Uenishi, M. Hamada, *Tetrahedron: Asymmetry* **2001**, *12*, 2999–3006.
[12] M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem. Int. Ed.* **2007**, *46*, 8274–8276.
[13] (a) L. Mantilli, C. Mazet, *Chem. Commun.* **2010**, *46*, 445−447; (b) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem.−Eur. J*. **2010**, *16*, 12736−12745.

outcome (Table 4.1, entries 4 and 8). Finally, reactions with chiral catalyst (*R*)-**60** displayed inferior reactivity to **235a** (Table 4.1, entries 5 and 9).



Entry	Substrate	Catalyst	Loading (%)	Reaction Time (h)	Products	Conversion[a] (isolated yield)
1		**3**•BAr_F	5	4	**234a**	>99% (33%)
2		**233**	1	4	**235a**	43%
3		**233**	5	4	**235a**	>99%
4		**233**[b]	5	4	**235a**	>99%
5		(*R*)-**60**	5	24	*n.r.*[c]	*n.d.*[d]
6		**3**•BAr_F	5	4	**234a**	67%
7		**233**	1	4	**235a**	>99%
8		**233**[b]	1	4	**235a**	>99%
9		(*R*)-**60**	5	24	**235a**	>99%

[a] Determined by ^{1}H NMR analysis of crude residue (400 MHz); [b] Using 1,2-dichloroethane as solvent; [c] n.r. = No reaction; [d] n.d. = Not determined.

Table 4.1. *Optimization table for vinylogous Peterson elimination of (Z) and (E)-**228a**.*

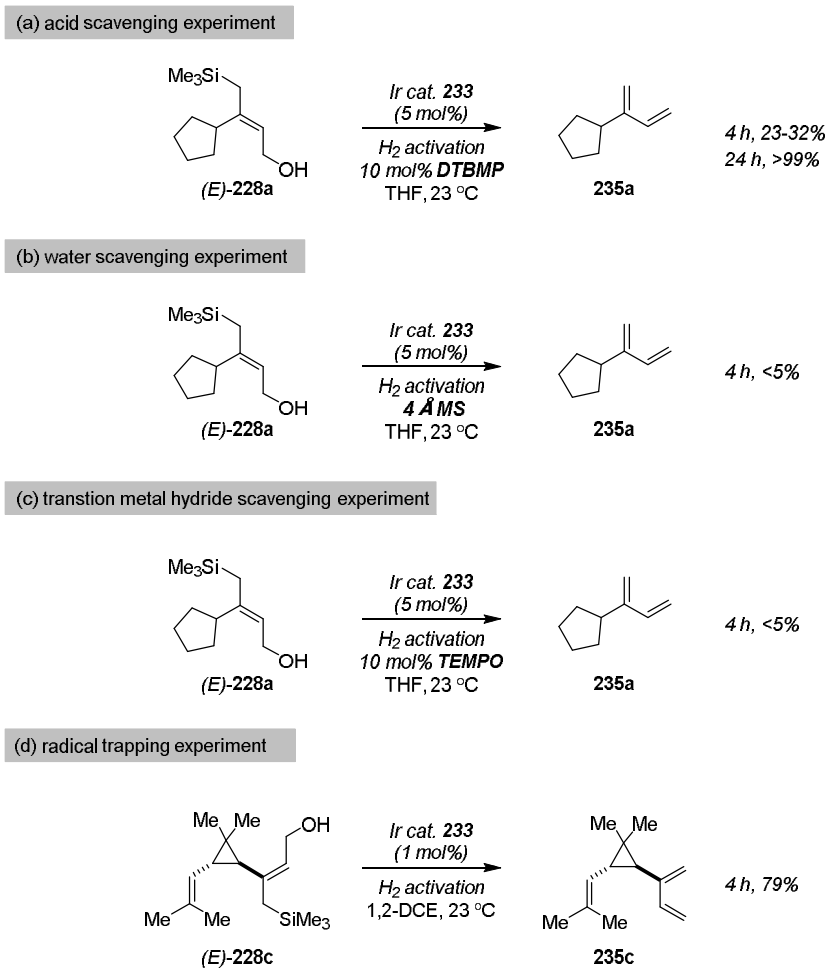
4.4 Proposed Reaction Mechanism

4.4.1 Control experiments

To gain mechanistic insights into this reaction, we next conducted several control experiments with (*E*)-**228a** (Scheme 4.8). Specifically, catalytic amounts of DTBMP were first added to the reaction to quench potential traces of acid that could be generated in-situ upon decomposition of the iridium dihydride intermediate (Scheme 4.8a).[14] Whereas the reaction with (*E*)-**228a** was slowed down to some extent after 4 h (23-32%), it still proceeded to full

[14] For the acidity of relevant iridium dihydride species, see: (a) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249−6253; (b) R. H. Morris, *J. Am. Chem. Soc*. **2014**, *136*, 1948−1959. For a similar observation see Chapter 2.6.1.

conversion after 24 h. This excluded the acid-promoted 1,4-elimination to be the major reaction pathway.



Scheme 4.8. *Control experiments.*

We also performed the reaction in the presence of 4 Å molecular sieves to quench potential traces of water (Scheme 4.8b). The reactivity was inhibited and only starting material was detected after 4 h. This result indicates that water may play a crucial role during the elimination.

In previous studies, TEMPO was commonly used to quench the transition metal hydrides during the reaction.[15] In our case, the reactivity was indeed suppressed and no desired product **235a** was formed after 4 h (Scheme 4.8c).

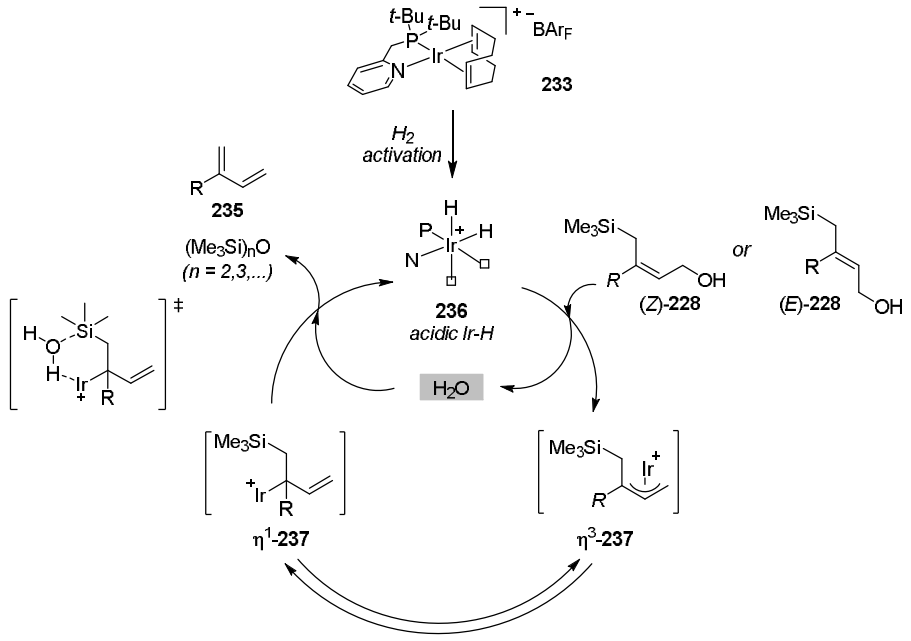
Finally, cyclopropyl substituted alcohol (*E*)-**228c** was also subjected to the reaction to evaluate whether a radical process may be at play or not (Scheme 4.8d). The reaction proceeded well and gave **235c** in good yield. No product resulting from a radical ring-opening process was detected. Combined with our previous reaction with TEMPO, we

[15] (a) A. C. Albéniz, P. Espinet, R. López-Fernández, A. Sen, *J. Am. Chem. Soc.* **2002**, *124*, 11278–11279; (b) H. Guan, M. Iimura, M. P. Magee, J. R. Norton, K. E. Janak, *Organometallics* **2003**, *22*, 4084-4089; (c) G. Li, A. Han, M. E. Pulling, D. P. Estes, J. R. Norton, *J. Am. Chem. Soc.* **2012**, *134*, 14662−14665; (d) Y. Hu, J. R. Norton, *J. Am. Chem. Soc.* **2014**, *136*, 5938−5948.

concluded that iridium hydride intermediates might be directly involved in the vinylogous Peterson elimination.

4.4.2 Proposed catalytic cycle

Taken together, we propose a mechanism which might be responsible for this iridium-catalyzed vinylogous Peterson elimination (Scheme 4.9). Iridium dihydride **236** is first generated in-situ upon the activation with molecular hydrogen. Through a yet unknown mechanism, this acidic hydride reacts with substrate **228** (both *Z* and *E*) to form η^1-**237** intermediate after π-to-σ-isomerization from η^3-**237** and release of one molecule of water. Subsequent elimination of η^1-**237** furnishes the final product **235** and at the same time regenerates the iridium dihydride **236**, presumably via a six-membered ring transition state involving participation of one molecule of water.



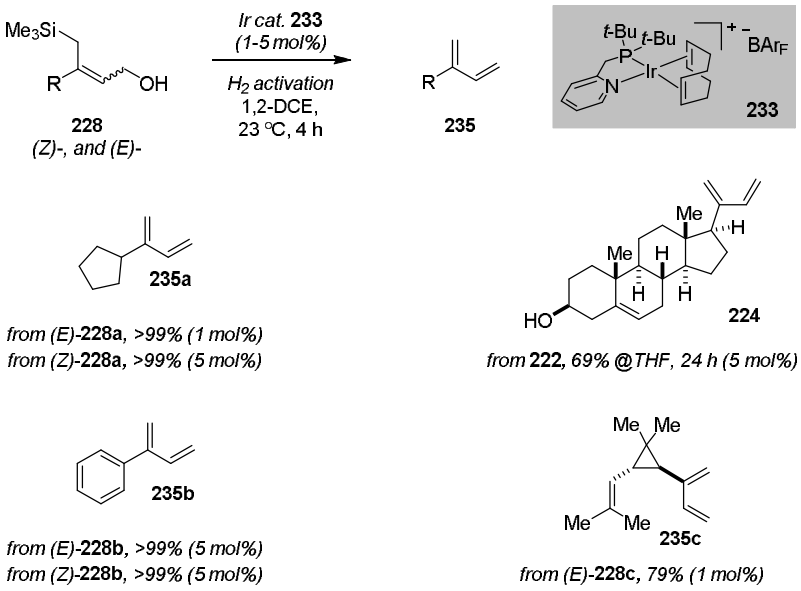
Scheme 4.9. *Proposed reaction mechanism.*

4.5 Reaction Scope

Applying the optimal conditions to our current collection of substrates led to similarly good results (Scheme 4.10). The corresponding products were systematically isolated in good yields using both alkyl/alkyl and aryl/alkyl allylic alcohols, independently of the geometry of the starting material.

Although extension of the scope of this transformation is certainly needed, at this stage of our investigations, the variety of dienyl products obtained already underscores the potential

of this unprecedented Ir-catalyzed vinylogous Peterson elimination of allylic alcohols. Whereas the previous vinylogous Peterson elimination commonly occurred under harsh reaction conditions (acid, base or fluoride at high temperature), the present system operates under mild reaction conditions, low catalyst loading (1 mol%) and is operationaly simple. Of note, the good results obtained with both steroidal allylic alcohol **222** and *rac*-chrysanthemic acid derivative (*E*)-**228c** already illustrate the potential application of our current protocol for late-stage functionalizations of complex molecular scaffolds.



Scheme 4.10. *Preliminary substrate scope*

4.6 Conclusion

In this chapter, an unprecedented Ir-catalyzed vinylogous Peterson elimination of allylic alcohols was discovered by serendipity. Based on a uniform yet modular synthetic route to access both geometrical isomers of allylic alcohols, we developed a simple vinylogous Peterson elimination reaction catalyzed by an analogue of Crabtree catalyst supported by a chelating ligand (**233**). Preliminary mechanistic studies support the involvement of the iridium hydride intermediate in the elimination reaction. Several representative substrates have been evaluated and usually gave good yields of the dienyl products. Further extension of the scope of this reaction is still in demand. Given the versatile synthetic applications of 1,3-dienes, we already expect our simple and unified protocol to become broadly applicable.

4.7 References

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(2) A. G. Angoh, D. L. Clive, *J. Chem. Soc. Chem. Commun*. **1984**, 534–536.

(3) For relevant examples, see: (a) R. Angell, P. J. Parsons, A. Naylor, E. Tyrrell, *Synlett* **1992**, 599–600; (b) H. Maeta, K. Suzuki, *Tetrahedron Lett*. **1992**, *33*, 5969–5972; (c) I. Fleming, I. T. Morgan, A. K. Sarkar, *J. Chem. Soc., Chem. Commun*. **1990**, 1575–1577; (d) I. Fleming, I. T. Morgan, A. K. Sarkar, *J. Chem. Soc., Perkin Trans. 1*, **1998**, *17*, 2749−2764; (e) M. Harmata, G. J. Bohnert, *Org. Lett.* **2003**, *5*, 59–61; (f) M. Ahmed, C. E. Atkinson, A. G. M. Barrett, K. Malagu, A. P. Procopiou, *Org. Lett*. **2003**, *5*, 669–672; (g) T. Borg, P. Tuzina, P. Somfai, *J. Org. Chem*. **2011**, *76*, 8070–8075; (h) P. A. Wender, D. N. Fournogerakis, M. S. Jeffreys, R. V. Quiroz, F. Inagaki, M. Pfaffenbach, *Nat. Chem*. **2014**, *6*, 448−452; (i) P. A. Wender, M. S. Jeffreys, A. G. Raub, *J. Am. Chem. Soc*. **2015**, *137*, 9088−9093.

(4) I. Fleming, A. Barbero, D. Walter, *Chem. Rev*. **1997**, *97*, 2063−2192.

(5) For selected examples using 1,3-dienes in transition metal-catalyzed transformations, see: (a) F. Shibahara, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc*. **2008**, *130*, 14120–14122; (b) J. Y. Wu; B. Moreau; T. Ritter, *J. Am. Chem. Soc*. **2009**, *131*, 12915–12917; (c) L. Liao, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 10209−10211; (d) J. Y. Wu, B. N. Stanzl, T. Ritter, *J. Am. Chem. Soc*. **2010**, *132*, 13214–13216; (e) J. Raynaud, J. Y. Wu, T. Ritter, *Angew. Chem. Int. Ed.* **2012**, *51*, 11805–11808; (f) S. Parker, J. Boergel, T. Ritter, *J. Am. Chem. Soc*. **2014**, *136*, 4857–4860; (g) V. Saini, M. O'Dair, M. S. Sigman, *J. Am. Chem. Soc*. **2015**, *137*, 608−611; (h) T.-Y. Chen, R. Tsutsumi, T. P. Montgomery, I. Volchkov, M. J. Krische, *J. Am. Chem. Soc*. **2015**, *137*, 1798–1801.

(6) For details see Chapter 3.5.

(7) For details see Scheme 3.17.

(8) J. B. Lambert, *Tetrahedron* **1990**, *46*, 2677–2689.

(9) H. Li, C. Mazet, *J. Am. Chem. Soc*. **2015**, *137*, 10720–10727. See also Chapter 3.2.

(10) (a) H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe, *Org. Lett.* **2008**, *10*, 2131−2134; (b) A. Manabe, Y. Ohfune, T. Shinada, *Synlett* **2012**, *23*, 1213−1216.

(11) J. Uenishi, M. Hamada, *Tetrahedron: Asymmetry* **2001**, *12*, 2999–3006.

(12) M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem. Int. Ed.* **2007**, *46*, 8274–8276.

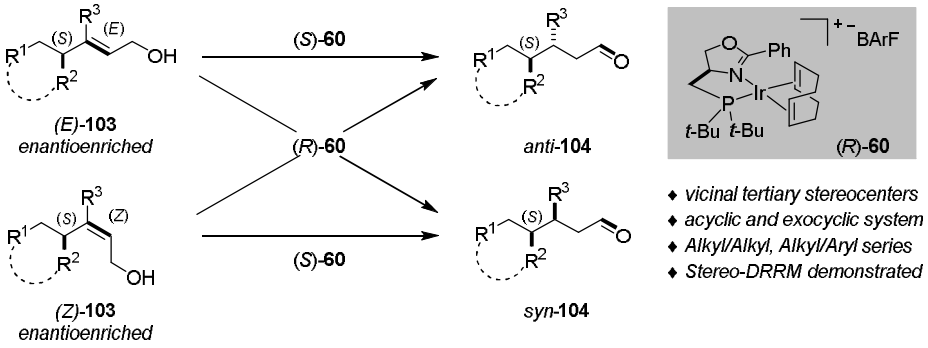
(13) (a) L. Mantilli, C. Mazet, *Chem. Commun.* **2010**, *46*, 445−447; (b) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem.−Eur. J*. **2010**, *16*, 12736−12745.

(14) For the acidity of relevant iridium dihydride species, see: (a) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249−6253; (b) R. H. Morris, *J. Am. Chem. Soc*. **2014**, *136*, 1948−1959. For a similar observation see Chapter 2.6.1.

(15) (a) A. C. Albéniz, P. Espinet, R. López-Fernández, A. Sen, *J. Am. Chem. Soc*. **2002**, *124*, 11278–11279; (b) H. Guan, M. Iimura, M. P. Magee, J. R. Norton, K. E. Janak, *Organometallics* **2003**, *22*, 4084-4089; (c) G. Li, A. Han, M. E. Pulling, D. P. Estes, J. R. Norton, *J. Am. Chem. Soc.* **2012**, *134*, 14662−14665; (d) Y. Hu, J. R. Norton, *J. Am. Chem. Soc*. **2014**, *136*, 5938−5948.

5. General Conclusion

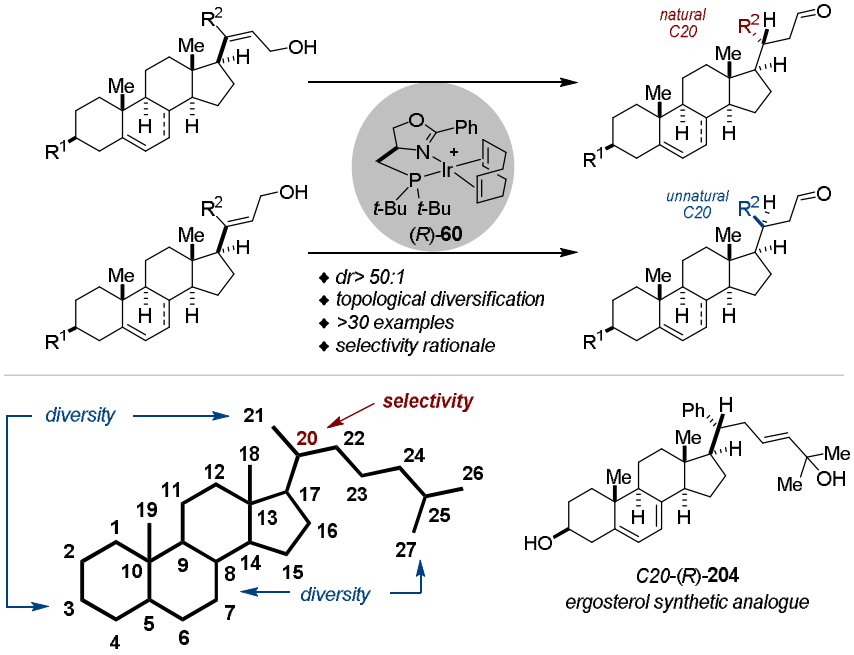
Efficient enantioselective isomerizations of prochiral allylic alcohols have been independently reported by our group and others in recent years. However, diastereoselective isomerization with chiral substrates had been barely documented at the beginning of this thesis. In our work, three different types of allylic alcohols have been employed in the Ir-catalyzed isomerization reaction and distinct reaction outcomes have been disclosed.



Scheme 5.1. *Catalyst-directed diastereoselective isomerization with enantioenriched substrates **103**.*

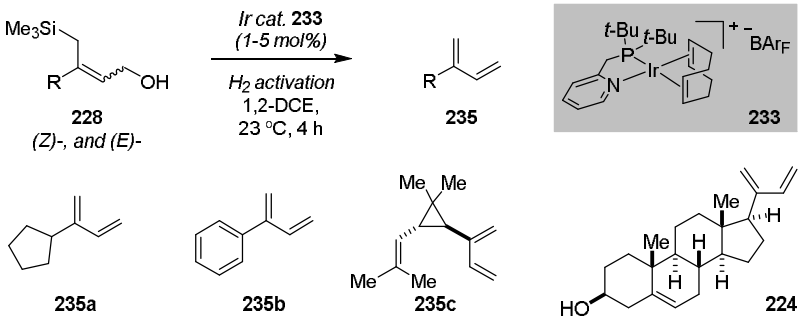
In chapter 2, we have conducted catalyst-directed diastereoselective isomerization with **enantioenriched allylic alcohols 103** using both enantiomers of catalyst **60** (Scheme 5.1). While good yields, perfect *dr* and excellent *ee* were commonly obtained with *acyclic* substrates, we also demonstrated the feasibility of stereodivergent reactions on racemic mixtures (stereo-DRRM) with two representative *acyclic* substrates. Extension of this study to *exocyclic* substrates resulted in the formal synthesis of the naturally occurring insecticidal sesquiterpenes (−)-juvabione (**87**) and (−)-epijuvabione (**88**).

In chapter 3, we evaluated **steroidal allylic alcohols** in the catalyst-directed diastereoselective isomerization for the stereocontrolled installation of C20, the first tertiary stereocenter of the acyclic domain in steroid derivatives (Scheme 5.2). Following a uniform yet modular synthetic route to prepare a variety of steroidal allylic alcohols, a range of allylic alcohols were employed in the diastereoselective isomerization. Catalyst (*R*)-**60** provided indifferently access to the natural C20-(*R*) and unnatural C20-(*S*) configurations – despite the strong innate bias imposed by the steroid scaffold (as measured by using the achiral Crabtree catalyst **3**•BAr_F). The scope of our method was further highlighted through topological diversification in the side chain and within the polycyclic domain of advanced and complex steroidal architectures. Subsequent post-isomerization topological diversification was also demonstrated to afford **204** as a synthetic analogue of ergosterol.



Scheme 5.2. *Stereoselective construction of C20 in steroid side chain using steroidal allylic alcohols.*

In chapter 4, we described the serendipitous discovery of an unprecedented Ir-catalyzed vinylogous Peterson elimination of **silane allylic alcohols 228** using a Crabtree catalyst analogue **233** (Scheme 5.3). Preliminary mechanistic studies are in support of a mechanism involving iridium hydride intermediates. Good yields were generally obtained with either geometry of the substrates. Application of this method to the late-stage functionalization of complex molecular architectures has already been demonstrated.



Scheme 5.3. *Ir-catalyzed vinylogous Peterson elimination of silane allylic alcohols.*

Collectively, the results discussed in this thesis have significantly extended the scope of reactions relying on the use of transition metal hydrides while providing a better understanding of the underlying principles of the mechanisms of these transforamtions. Ultimately this will inspire new discoveries.

6. Perspectives

Based on the work described in this thesis, we could consider many directions as the potential follow-up studies.

(1) As a continuation of **Chapter 2**, for the moment we have mainly evaluated alkyl/alkyl substrates in catalyst-directed diastereoselective isomerization using chiral catalyst **60**. Other enantioenriched substrates with distinct substitution patterns (alkyl/aryl, alkyl/heterocyclic, and aryl/aryl, etc) could also be prepared and then enganged into the isomerization. For the stereodivergent reactions on racemic mixtures, further extension of the scope of this reaction is still needed by employing different series of *acyclic* substrates (alkyl/alkyl, aryl/alkyl, (*Z*) and (*E*)).

(2) As a continuation of **Chapter 3**, whereas we obtained a perfect stereocontrol at C20 with aromatic steroidal allylic alcohols, alkyl containing substrates are more challenging as they affect regioselectivity of iridium-hydride insertion. Further efforts which will circumvent the site selectivity during the migratory insertion of the iridium dihydride would potentially facilitate the formation of desired aldehyde through the productive isomerization pathway. The design of novel ligands with modified steric and electronic properties might be crucial in the control of site selectivity for alkyl/alkyl substrates.

(3) In **Chapter 4**, we already demonstrated the feasibility of an unprecedented Ir-catalyzed vinylogous Peterson elimination of silane allylic alcohols. Further extension of the scope of this reaction is still needed with special focus on the *multifunctionalized* substrates as well as the *late-stage* functionalizations. Additional mechanistic studies should be carried out to firmly secure the involvement of the iridium hydride in this transformation.

7. Experimental Section

7.1 Genral Information

Solvents and reagents: Commercial reagents such as aryl halides, aldehydes and tBuOK (98% pure) were purchased from Aldrich, Fluka, Acros or Strem and used without purification, unless otherwise noted. Liquids and solutions were transferred with syringes or cannula. Solvents such as Dichloromethane (CH_2Cl_2), Diethylether (Et_2O), Hexane, toluene, triethyl amine (Et_3N) and Tetrahydrofuran (THF) were dried over activated alumina columns and further degassed by three successive "freeze-pump-thaw" cycles if necessary. Diethyl amine (Et_2NH) was dried over KOH. All reactions were carried out under an inert atmosphere of nitrogen using either two-manifold vacuum / inert gas lines or a M.Braun glove-box, unless otherwise noted. $[Ir(cod)Cl]_2$,[1] $NaBAr_F$[2] were prepared according to literature procedures. $NaBAr_F$ and all iridium catalysts are normally dried under vacuum over P_2O_5 for overnight ahead of usage.

Chromatography: Thin layer chromatography (TLC) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254} from *Merck*. Flash chromatography was performed using silica gel SiliaFlash® P60 (230–400 mesh) from *Silicycle*.

Nuclear magnetic resonance (NMR) spectra: NMR spectra were recorded on ARX-300, AMX–400 and AMX–500 Bruker Avance spectrometers. ^1H and $^{13}C\{^1H\}$ NMR chemical shifts are given in ppm relative to $SiMe_4$, with the solvent resonance used as internal reference. ^1H NMR spectra were referenced to $CDCl_3$ (7.26 ppm), CD_2Cl_2 (5.32 ppm) or THF–d_8 (3.58, 1.72 ppm) and $^{13}C\{^1H\}$ NMR spectra were referenced to $CDCl_3$ (77 ppm), CD_2Cl_2 (53.84 ppm), or THF–d_8 (67.21, 25.31 ppm). $^{19}F\{^1H\}$ NMR chemical shifts are reported in ppm with absolute reference relative to ^1H.

Melting points: Melting points were recorded on a Buchi SMP-20 melting point apparatus using open glass capillaries are not corrected.

IR Spectra: Infrared spectra were obtained on a Perkin–Elmer 1650 FT-IR spectrometer using neat samples on a diamond ATR Golden Gate sampler.

Optical rotations: Optical rotations were measured on a Perkin-Elmer 241 polarimeter equipped with a Na-lamp at 25 °C unless otherwise noted.

Mass spectrometry: The mass spectrometric data were obtained at the mass spectrometry facility of the University of Geneva (http://www.unige.ch/sciences/sms/). The

[1] J. Choudhury, S. Podder, S. Roy. *J. Am. Chem. Soc.* **2005**, *127*, 6162–6163.
[2] D. L. Reger, T. D. Wright, C. A. Little, J. J. S. Lamba, M. D. Smith, *Inorg. Chem.* **2001**, *40*, 3810–3814.

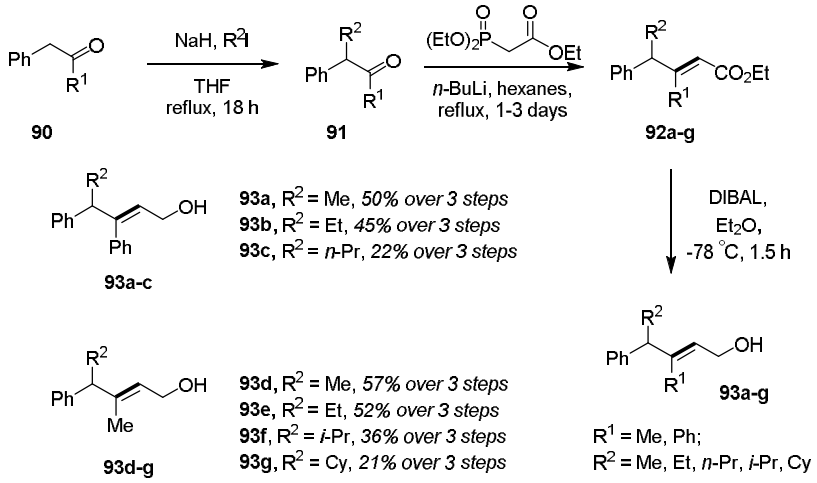
MALDI–TOF mass spectrometric data were recorded using a Brucker Daltonics Autoflex speed spectrometer operated by positive mode.

HPLC analysis: Chiral HPLC analyses were performed on an a Shimadzu CTO-20AA at at 25 °C unless otherwise noted.

Single crystal X-ray diffraction analysis: All the X-ray structures were resolved by Dr. Laure Guénée and Dr. Céline Besnard. The representations of all molecular structures reported in this manuscript were generated using CYLview (Legault, C. Y.: CYLview, version 1.0.561b; Université de Sherbrooke: Sherbrooke, QC, 2009, http://www.cylview.org.).

7.2 Catalyst-Directed Diastereoselective Isomerization of Allylic Alcohols for the Construction of Vicinal Tertiary Stereocenters

*7.2.1 General procedure for the synthesis of racemic substrates **93a-g***



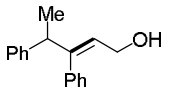
An oven-dried 100 mL round bottom flask was charged with 60% dispersion of NaH in mineral oil (0.6 g, 15 mmol), anhydrous THF (20 mL), phenyl acetone (1.4 mL, 10 mmol), and the corresponding alkyl iodide (20 mmol). The reaction mixture was refluxed overnight. After 18 h the resulting mixture was quenched at 0 °C by adding 1 M HCl (10 mL) and saturated $NaHCO_3$ (10 mL) sequentially, then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (Eluent: Petro ether/Ethyl acetate = 8/1) provided the desired ketone as a yellow oil.[3]

To a stirred solution of triethyl phosphonoacetate (2.0 eq.) in anhydrous hexanes was added dropwise *n*-BuLi (1.6 M in hexanes, 2.0 eq.) at 0 °C. After stirring for 0.5 h at 0 °C, the appropriate ketone (1 eq.) was added dropwise, and the reaction was refluxed for 1-3 days (tlc monitoring). After full consumption of the ketone, the reaction mixture was cooled to ambient temperature, quenched with a saturated aqueous Na_2CO_3 solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, concentrated and the crude mixture was purified by flash chromatography (Eluent: Petro ether/Ethyl acetate = 20/1). The (*E*)-enoate could be obtained pure as colorless oil, which was subsequently dissolved in anhydrous Et_2O (concentration: 0.1 M) and cooled to -78 °C. Dibal-H (1.0 M in hexanes, 2.2 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 1.5 h, and then quenched by adding a saturated aqueous NH_4Cl solution at 0 °C. The resulting

[3] M. L. McIntosh, C. M. Moore, T. B. Clark, *Org. Lett.* **2010**, *12*, 1996–1999.

suspension was kept stirring at room temperature for another hour before extraction with Et_2O, The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Eluent: Petro ether/Ethyl acetate = 4/1) yielded colorless oil.

(Z)-3,4-diphenylpent-2-en-1-ol (**93a**)



93a

489 mg, yield = 50%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

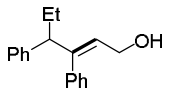
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.29-7.23 (m, 5H, arom C*H*), 7.21-7.18 (m, 3H, arom C*H*), 6.93 (dd, $^3J_{HH}$ = 7.3, 1.4 Hz, 2H, arom C*H*), 5.76 (td, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 0.8 Hz, 1H, C*H*CH_2OH), 4.02 (d, $^3J_{HH}$ = 6.8 Hz, 2H, C*H*$_2$OH), 3.81 (q, $^3J_{HH}$ = 7.1 Hz, 1H, C*H*Ph), 1.45 (d, $^3J_{HH}$ = 7.2 Hz, 3H, C*H*$_3$CH), 1.36 (s, 1H, OH).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 148.6 (*C*Ph), 144.0 (arom *C*), 139.7 (arom *C*), 128.5 (arom *C*H), 128.2 (arom *C*H), 127.9 (arom *C*H), 127.8 (arom *C*H), 126.9 (arom *C*H), 126.2 (arom *C*H), 125.5 (*C*HCH_2OH), 60.4 (*C*H_2OH), 47.2 (*C*HPh), 20.0 (*C*H_3CH).

HRMS (+ESI) calculated for $C_{17}H_{16}$ $[M\text{-}H_2O]^+$: 220.12465, found 220.12452.

IR (neat): ν (cm^{-1}) = 3318, 2968, 2930, 2871, 1600, 1492, 1451, 1370, 1102, 1073, 1023, 995, 965, 910, 774, 736, 697.

(Z)-3,4-diphenylhex-2-en-1-ol (**93b**)



93b

1.1 g, yield = 45%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

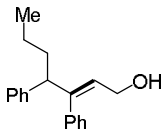
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.26-7.16 (m, 6H, arom C*H*), 7.11-7.10 (m, 2H, arom C*H*), 6.84-6.82 (m, 2H, arom C*H*), 5.79 (td, $^3J_{HH}$ = 6.7, $^4J_{HH}$ = 0.6 Hz, 1H, C*H*CH_2OH), 3.97 (d, $^3J_{HH}$ = 6.8 Hz, 2H, C*H*$_2$OH), 3.43 (t, $^3J_{HH}$ = 7.6 Hz, 1H, C*H*Ph), 1.91 (dt, $^2J_{HH}$ = 20.8, $^3J_{HH}$ = 7.1 Hz, 1H, C*H*$_2$$CH_3$), 1.82-1.74 (m, 1H, C*H*$_2$$CH_3$), 1.37 (br, 1H, OH), 0.91 (t, *J* = 7.3 Hz, 3H, C*H*$_3$$CH_2$).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 147.5 (*C*Ph), 142.5 (arom *C*), 139.8 (arom *C*), 128.5 (arom *C*H), 128.4 (arom *C*H), 128.1 (arom *C*H), 127.7 (arom *C*H), 126.8 (arom *C*H), 126.2 (arom *C*H), 126.0 (*C*HCH_2OH), 60.4 (*C*H_2OH), 55.6 (*C*HPh), 26.4 (*C*$H_2$$CH_3$), 12.6 (*C*$H_3$$CH_2$).

HRMS (+ESI) calculated for $C_{18}H_{18}$ $[M\text{-}H_2O]^+$: 234.14030, found 234.14045.

IR (neat): ν (cm^{-1}) = 3323, 2962, 2930, 2873, 1600, 1492, 1452, 1379, 1072, 1049, 1025, 990, 909, 789, 758, 732, 698.

(Z)-3,4-diphenylhept-2-en-1-ol (**93c**)



93c

500 mg, yield = 22%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

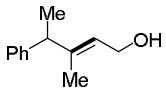
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.25-7.20 (m, 5H, arom C*H*), 7.19-7.15 (m, 1H, arom C*H*), 7.11-7.10 (m, 2H, arom C*H*), 6.82 (dd, $^3J_{HH}$ = 6.4, $^4J_{HH}$ = 3.2 Hz, 2H, arom C*H*), 5.79 (td, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 1.1 Hz, 1H, C*H*CH_2OH), 3.96 (d, $^3J_{HH}$ = 6.8 Hz, 2H, C*H*$_2$OH), 3.48 (t, $^3J_{HH}$ =7.5 Hz, 1H, C*H*Ph), 1.84 (ddt, $^2J_{HH}$ = 12.6, $^3J_{HH}$ = 9.9, 6.2 Hz, 1H, C*H*$_2CH_2$), 1.78-1.71 (m, 1H, C*H*$_2CH_2$), 1.37-1.24 (m, 3H, OH + C*H*$_2CH_3$), 0.90 (t, $^3J_{HH}$ = 7.4 Hz, 3H, C*H*$_3CH_2$).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 147.6 (*C*Ph), 142.7 (arom *C*), 139.8 (arom *C*), 128.5 (arom *C*H), 128.3 (arom *C*H), 128.1 (arom *C*H), 127.7 (arom *C*H), 126.8 (arom *C*H), 126.2 (arom *C*H), 125.8 (*C*HCH_2OH), 60.4 (*C*H_2OH), 53.4 (*C*HPh), 35.7 (*C*H_2CH), 21.0 (*C*H_2CH_3), 14.0 (*C*H_3CH_2).

HRMS (+ESI) calculated for $C_{19}H_{20}$ $[M\text{-}H_2O]^+$: 248.15595, found 248.15613.

IR (neat): ν (cm^{-1}) = 3311, 2956, 2930, 2870, 1600, 1492, 1452, 1379, 1073, 1010, 986, 909, 733, 698.

(E)-3-methyl-4-phenylpent-2-en-1-ol (**93d**)



93d

620 mg, yield = 57%

Colorless oil (Petro ether/ Ethyl acetate = 4/1, R_f = 0.20)

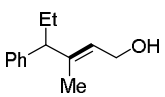
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.31-7.28 (m, 2H, arom C*H*), 7.22-7.18 (m, 3H, arom C*H*), 5.62 (m, 1H, C*H*CH_2), 4.23 (d, $^3J_{HH}$ = 6.6 Hz, 2H, C*H*$_2$OH), 3.42 (q, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*Ph), 1.54 (s, 3H, C*H*$_3$C), 1.44 (s, 1H, OH), 1.39 (d, $^3J_{HH}$ = 7.1 Hz, 3H, C*H*$_3$CH).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 144.7 (arom *C*), 142.7 (*C*CH_3), 128.2 (arom *C*H), 127.4 (arom *C*H), 126.1 (arom *C*H), 123.2 (*C*HCH_2), 59.5 (*C*H_2OH), 47.5 (*C*HPh), 19.4 (*C*H_3CH), 15.0 (*C*H_3C).

HRMS (+ESI) calculated for $C_{12}H_{16}ONa$ $[M+Na]^+$: 199.1093, found 199.1088.

IR (neat): ν (cm^{-1}) = 3324, 2967, 2873, 1664, 1601, 1493, 1451, 1375, 996, 762, 733, 698.

(E)-3-methyl-4-phenylhex-2-en-1-ol (**93e**)



93e

450 mg, yield = 52%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.30-7.27 (m, 2H, arom C*H*), 7.21-7.18

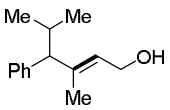
(m, 3H, arom C*H*), 5.66-5.62 (m, 1H, C*H*CH_2), 4.20 (d, $^3J_{HH}$ = 6.7 Hz, 2H, CH_2OH), 3.10 (t, $^3J_{HH}$ = 7.6 Hz, 1H, C*H*Ph), 1.90-1.712 (m, 2H, CH_2CH_3), 1.51 (s, 3H, CH_3C), 1.34 (s, 1H, OH), 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3CH_2).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 143.4 (arom *C*), 141.6 (*C*CH_3), 128.2 (arom *C*H), 127.9 (arom *C*H), 126.1 (arom *C*H), 123.9 (*C*HCH_2), 59.5 (*C*H_2OH), 55.8 (*C*HPh), 25.2 (*C*H_2CH_3), 14.5 (*C*H_3C), 12.4 (*C*H_3CH_2).

HRMS (+ESI) calculated for $C_{13}H_{18}ONa$ $[M+Na]^+$: 213.1249, found 213.1246.

IR (neat): ν (cm^{-1}) = 3312, 2962, 2930, 2872, 1668, 1599, 1493, 1451, 1379, 1075, 995, 760, 735, 698.

(E)-3,5-dimethyl-4-phenylhex-2-en-1-ol (**93f**)



93f

290 mg, yield = 36%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

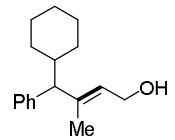
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.29-7.26 (m, 2H, arom C*H*), 7.21-7.17 (m, 3H, arom C*H*), 5.67-5.64 (m, 1H, C*H*CH_2), 4.15 (d, $^3J_{HH}$ = 6.7 Hz, 2H, CH_2OH), 2.82 (d, $^3J_{HH}$ = 10.9 Hz, 1H, C*H*Ph), 2.25 (ddd, $^3J_{HH}$ = 12.9, 6.5, 4.4 Hz, 1H, C*H*CH_3), 1.55 (s, 3H, CH_3C), 1.36 (br, 1H, OH), 0.96 (d, $^3J_{HH}$ = 6.4 Hz, 3H, CH_3CH), 0.77 (d, $^3J_{HH}$ = 6.5 Hz, 3H, CH_3CH).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 142.8 (arom *C*), 141.5 (*C*CH_3), 128.2 (arom *C*H), 128.1 (arom *C*H), 126.0 (arom *C*H), 124.4 (*C*HCH_2), 63.6 (*C*HPh), 59.4 (*C*H_2OH), 28.2 (*C*HCH_3), 21.5 (*C*H_3CH), 21.4 (*C*H_3CH), 13.5 (*C*H_3C).

HRMS (+ESI) calculated for $C_{14}H_{20}ONa$ $[M+Na]^+$: 227.1406, found 227.1401.

IR (neat): ν (cm^{-1}) = 3321, 2956, 2867, 1658, 1599, 1493, 1451, 1384, 1167, 1079, 997, 750, 699.

(E)-4-cyclohexyl-3-methyl-4-phenylbut-2-en-1-ol (**93g**)



93g

181 mg, yield = 21%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

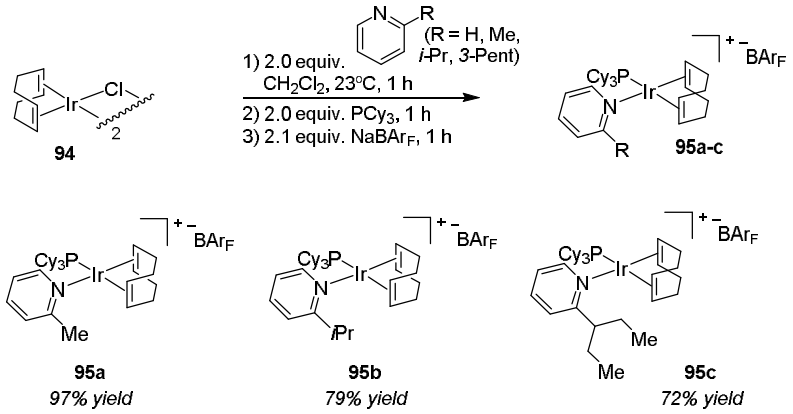
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.29-7.26 (m, 2H, arom C*H*), 7.20-7.16 (m, 3H, arom C*H*), 5.64 (td, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 1.3 Hz, 1H, C*H*CH_2), 4.14 (dd, $^3J_{HH}$ = 6.7, 2.3 Hz, 2H, CH_2OH), 2.91 (d, $^3J_{HH}$ = 10.9 Hz, 1H, C*H*Ph), 1.89 (qt, $^3J_{HH}$ = 11.0, 3.2 Hz, 1H, CH_{cy}), 1.80-1.74 (m, 2H, CH_{2cy}), 1.67-1.61 (m, 2H, CH_{2cy}), 1.54 (s, 3H, CH_3C), 1.52-1.48 (m, 1H, CH_{2cy}), 1.29-1.13 (m, 4H, CH_{2cy} + OH), 0.92-0.89 (m, 1H, , CH_{2cy}), 0.76 -0.68 (m, 1H, CH_{2cy}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 142.4 (arom *C*), 141.0 (*C*CH_3), 128.4 (arom *C*H), 128.1 (arom *C*H), 126.0 (arom *C*H), 124.5 (*C*HCH_2), 62.2 (*C*HPh), 59.4 (*C*H_2OH), 37.6 (*C*H_{cy}), 31.8 (*C*H_{2cy}), 31.7 (*C*H_{2cy}), 26.6 (*C*H_{2cy}), 26.4 (*C*H_{2cy}), 26.3 (*C*H_{2cy}), 13.5 (*C*H_3C).

HRMS (+ESI) calculated for $C_{17}H_{24}ONa$ $[M+Na]^+$: 267.1719, found 267.1714.

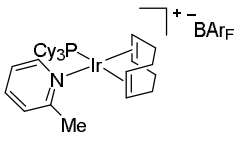
IR (neat): ν (cm^{-1}) = 3333, 2920, 2850, 1660, 1601, 1493, 1448, 1075, 996, 908, 732, 699.

*7.2.2 General procedure for the synthesis of Crabtree analogs **95a-c***[4]



In a glove box, the appropriate pyridine derivatives (0.1 mmol, 2 eq.) was added neat via micro-syringe to a solution of $[Ir(cod)Cl]_2$ (**94**) (33.6 mg, 0.05 mmol, 1 eq.) in CH_2Cl_2 (2 mL). The solution rapidly turned bright yellow. After 1 h, PCy_3 (28.1 mg, 0.1 mmol. 1 eq.) was added in one portion. The reaction was kept another hour before $NaBAr_F$ (93.3 mg, 0.105 mmol, 2.1 eq.) was added and the solution became slightly turbid. After 1-1.5 h the reaction was checked by TLC (Eluent: CH_2Cl_2, R_f = 0.9), the reaction mixture was concentrated and purified by flash chromatography (Eluent: CH_2Cl_2) to obtain orange-red powder.

Iridium complex **95a**



95a

152 mg, yield = 97%

Orange powder (CH_2Cl_2, R_f = 0.90)

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.40 (d, $^{3}J_{HH}$ = 5.4 Hz, 1H, arom C*H*), 7.71 (s, 8H, H_{BArF}), 7.62 (td, $^{3}J_{HH}$ = 7.8, $^{4}J_{HH}$ = 1.4 Hz, 1H, arom C*H*), 7.52 (s, 4H, H_{BArF}), 7.31 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, arom C*H*), 7.26-7.23 (m, 1H, arom C*H*), 4.46 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, CH_{cod}), 4.15-4.11 (m, 1H, CH_{cod}), 3.96-3.92 (m, 1H, CH_{cod}), 3.31-3.26 (m, 1H, CH_{cod}), 3.07 (s, 3H, CH_3), 2.35-0.92 (m, 41H, CH_{Cy}+CH_{2Cy}+CH_{2cod}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 161.7 (q, $^{1}J_{CB}$ = 49.9 Hz, $C_{ipsoBArF}$), 159.3 (s, C_{Ar}), 149.5 (s, CH_{Ar}), 138.0 (s, CH_{Ar}), 134.8 (s, CH_{BArF}), 129.3-128.5 (m, C_{CF3}), 128.2 (s, CH_{Ar}),

[4] L. Mantilli, D. Gérard, C. Besnard, C. Mazet, *Eur. J. Inorg. Chem.* **2012**, 3320–3330.

124.5 (q, $^{1}J_{CF}$ = 273.2 Hz, C_{CF3}), 123.3 (s, CH_{Ar}), 117.5-117.4 (m, CH_{BArF}), 90.1 (d, $^{2}J_{CP}$ = 9.6 Hz, CH_{cod}), 83.3 (d, $^{2}J_{CP}$ = 13.6 Hz, CH_{cod}), 67.3 (s, CH_{cod}), 61.4 (s, CH_{cod}), 35.2 (d, $^{1}J_{CP}$ = 22.9 Hz, CH_{Cy}), 33.4 (d, $^{3}J_{CP}$ = 3.1 Hz, CH_{2cod}), 32.2 (d, $^{3}J_{CP}$ = 2.0 Hz, CH_{2cod}), 30.1 (d, $^{3}J_{CP}$ = 17.8 Hz, CH_{2Cy}), 29.8 (s, CH_{2Cy}), 28.0 (d, $^{3}J_{CP}$ = 1.9 Hz, CH_{2Cy}), 27.66 (d, $^{3}J_{CP}$ = 10.3 Hz, CH_{2Cy}), 27.58 (d, $^{3}J_{CP}$ = 10.2 Hz, CH_{2Cy}), 26.8 (s, CH_3), 26.0 (s, CH_{2Cy}).

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz): δ (ppm) = -9.0

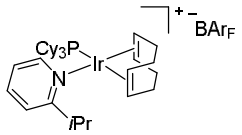
$^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 282 MHz): δ (ppm) = -62.4

HRMS (+ESI) calculated for $C_{26}H_{43}IrNP$ [M-2H-(N*ligand*)-BAr_F]$^{+}$: 579.2726, found 579.2715.

IR (neat): ν (cm^{-1}) = 2937, 2860, 1452, 1352, 1273, 1124, 1003, 887, 838, 764, 742, 714, 668.

m.p.: 129 °C (dec.)

Iridium complex **95b**



95b

126 mg, yield = 79%

Orange powder (CH_2Cl_2, R_f = 0.90)

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.37 (d, $^{3}J_{HH}$ = 5.3 Hz, 1H, arom C*H*), 7.74-7.71 (m, 9H, arom C*H*+H_{BArF}), 7.52 (s, 4H, H_{BArF}), 7.44 (d, $^{3}J_{HH}$ = 7.7 Hz, 1H, arom C*H*), 7.20-7.18 (m, 1H, arom C*H*), 4.78 (s, 1H, CH_{cod}), 4.30-4.27 (m, 1H, CH_{cod}), 4.08-4.05 (m, 1H, C*H*Me_2), 3.84-3.82 (m, 1H, CH_{cod}), 3.30-3.26 (m, 1H, CH_{cod}), 2.38-1.15 (m, 41H, CH_{Cy}+CH_{2Cy}+CH_{2cod}), 1.50 (d, $^{3}J_{HH}$ = 6.6 Hz, 3H, CH_3), 1.44 ($^{3}J_{HH}$ = 6.7 Hz, 3H, CH_3).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz): δ (ppm) = 169.5 (s, C_{Ar}), 161.7 (q, $^{1}J_{CB}$ = 49.6 Hz, $C_{ipso BArF}$), 149.2 (s, CH_{Ar}), 138.6 (s, CH_{Ar}), 134.8 (s, CH_{BArF}), 129.3-128.5 (m, C_{CF3}), 123.6 (q, $^{1}J_{CF}$ = 273.2 Hz, C_{CF3}), 125.1 (s, CH_{Ar}), 123.4 (s, CH_{Ar}), 117.5-117.3 (m, CH_{BArF}), 90.8 (d, $^{2}J_{CP}$ = 8.8 Hz, CH_{cod}), 81.8 (d, $^{2}J_{CP}$ = 14.7 Hz, CH_{cod}), 66.7 (s, CH_{cod}), 60.1 (s, CH_{cod}), 39.4 (s, $CHMe_2$), 35.3 (d, $^{1}J_{CP}$ = 21.7 Hz, CH_{Cy}), 33.2 (d, $^{3}J_{CP}$ = 2.4 Hz, CH_{2cod}), 32.8 (d, $^{3}J_{CP}$ = 2.2 Hz, CH_{2cod}), 30.2 (s, CH_{2Cy}), 29.4 (s, CH_{2Cy}), 29.2 (s, CH_{2Cy}), 27.6 (d, $^{3}J_{CP}$ = 9.5 Hz, CH_{2Cy}), 27.5 (d, $^{3}J_{CP}$ = 11.4 Hz, CH_{2Cy}), 25.9 (s, CH_{2Cy}), 24.1 (s, CH_3), 23.4 (s, CH_3).

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz): δ (ppm) = -7.2

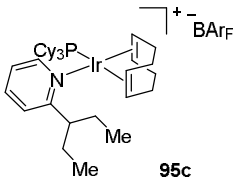
$^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 282 MHz): δ (ppm) = -62.4

HRMS (+ESI) calculated for $C_{26}H_{43}IrNP$ [M-2H-(N*ligand*)-BAr_F]$^{+}$: 579.2726, found 579.2741.

IR (neat): ν (cm^{-1}) = 2937, 2860, 1480, 1452, 1353, 1274, 1160, 1124, 1000, 886, 839, 713, 679, 668.

m.p.: 140 °C (dec.)

Iridium complex **95c**



95c

115 mg, yield = 72%

Orange powder (CH_2Cl_2, R_f = 0.90)

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.43 (d, $^3J_{HH}$ = 5.0 Hz, 1H, arom C*H*), 7.74-7.70 (m, 9H, arom C*H*+H_{BArF}), 7.52 (s, 4H, H_{BArF}), 7.38 (d, $^3J_{HH}$ = 7.6 Hz, 1H, arom C*H*), 7.21-7.18 (m, 1H, arom C*H*), 4.87 (t, $^3J_{HH}$ = 7.1 Hz, 1H, CH_{cod}), 4.41-4.40 (m, 1H, CH_{cod}), 3.78-3.74 (m, 2H, C*H*CH_2CH_3+ CH_{cod}), 3.21-3.16 (m, 1H, CH_{cod}), 2.43-1.10 (m, 45H, CH_{Cy}+CH_{2Cy}+CH_{2cod}+CH_2CH_3), 1.06 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3CH_2), 1.03 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3CH_2).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 167.5 (s, C_{Ar}), 161.7 (q, $^1J_{CB}$ = 49.7 Hz, $C_{ipso BArF}$), 149.5 (s, CH_{Ar}), 137.9 (s, CH_{Ar}), 134.8 (s, CH_{BArF}), 128.9 (q, $^2J_{CF}$ = 31.7 Hz, C_{CF3}), 126.8 (s, CH_{Ar}), 123.6 (q, $^1J_{CF}$ = 273.2 Hz, C_{CF3}), 123.2 (s, CH_{Ar}), 117.4 (m, CH_{BArF}), 91.9 (d, $^2J_{CP}$ = 8.3 Hz, CH_{cod}), 79.8 (d, $^2J_{CP}$ = 16.0 Hz, CH_{cod}), 68.2 (s, CH_{cod}), 59.0 (s, CH_{cod}), 50.5 (s, $CHCH_2CH_3$), 35.5 (d, $^1J_{CP}$ = 22.0 Hz, CH_{Cy}), 34.8 (d, $^3J_{CP}$ = 3.6 Hz, CH_{2cod}), 31.3 (d, $^3J_{CP}$ = 1.8 Hz, CH_{2cod}), 30.9 (s, CH_{2Cy}), 30.4 (s, CH_{2Cy}), 29.3 (s, CH_{2Cy}), 27.6 (d, $^3J_{CP}$ = 9.5 Hz, CH_{2Cy}), 27.5 (d, $^3J_{CP}$ = 10.9 Hz, CH_{2Cy}), 26.6 (d, $^3J_{CP}$ = 2.2 Hz, CH_{2Cy}), 25.9 (s, CH_{2Cy}), 25.8 (s, CH_2CH_3), 25.2 (s, CH_2CH_3), 11.4 (s, CH_3CH_2), 10.0 (s, CH_3CH_2).

^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ (ppm) = -7.5

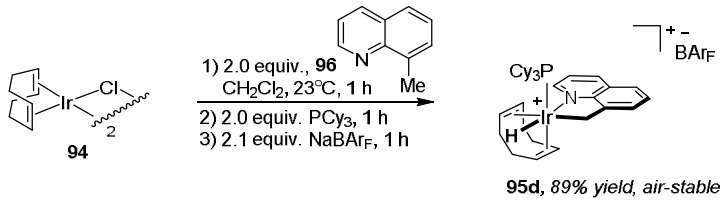
^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = -62.4

HRMS (+ESI) calculated for $C_{26}H_{43}IrNP$ [M-2H-(N*ligand*)-BAr_F]$^+$: 579.2726, found 579.2703.

IR (neat): ν (cm^{-1}) = 2938, 2860, 1609, 1508, 1449, 1352, 1274, 1158, 1123, 1002, 886, 838, 763, 742, 713, 668.

m.p.: 131 °C (dec.)

7.2.3 Procedure for the synthesis of iridium monohydride complex ***95d***



95d, *89% yield, air-stable*

In a glove box, 8-methylquinoline **96** (14.2 μL, 0.1 mmol, 2 eq.) was added neat via micro-syringe to a solution of $[Ir(cod)Cl]_2$ (**94**) (33.6 mg, 0.05 mmol, 1 eq.) in CH_2Cl_2 (2 mL). After 1 h, PCy_3 (28.5 mg, 0.1 mmol. 1 eq.) was added in one portion. The reaction was kept another hour before $NaBAr_F$ (93.0 mg, 0.105 mmol, 2.1 eq.) was added and the solution became slightly turbid. After 1-1.5 h the reaction was checked by TLC (Eluent: CH_2Cl_2, R_f = 0.9), the

reaction mixture was concentrated and purified by flash chromatography (Eluent: CH_2Cl_2) to obtain a light yellow powder **95d** in 89% yield (141 mg).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 9.31 (d, $^3J_{HH}$ = 5.1 Hz, 1H, arom C*H*), 8.33 (d, $^3J_{HH}$ = 8.3 Hz, 1H, arom C*H*), 7.73-7.71 (m, 9H, arom C*H*+H_{BArF}), 7.69-7.68 (m, 1H, arom C*H*), 7.63-7.56 (2H, arom C*H*), 7.52 (s, 4H, H_{BArF}), 7.51-7.49 (m, 1H, arom C*H*), 5.05-5.04 (m, 1H, CH_{cod}), 4.92 (t, $^3J_{HH}$ = 7.3 Hz, 1H, CH_{cod}), 4.45 (td, $^3J_{HH}$ = 8.7, 5.4 Hz, 1H, CH_{cod}), 3.41 (dd, $^2J_{HH}$ = 15.5, $^3J_{HH}$ = 8.0 Hz, 1H, CH_{2cod}), 3.29-3.24 (m, 2H, CH_{cod} + Ir-CH_2), 2.73-2.65 (m, 1H, CH_{2cod}), 2.61-1.12 (m , 39H, CH_{Cy}+CH_{2Cy}+CH_{2cod}), -15.95 (d, $^2J_{PH}$ = 16.2 Hz, 1H, Ir-*H*).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 161.7 (q, $^1J_{CB}$ = 50.1 Hz, $C_{ipso BArF}$), 154.4 (s, CH_{Ar}), 152.4 (s, C_{Ar}), 149.6 (s, C_{Ar}), 139.5 (s, CH_{Ar}), 134.8 (s, CH_{BArF}), 133.8 (s, CH_{Ar}), 129.9 (s, C_{Ar}), 129.2 (s, CH_{Ar}), 129.2-128.5 (m, C_{CF3}), 125.6 (s, CH_{Ar}), 123.5 (q, $^1J_{CF}$ = 272.2 Hz, C_{CF3}), 122.6 (s, CH_{Ar}), 117.5-117.4 (m, CH_{BArF}), 94.1 (d, $^2J_{PC}$ = 10.9 Hz, CH_{cod}), 93.1 (d, $^2J_{PC}$ = 14.4 Hz, CH_{cod}), 88.9 (s, CH_{cod}), 85.7 (s, CH_{cod}), 39.5 (d, $^3J_{CP}$ = 3.4 Hz, CH_{2cod}), 31.1 (s, CH_{2cod}), 30.1 (s, CH_{2Cy}), 27.4 (s, CH_{2cod}), 27.1 (d, $^3J_{CP}$ = 10.0 Hz, CH_{2Cy}), 26.0 (d, $^3J_{CP}$ = 6.7 Hz, CH_{2cod}), 12.1 (d, $^2J_{PC}$ = 5.4 Hz, Ir-CH_2).

^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ (ppm) = -7.2

^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz): δ (ppm) = -63.0

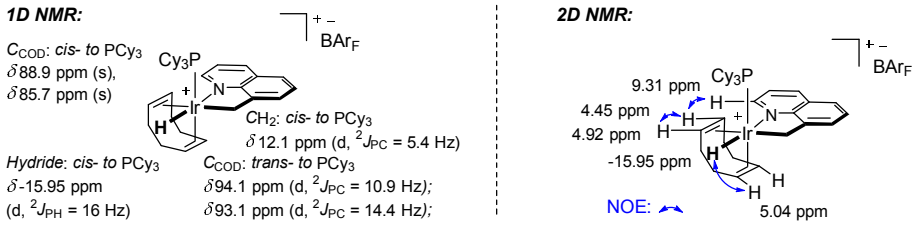
HRMS (+ESI) calculated for $C_{26}H_{43}IrNP$ [M-3H-(N*ligand*)-BAr_F]$^+$: 579.2726, found 579.2742.

IR (neat): ν (cm^{-1}) = 2938, 2859, 2242, 1610, 1508, 1449, 1353, 1272, 1160, 1116, 1008, 908, 887, 839, 797, 770, 735, 713, 682, 670.

m.p. 110-112 °C

The structure of **95d** was assigned based on the NMR spectra and confirmed by single crystal X-ray diffraction analysis.[5]

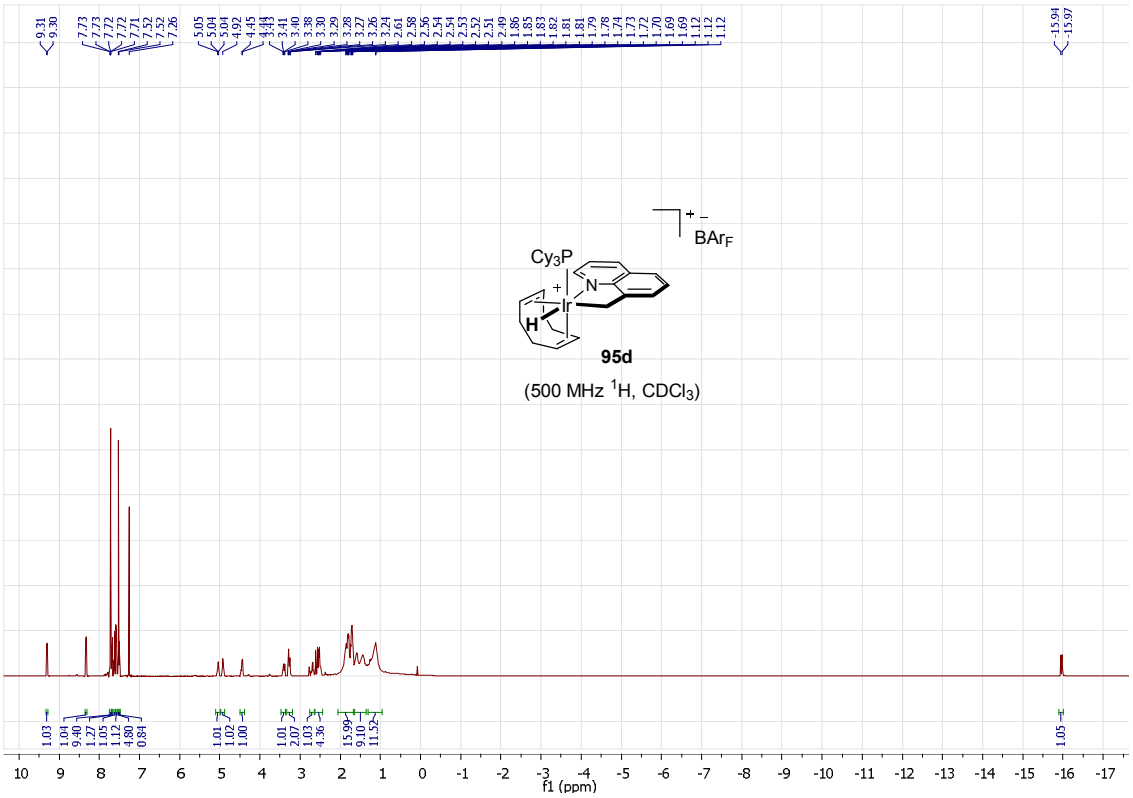
Key signals from the NMR spectra were listed as below:



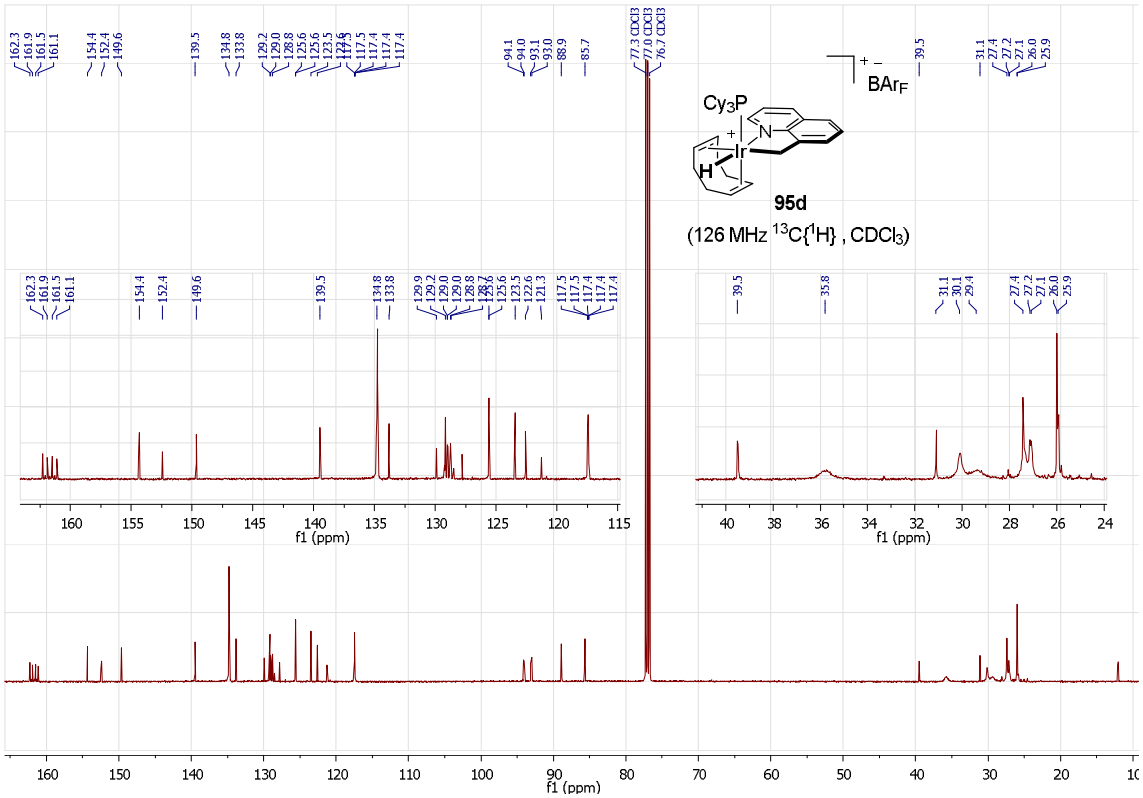
[5] The X-ray structure of **95d** was obtained by Dr. Devendra Vyas and later resolved by Dr. Céline Besnard. See: N. Humbert, D. J. Vyas, C. Besnard, C. Mazet, *Chem. Commun*. **2014**, *50*, 10592–10595.

The original NMR spectra of **95d** were shown as below:

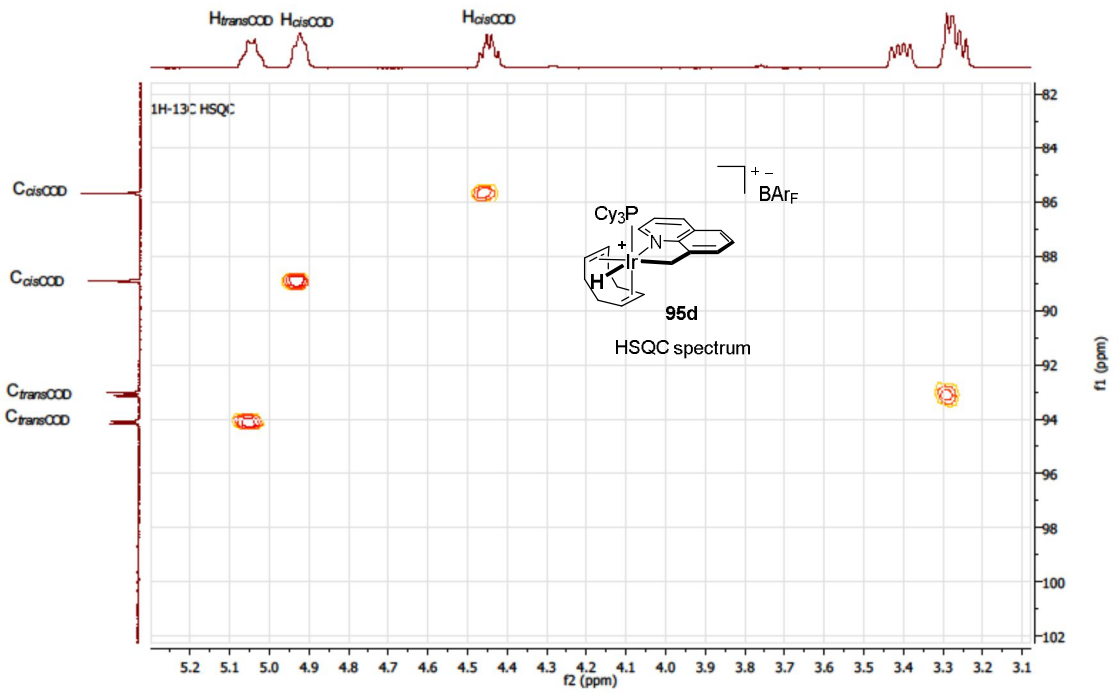
a) **^{1}H NMR**:



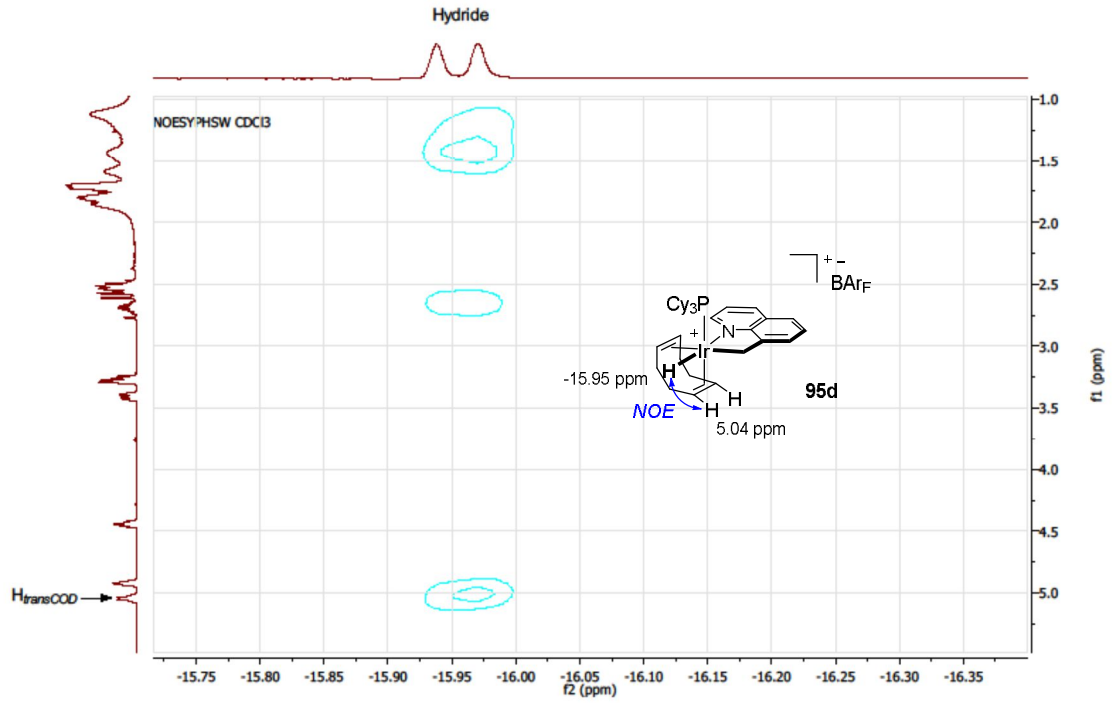
b) **^{13}C{^{1}H} NMR**:

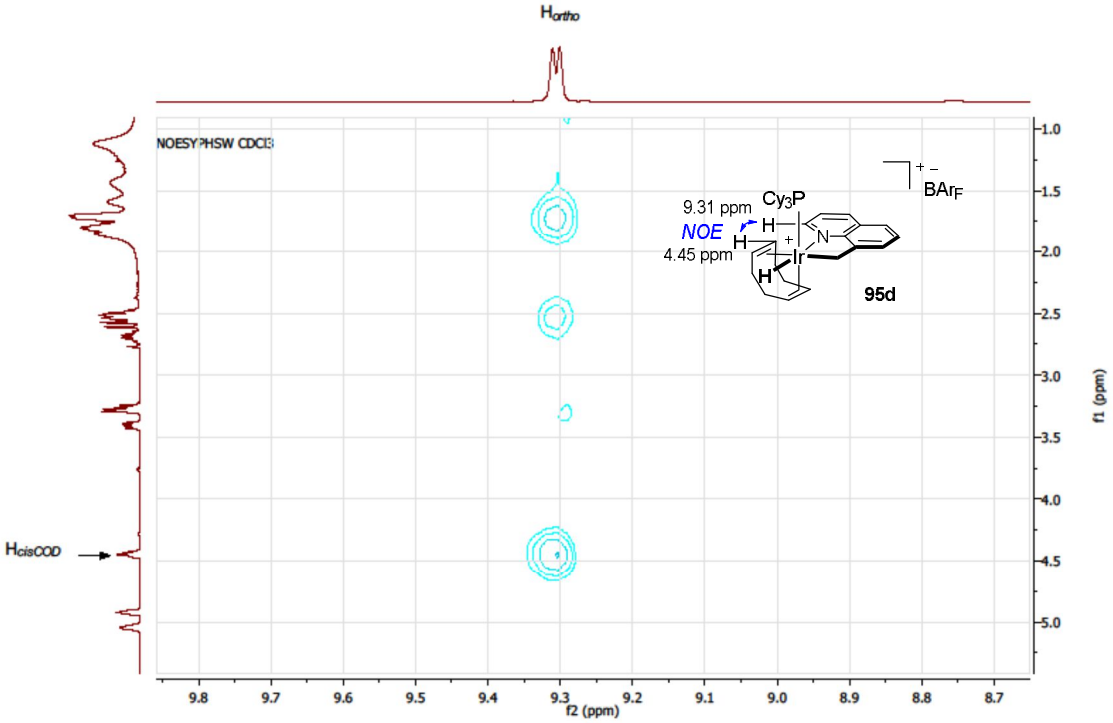


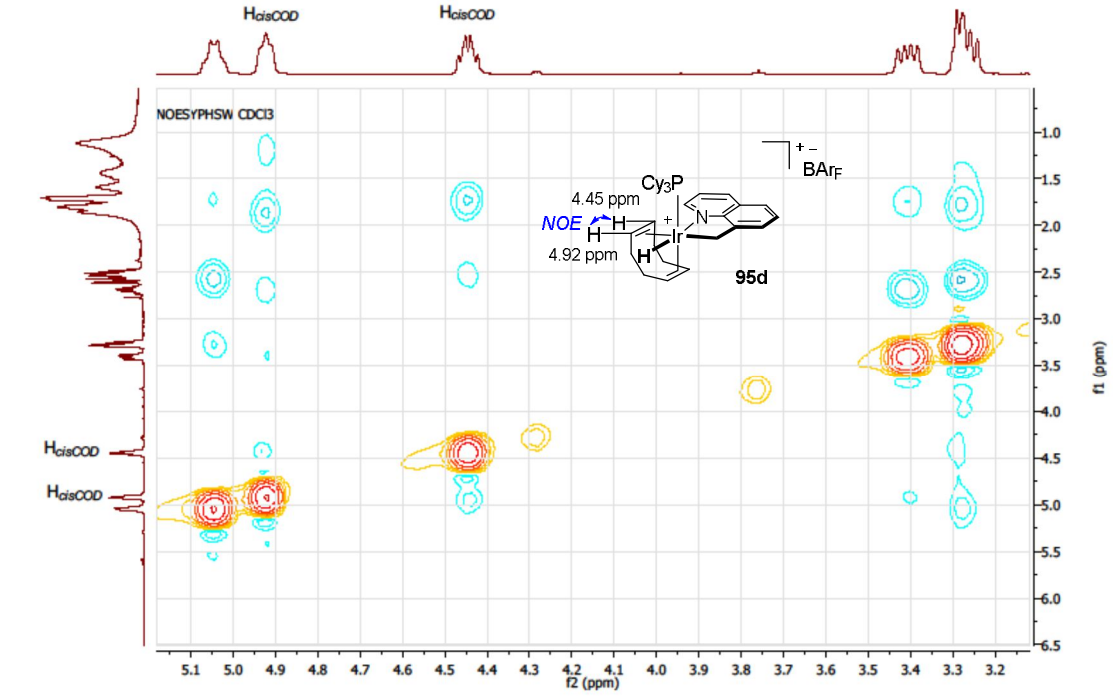
c) **HSQC NMR**:



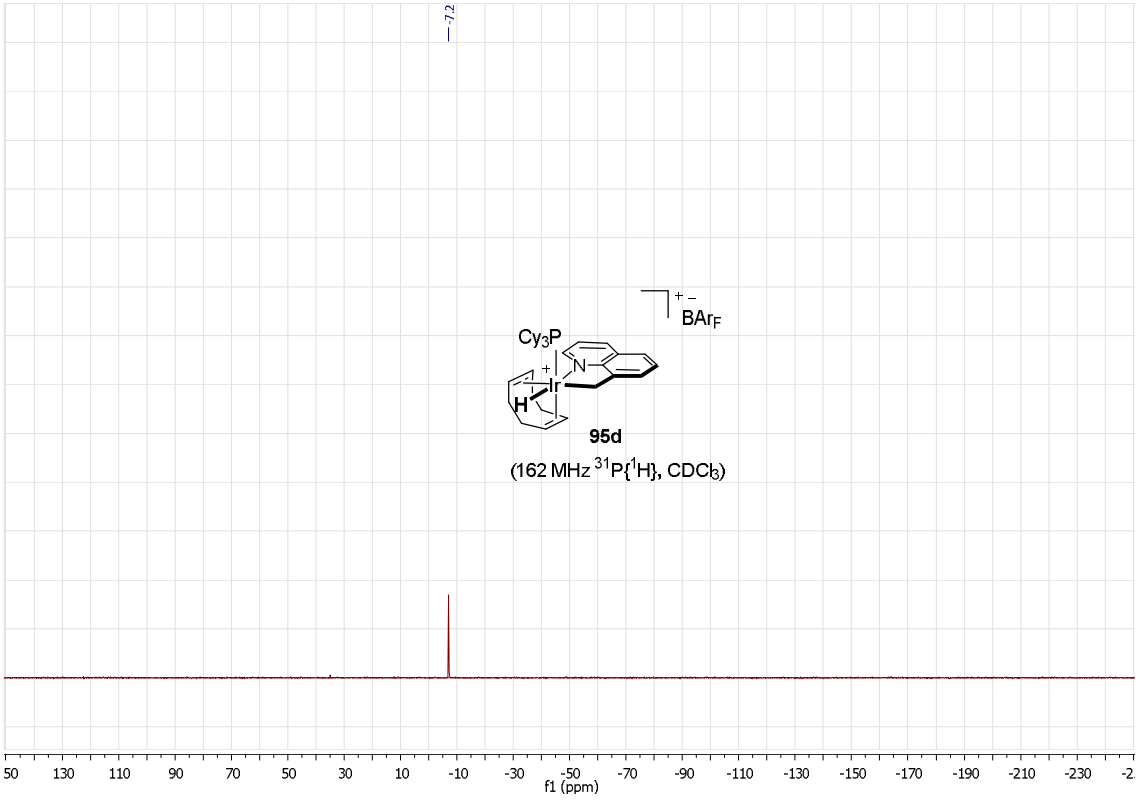
d) **2D-NOESY NMR**:



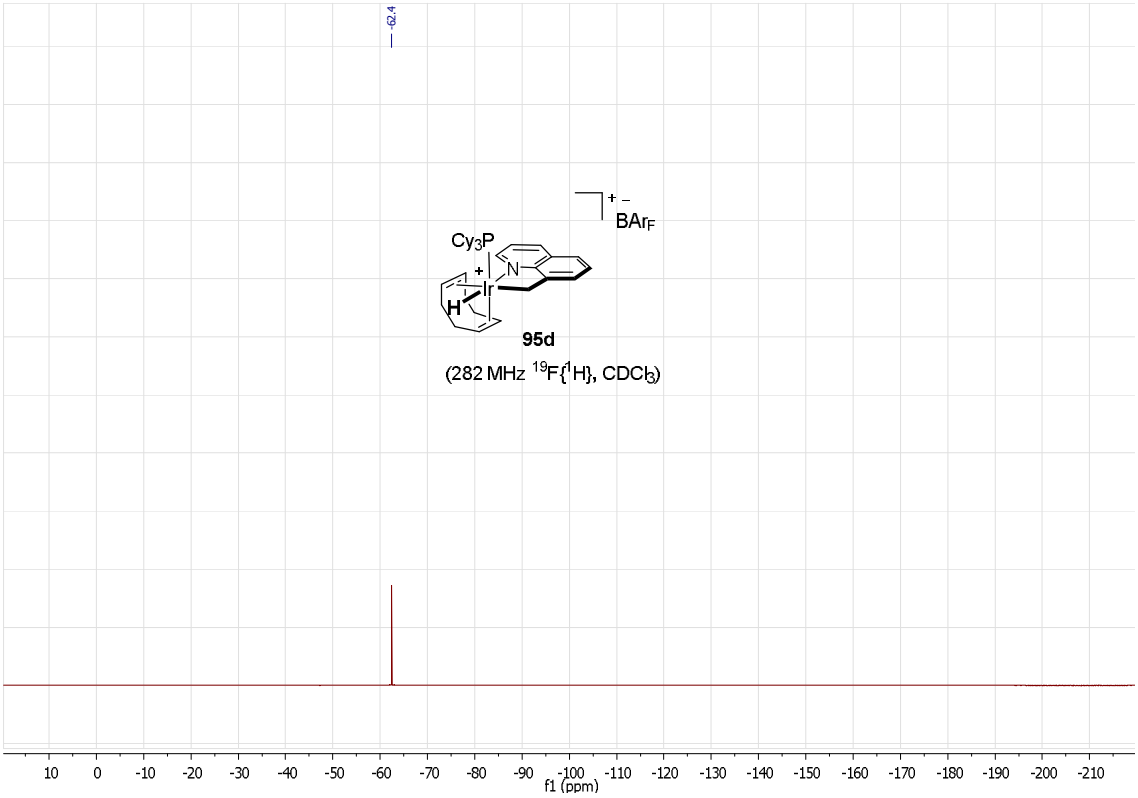

Hortho
NOESYPHSW CDCl3
HcisCOD
9.31 ppm
NOE
4.45 ppm
Cy3P
BArF
95d
f2 (ppm)
f1 (ppm)


HcisCOD
HcisCOD
NOESYPHSW CDCl3
HcisCOD
HcisCOD
4.45 ppm
NOE
4.92 ppm
Cy3P
BArF
95d
f2 (ppm)
f1 (ppm)

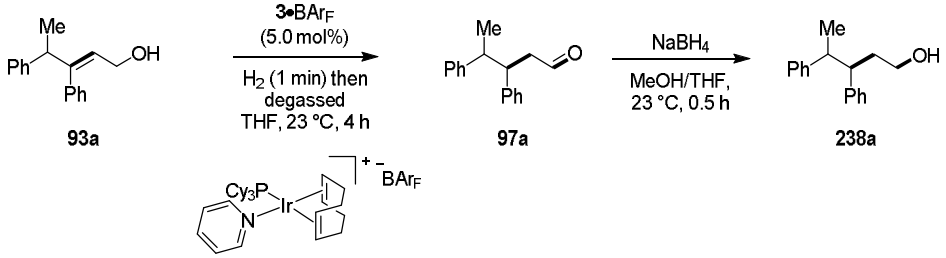
e) **$^{31}P\{^{1}H\}$ NMR**:



f) **$^{19}F\{^{1}H\}$ NMR**:

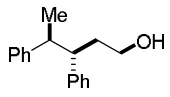


7.2.4 Representative procedure for Crabtree-catalyzed diastereoselective isomerization of primary allylic alcohols



A 10 mL Schlenk containing catalyst **3**•BAr_F (7.6 mg, 5.0 mol%,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed anhydrous THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution rapidly discolored. After 1 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, **93a** (23.5 mg, 0.1 mmol) was added by micro-syringe. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at ambient temperature for 4 h. After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. The aldehyde was then re-dissolved in 2 mL of anhydrous MeOH, cooled to 0^{o}C, and $NaBH_4$ (7.7 mg, 2 eq.) was added in one portion. The resulting solution was kept at ambient temperature for 30 minutes. The reaction was stopped and quenched by adding a saturated aqueous NH_4Cl solution (3 mL), the water phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude yellow oil was dissolved in pentane, the resulting suspension was passed through a syringe filter and the filtrate was concentrated to give pure desired alcohols **238a** (18.6 mg, yield = 78%, *syn/anti* = 1/2.6).

3,4-diphenylpentan-1-ol (**238a**)



238a

18.6 mg, yield = 78%, *syn/anti* = 1/2.6, from **93a** (23.5 mg, 0.1 mmol).

Yellow oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

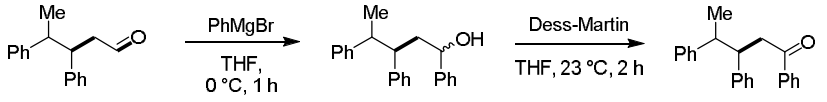
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.38-7.29 (m, 1H, arom C*H*), 7.28-7.20 (m, 2H, arom C*H*), 7.19-7.05 (m, 4H, arom C*H*), 6.98-6.94 (m, 3H, arom C*H*), 3.50-3.46 (m, 1H, *anti*-CH_2OH), 3.40-3.34 (m, 1H, CH_2OH), 3.26-3.20 (m, 1H, *syn*-CH_2OH), 3.03-2.78 (m, 2H, C*H*CH_3+C*H*Ph), 2.18-2.10 (m, 1H, *anti*-C$H_2$$CH_2$OH), 1.93-1.84 (m, 1H, *anti*-C$H_2$$CH_2$OH), 1.70-1.64 (m, 2H, *syn*-C$H_2$$CH_2$OH), 1.34 (d, $^3J_{HH}$ = 6.9 Hz, 3H, *anti*-CH_3CH), 1.27 (br, O*H*), 1.00 (d, $^3J_{HH}$ = 6.6 Hz, 3H, *syn*-CH_3CH).

^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) = 146.3, 145.1, 143.6, 142.5, 128.6, 128.5, 128.5, 128.2, 128.0, 127.9, 127.7, 127.6, 126.4, 126.2, 126.1, 125.8, 61.4, 61.3, 49.7, 49.2, 46.4, 45.6, 37.4, 35.1, 21.1, 18.8.

HRMS (+ESI) calculated for $C_{17}H_{24}NO$ $[M+NH_4]^+$: 258.1852, found 258.1802.

IR (neat): ν (cm^{-1}) = 3345, 3028, 2963, 2932, 2874, 1602, 1494, 1452, 1376, 1354, 1278, 1127, 1028, 908, 761, 732.

The relative configuration of **97a**/**238a** was determined after converting into known compound,[6] others were assigned by analogy.



97a **239a** **240a**
known compound
syn/anti 1/3.2 (crude)
1/3.6 (purified)

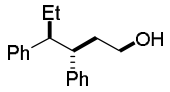
93a (24 mg, 0.1 mmol) was engaged in the isomerization with **3**•BAr_F (5 mol%) following the standard procedure. The reaction mixture was cooled to 0°C after **93a** was consumed 4 h later, and PhMgBr (0.1 mmol, 1 eq.) was added to the solution. Then the reaction was kept at 0°C for another 1 h before quenching by adding sat. aq. NH_4Cl solution. The aqueous phase was extracted with Et_2O (10 mL×3), the combined extracts were dried over anhydrous Na_2SO_4, filtration and concentration in vacuum yielded **239a** as an oil residue.

To the CH_2Cl_2 (2 mL) solution of **239a** was added Dess-Martin Periodiane (64 mg, 1.5 eq), the resulted reaction mixture was stirred at ambient temperature for 2 h. Then the reaction was quenched by adding sat. aq. Na_2SO_3 solution, after stirring at ambient temperature for another 1 h, the water phase was extracted with CH_2Cl_2 (10 mL×3) and the organic extracts were combined and dried over anhydrous Na_2SO_4, filtration and concentration in vacuum gave a crude oil. Purification by flash chromatography (Eluent: Petro ether/Ethyl acetate = 70/1) yielded colorless oil **240a** (20 mg, 64% yield for 3 steps).[7]

^{1}H NMR ($CDCl_3$, 500 MHz,) δ (ppm) = 7.84-7.83 (m, 2H, *anti*-arom C*H*), 7.65-7.64 (m, 2H, *syn*-arom C*H*), 7.52 (s, 1H), 7.65-7.07 (m, 14H, arom C*H*), 6.99 (d, $^3J_{HH}$ = 7.3 Hz, 2H, *anti*-arom C*H*), 3.70-3.66 (m, 1H, *anti*-C*H*CH_2), 3.51 (td, $^3J_{HH}$ = 10.5, 3.5 Hz, 1H, *syn*-C*H*CH_2), 3.35 (d, $^3J_{HH}$ = 7.0 Hz, 2H, *anti*-CH_2), 3.25 (dd, $^2J_{HH}$ = 16.5, $^3J_{HH}$ = 10.2 Hz, 1H, *syn*-CH_2), 3.18-3.13 (m, 1H, *anti*-C*H*CH_3), 3.04-2.94 (m, 2H, *syn*-CH_2+ *syn*-C*H*CH_3), 1.32 (d, $^3J_{HH}$ = 7.1 Hz, 3H, *anti*-CH_3), 1.04 (d, $^3J_{HH}$ = 6.9 Hz, 3H, *syn*-CH_3).

[6] E. Hupe, D. Denisenko, P. Knochel. *Tetrahedron* **2003**, *59*, 9187-9198.

3,4-diphenylhexan-1-ol (**238b**)



238b

22.4 mg, yield = 89%, *syn/anti* = 1/2.1, from **93b** (25.2 mg, 0.1 mmol).

Yellow oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

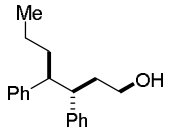
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) =7.35-7.31 (m, 1H, arom C*H*), 7.26-7.20 (m, 2H, arom C*H*), 7.16-7.06 (m, 4H, arom C*H*), 6.91-6.87 (m, 3H, arom C*H*), 3.52- 3.45 (m, 1H, *anti*-CH_2OH), 3.41-3.36 (m, 1H, *anti*-CH_2OH), 3.32-3.36 (m, 1H, *syn*-CH_2OH), 3.22-3.16 (m, 1H, *syn*-CH_2OH), 3.02-2.97 (m, 1H, *anti*-C*H*CH_2CH_2OH), 2.86 (td, $^3J_{HH}$ = 10.2, 5.2 Hz, 1H, *syn*-C*H*CH_2CH_2OH), 2.75-2.70 (m, 1H, *anti*-C*H*CH_2CH_3), 2.61 (td, $^3J_{HH}$ = 10.5, 4.1 Hz, 1H, *syn*-C*H*CH_2CH_3), 2.18-2.13 (m, 1H, *anti*-CH_2CH_2OH), 1.92-1.83 (m, 2H, *anti*-CH_2CH_2OH+ *anti*-CH_2CH_3), 1.64-1.60 (m, 3H, *anti*-CH_2CH_3+*syn*-CH_2CH_2OH), 1.40-1.32 (m, 2H, *syn*-CH_2CH_3), 1.27 (br, 1H, O*H*), 0.75 (t, $^3J_{HH}$ = 7.3 Hz, 3H, *anti*-CH_3CH_2), 0.54 (t, $^3J_{HH}$ = 7.4 Hz, 3H, *syn*-CH_3CH_2).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 144.0, 144.0, 142.5, 142.2, 129.0, 128.8, 128.5, 128.4, 128.2, 127.7, 127.5, 126.4, 126.2, 126.0, 125.8, 61.4, 61.3, 54.2, 53.5, 48.8, 47.8, 37.5, 35.9, 27.3, 25.7, 12.3, 12.1.

HRMS (+ESI) calculated for $C_{18}H_{26}NO$ $[M+NH_4]^+$: 272.2009, found 272.1952.

IR (neat): ν (cm^{-1}) = 3346, 3027, 2959, 2930, 2874, 1602, 1494, 1453, 1354, 1278, 1127, 1032, 909, 763, 732.

3,4-diphenylheptan-1-ol (**238c**)



238c

21.5 mg, yield = 81%, *syn/anti* = 1/2.0, from **93c** (26.6 mg, 0.1 mmol).

Yellow oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

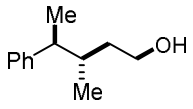
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.35-7.30 (m, 1H, arom C*H*), 7.24-7.19 (m, 2H, arom C*H*), 7.16-7.06 (m, 4H, arom C*H*), 6.90-6.86 (m, 3H, arom C*H*), 3.52-3.45 (m, 1H, *anti*-CH_2OH), 3.41-3.35 (m, 1H, *anti*-CH_2OH), 3.31-3-25 (m, 1H, *syn*-CH_2OH), 3.22-3.16 (m, 1H, *syn*-CH_2OH), 2.97 (dd, $^3J_{HH}$ = 11.3, 4.0 Hz, 1H, *anti*-C*H*CH_2CH_2OH), 2.87-2.79 (m, 2H, *syn*-C*H*CH_2CH_2OH+ *anti*-C*H*CH_2CH_2CH_3), 2.71 (td, *J* = 10.7, 3.7 Hz, 1H, *syn*-C*H*CH_2CH_2CH_3), 2.21-2.13 (m, 1H, *anti*-CH_2CH_2OH), 1.89-1.77 (m, 2H, *anti*-CH_2CH_2OH+ *anti*-CH_2CH_2CH_3), 1.66-1.56 (m, 3H, *anti*-CH_2CH_2CH_3+ *syn*-CH_2CH_2OH), 1.42-0.88 (m, 4H, *syn*-CH_2CH_2CH_3+ *syn*-CH_2CH_3), 0.85 (t, $^3J_{HH}$ = 7.3 Hz, 3H, *anti*-CH_3), 0.66 (t, $^3J_{HH}$ = 7.3 Hz, 3H, *syn*-CH_3).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 144.3, 143.9, 142.8, 142.2, 128.9, 128.8, 128.5, 128.4, 128.3, 128.2, 127.7, 127.5, 126.4, 126.2, 126.0, 125.8, 61.4, 61.3, 52.0, 51.5, 49.0, 48.1, 37.5, 36.5, 36.0, 35.2, 20.8, 20.5, 14.1, 13.8.

HRMS (+ESI) calculated for $C_{19}H_{22}$ $[M-H_2O]^+$: 250.17160, found 250.17174.

IR (neat): ν (cm^{-1}) = 3373, 3028, 2956, 2930, 2872, 1601, 1494, 1453, 1377, 1265, 1030, 908, 730, 698.

3-methyl-4-phenylpentan-1-ol (**238d**)



238d

16.5 mg, yield = 94%, *syn/anti* = 1/2.2, from **93d** (17.6 mg, 0.1 mmol)

Yellow oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

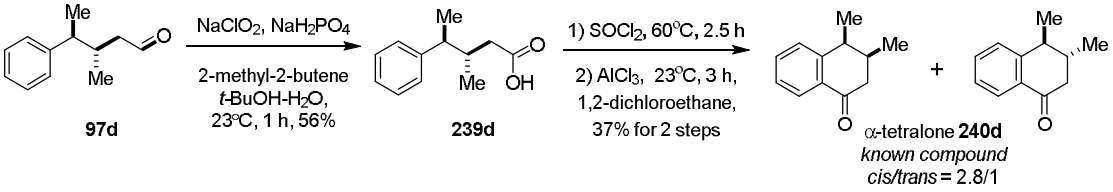
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.30-7.27 (m, 2H, arom C*H*), 7.20-7.16 (m, 3H, arom C*H*), 3.74-3.54 (m, 2H, CH_2OH), 2.63-2.60 (m, 1H, C*H*Ph), 1.81-1.56 (m, 2H, CH_2CH), 1.32-1.30 (m, 1H, C*H*CH$_2$), 1.28 (d, $^3J_{HH}$ = 7.1 Hz, 3H, *anti*-CH_3CHPh), 1.24 (d, $^3J_{HH}$ = 7.0 Hz, 3H, *syn*-CH_3CHPh), 0.92 (d, $^3J_{HH}$ = 6.7 Hz, 3H, *syn*-CH_3CHCH$_2$), 0.80 (d, $^3J_{HH}$ = 6.8 Hz, 3H, *anti*-CH_3CHCH$_2$).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 146.64, 145.95, 128.15, 128.02, 127.84, 127.63, 125.84, 61.31, 45.14, 45.12, 37.88, 36.68, 35.88, 18.22, 17.73, 17.30, 16.36.

HRMS (+ESI) calculated for $C_{12}H_{18}O$ $[M]^+$: 178.13522, found 178.13536.

IR (neat): ν (cm^{-1}) = 3326, 2963, 2926, 2872, 1601, 1493, 1452, 1377, 1278, 1128, 1051, 1001, 769, 699.

The relative configuration of **97d**/**238d** was determined after converting into known compound,[7] others were assigned by analogy.



97d (70 mg, 0.4 mmol) was engaged in the isomerization with **3**•BAr_F (5 mol%) following the standard procedure, THF was evaporated after 4 h to yield **3d** as crude yellow oil, which was dissolved in *t*BuOH (2.5 mL), then 2-methyl-2-butene (3.6 mL, 70 eq.) was added, followed by the solution of $NaClO_2$ (678 mg, 15 eq.) and NaH_2PO_4•H_2O (586 mg, 9 eq.) in H_2O (5.0 mL). The resulted solution was stirred vigorously at ambient temperature for 2-3 h and then extracted with EtOAc (10 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the crude oil. Purification by flash chromatography (Eluent: Petro ether/Ethyl acetate = 4/1) yielded colorless oil **239d** (39.2 mg, 56% yield for 2 steps).

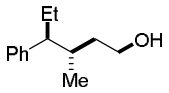
To a 10 mL round-bottle flask containing acid **239d** was added 0.6 mL of thionyl chloride, the reaction mixture was heated to 60°C and stirred for another 2.5 h. After **239d** was

[7] A. Boudier, C. Darcel, F. Flachsmann, L. Micouin, M. Oestreich, P. Knochel. *Chem. Eur. J.* **2000**, *6*, 2748-2761.

comsumed, the excess $SOCl_2$ was evaporated to give a brown residue, which was redissolved in 1,2-dichloroethane (1.5 mL) and $AlCl_3$ (48 mg, 1.8 eq.) was added in one portion.The reaction mixture was stirred at room temperature for another 3 h before quenching with water, the water phase was extracted with Et_2O (10 mL×3) and the organic extracts were combined and dried over anhydrous Na_2SO_4, filtration and concentration in vacuum gave a crude oil. Purification by flash chromatography (Eluent: Petro ether/Ethyl acetate = 10/1) yielded colorless oil **240d** (12.1 mg, 37% yield for 2 steps).[7]

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.02-8.00 (m, 1H, arom C*H*), 7.53-7.48 (m, 1H, arom C*H*), 7.34-7.26 (m, 2H, arom C*H*), 3.05-3.00 (m, 1H, *cis*-C*H*Ph), 2.87 (dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, *trans*-CH_2CO), 2.83-2.78 (m, 1H, *trans*-C*H*Ph), 2.56-2.55 (m, *2*H, *cis*-CH_2CO), 2.52-2.45 (m, 1H, *cis*-C*H*CH_2), 2.41 (dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, *trans*-CH_2CO), 2.19-2.09 (m, 1H, *trans*-C*H*CH_2), 1.42 (d, $^3J_{HH}$ = 7.0 Hz, 3H, *trans*-CH_3CHPh), 1.23 (d, $^3J_{HH}$ = 7.2 Hz, 3H, *cis*-CH_3CHPh), 1.10 (d, $^3J_{HH}$ = 6.8 Hz, 3H, *trans*-CH_3CHCH_2), 1.07 (d, $^3J_{HH}$ = 6.6 Hz, 3H, *cis*-CH_3CHCH_2).

3-methyl-4-phenylhexan-1-ol (**238e**)



238e

18.5 mg, yield = 96%, *syn/anti* = 1/1.2, from **93e** (19.2 mg, 0.1 mmol)

Yellow oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

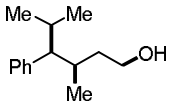
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.30-7.26 (m, 2H, arom C*H*), 7.20-7.17 (m, 1H, arom C*H*), 7.14-7.11 (m, 2H, arom C*H*), 3.75 (ddd, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 7.8, 5.3 Hz, 1H, *anti*-CH_2OH), 3.67-3.61 (m, 1H, CH_2OH), 3.54 (dt, $^2J_{HH}$ = 10.5, $^3J_{HH}$ = 7.4 Hz, 1H, *syn*-CH_2OH), 2.35 (ddd, $^3J_{HH}$ = 10.7, 6.4, 4.6 Hz, 1H, *anti*-C*H*Ph), 2.30-2.26 (m, 1H, *syn*-C*H*Ph), 1.89-1.54 (m, 5H, C$H_2$$CH_3$+C$H_2$CH+C*H*$CH_3$), 0.96 (d, $^3J_{HH}$ = 6.7 Hz, 3H, *syn*-CH_3CH), 0.77-0.70 (m, 9H, *anti*-CH_3CH+*anti*-C$H_3$$CH_2$ +*syn*-C$H_3$$CH_2$).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 144.1, 143.3, 128.8, 128.6, 128.0, 127.9, 125.8, 61.3, 61.2, 53.7, 53.1, 37.7, 37.5, 34.9, 34.4, 25.6, 25.0, 17.4, 16.6, 12.5, 12.3.

HRMS (+ESI) calculated for $C_{13}H_{24}NO$ $[M+NH_4]^+$: 210.1852, found 210.1821.

IR (neat): ν (cm^{-1}) = 3361, 2956, 2927, 2873, 1600, 1492, 1453, 1378, 1354, 1278, 1128, 1050, 1003, 762, 734, 700.

3,5-dimethyl-4-phenylhexan-1-ol (**238f**)



238f

17.8 mg, yield = 92%, *syn/anti* = 22/1, from **93f** (19.3 mg, 0.1 mmol)

Yellow oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.28-7.24 (m, 2H, arom C*H*), 7.21-7.17 (m, 1H, arom C*H*), 7.10-7.07 (m, 1H, arom C*H*), 3.72-3.51 (m, 2H, CH_2OH), 2.21-2.07 (m, 3H, C*H*Ph+C*H*CH_3+C*H*Me_2), 1.68-1.60 (m, 1H, CH_2CH), 1.15-1.06 (m, 1H,

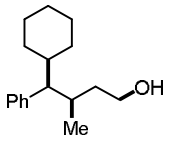
CH_2CH), 0.90 (d, $^3J_{HH}$ = 6.5 Hz, 3H, CH_3CHCH$_2$), 0.85 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CH_3CHCH$_3$), 0.75 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CH_3CHCH$_3$).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ(ppm) = 141.5, 129.8, 127.6, 125.9, 61.4, 58.6, 36.2, 30.5, 28.4, 21.7, 18.9, 18.3.

HRMS (+ESI) calculated for $C_{14}H_{22}ONa$ $[M+Na]^+$: 229.1563, found 229.1513.

IR (neat): ν (cm^{-1}) = 3340, 3028, 2958, 2929, 2872, 1602, 1493, 1453, 1354, 1277, 1162, 1127, 1053, 1004, 773, 749, 702.

4-cyclohexyl-3-methyl-4-phenylbutan-1-ol (**238g**)



238g

23.4 mg, yield = 94%, *syn/anti* = 30/1, from **93g** (25.0 mg, 0.1 mmol)

Yellow oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

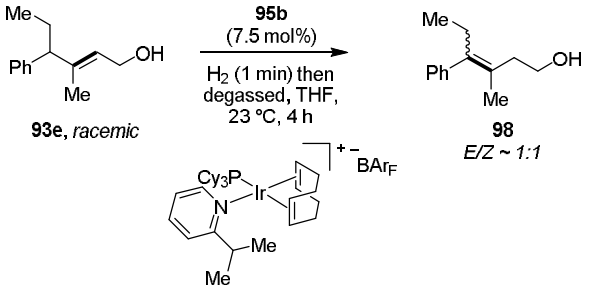
^{1}H NMR ($CDCl_3$, 400 MHz): δ(ppm) = 7.27-7.23 (m, 2H, arom C*H*), 7.20-7.16 (m, 1H, arom C*H*), 7.09-7.06 (m, 2H, arom C*H*), 3.75-3.51 (m, 2H, *C*H_2OH), 2.23 (t, $^3J_{HH}$ = 7.4 Hz, 1H, C*H*Ph), 2.16-2.10 (m, 1H, CH_2CH), 1.76-0.94 (m, 13H, CH_{Cy}+ CH_{2Cy}+C*H*CH$_3$+CH_2CH), 0.87 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3CH).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ(ppm) = 141.9, 129.7, 127.6, 125.8, 61.4, 58.0, 38.6, 36.0, 32.1, 29.6, 29.5, 26.7, 26.6, 26.6, 18.4.

HRMS (+ESI) calculated for $C_{17}H_{26}ONa$ $[M+Na]^+$: 269.1876, found 269.1874.

IR (neat): ν (cm^{-1}) = 3338, 2924, 2852, 1602, 1493, 1449, 1354, 1277, 1127, 1051, 9084, 773, 733, 702.

7.2.5 Representative procedure for the regioselective isomerization of primary allylic alcohol



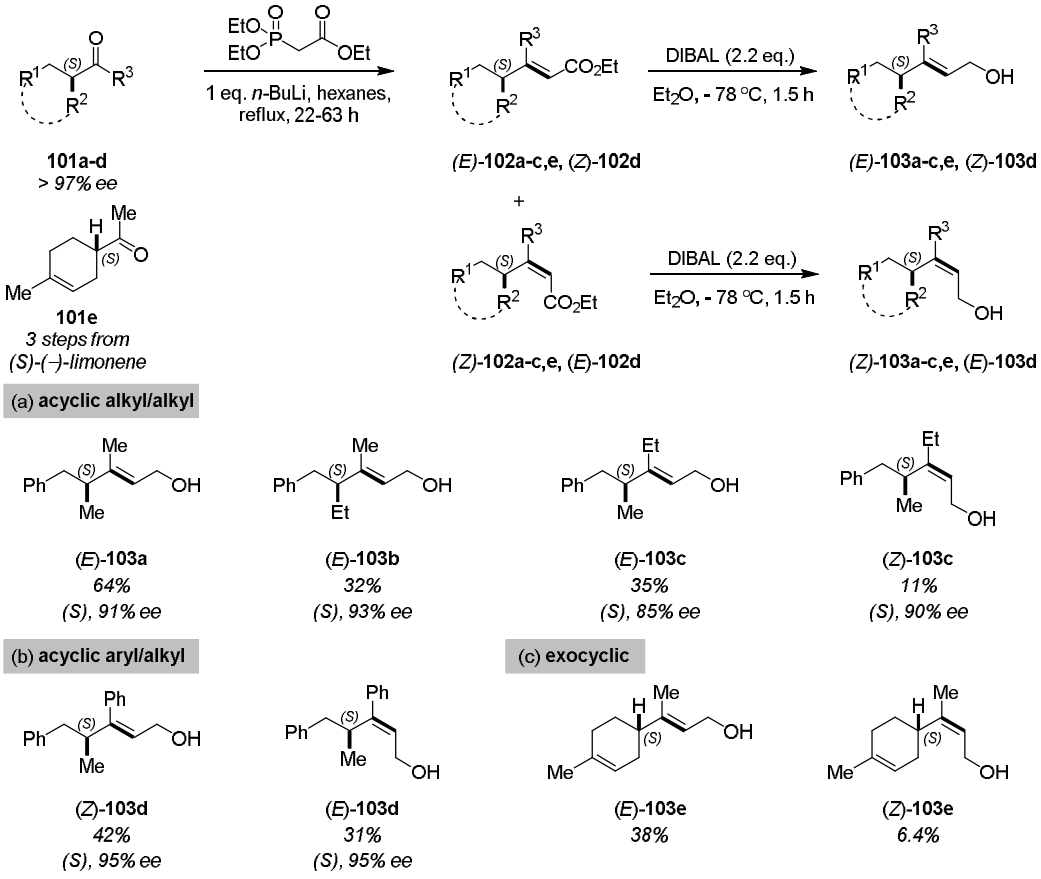
A 10 mL Schlenk containing catalyst **95b** (11.7 mg, 7.5 mol%,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed anhydrous THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution rapidly discolored. After 1 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, **93e** (19.0 mg, 0.1 mmol) was added by micro-syringe. The

rubber septum was replaced with a polyethylene stopper and the reaction was stirred at ambient temperature for 4 h**.** Then the reaction mixture was concentrated to give crude yellow oil, purification by flash chromatography (Eluent: Cyclohexane/Diethyl ether = 3/2) yielded colorless oil **98** (11 mg, 58% yield, *E/Z* ~ 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ(ppm) = 7.33-7.06 (m, 5H, arom C*H*), 3.77 (t, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2OH), 3.58 (t, $^3J_{HH}$ = 6.9 Hz, 2H, CH_2OH), 2.50 (t, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2CH$_2$OH), 2.43-2.33 (m, 2H, CH_2CH$_3$), 2.16 (t, $^3J_{HH}$ = 6.9 Hz, 2H, CH_2CH$_2$OH), 1.84 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 0.91-0.86 (m, 3H, CH_3CH$_2$).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ(ppm) = 143.4, 143.4, 140.7, 140.7, 129.1, 128.8, 128.0, 127.9, 126.3, 126.3, 126.2, 126.0, 126.0, 125.8, 61.1, 61.1, 53.7, 53.1, 38.6, 37.0, 27.9, 27.2, 20.1, 19.9, 17.3, 16.6, 13.3, 12.5.

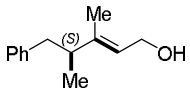
*7.2.6 General procedure for the synthesis of enantioenriched substrates **103a-e***



To a stirred solution of triethylphosphonoacetate (1.0 eq.) in anhydrous hexanes (concentration: 0.1 M) was added dropwise *n*-BuLi (1.6 M in hexanes, 0.95 eq.) at 0 °C.

After stirring for 0.5 h at 0 °C, the ketone (*S*)-**101** (1 eq.)[8] was added dropwise, and the reaction was refluxed for 22-63 h. The reaction mixture was then cooled to ambient temperature, quenched with a saturated aqueous Na_2CO_3 solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated, the crude mixture was purified by flash chromatography (Eluent: Pentane/Ethyl acetate = 20/1). Either (*Z*)- or (*E*)-enoate could be obtained pure as colorless oil, which was subsequently dissolved in anhydrous Et_2O (concentration: 0.1 M) and cooled down to -78 °C. Dibal-H (1.0 M in hexanes, 2.2 eq.) was added dropwise. The reaction mixture was stirred at -78 °C for 1.5 h, and then quenched by adding a saturated aqueous NH_4Cl solution at 0 °C. The resulting suspension was kept stirring at room temperature for another hour before extracting with Et_2O, The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification of crude oil by flash chromatography (Eluent: Pentane/Ethyl acetate = 4/1) yielded colorless oils. Configurations were assessed by 2D-NMR experiments. Racemic allylic alcohols were also synthesized using the same procedure started from racemic ketone.[8]

(S,E)-3,4-dimethyl-5-phenylpent-2-en-1-ol ((*E*)-**103a**)



(*E*)-**103a**

675 mg, yield = 64%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

HPLC: 91% *ee*, Chiral HPLC OJ-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 254 nm, Rt_1 = 21.55 (*R, minor*), Rt_2 = 23.66 (*S, major*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.28-7.24 (m, 2H, arom C*H*), 7.19-7.16 (m, 1H, arom C*H*), 7.14 -7.11 (m, 2H, arom C*H*), 5.35 (ddt, *J* = 6.8, 5.9, 1.1 Hz, 1H, C*H*CH_2OH), 4.10 (dd, *J* = 6.9, 1.4 Hz, 2H, C*H*$_2$OH), 2.74 (dd, *J* = 13.3, 6.7 Hz, 1H, C*H*$_2$Ph), 2.53 (dd, *J* = 13.4, 8.0 Hz, 1H, C*H*$_2$Ph), 2.42 (sext, *J* = 7.0 Hz, 1H, C*H*CH_3), 1.67 (d, *J* = 1.2 Hz, 3H, C*H*$_3$C), 1.14 (br, 1H, OH), 1.01 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 143.2 (arom *C*), 141.0 (*C*CH_3), 129.0 (arom *C*H), 128.1 (arom *C*H), 125.8 (arom *C*H), 123.2 (*C*HCH_2OH), 59.2 (*C*H_2OH), 44.4 (*C*HCH_3), 41.7 (*C*H_2Ph), 18.7 (*C*H_3CH), 13.4 (*C*H_3C).

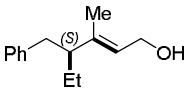
HRMS (+ESI) calculated for $C_{13}H_{18}ONa$ $[M+Na]^+$: 213.1249, found 213.1246.

IR (neat): ν (cm^{-1}) = 3324, 2961, 2928, 2869, 1664, 1601, 1494, 1453, 1376,995, 736, 697.

$[\alpha]^{22}_D$ = +24.9 (*c* 1.0, CH_2Cl_2)

[8] S. Lu, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 8920–8923.

(S,E)-4-benzyl-3-methylhex-2-en-1-ol ((*E*)-**103b**)



(*E*)-**103b**

224 mg, yield = 32%

Colorless oil (Petro ether/Ethyl acetate = 4/1, R_f = 0.20)

HPLC: 93% *ee*, Chiral HPLC OJ-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 254 nm, Rt_1 = 14.94 (*R, minor*), Rt_2 = 16.95 (*S, major*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.27-7.23 (m, 2H, arom C*H*), 7.18 -7.15 (m, 1H, arom C*H*), 7.12-7.10 (m, 2H, arom C*H*), 5.28 (ddd, *J* = 8.3, 6.2, 1.5 Hz, 1H, C*H*CH_2OH), 4.10-4.03 (m, 2H, CH_2OH), 2.65 (dd, *J* = 8.6, 7.6 Hz, 2H, CH_2Ph), 2.20 (dtd, *J* = 9.3, 7.5, 5.0 Hz, 1H, C*H*CH_2), 1.59 (d, *J* = 1.3 Hz, 3H, CH_3C), 1.46-1.39 (m, 2H, CH_2CH_3), 1.19-1.10 (m, 1H, OH), 0.81 (t, *J* = 7.4 Hz, 3H, CH_3CH_2).

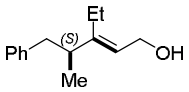
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 141.0 (arom *C*), 140.5 (*C*CH_3), 129.0 (arom *C*H), 128.0 (arom *C*H), 125.7 (arom *C*H), 125.6 (*C*HCH_2OH), 59.1 (*C*H_2OH), 52.4 (*C*HCH_2), 40.2 (*C*H_2Ph), 25.2 (*C*H_2CH_3), 12.4 (*C*H_3C), 12.0 (*C*H_3CH_2).

HRMS (+ESI) calculated for $C_{14}H_{20}ONa$ $[M+Na]^+$: 227.1406, found 227.1401.

IR (neat): ν (cm^{-1}) = 3350, 2958, 2928, 2873, 1664, 1601, 1494, 1454, 1379, 1074, 992, 732, 697.

$[\alpha]^{22}_D$ = +35.5 (*c* 1.0, CH_2Cl_2)

(S,E)-3-ethyl-4-methyl-5-phenylpent-2-en-1-ol ((*E*)-**103c**)



(*E*)-**103c**

300 mg, yield = 35%.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: 85% *ee*, Chiral HPLC OJ-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 205 nm, Rt_1 = 17.56 (*R, minor*), Rt_2 = 19.72 (*S, major*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.28-7.24 (m, 2H, arom C*H*), 7.19-7.12 (m, 3H, arom C*H*), 5.36 (t, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*CH_2OH), 4.16 (d, $^2J_{HH}$ = 6.9 Hz, 2H, CH_2OH), 2.79 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, CH_2Ph), 2.50 (dd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 8.6 Hz, 1H, CH_2Ph), 2.40 (dt, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.5 Hz, 1H, C*H*CH_3), 2.13-1.99 (m, 2H, CH_2CH_3), 1.25 (br, 1H, O*H*), 1.01-0.96 (m, 6H, CH_3CH+CH_3CH_2).

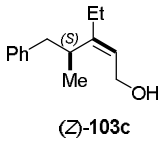
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 149.8 (*C*Et), 141.1 (arom *C*), 129.1 (arom *C*), 128.0 (arom *C*), 125.8 (arom *C*), 122.5 (*C*HCH_2OH), 59.2 (*C*H_2OH), 42.6 (*C*H_2Ph), 42.0 (*C*HMe), 23.0 (*C*H_2Me), 19.4 (*C*H_3CH), 14.6 (*C*H_3CH_2).

HRMS (+ESI) calculated for $C_{14}H_{20}ONa$ $[M+Na]^+$: 227.1406, found 227.1414.

IR (neat): ν (cm^{-1}) = 3316, 2964, 2929, 2872, 1660, 1601, 1492, 1453, 1373, 1002, 962, 732, 698.

$[\alpha]^{25}_D$ = +19.0 (*c* 1.0, $CHCl_3$).

(S,Z)-3-ethyl-4-methyl-5-phenylpent-2-en-1-ol ((*Z*)-**103c**)



(*Z*)-**103c**

100 mg, yield = 11%.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20)

HPLC: 90% *ee*, Chiral HPLC OJ-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 254 nm, Rt_1 = 14.11 (*R, minor*), Rt_2 = 14.50 (*S, major*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.29-7.26 (m, 2H, arom C*H*), 7.20-7.17 (m, 1H, arom C*H*), 7.12-7.10 (m, 2H, arom C*H*), 5.31 (tt, $^3J_{HH}$ = 7.1, 1.7 Hz, 1H, C*H*CH_2OH), 3.84 (d, $^3J_{HH}$ = 7.3 Hz, 2H, C*H*$_2$OH), 2.98 (dt, $^2J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 6.6 Hz, 1H, C*H*$_2$Ph), 2.67-2.58 (m, 2H, C*H*$_2$Ph+C*H*CH_3), 2.08 (q, $^3J_{HH}$ = 7.5 Hz, 2H, C*H*$_2CH_3$), 1.57 (s, 1H, O*H*), 1.09-1.05 (m, 6H, C*H*$_3$CH+C*H*$_3CH_2$).

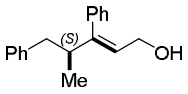
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 146.9 (*C*Et), 141.1 (arom *C*), 129.0 (arom *C*), 128.2 (arom *C*), 126.0 (arom *C*), 122.6 (*C*HCH_2OH), 58.5 (*C*H$_2$OH), 41.7 (*C*H$_2$Ph), 37.4 (*C*HMe), 22.8 (*C*H$_2$Me), 19.2 (*C*H$_3$CH), 12.6 (*C*H$_3CH_2$).

HRMS (+ESI) calculated for $C_{14}H_{20}O$ $[M]^+$: 204.1509, found 204.1512.

IR (neat): ν (cm^{-1}) = 3329, 2963, 2932, 2878, 1658, 1601, 1494, 1454, 1373, 1057, 1000, 751, 728, 698.

$[\alpha]^{25}_D$ = +2.1 (*c* 1.0, $CHCl_3$).

(S,Z)-4-methyl-3,5-diphenylpent-2-en-1-ol ((*Z*)-**103d**)



(*Z*)-**103d**

260 mg, yield = 42%.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: 95% *ee*, Chiral HPLC AD-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 205 nm, Rt_1 = 39.36 (*R, minor*), Rt_2 = 45.65 (*S, major*).

^{1}H NMR ($CDCl_3$, 500 MHz**)**: δ (ppm) = 7.36-7.32 (m, 2H, arom C*H*), 7.30-7.24 (m, 3H, arom C*H*), 7.20-7.16 (m, 1H, arom C*H*), 7.14-7.08 (m, 4H, arom C*H*), 5.70 (t, $^3J_{HH}$ = 6.7 Hz, 1H, C*H*CH_2OH), 3.97 (t, $^2J_{HH}$ = 5.4 Hz, 2H, C*H*$_2$OH), 2.88 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 5.4 Hz, 1H, C*H*$_2$Ph), 2.78-2.74 (m, 1H, C*H*CH_3), 2.42 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, C*H*$_2$Ph), 1.16-1.15 (m, 1H, O*H*), 1.02 (d, $^3J_{HH}$ = 6.8 Hz, 3H, C*H*$_3$CH).

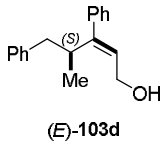
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz**)**: δ (ppm) = 149.1 (*C*Ph), 140.8 (arom *C*), 139.9 (arom *C*), 129.1 (arom *C*), 128.6 (arom *C*), 128.1 (arom *C*), 128.0 (arom *C*), 127.0 (arom *C*), 125.8 (arom *C*), 124.9 (*C*HCH_2OH), 60.4 (*C*H$_2$OH), 43.1 (*C*H$_2$Ph), 42.0 (*C*HMe), 18.9 (*C*H$_3$CH).

LRMS (ESI) calculated for $C_{18}H_{20}O$ $[M]^+$: 252.2, found $[M+NH_4]^+$: 270.3.

IR (neat): ν (cm^{-1}) = 3306, 2962, 2927, 2871, 1651, 1602, 1494, 1453, 1014, 975, 770, 748, 698.

$[\alpha]^{25}_D$ = +19.0 (*c* 1.0, $CHCl_3$).

(S,E)-4-methyl-3,5-diphenylpent-2-en-1-ol ((*E*)-**103d**)



(*E*)-**103d**

190 mg, yield = 31%.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: 95% *ee*, Chiral HPLC AD-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 205 nm, Rt_1 = 39.03 (*S, major*), Rt_2 = 48.93 (*R, minor*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.35-7.28 (m, 5H, arom C*H*), 7.24-7.17 (m, 5H, arom C*H*), 5.52 (t, $^3J_{HH}$ = 7.0 Hz, 1H, C*H*CH_2OH), 4.15-4.03 (m, 2H, CH_2OH), 3.22-3.15 (m, 1H, C*H*CH_3), 2.76 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, CH_2Ph), 2.64 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, CH_2Ph), 1.12 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3CH), 0.88-0.85 (m, 1H, O*H*).

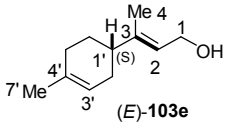
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 147.1 (*C*Ph), 142.2 (arom *C*), 140.8 (arom *C*), 129.2 (arom *C*), 129.2 (arom *C*), 128.5 (arom *C*), 128.3 (arom *C*), 127.7 (arom *C*), 126.8 (arom *C*), 126.1 (*C*HCH_2OH), 58.9 (*C*H_2OH), 42.1 (*C*H_2Ph), 37.4 (*C*HMe), 19.9 (*C*H_3CH).

LRMS (ESI) calculated for $C_{18}H_{20}O$ $[M]^+$: 252.2, found $[M+NH_4]^+$: 270.1.

IR (neat): ν (cm^{-1}) = 3311, 3026, 2964, 2929, 2872, 1601, 1492, 1453, 1374, 1006, 751, 725, 697.

$[\alpha]^{25}_D$ = +2.1 (*c* 1.0, $CHCl_3$).

(S,E)-3-(4-methylcyclohex-3-en-1-yl)but-2-en-1-ol ((*E*)-**103e**)



(*E*)-**103e**

1.06 g, yield = 38%.

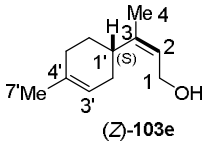
Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 5.45-5.42 (m, 1H, *H* at C2), 5.40-5.38 (m, 1H, *H* at C3'), 4.18 (d, $^3J_{HH}$ = 6.8 Hz, 2H, *H* at C1), 2.13-1.88 (m, 5H, *H* at C1', C2' and C5'), 1.77-1.73 (m, 1H, *H* at C6'), 1.66 (s, 3H, *H* at C4), 1.65 (s, 3H, *H* at C7'), 1.53-1.45 (m, 1H, *H* at C6'), 1.29-1.23 (m, 1H, O*H*).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 143.9 (*C*3), 133.8 (*C*4'), 122.0 (*C*2), 120.5 (*C*3'), 59.5 (*C*1), 42.7 (*C*1'), 30.6 (*C*2' + *C*5'), 27.7 (*C*6'), 23.4 (*C*7'), 14.5 (*C*4).

$[\alpha]^{20}_D$ = +80.1 (*c* 0.1, EtOH).

(S,Z)-3-(4-methylcyclohex-3-en-1-yl)but-2-en-1-ol ((*Z*)-**103e**)



(*Z*)-**103e**

176 mg, yield = 6.4%.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 5.41-5.38 (m, 2H, *H* at C2 + *H* at C3'), 4.20-4.12 (m, 2H, *H* at C1), 2.68-2.62 (m, 1H, *H* at C1'), 2.07-1.77 (m, 4H, *H* at C2' and C5'), 1.68 (s, 3H, *H* at C4), 1.65 (s, 3H, *H* at C7'), 1.62-1.57 (m, 2H, *H* at C6'), 1.16 (s, 1H, O*H*).

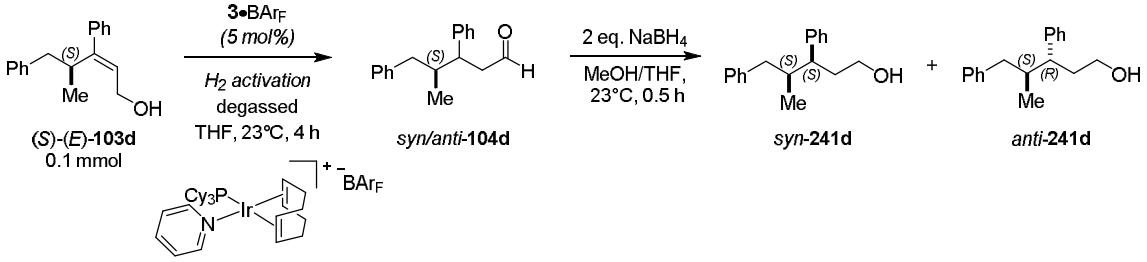
$^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ (ppm) = 144.2 (*C*3), 133.9 (*C*4'), 123.9 (*C*2), 120.6 (*C*3'), 58.5 (*C*1), 35.6 (*C*1'), 30.4 (*C*2'), 30.0 (*C*5'), 27.5 (*C*6'), 23.5 (*C*7'), 19.3 (*C*4).

$[\alpha]^{20}_D$ = -22.3 (*c* 0.1, EtOH).

Both (*E*)-**103e** and (*Z*)-**103e** are known compounds and all spectrocopic and spectrometric analyses are consitent with those reported in the literature.[9]

*7.2.7 Representative procedure for the isomerization of acyclic substrates **103a-d***

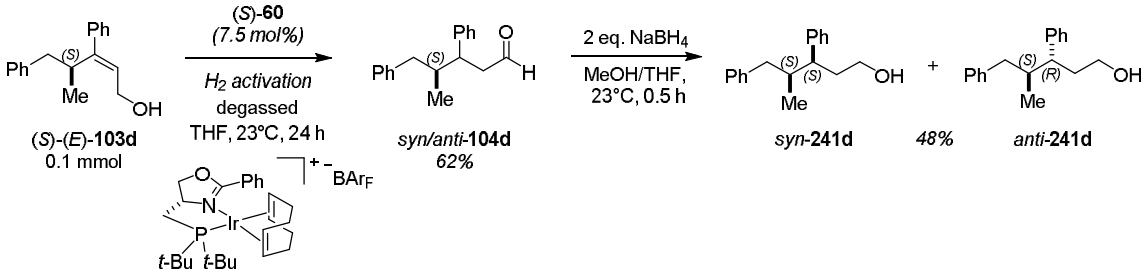
Representative Procedure A: *Crabtree (**3**•BAr$_F$) catalyzed isomerization*[10]



A 10 mL Schlenk containing Crabtree catalyst **3**•BAr$_F$ (7.6 mg, 5 mol%) was purged by three successive vacuum/nitrogen sequences and refilled with nitrogen. Degassed anhydrous tetrahydrofuran (1.5 mL) was added next and hydrogen gas was gently bubbled directly through the solution (2-3 bubbles per second) via a stainless-steel needle at room temperature. The orange solution rapidly discolored. After 1 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol (*S*)-(*E*)-**103d** (23.0 mg, 0.1 mmol) was added immediately to the cold solution by micro-syringe. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 4 h. After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. The aldehyde was then re-dissolved in 2 mL of anhydrous MeOH, cooled to 0^{o}C,, and $NaBH_4$ (7.7 mg, 2 eq.) was added in one portion. The resulting solution was kept at ambient temperature for 30 minutes. The reaction was stopped and quenched by adding a saturated aqueous NH_4Cl solution (3 mL), the water phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude yellow oil was dissolved in pentane, the resulting suspension was passed through a syringe filter and the filtrate was concentrated to give pure desired alcohols **241d** as inseparable mixture (23.0 mg, quant., *syn/anti* = 1/1).

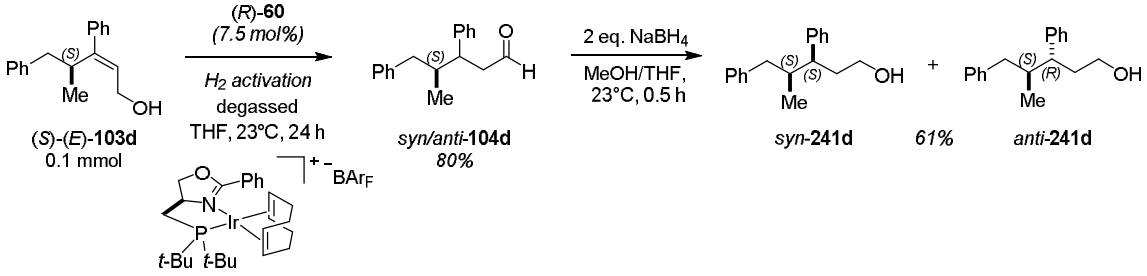
[9] V. J. Davisson, C. D. Poulter, *J. Am. Chem. Soc.* **1993**, *115*, 1245–1260.
[10] L. Mantilli, C. Mazet, *Tetrahedron Lett.* **2009**, *50*, 4141–4144.

Representative Procedure B: *(S)-**60**–catalyzed isomerization*



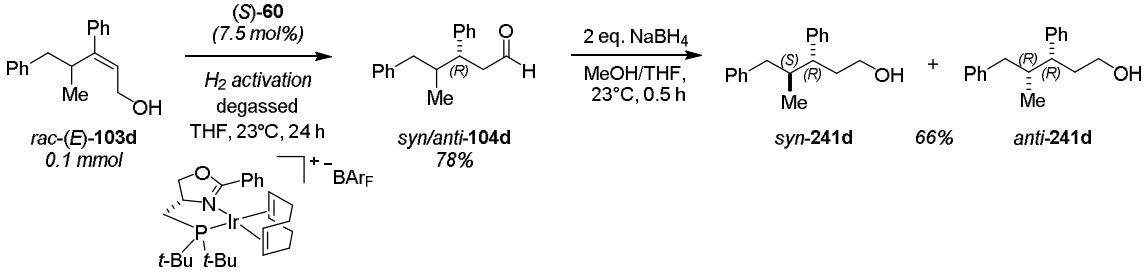
A 10 mL Schlenk containing (*S*)-**60** (11.0 mg, 7.5 mol %,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol (*S*)-(*E*)-**103d** (25.2 mg, 0.1 mmol) was added immediately to the cold solution by micro-syringe. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h**.** After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. Purification by flash chromatography (Eluent: Pentane/Ethyl acetate = 40/1) afforded desired aldehyde **104d** as colorless oil (15.7 mg, 62%). The unstable aldehyde **104d** was immediately dissolved in anhydrous MeOH (1.0 mL), then 7.7 mg of $NaBH_4$ was added at 0 ^{o}C. The resulted solution was kept at ambient temperature for another 30 minutes. The reaction was stopped and quenched by adding a saturated aqueous NH_4Cl solution (5 mL), the water phase was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude yellow oil was purified by flash chromatography (Eluent: Pentane/Ethyl acetate = 4/1) to give pure desired alcohols *anti*-**241d** (12.0 mg, 48%, *syn/anti* = 1/21).

Representative Procedure C: *(R)-**60**–catalyzed isomerization*



A 10 mL Schlenk containing (*R*)-**60** (11.0 mg, 7.5 mol %,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol (*S*)-(*E*)-**103d** (25.2 mg, 0.1 mmol) was added immediately to the cold solution by micro-syringe. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h**.** After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. Purification by flash chromatography (Eluent: Pentane/Ethyl acetate = 40/1) afforded desired aldehyde **104d** as colorless oil (20.1 mg, 80%). The unstable aldehyde **104d** was immediately dissolved in anhydrous MeOH (1.0 mL), then 7.7 mg of $NaBH_4$ was added at 0 ^{o}C. The resulted solution was kept at ambient temperature for another 30 minutes. The reaction was stopped and quenched by adding a saturated aqueous NH_4Cl solution (5 mL), the water phase was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude yellow oil was purified by flash chromatography (Eluent: Pentane/Ethyl acetate = 4/1) to give pure desired alcohols *syn*-**241d** (15.4 mg, 61%, *syn/anti* = 23/1).

Representative Procedure D: *(S)-**60**–catalyzed divergent reaction on a racemic mixture*

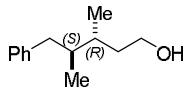


A 10 mL Schlenk containing (*S*)-**60** (11.0 mg, 7.5 mol %,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol *rac*-(*E*)-**103d** (25.2 mg, 0.1 mmol) was added immediately to the cold solution by micro-syringe. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h**.** After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. Purification by

flash chromatography (Eluent: Pentane/Ethyl acetate = 40/1) afforded desired aldehyde **104d** as colorless oil (19.6 mg, 78%). The unstable aldehyde **104d** was immediately dissolved in anhydrous MeOH (1.0 mL), then 7.7 mg of $NaBH_4$ was added at 0 °C. The resulted solution was kept at ambient temperature for another 30 minutes. The reaction was stopped and quenched by adding a saturated aqueous NH_4Cl solution (5 mL), the water phase was extracted with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude yellow oil was purified by flash chromatography (Eluent: Pentane/Ethyl acetate = 4/1) to give pure desired alcohols **241d** (16.5 mg, 66%, *syn/anti* = 1.1/1).

*Note: The relative configurations of **104/241** were assigned by analogy to the previous racemic products **97/238** based on the NMR spectroscopy.*

(3R,4S)-3,4-dimethyl-5-phenylpentan-1-ol (*anti*-**241a**)



anti-**241a**

Following procedure B using (*S*)-(*E*)-**103a**, 11.4 mg, yield = 60%, *syn/anti* = 1/12.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: 99.2% *ee*, Chiral HPLC OJ-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 254 nm, Rt_1 = 24.35 ((3*S*,4*R*)*, minor*), Rt_2 = 25.06 ((3*R*,4*S*)*, major*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.28-7.24 (m, 2H, arom C*H*), 7.18-7.13 (m, 3H, arom C*H*), 3.75-3.72 (m, 1H, CH_2OH), 3.67-3.62 (m, 1H, CH_2OH), 2.70 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 5.2 Hz, 1H, CH_2Ph), 2.29 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 9.5 Hz, 1H, CH_2Ph), 1.78-1.71 (m, 2H, C*H*Bn+ CH_2CH_2OH), 1.61-1.59 (m, 1H, C*H*Me), 1.43-1.37 (m, 1H, CH_2CH_2OH), 1.32-1.27 (br, 1H, O*H*), 0.92 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3CHCH_2CH_2OH), 0.80 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3CHBn).

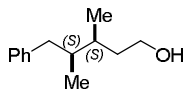
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 141.8 (arom *C*), 129.1 (arom *C*), 128.1 (arom *C*), 125.6 (arom *C*), 61.7 (*C*H_2OH), 40.2 (*C*HBn), 39.6 (*C*H_2Ph), 35.7 (*C*H_2CH_2OH), 33.5 (*C*HMe), 16.7 (*C*H_3CHCH_2CH_2OH), 15.7 (*C*H_3CHBn).

HRMS (+ESI) calculated for $C_{13}H_{20}O$ $[M]^+$: 192.1509, found 192.1511.

IR (neat): ν (cm^{-1}) = 3331, 2957, 2931, 2872, 1601, 1492, 1453, 1379, 1052, 734, 698.

$[\alpha]^{25}_D$ = +3.9 (*c* 1.0, $CHCl_3$).

(3S,4S)-3,4-dimethyl-5-phenylpentan-1-ol (*syn*-**241a**)



syn-**241a**

Following procedure C using (*S*)-(*E*)-**103a**, 7.9 mg, yield = 42%, *syn/anti* = 5.4/1.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: 99.3% *ee*, Chiral HPLC OJ-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 254 nm, Rt_1 = 23.14 ((3*R*,4*R*)*, minor*), Rt_2 = 27.31 ((3*S*,4*S*)*, major*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.29-7.26 (m, 2H, arom C*H*), 7.19-7.14 (m, 3H, arom C*H*), 3.68-3.61 (m, 2H, CH_2OH), 2.66 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, CH_2Ph), 2.40 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.8 Hz, 1H, CH_2Ph), 1.78-1.76 (m, 1H, C*H*Bn), 1.64-1.62 (m, 1H, C*H*Me+ CH_2CH$_2$OH), 1.46-1.44 (m, 1H, CH_2CH$_2$OH), 1.30-1.26 (br, 1H, O*H*), 0.89 (d, $^3J_{HH}$ = 6.7 Hz, 3H, CH_3CHCH$_2$CH$_2$OH), 0.78 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3CHBn).

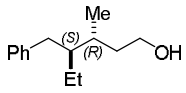
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 141.7 (arom *C*), 129.0 (arom *C*), 128.2 (arom *C*), 125.6 (arom *C*), 61.4 (*C*H_2OH), 41.1 (*C*H_2Ph), 39.2 (*C*HBn), 37.9 (*C*H_2CH$_2$OH), 32.7 (*C*HMe), 14.3 (*C*H_3CHCH$_2$CH$_2$OH), 14.0 (*C*H_3CHBn).

HRMS (+ESI) calculated for $C_{13}H_{18}$ $[M\text{-}H_2O]^+$: 174.1403, found 174.1404.

IR (neat): ν (cm^{-1}) = 3318, 2957, 2926, 2872, 1601, 1494, 1454, 1380, 1112, 1053, 733, 698.

$[\alpha]^{25}_D$ = +1.8 (*c* 1.0, $CHCl_3$).

(3*R*,4*S*)-4-benzyl-3-methylhexan-1-ol (*anti*-**241b**)



anti-**241b**

Following procedure B using (*S*)-(*E*)-**103b**, 4.4 mg, yield = 22%, *syn/anti* = 1/10.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: >99.9% *ee*, Chiral HPLC OD-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 205 nm, Rt_1 = 23.98 ((3*R*,4*S*)).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.28-7.25 (m, 2H, arom C*H*), 7.19-7.14 (m, 3H, arom C*H*), 3.76-3.63 (m, 2H, CH_2OH), 2.62 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, CH_2Ph), 2.39 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, CH_2Ph), 1.78-1.69 (m, 2H, C*H*Me+CH_2CH$_2$OH), 1.51-1.45 (m, 2H, C*H*Et+CH_2CH$_2$OH), 1.34-1.22 (m, 3H, CH_2Me+O*H*), 0.87 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3CH), 0.85 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3CH$_2$).

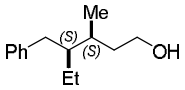
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 142.1 (arom *C*), 129.1 (arom *C*), 128.2 (arom *C*), 125.6 (arom *C*), 61.7 (*C*H_2OH), 46.8 (*C*HEt), 36.9 (*C*H_2CH$_2$OH), 36.3 (*C*H_2Ph), 29.7 (*C*HMe), 22.9 (*C*H_2Me), 15.5 (*C*H_3CH), 12.2 (*C*H_3CH$_2$).

HRMS (+ESI) calculated for $C_{14}H_{22}O$ $[M]^+$: 206.1665, found 206.1662.

IR (neat): ν (cm^{-1}) = 3335, 2957, 2929, 2872, 1601, 1492, 1455, 1381, 1054, 1031, 1005, 730, 698.

$[\alpha]^{25}_D$ = +5.1 (*c* 1.0, $CHCl_3$).

(3*S*,4*S*)-4-benzyl-3-methylhexan-1-ol (*syn*-**241b**)



syn-**241b**

Following procedure C using (*S*)-(*E*)-**103b**, 5.1 mg, yield = 25%, *syn/anti* = 13/1.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: 96.0% *ee*, Chiral HPLC OD-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 205 nm, Rt_1 = 25.33 ((3*S*,4*S*)*, major*), Rt_2 = 32.64 ((3*R*,4*R*)*, minor*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.28-7.25 (m, 2H, arom C*H*), 7.19-7.15 (m, 3H, arom C*H*), 3.66-3.54 (m, 2H, CH_2OH), 2.54 (dd, $^3J_{HH}$ = 7.2, 5.6 Hz, 2H, CH_2Ph), 1.67-1.58 (m, 2H, C*H*Me+CH_2CH$_2$OH), 1.52-1.48 (m, 1H, C*H*Et), 1.42-1.26 (m, 3H, CH_2CH$_2$OH+CH_2Me+O*H*), 1.26-1.15 (m, 1H, CH_2Me), 0.91-0.88 (m, 6H, CH_3CH+CH_3CH$_2$).

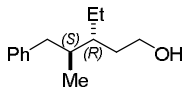
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 142.0 (arom *C*), 129.0 (arom *C*), 128.2 (arom *C*), 125.6 (arom *C*), 61.6 (*C*H$_2$OH), 46.6 (*C*HEt), 37.1 (*C*H$_2$Ph), 36.7 (*C*H$_2$CH$_2$OH), 29.8 (*C*HMe), 22.1 (*C*H$_2$Me), 15.6 (*C*H$_3$CH), 12.4 (*C*H$_3$CH$_2$).

HRMS (+ESI) calculated for $C_{14}H_{20}$ $[M\text{-}H_2O]^+$: 188.1560, found 188.1557.

IR (neat): ν (cm^{-1}) = 3347, 2957, 2931, 2876, 1601, 1492, 1455, 1379, 1055, 1031, 1005, 730, 697.

$[\alpha]^{25}_D$ = +11.3 (*c* 1.0, $CHCl_3$).

(3R,4S)-3-ethyl-4-methyl-5-phenylpentan-1-ol (*anti*-**241c**)



anti-**241c**

Following procedure C using (*S*)-(*Z*)-**103c**, 11.4 mg, yield = 58%, *syn/anti* = 1/12.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: 99.2% *ee*, Chiral HPLC OD-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 205 nm, Rt_1 = 38.85 ((3*R*,4*S*)*, major*), Rt_2 = 43.18 ((3*S*,4*R*)*, minor*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.29-7.26 (m, 2H, arom C*H*), 7.19-7.14 (m, 3H, arom C*H*), 3.74-3.62 (m, 2H, CH_2OH), 2.66 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, CH_2Ph), 2.39 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 9.1 Hz, 1H, CH_2Ph), 1.95-1.90 (m, 1H, C*H*Me), 1.75-1.68 (m, 1H, CH_2CH$_2$OH), 1.46-1.25 (m, 3H, C*H*Et+CH_2CH$_2$OH +O*H*), 0.87 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3CH$_2$), 0.78 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3CH).

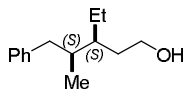
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 141.8 (arom *C*), 129.0 (arom *C*), 128.2 (arom *C*), 125.6 (arom *C*), 62.0 (*C*H$_2$OH), 40.6 (*C*H$_2$Ph), 40.1 (*C*HEt), 36.2 (*C*HMe), 33.0 (*C*H$_2$CH$_2$OH), 24.2 (*C*H$_2$Me), 14.7 (*C*H$_3$CH), 12.2 (*C*H$_3$CH$_2$).

HRMS (+ESI) calculated for $C_{14}H_{22}ONa$ $[M+Na]^+$: 229.1562, found 229.1557.

IR (neat): ν (cm^{-1}) = 3306, 2959, 2929, 2872, 1601, 1494, 1454, 1379, 1053, 1017, 732, 698.

$[\alpha]^{25}_D$ = +17.5 (*c* 1.0, $CHCl_3$).

(3S,4S)-3-ethyl-4-methyl-5-phenylpentan-1-ol (*syn*-**241c**)



syn-**241c**

Following procedure B using (*S*)-(*Z*)-**103c**, 11 mg, yield = 54%, *syn/anti* = 5.7/1.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: > 99.9% *ee*, Chiral HPLC OD-H, *n*-hexane: *i*-PrOH = 99:1, 1 mL/min, $\lambda 1$ = 205 nm, Rt_1 = 29.15 ((3*S*,4*S*)).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.29-7.26 (m, 2H, arom C*H*), 7.19-7.13 (m, 3H, arom C*H*), 3.64 (t, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2OH), 2.68 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, CH_2Ph), 2.34 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 9.2 Hz, 1H, CH_2Ph), 1.88-1.85 (m, 1H, C*H*Me), 1.66-1.43 (m, 3H, CH_2CH$_2$OH+ CH_2Me), 1.41-1.16 (m, 3H, C*H*Et+CH_2Me+O*H*), 0.93 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3CH$_2$), 0.80 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3CH).

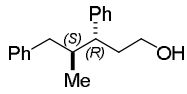
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 141.9 (arom *C*), 129.0 (arom *C*), 128.2 (arom *C*), 125.6 (arom *C*), 61.8 (*C*H$_2$OH), 40.3 (*C*HEt), 40.1 (*C*H$_2$Ph), 36.9 (*C*HMe), 34.0 (*C*H$_2$CH$_2$OH), 22.7 (*C*H$_2$Me), 15.4 (*C*H$_3$CH), 12.3 (*C*H$_3$CH$_2$).

HRMS (+ESI) calculated for $C_{14}H_{22}ONa$ $[M+Na]^+$: 229.1562, found 229.1566.

IR (neat): ν (cm^{-1}) = 3318, 2958, 2929, 2872, 1601, 1494, 1454, 1379, 1053, 1015, 732, 698.

$[\alpha]^{25}_D$ = -1.7 (*c* 1.0, $CHCl_3$).

(3R,4S)-4-methyl-3,5-diphenylpentan-1-ol (*anti*-**241d**)



anti-**241d**

Following procedure B using (*S*)-(*Z*)-**103d**, 12.0 mg, yield = 48%, *syn/anti* = 1/21.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: > 99% *ee*, Chiral HPLC AS-H, *n*-hexane: *i*-PrOH = 99.5:0.5, 1 mL/min, $\lambda 1$ = 195 nm, Rt = 61.11 (3*R*,4*S*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.33-7.25 (m, 4H, arom C*H*), 7.24-7.21 (m, 1H, arom C*H*), 7.20-7.16 (m, 3H, arom C*H*), 7.14-7.12 (m, 2H, arom C*H*), 3.54 (ddd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, CH_2OH), 3.45 (ddd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, CH_2OH), 2.90 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 4.6 Hz, 1H, CH_2Ph), 2.71 (ddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 4.2 Hz, 1H, C*H*Ph), 2.21-2.11 (m, 2H, CH_2Ph + CH_2CH$_2$OH), 2.06-1.97 (m, 2H, C*H*Me+ CH_2CH$_2$OH), 1.29 (s, 1H, O*H*), 0.69 (d, $^3J_{HH}$ = 6.7 Hz, 3H, CH_3CHBn).

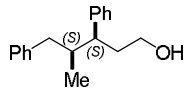
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 142.6 (arom *C*), 141.3 (arom *C*), 129.1 (arom *C*), 128.8 (arom *C*), 128.2 (arom *C*), 126.3 (arom *C*), 125.7 (arom *C*), 61.5 (*C*H$_2$OH), 47.4 (*C*HPh), 41.3 (*C*H$_2$Ph), 40.3 (*C*HMe), 36.1 (*C*H$_2$CH$_2$OH), 16.3 (*C*H$_3$CHBn).

LRMS (ESI) calculated for $C_{18}H_{22}O$ $[M]^+$: 254.2, found $[M+NH_4]^+$: 272.8.

IR (neat): ν (cm^{-1}) = 3329, 3026, 2960, 2929, 2876, 1602, 1494, 1453, 1378, 1041, 1029, 909, 767, 734, 698.

$[\alpha]^{25}_D$ = +3.9 (*c* 1.0, $CHCl_3$).

(3S,4S)-4-methyl-3,5-diphenylpentan-1-ol (*syn*-**241d**)



syn-**241d**

Following procedure C using (*S*)-(*Z*)-**103d**, 15.4 mg, yield = 61%, *syn/anti* = 23/1.

Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

HPLC: > 99% *ee*, Chiral HPLC AS-H, *n*-hexane: *i*-PrOH = 99.5:0.5, 1 mL/min, $\lambda 1$ = 210 nm, Rt = 42.82 (3*S*,4*S*).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.34-7.31 (m, 2H, arom C*H*), 7.26-7.20 (m, 5H, arom C*H*), 7.17-7.14 (m, 1H, arom C*H*), 7.06-7.04 (m, 2H, arom C*H*), 3.51 (ddd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, CH_2OH), 3.41 (dt, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, CH_2OH), 2.68 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 4.0 Hz, 1H, CH_2Ph), 2.60 (ddd, $^3J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, C*H*Ph), 2.17-2.07 (m, 2H, CH_2Ph + CH_2CH_2OH), 1.98 (dtq, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 3.3 Hz, $^3J_{HH}$ = 2.7 Hz, 1H, C*H*Me), 1.90 (dddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, CH_2CH_2OH), 1.14 (s, 1H, O*H*), 0.89 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3CHBn).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 143.7 (arom *C*), 141.5 (arom *C*), 129.0 (arom *C*), 128.4 (arom *C*), 128.4 (arom *C*), 128.1 (arom *C*), 126.3 (arom *C*), 125.6 (arom *C*), 61.6 (*C*H_2OH), 47.9 (*C*HPh), 41.1 (*C*HMe), 41.0 (*C*H_2Ph), 35.0 (*C*H_2CH_2OH), 16.7 (*C*H_3CHBn).

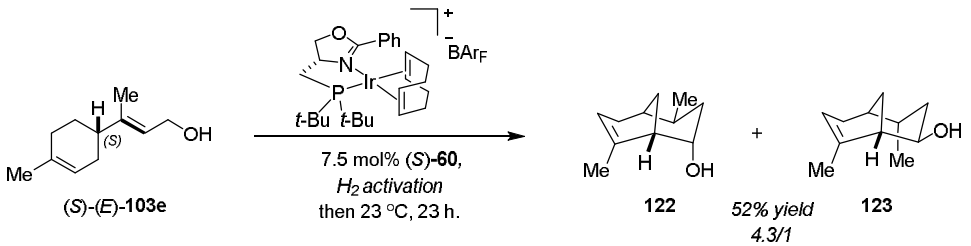
LRMS (ESI) calculated for $C_{18}H_{22}O$ $[M]^+$: 254.2, found $[M+NH_4]^+$: 272.5.

IR (neat): ν (cm^{-1}) = 3285, 3027, 2960, 2924, 2858, 1734, 1601, 1493, 1452, 1374, 1029, 768, 748, 736, 698.

$[\alpha]^{25}_D$ = +1.8 (*c* 1.0, $CHCl_3$).

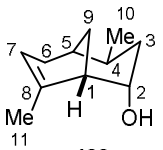
*7.2.8 Isomerization of exocyclic substrates **103d***

Procedure A: *(S)-**60**–catalyzed tandem isomerization/intramolecular carbonyl-ene reaction*



A 10 mL Schlenk containing (*S*)-**60** (11.0 mg, 7.5 mol %,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol (*S*)-(*E*)-**103e** (16.6 mg, 0.1 mmol) was added immediately to the cold solution by micro-syringe. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h**.** After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. Purification by flash chromatography (Eluent: Pentane/Ethyl acetate = 6/1) afforded alcohols **122** and **123** as inseparable mixture (8.6 mg, 52%, **122**/**123** = 4.3/1).

(1S,2S,4S,5S)-4,8-dimethylbicyclo[3.3.1]non-7-en-2-ol (**122**)



122

8.5 mg, yield = 52%.

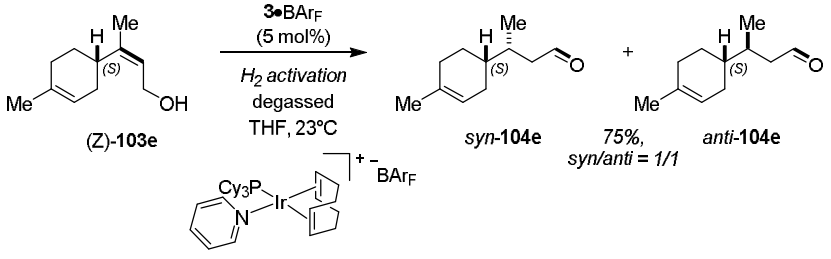
Colorless oil (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 5.58-5.55 (m, 1H, H_7), 3.88-3.84 (m, 1H, H_2), 2.35-2.32 (m, 1H, H_1), 2.04-1.94 (m, 2H, H_6), 1.79 (d, $^4J_{HH}$ = 1.8 Hz, 3H, Me_{11}), 1.75 (dt, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.4 Hz, 1H, H_9), 1.50 (dt, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 2.7 Hz, 1H, H_9),1.69-1.55 (m, 4H, H_3 + H_4 + H_5), 0.92 (d, $^2J_{HH}$ = 6.5 Hz, 3H, Me_{10}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 134.2 (C_8), 124.3 (C_7), 74.6 (C_2), 40.9 (C_1), 36.5 (C_3), 35.6 (C_5), 31.9 (C_9), 31.1 (C_4), 25.7 (C_{11}), 25.4 (C_6), 19.5 (C_{10}).

122 is a known compound and all spectrocopic and spectrometric analyses are consitent with those reported in the literature.[11]

Procedure B: *Crabtree (**3**•BAr$_F$) catalyzed isomerization*

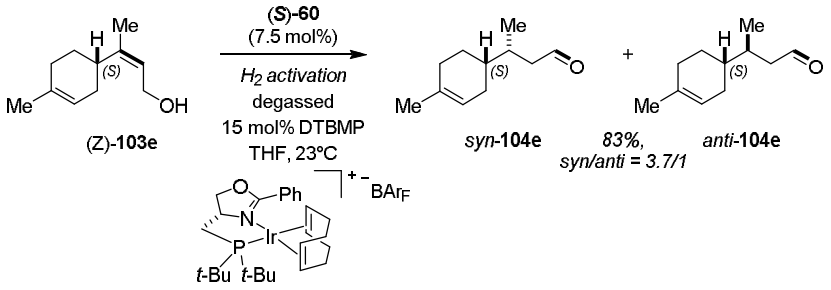


A 10 mL Schlenk containing Crabtree catalyst **3**•BAr$_F$ (7.6 mg, 5 mol%) was purged by three successive vacuum/nitrogen sequences and refilled with nitrogen. Degassed

[11] (a) A. de O. Dias, R. Augusti, E. N. dos Santos, E. V. Gusevskaya, *Tetrahedron Lett.* **1997**, *38*, 41–44; (b) C. G. Vieira, M. C. de Freitas, E. N. dos Santos, E. V. Gusevskaya, *ChemCatChem* **2012**, *4*, 795–801.

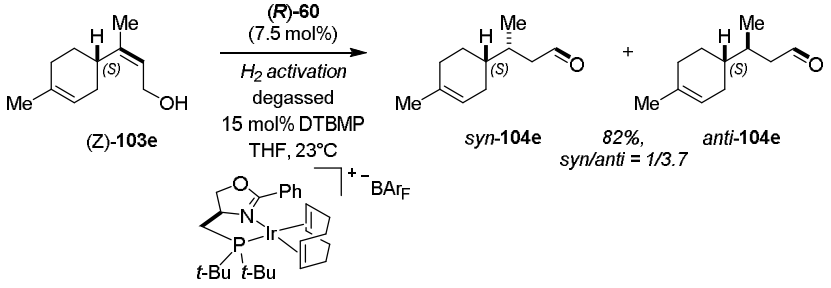
anhydrous tetrahydrofuran (1.5 mL) was added next and hydrogen gas was gently bubbled directly through the solution (2-3 bubbles per second) via a stainless-steel needle at room temperature. The orange solution rapidly discolored. After 1 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol (*S*)-(*E*)-**103e** (16.6 mg, 0.1 mmol) was added immediately to the cold solution by micro-syringe. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 4 h. After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. The crude yellow oil was dissolved in pentane, the resulting suspension was passed through a syringe filter and the filtrate was concentrated to give pure desired alcohols **104e** as inseparable mixture (12.5 mg, 75%, *syn/anti* = 1/1).

Procedure C: *(S)-**60**–catalyzed isomerization in the presence of DTBMP*



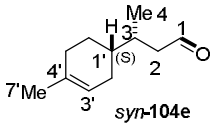
A 10 mL Schlenk containing (*S*)-**60** (11.0 mg, 7.5 mol %,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol (*S*)-(*Z*)-**103e** (16.6 mg, 0.1 mmol) and 2,6-di*t*-butyl-4-methylpyridine (3.1 mg, 15 mol%) were added immediately to the cold solution. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h**.** After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. The crude yellow oil was dissolved in pentane, the resulting suspension was passed through a syringe filter and the filtrate was concentrated to give pure desired aldehyde *syn*-**104e** as colorless oil (16.9 mg, 83%, *syn/anti* = 3.7/1).

Procedure D: *(R)-**60**–catalyzed isomerization in the presence of DTBMP*



A 10 mL Schlenk containing (*R*)-**60** (11.0 mg, 7.5 mol %,) was purged by three successive vacuum/N_2 sequences and refilled with N_2. Degassed THF (1.5 mL) was added next and H_2 gas was gently bubbled directly through the solution via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol (*S*)-(*Z*)-**103e** (16.6 mg, 0.1 mmol) and 2,6-di*t*-butyl-4-methylpyridine (3.1 mg, 15 mol%) were added immediately to the cold solution. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h**.** After evaporation of the volatiles, the *syn/anti* selectivity was accessed by ^{1}H NMR. The crude yellow oil was dissolved in pentane, the resulting suspension was passed through a syringe filter and the filtrate was concentrated to give pure desired aldehyde *syn*-**104e** as colorless oil (16.8 mg, 82%, *syn/anti* = 3.7/1).

(R)-3-((S)-4-methylcyclohex-3-en-1-yl)butanal (*syn*-**104e**)



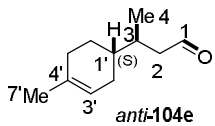
syn-**104e**

16.9 mg, yield = 83%.

Colorless oil (Pentane/Ethyl acetate = 10/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.76 (dd, $^3J_{HH}$ = 3.0, 1.8 Hz, 1H, C*H*O$_1$), 5.37-5.34 (m, 1H, $H_{3'}$), 2.52-2.45 (m, 1H, H_2), 2.30-2.18 (m, 1H, H_2), 1.64 (s, 3H, $Me_{7'}$), 2.10-1.20 (m, 8H), 0.95 (d, $^2J_{HH}$ = 6.9 Hz, 3H, Me_4).

(S)-3-((S)-4-methylcyclohex-3-en-1-yl)butanal (*anti*-**104e**)



anti-**104e**

16.8 mg, yield = 82%.

Colorless oil (Pentane/Ethyl acetate = 10/1, R_f = 0.20).

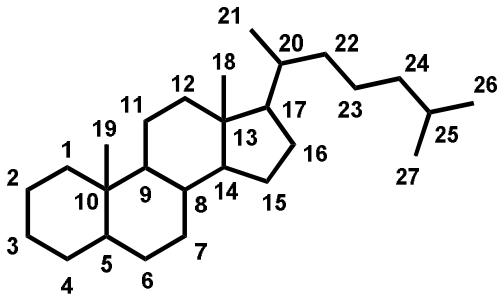
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.77 (dd, $^3J_{HH}$ = 3.0, 1.8 Hz, 1H, C*H*O$_1$), 5.39-5.35 (m, 1H, $H_{3'}$), 2.53-2.46 (m, 1H, H_2), 2.30-2.18 (m, 1H, H_2), 1.64 (s, 3H, $Me_{7'}$), 2.10-1.20 (m, 8H), 0.94 (d, $^2J_{HH}$ = 6.9 Hz, 3H, Me_4).

Both *syn*- and *anti*-**104e** are known compounds and all spectrocopic and spectrometric analyses are consitent with those reported in the literature.[12]

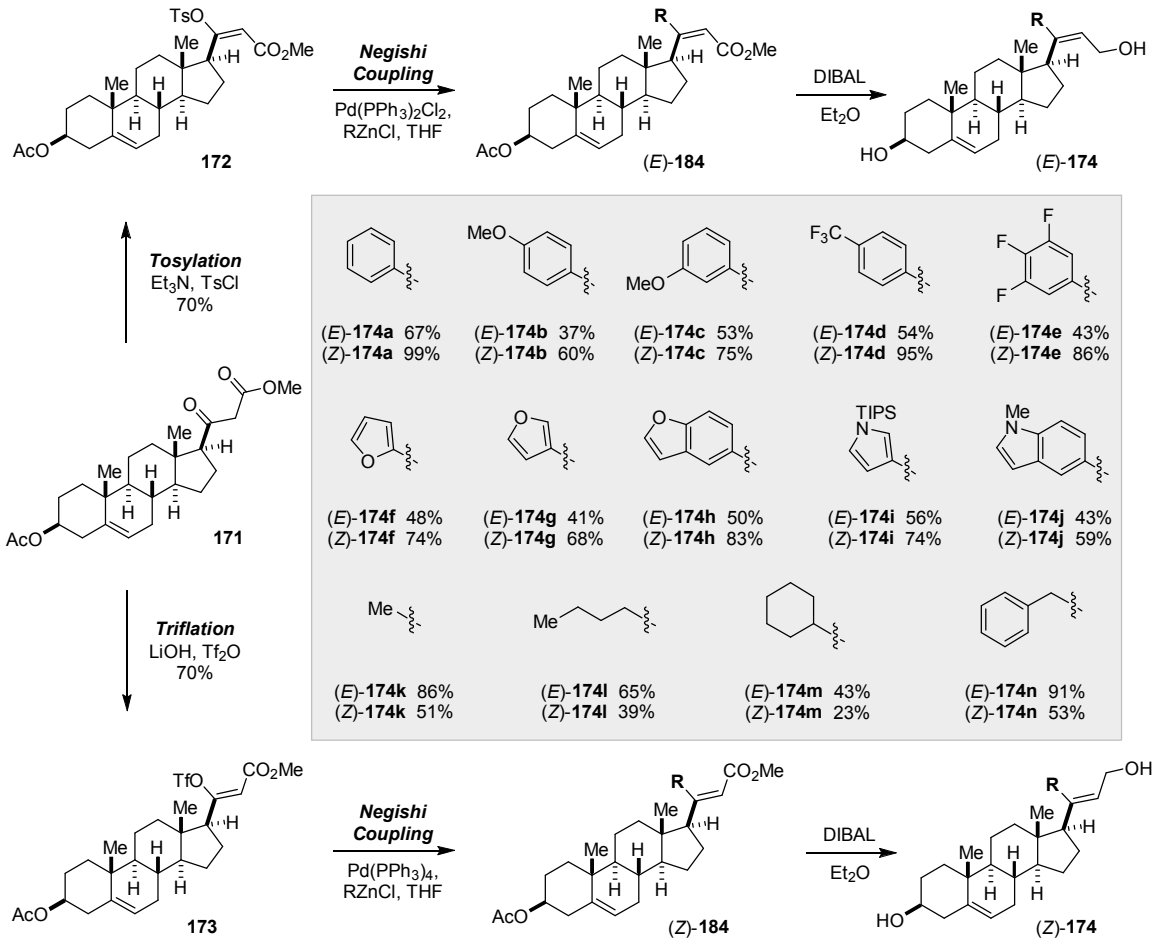
[12] (a) L. Kollár, J. Bakos, B. Heil, P. Sándor, G. Szalontai, *J. Organmet. Chem.* **1990**, *385*, 147−152; (b) C. Fuganti, S. Serra, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 97−101.

7.3 Stereoselective Construction of C20 in Steroid Side Chain and Topological Diversification

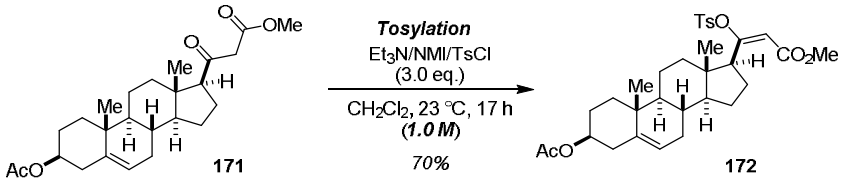
Nomenclature of steroid skeleton:



*7.3.1. General procedures for the syntheses of (E) and (Z)-steroidal allylic alcohols **174***



*7.3.1.1. Stereoselective synthesis of (E)-enol tosylate (**172**)*[13]



To a solution of **171** (2.0 g, 4.8 mmol)[14] in dichloromethane (4.8 mL, 1.0 M) were successively added *N*-methylimidazole (1.1 mL, 14.4 mmol), triethylamine (2.0 mL, 14.4 mmol) and *p*-toluenesulfonyl chloride (2.8 g, 14.4 mmol) at 0 °C. The mixture was stirred at 23 °C for 17 h. Next, 1 M HCl (15 mL) was added at 0 °C, the resulting mixture was extracted twice with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 6:1) gave the desired (*E*)-enol tosylate (**172**) (1.9 g, 70%).

White solid, m.p. = 67–70 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.35).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.82 (d, $^3J_{HH}$ = 8.4 Hz, 2H, $H_{ortho\text{-}Ph}$), 7.17-7.14 (d, $^3J_{HH}$ = 8.4 Hz, 2H, $H_{meta\text{-}Ph}$), 6.08 (s, 1H, H_{22}), 5.38-5.34 (m, 1H, H_6), 4.60-4.58 (m, 1H, H_3), 3.75 (t, $^3J_{HH}$ = 9.4 Hz, 1H, H_{17}), 3.68 (s, 3H, O*Me*), 2.47 (s, 3H, *Me*Ph), 2.35-2.25 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.99-1.92 (m, 1H, H_7), 1.88-1.75 (m, 3H, H_2+H_{12}+H_{16}), 1.71-1.50 (m, 6H, H_1+H_2+H_8+H_{11}+H_{15}+H_{16}), 1.46-1.30 (m, 3H, H_1+H_8+H_{11}), 1.28-1.06 (m, 3H, H_{12}+H_{14}+H_{15}), 1.02-0.93 (m, 4H, H_9+Me_{19}), 0.67 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 166.1 (*C*O_2Me), 165.6 (C_{20}), 145.6 ($C_{Ph}SO_2$), 139.7 (C_5), 133.4 (C_{Ph}Me), 130.0 ($C_{meta\text{-}Ph}$), 128.1 ($C_{ortho\text{-}Ph}$), 122.3 (C_6H), 108.2 (C_{22}H), 73.8 (C_3H), 55.8 (C_{14}H), 51.4 (*Me*O), 50.0 (C_9H), 49.6 (C_{17}H), 47.0 (C_{13}), 38.1 (C_4H_2), 36.9 ($C_{12}H_2$), 36.7 (C_1H_2), 36.6 (C_{10}), 31.8 (C_8H), 31.8 (C_7H_2), 27.7(C_2H_2), 24.6 ($C_{15}H_2$), 23.5 ($C_{16}H_2$), 21.7 (*Me*Ph), 21.4 (*Me*CO), 20.6 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 13.6 ($C_{18}H_3$).

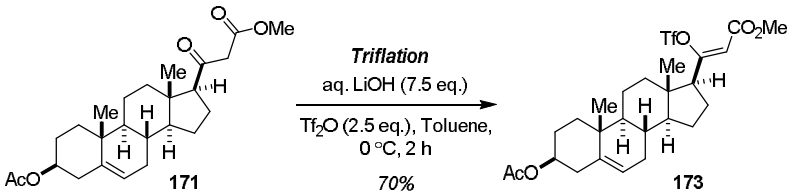
HRMS (MALDI–TOF) calculated for $C_{32}H_{42}O_7SNa$ $[M+Na]^+$: 593.2543, found 593.2505.

IR (neat): ν (cm^{-1}) = 2945, 1726, 1636, 1434, 1365, 1242, 1193, 1179, 1136, 1088, 1029, 928, 883, 814, 770, 732, 692.

$[\alpha]^{25}_D$ = –67.0 (*c* 0.10, CH_2Cl_2).

[13] (a) H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe, *Org. Lett.* **2008**, *10*, 2131–2134; (b) A. Manabe, Y. Ohfune, T. Shinada, *Synlett* **2012**, *23*, 1213–1216.
[14] K. M. Allan, B. D. Hong, B. M. Stoltz, *Org. Biomol. Chem.* **2009**, *7*, 4960–4964.

*7.3.1.2. Stereoselective synthesis of (Z)-enol triflate (**173**)*[15]



To a solution of **171** (5.8 g, 13.8 mmol; toluene (55 mL, 0.25 M)) was added a freshly prepared saturated aqueous solution of lithium hydroxide (5.0 M, 21 mL, 104 mmo,) in one portion at 0 °C. The resulting biphasic mixture was vigorously stirred at 0 °C for 5 minutes before dropwise addition of triflic anhydride (5.9 mL, 34.6 mmol). After 2 h at 0 °C, the biphasic solution was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 80 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 10/1, buffered with 0.1% triethylamine) gave the desired (*Z*)-enol triflate (**173**) (5.4 g, 70%).

White solid, m.p. = 58–60 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.83 (d, *J* = 1.2 Hz, 1H, H_{22}), 5.38-5.35 (m, 1H, H_6), 4.62-4.59 (m, 1H, H_3), 3.78 (s, 3H, O*Me*), 2.40 (t, $^3J_{HH}$ = 8.8 Hz, 1H, H_{17}), 2.35-2.26 (m, 2H, H_4), 2.03 (s, 3H, *Me*CO), 2.01-1.91 (m, 3H, H_7+H_{12}+H_{16}), 1.89-1.84 (m, 2H, H_1+H_2), 1.82-1.72 (m, 1H, H_{15}), 1.70-1.53 (m, 4H, H_2+H_7+H_{11}+H_{16}), 1.52-1.39 (m, 2H, H_8+H_{11}), 1.35-1.10 (m, 4H, H_{1a}+H_{12a}+H_{14}+H_{15}), 1.05-0.98 (m, 4H, H_9+Me_{19}), 0.69 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 163.3 (*C*O_2Me), 160.4 (C_{20}), 139.8 (C_5), 122.0 (C_6H), 118.3 (q, $^1J_{CF}$ = 323 Hz, C_{CF3}), 110.8 (C_{22}H), 73.7 (C_3H), 56.2 (C_{14}H), 55.1 (C_{17}H), 52.0 (*Me*O), 49.7 (C_9H), 45.0 (C_{13}), 38.0 (C_4H_2), 37.6 ($C_{12}H_2$), 36.9 (C_1H_2), 36.6 (C_{10}), 32.3 (C_8H), 31.6 (C_7H_2), 27.7(C_2H_2), 25.2 ($C_{16}H_2$), 24.1 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = –74.0.

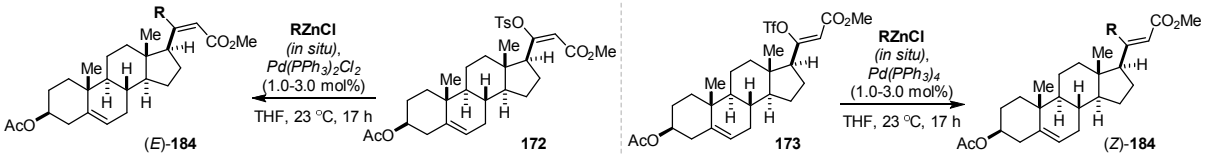
HRMS (+ESI) calculated for $C_{26}H_{40}F_3NO_4S$ $[M+NH_4]^+$: 566.2394, found 566.2421.

IR (neat): ν (cm^{-1}) = 2948, 1729, 1670, 1426, 1371, 1305, 1244, 1203, 1177, 1138, 1030, 911, 890.

$[\alpha]^{25}_D$ = +19.0 (*c* 0.11, CH_2Cl_2).

[15] D. Babinski, O. Soltani, D. E. Frantz, *Org. Lett.* **2008**, *10*, 2901–2904.

*7.3.1.3. Negishi coupling reactions of (E)-enol tosylate (**172**) and (Z)-enol triflate (**173**)*[14,16]



(*E*)-**184** **172** **173** (*Z*)-**184**

General Procedure A (Magnesium-Zinc Exchange)

The appropriate Grignard reagent (4.2 mmol) was added to an anhydrous zinc chloride solution (4.2 mmol, 1.0 M solution in THF) at 0 °C. The resulting white suspension was stirred at the same temperature for 1 h. To this mixture were then successively added the appropriate enoate (**172 or 173**, 3.5 mmol) and the palladium catalyst (25 mg of $[(Ph_3P)_2PdCl_2]$ for **172**, or 42 mg of $[(Ph_3P)_4Pd]$ for **173**, 1 mol%) in anhydrous THF (35 mL, 0.1 M). The reaction mixture was stirred at 23 °C for 17 h. A saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction, which was subsequently extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash chromatography.

General Procedure B (Magnesium-Zinc Exchange)

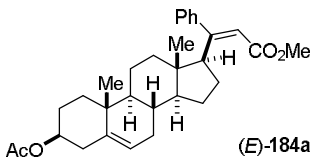
To a solution of the appropriate (hetero)aryl bromide (0.57 mmol) in anhydrous THF (2 mL) at 0 °C, isopropyl magnesium chloride (0.63 mmol, 2.0 M in THF) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 1 h. An anhydrous solution of zinc chloride (0.68 mmol, 1.0 M solution in THF) was added dropwise at 0 °C. The resulting mixture was stirred at ambient temperature for 1 h. To this mixture were then successively added the appropriate enoate (**172 or 173**, 0.44 mol) and the palladium catalyst (9.3 mg of $[(Ph_3P)_2PdCl_2]$ for **172**, or 15.2 mg of $[(Ph_3P)_4Pd]$ for **173**, 3 mol%) in THF (6.0 mL, 0.05 M). The reaction mixture was stirred at 23 °C for 17 h. A saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction, which was subsequently extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash chromatography.

General Procedure C (Lithium-Zinc Exchange)

To a solution of the appropriate (hetero)aryl bromide (0.55 mmol) in anhydrous THF (2 mL) at −78 °C, *n*-butyl lithium (0.60 mmol, 1.35 M in hexanes based on titration) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h. An anhydrous solution of zinc chloride (0.66 mmol, 1.0 M solution in THF) was added dropwise at −78 °C. The resulting

[16] Y. Yang, N. J. Oldenhuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 615–619.

homogeneous solution was stirred at ambient temperature for 1 h. To this mixture were then successively added the appropriate enoate (**172 or 173**, 0.42 mmol) and the palladium catalyst (8.9 mg of $[(Ph_3P)_2PdCl_2]$ for **172**, or 14.6 mg of $[(Ph_3P)_4Pd]$ for **173**, 3 mol%) in THF (6.0 mL, 0.05 M). The reaction mixture was stirred at 23 °C for 17 h. A saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction, which was subsequently extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash chromatography.



(*E*)-**184a**

Following general procedure A using phenyl magnesium bromide (2.8 M in Et_2O, 1.5 mL, 4.2 mmol), an anhydrous zinc chloride solution (4.2 mL, 4.2 mmol), enoate **172** (1.9 g, 3.5 mmol) and bis(triphenylphosphine)palladium chloride (25 mg, 1.0 mol%) in THF (35 mL, 0.1 M). Purification by flash chromatography (Pentane/Ethyl acetate = 15/1) gave (*E*)-**184a** (1.1 g, 64%).

Colorless foam (Pentane/Ethyl acetate = 15/1, R_f = 0.30).

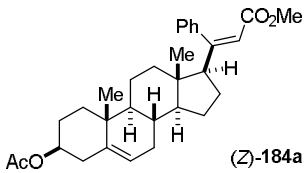
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.31-7.26 (m, 3H, $2H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.17-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.79 (s, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 3.99 (dd, $^3J_{HH}$ = 10.9, 8.5 Hz, 1H, H_{17}), 3.72 (s, 3H, O*Me*), 2.34-2.24 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.99-1.82 (m, 5H, H_2+H_7+H_{12}+$2H_{16}$), 1.80-1.71 (m, 1H, H_{15}), 1.66-1.50 (m, 4H, H_1+H_2+H_7+H_{11}), 1.43-1.34 (m, 3H, H_1+H_8+H_{11}), 1.28-1.21 (m, 1H, H_{14}), 1.17-1.07 (m, 2H, H_{12}+H_{15}), 1.02-0.94 (m, 4H, H_9+Me_{19}), 0.38 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.1 (*C*O_2Me), 162.1 (C_{20}), 143.0 (C_{Ph}), 139.7 (C_5), 128.5 ($C_{ortho\text{-}Ph}$),127.5 ($C_{meta\text{-}Ph}$), 127.1 ($C_{para\text{-}Ph}$), 122.5 (C_6H), 122.4 (C_{22}H), 73.9 (C_3H), 55.9 (C_{14}H), 51.1 (*Me*O), 50.4 (C_{17}H), 50.0 (C_9H), 47.3 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.9 (C_1H_2), 36.6 (C_{10}), 31.9 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 25.4 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{31}H_{41}O_4$ $[M+H]^+$: 477.2999, found 477.3007.

IR (neat): ν (cm^{-1}) = 2942, 1724, 1615, 1435, 1366, 1240, 1195, 1161, 1028, 956, 905, 877.

$[\alpha]^{25}_D$ = −154.8 (*c* 0.11, CH_2Cl_2).



(*Z*)-**184a**

Following general procedure A using phenyl magnesium bromide (2.8 M in Et_2O, 1.6 mL, 4.4 mmol), an anhydrous zinc chloride solution (4.4 mL, 4.4 mmol), enoate **173** (2.0 g, 3.6 mmol) and tertakis(triphenylphosphine)palladium (42 mg, 1.0 mol%) in THF (15 mL, 0.2 M). Purification by flash chromatography (Pentane/Ethyl acetate = 15/1) gave (*Z*)-**184a** (1.7 g, >99%).

White solid, m.p. = 196−197 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

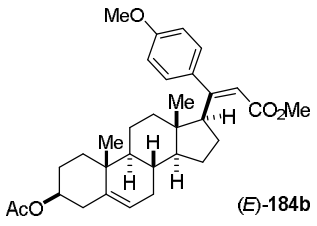
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34-7.28 (m, 3H, 2$H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.16-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.91 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.60-4.52 (m, 1H, H_3), 3.52 (s, 3H, O*Me*), 2.62 (t, $^3J_{HH}$ = 8.8 Hz, 1H, H_{17}), 2.33-2.23 (m, 2H, H_4), 2.01 (s, 3H, *Me*CO), 1.96-1.70 (m, 6H, H_1+H_2+H_7+H_{15}+2H_{16}), 1.57-1.48 (m, 2H, H_2+H_7), 1.46-1.36 (m, 1H, H_8), 1.31-1.10 (m, 4H, H_{11}+H_{14}+H_{15}), 1.06-0.98 (m, 1H, H_1), 0.94 (s, 3H, Me_{19}), 0.88-0.81 (m, 2H, H_9+H_{12}), 0.71-0.63 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 166.9 (*C*O_2Me), 159.8 (C_{20}), 141.5 (C_{Ph}), 139.7 (C_5), 127.6 ($C_{meta\text{-}Ph}$+$C_{para\text{-}Ph}$), 127.5 ($C_{ortho\text{-}Ph}$), 122.3 (C_6H), 117.2 (C_{22}H), 73.8 (C_3H), 58.9 (C_{17}H), 56.9 (C_{14}H), 51.0 (*Me*O), 49.9 (C_9H), 44.1 (C_{13}), 38.0 (C_4H_2), 37.9 ($C_{12}H_2$), 36.9 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.6 (C_7H_2), 27.7(C_2H_2), 25.5 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{31}H_{41}O_4$ $[M+H]^+$: 477.2999, found 477.3006.

IR (neat): ν (cm^{-1}) = 2943, 1728, 1635, 1436, 1374, 1320, 1240, 1164, 1132, 938.

$[\alpha]^{25}_D$ = +10.1 (*c* 0.13, CH_2Cl_2).



(*E*)-**184b**

Following general procedure A using *p*-methoxylphenyl magnesium bromide (1.0 M in THF, 0.51 mL, 0.51 mmol), an anhydrous zinc chloride solution (0.51 mL, 0.51 mmol), enoate **172** (240 mg, 0.42 mmol) and bis(triphenylphosphine)palladium chloride (3.0 mg, 1.0 mol%) in THF (2.0 mL, 0.2 M). Purification by flash chromatography (Pentane/Ethyl acetate = 10/1) gave (*E*)-**184b** (130 mg, 61%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.45).

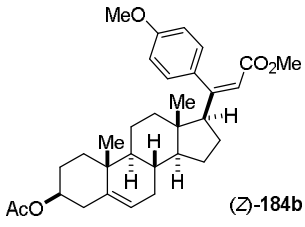
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.08 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{ortho\text{-}Ph}$), 6.82 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{meta\text{-}Ph}$), 5.78 (s, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.61-4.58 (m, 1H, H_3), 3.96 (dd, $^3J_{HH}$ = 10.9, 8.4 Hz, 1H, H_{17}), 3.80 (s, 3H, *Me*OC_6H_4), 3.71 (s, 3H, O*Me*), 2.34-2.24 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.99-1.81 (m, 5H), 1.79-1.71 (m, 1H, H_{15}), 1.64-1.49 (m, 4H), 1.43-1.30 (m, 3H), 1.28-1.20 (m, 1H, H_{14}), 1.19-1.07 (m, 2H), 1.02-0.95 (m, 4H, H_9+Me_{19}), 0.37 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.2 (*C*O_2Me), 161.9 (C_{20}), 158.7 ($C_{para\text{-}Ph}$), 139.7 (C_5), 135.6 (C_{Ph}), 129.7 ($C_{ortho\text{-}Ph}$), 122.5 (C_6H), 122.1 (C_{22}H), 112.9 ($C_{meta\text{-}Ph}$), 73.9 (C_3H), 55.9 (C_{14}H), 55.2 (*Me*OC_6H_4), 51.1 (*Me*O), 50.6 (C_{17}H), 50.0 (C_9H), 47.3 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.9 (C_1H_2), 36.7 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 27.7(C_2H_2), 25.3 ($C_{16}H_2$), 24.7 ($C_{15}H_2$), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{32}H_{43}O_5$ $[M+H]^+$: 507.3105, found 507.2962.

IR (neat): ν (cm^{-1}) = 2944, 1721, 1609, 1509, 1460, 1436, 1367, 1242, 1160, 1029, 957, 911, 879, 833, 814, 731.

$[\alpha]^{25}_D$ = −160.8 (*c* 0.10, CH_2Cl_2).



(*Z*)-**184b**

Following general procedure A using *p*-methoxylphenyl magnesium bromide (1.0 M in THF, 0.44 mL, 0.44 mmol), an anhydrous zinc chloride solution (0.44 mL, 0.44 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (4.2 mg, 1.0 mol%) in THF (1.5 mL, 0.2 M). Purification by flash chromatography (Pentane/Ethyl acetate = 5/1) gave (*Z*)-**184b** (194 mg, 96%).

White solid, m.p. = 67−70 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.30).

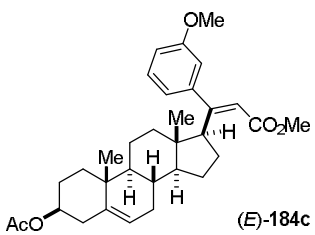
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.09 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{ortho\text{-}Ph}$), 6.84 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{meta\text{-}Ph}$), 5.87 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.60-4.52 (m, 1H, H_3), 3.81 (s, 3H, *Me*OC_6H_4), 3.55 (s, 3H, O*Me*), 2.61 (t, $^3J_{HH}$ = 9.1 Hz, 1H, H_{17}), 2.34-2.23 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.96-1.70 (m, 6H), 1.60-1.48 (m, 2H), 1.45-1.36 (m, 1H, H_8), 1.32-1.10 (m, 4H), 1.03 (td, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, H_1), 0.95 (s, 3H, Me_{19}), 0.89-0.81 (m, 2H), 0.72-0.63 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.1 (*C*O_2Me), 159.6 (C_{20}), 159.2 ($C_{para\text{-}Ph}$), 139.7 (C_5), 133.7 (C_{Ph}), 128.9 ($C_{ortho\text{-}Ph}$), 122.3 (C_6H), 116.7 (C_{22}H), 113.0 ($C_{meta\text{-}Ph}$), 73.9 (C_3H), 59.0 (C_{17}H), 56.9 (C_{14}H), 55.1 (*Me*OC_6H_4), 51.0 (*Me*O), 50.0 (C_9H), 44.1 (C_{13}), 38.1 (C_4H_2), 38.1 ($C_{12}H_2$), 36.9 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.6 (C_7H_2), 27.7(C_2H_2), 25.4 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{32}H_{43}O_5$ $[M+H]^+$: 507.3105, found 507.3102.

IR (neat): ν (cm^{-1}) = 2948, 1725, 1606, 1510, 1441, 1374, 1290, 1242, 1157, 1029, 939, 904, 861, 829, 729.

$[\alpha]^{25}_D$ = +34.3 (*c* 0.14, CH_2Cl_2).



(*E*)-**184c**

Following general procedure A using *m*-methoxylphenyl magnesium bromide (0.5 M in THF, 1.0 mL, 0.51 mmol),[17] an anhydrous zinc chloride solution (0.51 mL, 0.51 mmol), enoate **172** (240 mg, 0.42 mmol) and bis(triphenylphosphine)palladium chloride (8.9 mg, 3.0 mol%) in THF (8.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Diehtyl ether = 10/1) gave (*E*)-**184c** (132 mg, 62%).

[17] A. Tarui, S. Kondo, K. Sato, M. Omote, H. Minami, Y. Miwa, A. Ando, *Tetrahedron* **2013**, *69*, 1559−1565.

White solid, m.p. = 59–60 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

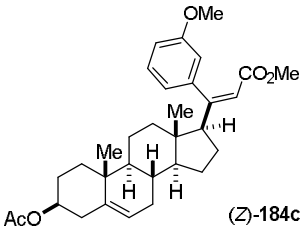
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.20 (t, $^3J_{HH}$ = 7.9 Hz, 1H, $H_{meta\text{-}Ph}$), 6.83-6.80 (m, 1H, H_{Ar}), 6.76-6.74 (m, 1H, H_{Ar}), 6.71-6.70 (m, 1H, H_{Ar}), 5.81 (s, 1H, H_{22}), 5.37-5.36 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 3.96 (dd, $^3J_{HH}$ = 10.9, 8.5 Hz, 1H, H_{17}), 3.80 (s, 3H, *Me*OC_6H_4), 3.72 (s, 3H, O*Me*), 2.35-2.24 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 2.00-1.81 (m, 5H), 1.79-1.71 (m, 1H, H_{15}), 1.66-1.50 (m, 4H), 1.44-1.08 (m, 6H), 1.02-0.96 (m, 4H, H_9+Me_{19}), 0.41 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.1 (*C*O_2Me), 161.8 (C_{20}), 158.7 ($C_{meta\text{-}Ph}$OMe), 144.4 (C_{Ph}), 139.7 (C_5), 128.5 ($C_{meta\text{-}Ph}$H), 122.5 (C_6H), 122.2 (C_{22}H), 121.1 (C_{Ar}H), 114.6 (C_{Ar}H), 112.3 (C_{Ar}H), 73.9 (C_3H), 55.9 (C_{14}H), 55.3 (*Me*OC_6H_4), 51.1 (*Me*O), 50.5 (C_{17}H), 50.0 (C_9H), 47.2 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.9 (C_1H_2), 36.7 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 27.7(C_2H_2), 25.6 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{32}H_{43}O_5$ $[M+H]^+$: 507.3105, found 507.3114.

IR (neat): ν (cm^{-1}) = 2940, 1724, 1598, 1575, 1484, 1457, 1433, 1366, 1288, 1239, 1210, 1160, 1030, 875, 789, 721.

$[\alpha]^{25}_D$ = –135.8 (*c* 0.12, CH_2Cl_2).



(*Z*)-**184c**

Following general procedure A using *m*-methoxylphenyl magnesium bromide (0.5 M in THF, 0.87 mL, 0.44 mmol),[17] an anhydrous zinc chloride solution (0.44 mL, 0.44 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (12.6 mg, 3.0 mol%) in THF (7.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 10/1 to 6/1) gave (*Z*)-**184c** (150 mg, 81%).

White solid, m.p. = 143–146 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.30).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.22 (d, $^3J_{HH}$ = 7.9 Hz, 1H, $H_{meta\text{-}Ph}$), 6.84-6.81 (m, 1H, H_{Ar}), 6.76-6.73 (m, 1H, H_{Ar}), 6.70-6.69 (m, 1H, H_{Ar}), 5.89 (d, $^3J_{HH}$ = 1.5 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.60-4.52 (m, 1H, H_3), 3.80 (s, 3H, *Me*OC_6H_4), 3.54 (s, 3H, O*Me*), 2.61 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 2.33-2.23 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 2.02-1.71 (m, 6H), 1.58-1.49 (m, 2H), 1.46-1.37 (m, 1H, H_8), 1.33-1.10 (m, 5H), 1.03 (td, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, H_1), 0.95 (s, 3H, Me_{19}), 0.93-0.82 (m, 2H), 0.75-0.65 (m, 4H, H_{12}+Me_{18}).

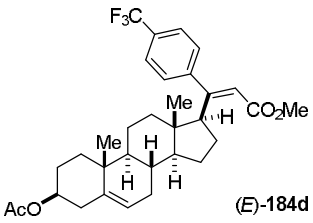
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 166.9 (*C*O_2Me), 159.2 (C_{20}), 158.9 ($C_{meta\text{-}Ph}$OMe), 143.0 (C_{Ph}), 139.7 (C_5), 128.6 ($C_{meta\text{-}Ph}$H), 122.3 (C_6H), 120.3 (C_{Ar}H), 117.4 (C_{22}H), 113.5 (C_{Ar}H), 112.7 (C_{Ar}H), 73.9 (C_3H), 58.7 (C_{17}H), 56.9 (C_{14}H), 55.2 (*Me*OC_6H_4), 51.1 (*Me*O), 50.0 (C_9H), 44.1 (C_{13}), 38.1 (C_4H_2), 37.9 ($C_{12}H_2$), 36.9 (C_1H_2), 36.5

(*C*$_{10}$), 32.2 (*C*$_8$H), 31.6 (*C*$_7$H$_2$), 27.7(*C*$_2$H$_2$), 25.5 (*C*$_{16}$H$_2$), 23.8 (*C*$_{15}$H$_2$), 21.4 (*Me*CO), 20.9 (*C*$_{11}$H$_2$), 19.3 (*C*$_{19}$H$_3$), 12.7 (*C*$_{18}$H$_3$).

HRMS (+ESI) calculated for $C_{32}H_{43}O_5$ $[M+H]^+$: 507.3105, found 507.3109.

IR (neat): ν (cm^{-1}) =.2941, 1729, 1630, 1575, 1432, 1371, 1241, 1207, 1149, 1030, 875, 790, 699.

$[\alpha]^{25}_D$ = +15.0 (*c* 0.10, CH_2Cl_2).



(*E*)-**184d**

Following general procedure A using *p*-trifluoromethylphenyl magnesium bromide (0.5 M in THF, 1.1 mL, 0.51 mmol),[17] an anhydrous zinc chloride solution (0.51 mL, 0.51 mmol) enoate **172** (240 mg, 0.42 mmol) and bis(triphenylphosphine)palladium chloride (3.0 mg, 1.0 mol%) in THF (2.0 mL, 0.2 M). Purification by flash chromatography (Pentane/Ethyl acetate = 10/1) gave (*E*)-**184d** (142 mg, 62%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.50).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.56 (d, $^3J_{HH}$ = 8.0 Hz, 2H, *H*$_{meta\text{-}Ph}$), 7.28 (d, $^3J_{HH}$ = 8.0 Hz, 2H, *H*$_{ortho\text{-}Ph}$), 5.78 (s, 1H, *H*$_{22}$), 5.38-5.35 (m, 1H, *H*$_6$), 4.64-4.56 (m, 1H, *H*$_3$), 3.99 (t, $^3J_{HH}$ = 11 Hz, 1H, *H*$_{17}$), 3.73 (s, 3H, O*Me*), 2.34-2.27 (m, 2H, *H*$_4$), 2.02 (s, 3H, *Me*CO), 1.99-1.73 (m, 6H), 1.66-1.51 (m, 4H), 1.41-1.08 (m, 8H), 1.04-0.95 (m, 4H, *H*$_9$+*Me*$_{19}$), 0.38 (s, 3H, *Me*$_{18}$).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 170.6 (Me*C*O), 166.8 (*C*O_2Me), 160.5 (*C*$_{20}$), 146.6 (*C*$_{Ph}$), 139.7 (*C*$_5$), 129.4 (q, $^2J_{CF}$ = 32.5 Hz, *C*$_{para\text{-}Ph}$$CF_3$), 129.0 (*C*$_{ortho\text{-}Ph}$), 124.6 (q, $^3J_{CF}$ = 3.6 Hz, *C*$_{meta\text{-}Ph}$), 124.4 (q, $^1J_{CF}$ = 272 Hz, *C*F_3), 123.2 (*C*$_{22}$H), 122.5 (*C*$_6$H), 73.9 (*C*$_3$H), 55.9 (*C*$_{14}$H), 51.3 (*Me*O), 50.3 (*C*$_{17}$H), 50.0 (*C*$_9$H), 47.5 (*C*$_{13}$), 38.1 (*C*$_4$H$_2$), 37.0 (*C*$_{12}$H$_2$), 37.0 (*C*$_1$H$_2$), 36.7 (*C*$_{10}$), 31.9 (*C*$_8$H), 31.8 (*C*$_7$H$_2$), 27.7(*C*$_2$H$_2$), 25.5 (*C*$_{16}$H$_2$), 24.7 (*C*$_{15}$H$_2$), 21.5 (*Me*CO), 20.7 (*C*$_{11}$H$_2$), 19.3 (*C*$_{19}$H$_3$), 14.4 (*C*$_{18}$H$_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = –61.8.

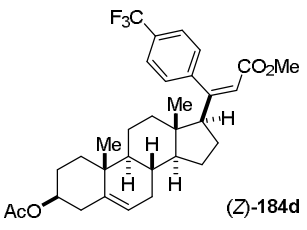
HRMS (+ESI) calculated for $C_{32}H_{43}O_5$ $[M+H]^+$: 507.3105, found 507.2962.

IR (neat): ν (cm^{-1}) = 2944, 1721, 1609, 1509, 1460, 1436, 1367, 1242, 1160, 1029, 957, 911, 879, 833, 814, 731.

HRMS (+ESI) calculated for $C_{32}H_{39}F_3O_4$ $[M+H]^+$: 545.2873, found 545.2886.

IR (neat): ν (cm^{-1}) =.2946, 1724, 1613, 1436, 1368, 1323, 1244, 1192, 1164, 1126, 1068, 1026, 957, 910, 847.

$[\alpha]^{25}_D$ = –124.2 (*c* 0.11, CH_2Cl_2).



(*Z*)-**184d**

Following general procedure A using *p*-trifluoromethylphenyl magnesium bromide (0.5 M in THF, 0.88 mL, 0.44 mmol),[17] an anhydrous zinc chloride solution (0.44 mL, 0.44 mmol), enoate **173** (195 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (4.2 mg, 1.0 mol%) in THF (3.0 mL, 0.1 M). Purification by flash chromatography (Pentane/Ethyl acetate = 8/1) gave (*Z*)-**184d** (184 mg, 95%).

White solid, m.p. = 146−148 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.56 (d, $^3J_{HH}$ = 8.0 Hz, 2H, $H_{meta\text{-}Ph}$), 7.27 (d, $^3J_{HH}$ = 8.0 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.97 (d, $^3J_{HH}$ = 1.5 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.59-4.54 (m, 1H, H_3), 3.54 (s, 3H, *Me*OC_6H_4), 3.55 (s, 3H, O*Me*), 2.59 (t, $^3J_{HH}$ = 9.0 Hz, 1H, H_{17}), 2.33-2.23 (m, 2H, H_4), 2.01 (s, 3H, *Me*CO), 1.96-1.72 (m, 6H), 1.60-1.49 (m, 2H), 1.47-1.37 (m, 1H, H_8), 1.34-1.10 (m, 4H), 1.07-1.10 (m, 1H, H_1), 0.95 (s, 3H, Me_{19}), 0.89-0.81 (m, 2H), 0.72-0.64 (m, 4H, H_{12}+Me_{18}).

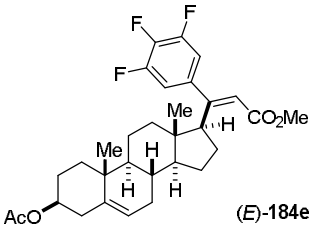
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 166.4 (*C*O_2Me), 158.6 (C_{20}), 145.4 (C_{Ph}), 139.7 (C_5), 129.6 (q, $^2J_{CF}$ = 32.4 Hz, $C_{para\text{-}Ph}CF_3$), 128.0 ($C_{ortho\text{-}Ph}$), 124.6 (q, $^3J_{CF}$ = 3.8 Hz, $C_{meta\text{-}Ph}$), 124.2 (q, $^1J_{CF}$ = 272 Hz, *C*F_3), 122.2 (C_6H), 118.2 (C_{22}H), 73.8 (C_3H), 59.0 (C_{17}H), 56.9 (C_{14}H), 51.2 (*Me*O), 49.9 (C_9H), 44.2 (C_{13}), 38.1 (C_4H_2), 38.1 ($C_{12}H_2$), 36.9 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.6 (C_7H_2), 27.7(C_2H_2), 25.7 ($C_{16}H_2$), 23.7 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.9 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −61.6.

HRMS (+ESI) calculated for $C_{32}H_{39}F_3O_4$ $[M+H]^+$: 545.2873, found 545.2880.

IR (neat): ν (cm^{-1}) =.2945, 1729, 1632, 1435, 1371, 1324, 1242, 1162, 1123, 1064, 1030, 847, 736.

$[\alpha]^{25}_D$ = −1.2 (*c* 0.10, CH_2Cl_2).



(*E*)-**184e**

Following general procedure B using 3,4,5-trifluorobromobenzene (69 μL, 0.57 mmol), isopropyl magnesium chloride (0.31 mL, 0.63 mmol), an anhydrous zinc chloride solution (0.68 mL, 0.68 mmol), enoate **172** (250 mg, 0.44 mmol) and bis(triphenylphosphine)palladium chloride (9.3 mg, 3.0 mol%) in THF (8.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 20/1) gave (*E*)-**184e** (108 mg, 47%).

White solid, m.p. = 157−159 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.50).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.80 (dd, $^3J_{HH}$ = 8.0, 6.3 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.77 (s, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 3.91 (t, $^3J_{HH}$ = 9.7 Hz, 1H, H_{17}), 3.73 (s,

3H, O*Me*), 2.34-2.27 (m, 2H, H_4), 2.03 (s, 3H, *Me*CO), 2.01-1.75 (m, 6H), 1.61-1.51 (m, 4H), 1.43-1.08 (m, 8H), 1.04-0.96 (m, 4H, H_9+Me_{19}), 0.41 (s, 3H, Me_{18}).

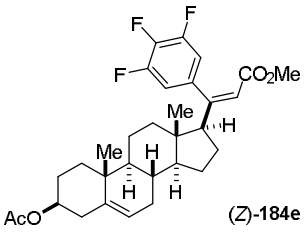
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 166.5 (*C*O_2Me), 158.3 (C_{20}), 150.3 (ddd, $^1J_{CF}$ = 250.5 Hz, $^2J_{CF}$ = 10.1 Hz, $^3J_{CF}$ = 4.2 Hz, $C_{meta\text{-}Ph}$F), 139.7 (C_5), 138.7 (m, C_{Ph}), 123.7 (C_{22}H), 122.4 (C_6H), 113.0 (dd, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 6.2 Hz, $C_{ortho\text{-}Ph}$), 73.9 (C_3H), 55.8 (C_{14}H), 51.4 (*Me*O), 50.3 (C_{17}H), 50.0 (C_9H), 47.4 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.9 (C_1H_2), 36.7 (C_{10}), 31.9 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 25.5 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.4 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −133.8 (d, $^3J_{FF}$ = 20.7 Hz), −161.3 (t, $^3J_{FF}$ = 20.6 Hz).

HRMS (MALDI−TOF) calculated for $C_{31}H_{37}F_3O_4Na$ $[M+Na]^+$: 553.2536, found 553.2552.

IR (neat): ν (cm^{-1}) = 2938, 1729, 1613, 1526, 1430, 1365, 1241, 1196, 1156, 1040, 866, 787, 760, 631.

$[\alpha]^{25}_D$ = −102.7 (*c* 0.10, CH_2Cl_2).



(*Z*)-**184e**

Following general procedure B using 3,4,5-trifluorobromobenzene (58 μL, 0.47 mmol), isopropyl magnesium chloride (0.26 mL, 0.52 mmol), an anhydrous zinc chloride solution (0.57 mL, 0.57 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (12.6 mg, 3.0 mol%) in THF (7.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 10/1) gave (*Z*)-**184e** (176 mg, 91%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.78 (dd, $^3J_{HH}$ = 8.1, 6.3 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.93 (d, *J* = 1.5 Hz, 1H, H_{22}), 5.36-5.35 (m, 1H, H_6), 4.61-4.53 (m, 1H, H_3), 3.58 (s, 3H, O*Me*), 2.49 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 2.34-2.24 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.97-1.70 (m, 6H), 1.60-1.02 (m, 8H), 0.97 (s, 3H, Me_{19}), 0.93-0.74 (m, 3H), 0.64 (s, Me_{18}).

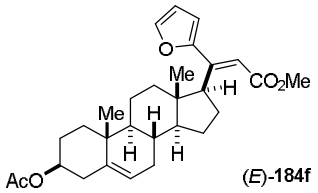
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 166.1 (*C*O_2Me), 156.4 (C_{20}), 150.6 (ddd, $^1J_{CF}$ = 249.9 Hz, $^2J_{CF}$ = 10.2 Hz, $^3J_{CF}$ = 4.1 Hz, $C_{meta\text{-}Ph}$F), 139.7 (C_5), 137.4 (m, C_{Ph}), 122.2 (C_6H), 118.8 (C_{22}H), 112.0 (dd, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 5.8 Hz, $C_{ortho\text{-}Ph}$),, 73.8 (C_3H), 58.8 (C_{17}H), 56.9 (C_{14}H), 51.3 (*Me*O), 49.9 (C_9H), 44.2 (C_{13}), 38.2 (C_4H_2), 38.1 ($C_{12}H_2$), 36.9 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.6 (C_7H_2), 27.7(C_2H_2), 25.6 ($C_{16}H_2$), 23.7 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −134.1 (d, $^3J_{FF}$ = 20.6 Hz), −160.7 (t, $^3J_{FF}$ = 20.6 Hz).

HRMS (+ESI) calculated for $C_{31}H_{37}F_3O_4$ $[M+H]^+$: 531.2717, found 531.2722.

IR (neat): ν (cm^{-1}) =.2941, 1728, 1614, 1527, 1431, 1381, 1304, 1240, 1199, 1145, 1037, 865.

$[\alpha]^{25}_D$ = +6.3 (*c* 0.80, CH_2Cl_2).



(*E*)-**184f**

Following general procedure C using 2-bromofuran (51 μL, 0.55 mmol), *n*-butyl lithium (0.45 mL, 0.60 mmol), an anhydrous zinc chloride solution (0.66 mL, 0.66 mmol), enoate **172** (240 mg g, 0.42 mmol) and bis(triphenylphosphine)palladium chloride (8.9 mg, 3.0 mol%) in THF (6 mL, 0.05 M). Purification by flash chromatography (Pentane/Diethyl ether = 10/1) gave (*E*)-**184f** (108 mg, 55%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.50).

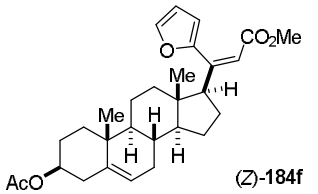
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.42 (dd, $^3J_{HH}$ = 1.8, 0.7 Hz, 1H, H_{Ar}), 6.57 (dd, $^3J_{HH}$ = 3.5, 0.8 Hz, 1H, H_{Ar}), 6.40 (dd, $^3J_{HH}$ = 3.5, 1.8 Hz, 1H, H_{Ar}), 6.36 (s, 1H, H_{22}), 5.39-5.38 (m, 1H, H_6), 4.65-4.57 (m, 1H, H_3), 4.14 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 3.72 (s, 3H, O*Me*), 2.46-2.26 (m, 3H), 2.06-1.98 (m, 4H), 1.90-1.75 (m, 4H), 1.80-1.71 (m, 1H, H_{15}), 1.64-1.19 (m, 9H), 1.12 (td, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 12.9, 4.1 Hz, 1H, H_1), 1.06-0.99 (m, 4H, H_9+Me_{19}), 0.56 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 170.5 (Me*C*O), 167.2 (*C*O_2Me), 154.8 (C_{Ar}), 148.4 (C_{20}), 142.7 (C_{Ar}H), 139.7 (C_5), 122.5 (C_6H), 118.0 (C_{22}H), 111.4 (C_{Ar}H), 73.9 (C_3H), 55.9 (C_{14}H), 51.2 (*Me*O), 50.1 (C_9H), 48.8 (C_{17}H), 46.6 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.8 (C_1H_2), 36.7 (C_{10}), 32.0 (C_7H_2), 31.9 (C_8H), 27.7(C_2H_2), 25.4 ($C_{16}H_2$), 25.2 ($C_{15}H_2$), 21.4 (*Me*CO), 20.8 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 13.9 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{29}H_{39}O_5$ $[M+H]^+$: 467.2792, found 467.2793.

IR (neat): ν (cm^{-1}) =.2943, 1729, 1716, 1597, 1434, 1368, 1241, 1189, 1160, 1025, 916, 878, 810, 736.

$[\alpha]^{25}_D$ = −177.1 (*c* 0.15, CH_2Cl_2).



(*Z*)-**184f**

Following general procedure C using 2-bromofuran (51 μL, 0.55 mmol), *n*-butyl lithium (0.41 mL, 0.55 mmol), an anhydrous zinc chloride solution (0.57 mL, 0.57 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (12.6 mg, 3.0 mol%) in THF (7 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 8/1) gave (*Z*)-**184f** (134 mg, 79%).

White solid, m.p. = 163−166 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.41 (dd, $^3J_{HH}$ = 1.9, 0.8 Hz, 1H, H_{Ar}), 6.63 (dd, $^3J_{HH}$ = 3.5, 0.8 Hz, 1H, H_{Ar}), 6.41 (dd, $^3J_{HH}$ = 3.4, 1.8 Hz, 1H, H_{Ar}), 5.86 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H_{22}),

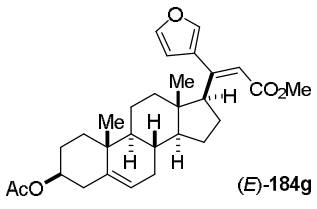
5.37-5.36 (m, 1H, H_6), 4.63-4.54 (m, 1H, H_3), 3.68 (s, 3H, O*Me*), 2.86 (t, $^3J_{HH}$ = 9.4 Hz, 1H, H_{17}), 2.34-2.25 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.99-1.96 (m. 1H, H_7), 1.88-1.74 (m, 5H), 1.61-1.38 (m, 4H), 1.33-1.19 (m, 3H), 1.12-0.90 (m, 6H), 0.60 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.2 (*C*O_2Me), 151.8 (C_{Ar}), 144.1 (C_{20}), 142.1 (C_{Ar}H), 139.7 (C_5), 122.3 (C_6H), 116.8 (C_{22}H), 111.3 (C_{Ar}H), 111.2 (C_{Ar}H), 73.9 (C_3H), 56.7 (C_{14}H), 55.1 (C_{17}H), 51.3 (*Me*O), 50.1 (C_9H), 44.2 (C_{13}), 38.1 (C_4H_2), 37.2 ($C_{12}H_2$), 36.9 (C_1H_2), 36.6 (C_{10}), 32.3 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 25.1 ($C_{16}H_2$), 24.1 ($C_{15}H_2$), 21.4 (*Me*CO), 21.0 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.5 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{29}H_{39}O_5$ $[M+H]^+$: 467.2792, found 467.2795.

IR (neat): ν (cm^{-1}) =.2945, 1729, 1632, 1436, 1316, 1236, 1170, 1034, 1015, 903, 750.

$[\alpha]^{25}_D$ = +33.8 (*c* 0.10, CH_2Cl_2).



(*E*)-**184g**

Following general procedure C using 3-bromofuran (51 μL, 0.55 mmol), *n*-butyl lithium (0.45 mL, 0.60 mmol), an anhydrous zinc chloride solution (0.66 mL, 0.66 mmol), enoate **172** (240 mg g, 0.42 mmol) and bis(triphenylphosphine)palladium chloride (8.9 mg, 3.0 mol%) in THF (8 mL, 0.05 M). Purification by flash chromatography (Pentane/Diethyl ether = 10/1) gave (*E*)-**184g** (105 mg, 54%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.50).

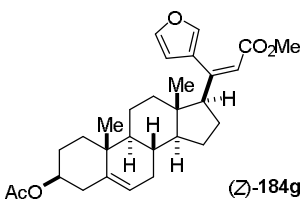
^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.41 (dd, $^3J_{HH}$ = 1.6, 0.9 Hz, 1H, H_{Ar}), 7.36 (t, $^3J_{HH}$ = 1.7 Hz, 1H, H_{Ar}), 6.40 (dd, $^3J_{HH}$ = 1.9, 0.9 Hz, 1H, H_{Ar}), 5.97 (s, 1H, H_{22}), 5.39-5.36 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 4.04 (t, $^3J_{HH}$ = 7.2 Hz, 1H, H_{17}), 3.71 (s, 3H, O*Me*), 2.36-2.25 (m, 2H, H_4), 2.10-1.95 (m, 5H), 1.89-1.76 (m, 4H), 1.63-1.52 (m, 4H), 1.46-1.23 (m, 5H), 1.12 (td, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 12.8, 4.2 Hz, 1H, H_1), 1.04-0.97 (m, 4H, H_9+Me_{19}), 0.51 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.0 (*C*O_2Me), 153.0 (C_{20}), 142.3 (C_{Ar}H), 140.3 (C_{Ar}H), 139.7 (C_5), 127.4 (C_{Ar}), 122.5 (C_6H), 120.9 (C_{22}H), 111.6 (C_{Ar}H), 73.9 (C_3H), 55.8 (C_{14}H), 51.1 (*Me*O), 50.1 (C_9H), 49.7 (C_{17}H), 47.2 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.7 (C_1H_2), 36.7 (C_{10}), 31.9 (C_7H_2), 31.9 (C_8H), 27.7(C_2H_2), 25.2 ($C_{16}H_2$), 24.9 ($C_{15}H_2$), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.3 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{29}H_{39}O_5$ $[M+H]^+$: 467.2792, found 467.2805.

IR (neat): ν (cm^{-1}) =.2945, 1722, 1608, 1434, 1369, 1242, 1191, 1161, 1027, 871, 794, 732.

$[\alpha]^{25}_D$ = −177.5 (*c* 0.11, CH_2Cl_2).



(*Z*)-**184g**

Following general procedure C using 3-bromofuran (44 μL, 0.47 mmol), *n*-butyl lithium (0.39 mL, 0.52 mmol), an anhydrous zinc chloride solution (0.57 mL, 0.57 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (12.6 mg, 3.0 mol%) in THF (7 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 15/1) gave (*Z*)-**184g** (150 mg, 74%).

White solid, m.p. = 96–98 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

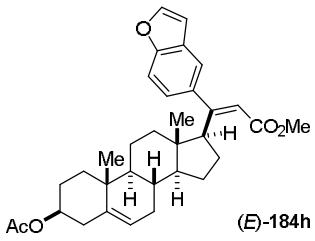
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.44 (dd, $^3J_{HH}$ = 1.5, 0.9 Hz, 1H, H_{Ar}), 7.38 (t, $^3J_{HH}$ = 1.7 Hz, 1H, H_{Ar}), 6.39 (dd, $^3J_{HH}$ = 1.9, 0.9 Hz, 1H, H_{Ar}), 5.87 (d, $^3J_{HH}$ = 1.3 Hz, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.62-4.54 (m, 1H, H_3), 3.64 (s, 3H, O*Me*), 2.51 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.35-2.24 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.98-1.95 (m. 1H, H_7), 1.91-1.70 (m, 5H), 1.58-1.38 (m, 4H), 1.30-1.02 (m, 6H), 0.97-0.88 (m, 5H), 0.60 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 166.9 (CO_2Me), 149.2 (C_{20}), 141.9 (C_{Ar}H), 140.7 (C_{Ar}H), 139.7 (C_5), 124.9 (C_{Ar}), 122.3 (C_6H), 116.8 (C_{22}H), 111.4 (C_{Ar}H), 73.8 (C_3H), 58.8 (C_{17}H), 56.8 (C_{14}H), 51.1 (*Me*O), 50.0 (C_9H), 44.3 (C_{13}), 38.4 (C_4H_2), 38.1 ($C_{12}H_2$), 36.9 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 25.3 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 21.4 (*Me*CO), 21.0 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{29}H_{39}O_5$ $[M+H]^+$: 467.2792, found 467.2788.

IR (neat): ν (cm^{-1}) =.2943, 2897, 1730, 1638, 1423, 1373, 1230, 1156, 1124, 1030, 926, 871, 810, 741.

$[\alpha]^{25}_D$ = +9.8 (*c* 0.11, CH_2Cl_2).



(*E*)-**184h**

Following general procedure A using 5-benzofuran magnesium bromide (0.5 M in THF, 1.1 mL, 0.51 mmol),[17] an anhydrous zinc chloride solution (0.51 mL, 0.51 mmol), enoate **172** (240 mg, 0.42 mmol) and bis(triphenylphosphine)palladium chloride (3.0 mg, 1.0 mol%) in THF (2.0 mL, 0.2 M). Purification by flash chromatography (Pentane/Ethyl acetate = 15/1) gave (*E*)-**184h** (136 mg, 63%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.50).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.63 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H_{Ar}), 7.43-7.38 (m, 2H, H_{Ar}), 7.10 (dd, $^3J_{HH}$ = 8.5, 1.8 Hz, 1H, H_{Ar}), 6.75-6.74 (dd, $^3J_{HH}$ = 2.1, 0.9 Hz, 1H, H_{Ar}), 5.84 (s, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 4.03 (dd, $^3J_{HH}$ = 10.9, 8.5 Hz, 1H, H_{17}), 3.72 (s, 3H, O*Me*), 2.39-2.24 (m, 2H, H_4), 2.08-1.91 (m, 6H), 1.88-1.74 (m, 3H), 1.68-1.50 (m, 4H), 1.41-1.24 (m, 4H), 1.16-1.08 (m, 2H), 1.03-0.96 (m, 4H), 0.38 (s, 3H, Me_{18}).

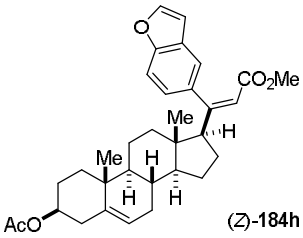
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.1 (CO_2Me), 162.3 (C_{20}), 154.0 (C_{Ar}), 145.5 (C_{Ar}H), 139.7 (C_5), 137.8 (C_{Ar}), 126.7 (C_{Ar}), 125.2 (C_{Ar}H), 122.7 (C_{22}H),

122.5 (C_6H), 121.0 (C_{Ar}H), 110.3 (C_{Ar}H), 106.6 (C_{Ar}H), 73.9 (C_3H), 55.9 (C_{14}H), 51.1 (*Me*O), 50.7 (C_{17}H), 50.0 (C_9H), 47.3 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.9 (C_1H_2), 36.6 (C_{10}), 31.9 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 25.5 ($C_{16}H_2$), 24.7 ($C_{15}H_2$), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 14.3 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{33}H_{41}O_5$ $[M+H]^+$: 517.2949, found 517.2962.

IR (neat): ν (cm^{-1}) =.2945, 1720, 1612, 1465, 1434, 1368, 1245, 1171, 1153, 1132, 1110, 1029, 957, 908, 880, 816, 771, 729.

$[\alpha]^{25}_D$ = −109.6 (*c* 0.11, CH_2Cl_2).



(*Z*)-**184h**

Following general procedure A using 5-benzofuran magnesium bromide (0.5 M in THF, 0.87 mL, 0.44 mmol),[17] an anhydrous zinc chloride solution (0.44 mL, 0.44 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (4.2 mg, 1.0 mol%) in THF (2.0 mL, 0.2 M). Purification by flash chromatography (Pentane/Ethyl acetate = 12/1) gave (*Z*)-**184h** (188 mg, 83%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.30).

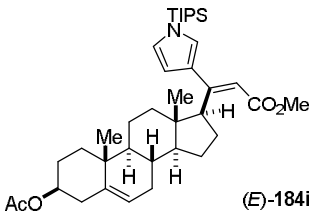
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.60 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H_{Ar}), 7.45-7.39 (m, 2H, H_{Ar}), 7.10 (dd, $^3J_{HH}$ = 8.5, 1.8 Hz, 1H, H_{Ar}), 6.74 (dd, $^3J_{HH}$ = 2.2, 0.9 Hz, 1H, H_{Ar}),, 5.95 (d, $^3J_{HH}$ = 1.5 Hz, 1H, H_{22}), 5.35-5.33 (m, 1H, H_6), 4.59-4.51 (m, 1H, H_3), 3.51 (s, 3H, O*Me*), 2.69 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.32-2.22 (m, 2H, H_4), 2.05-1.85 (m, 6H), 1.81-1.67 (m, 3H), 1.57-1.36 (m, 3H), 1.28-1.11 (m, 4H), 1.06-0.96 (m, 1H, H_1), 0.93 (s, 3H, Me_{19}), 0.86-0.68 (m, 2H, H_9+H_{12}), 0.68-0.59 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.1 (CO_2Me), 159.9 (C_{20}), 154.5 (C_{Ar}), 145.1 (C_{Ar}H), 139.7 (C_5), 136.3 (C_{Ar}), 126.9 (C_{Ar}), 124.4 (C_{Ar}H), 122.3 (C_6H), 120.0 (C_{Ar}H), 117.3 (C_{22}H), 110.5 (C_{Ar}H), 106.8 (C_{Ar}H), 73.8 (C_3H), 59.5 (C_{17}H), 56.9 (C_{14}H), 51.0 (*Me*O), 49.9 (C_9H), 44.1 (C_{13}), 38.0 (C_4H_2), 38.0 ($C_{12}H_2$), 36.8 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.6 (C_7H_2), 27.7(C_2H_2), 25.6 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.4 (*Me*CO), 20.8 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{33}H_{41}O_5$ $[M+H]^+$: 517.2949, found 517.2948.

IR (neat): ν (cm^{-1}) =.2945, 1725, 1628, 1537, 1468, 1434, 1373, 1244, 1172, 1139, 1110, 1066, 1029, 909, 880, 815, 768, 729, 647, 610.

$[\alpha]^{25}_D$ = +29.5 (*c* 0.12, CH_2Cl_2).



(*E*)-**184i**

Following general procedure C using 3-bromo-1-tri(*iso*propylsilyl)pyrrole (0.20 mL, 0.75 mmol), *n*-butyl lithium (0.51 mL, 0.68 mmol), an anhydrous zinc chloride solution (0.82 mL, 0.82 mmol), enoate **172** (300 mg, 0.53 mmol) and bis(triphenylphosphine)palladium chloride (11.2 mg, 3.0 mol%) in THF (10 mL, 0.05 M). Purification by flash chromatography (Pentane/Diethyl ether = 20/1) gave (*E*)-**184i** (224 mg, 69%).

Colorless foam (Pentane/Ethyl acetate = 9/1, R_f = 0.30).

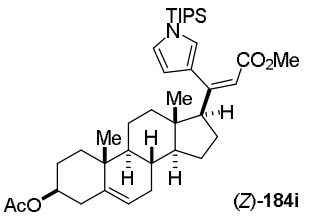
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 6.71 (t, $^3J_{HH}$ = 1.8 Hz, 1H, H_{Ar}), 6.61 (dd, $^3J_{HH}$ = 2.8, 2.1 Hz, 1H, H_{Ar}), 6.24 (dd, $^3J_{HH}$ = 2.8, 1.4 Hz, 1H, H_{Ar}), 5.90 (s, 1H, H_{22}), 5.31-5.29 (m, 1H, H_6), 4.50-4.42 (m, 1H, H_3), 4.01 (t, $^3J_{HH}$ = 8.8 Hz, 1H, H_{17}), 3.57 (s, 3H, O*Me*), 2.22-2.20 (m, 2H, H_4), 1.96-1.88 (m, 4H), 1.80-1.68 (m, 3H), 1.57-1.12 (m, 11H), 1.09-0.93 (m, 24H), 0.91 (s, 3H, Me_{19}), 0.42 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 170.6 (Me*C*O), 167.8 (*C*O_2Me), 157.2 (C_{20}), 140.4 (C_5), 128.8 (C_{Ar}), 124.3 (C_{Ar}H), 124.3 (C_{Ar}H), 122.8 (C_6H), 117.9 (C_{22}H), 112.0 (C_{Ar}H), 74.3 (C_3H), 56.5 (C_{14}H), 51.0 (*Me*O), 50.7 (C_9H), 50.6 (C_{17}H), 47.2 (C_{13}), 38.5 (C_4H_2), 37.4 ($C_{12}H_2$), 37.3 (C_1H_2), 37.1 (C_{10}), 32.4 (C_7H_2), 32.3 (C_8H), 28.2(C_2H_2), 25.7 ($C_{16}H_2$), 25.4 ($C_{15}H_2$), 21.6 (*Me*CO), 21.2 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 17.9 (Me_2CHSi), 17.9 (Me_2CHSi), 14.5 ($C_{18}H_3$), 12.0 (*C*HSi).

HRMS (MALDI–TOF) calculated for $C_{38}H_{59}NO_4SiNa$ $[M+Na]^+$: 644.4106, found 644.4141.

IR (neat): ν (cm^{-1}) = 2945, 2868, 1732, 1714, 1595, 1464, 1434, 1369, 1306, 1242, 1164, 1113, 1089, 1023, 960, 923, 882, 795, 737, 691, 657.

$[\alpha]^{25}_D$ = –55.3 (*c* 1.1, CH_2Cl_2).



(*Z*)-**184i**

Following general procedure C using 3-bromo-1-tri(*iso*propylsilyl)pyrrole (0.18 mL, 0.63 mmol), *n*-butyl lithium (0.44 mL, 0.59 mmol), an anhydrous zinc chloride solution (0.71 mL, 0.71 mmol), enoate **173** (250 mg, 0.46 mmol) and tertakis(triphenylphosphine)palladium (15.8 mg, 3.0 mol%) in THF (9 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 20/1) gave (*Z*)-**184i** (220 mg, 78%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.50).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.77 (dd, $^3J_{HH}$ = 2.1, 1.4 Hz, 1H, H_{Ar}), 6.68 (dd, $^3J_{HH}$ = 2.8, 2.1 Hz, 1H, H_{Ar}), 6.27 (dd, $^3J_{HH}$ = 2.8, 1.4 Hz, 1H, H_{Ar}), 5.73 (d, $^3J_{HH}$ = 1.1 Hz, 1H, H_{22}), 5.36-5.35 (m, 1H, H_6), 4.62-4.54 (m, 1H, H_3), 3.58 (s, 3H, O*Me*), 2.64 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.34-2.24 (m, 2H, H_4), 2.02 (s, 3H, *Me*CO), 1.98-1.95 (m. 1H, H_7), 1.92-1.70 (m, 5H),

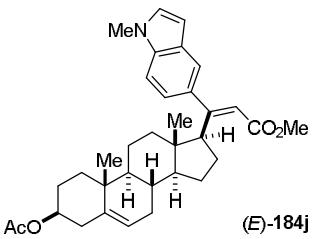
1.60-1.37 (m, 5H), 1.29-1.16 (m, 4H), 1.12-1.03 (m, 22H), 0.99-0.83 (m, 6H), 0.58 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 168.4 (*C*O_2Me), 152.1 (C_{20}), 139.7 (C_5), 125.7 (C_{Ar}), 123.7 (C_{Ar}H), 123.4 (C_{Ar}H), 122.4 (C_6H), 113.8 (C_{22}H), 111.6 (C_{Ar}H), 73.9 (C_3H), 58.4 (C_{17}H), 56.9 (C_{14}H), 50.9 (*Me*O), 50.1 (C_9H), 44.1 (C_{13}), 38.5 (C_4H_2), 38.1 ($C_{12}H_2$), 36.9 (C_1H_2), 36.6 (C_{10}), 32.3 (C_8H), 31.8 (C_7H_2), 27.7(C_2H_2), 25.4 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 17.8 (Me_2CHSi), 17.8 (Me_2CHSi), 12.6 ($C_{18}H_3$), 11.6 (*C*HSi).

HRMS (ESI) calculated for $C_{38}H_{59}NO_4SiNa$ $[M+Na]^+$: 644.4106, found 644.4135.

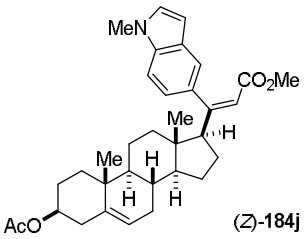
IR (neat): ν (cm^{-1}) = 2944, 2868, 1730, 1616, 1464, 1370, 1240, 1168, 1083, 1016, 922, 882, 801, 770, 732, 690, 658.

$[\alpha]^{25}_D$ = +14.0 (*c* 1.7, CH_2Cl_2).



(*E*)-**184j**

Following general procedure A using 5-(*N*-methyl)indole magnesium bromide (0.5 M in THF, 1.1 mL, 0.51 mmol),[17] an anhydrous zinc chloride solution (0.51 mL, 0.51 mmol), enoate **172** (240 mg, 0.42 mmol) and bis(triphenylphosphine)palladium chloride (8.9 mg, 3.0 mol%) in THF (8.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 8/1 to 4/1) gave (*E*)-**184j** as colorless foam (149 mg, Pentane/Ethyl acetate = 4/1, R_f = 0.35).[18]



(*Z*)-**184j**

Following general procedure A using 5-(*N*-methyl)indole magnesium bromide (0.5 M in THF, 0.87 mL, 0.44 mmol),[17] an anhydrous zinc chloride solution (0.44 mL, 0.44 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (12.6 mg, 3.0 mol%) in THF (7.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 6/1 to 4/1) gave (*Z*)-**184j** (113 mg, 59%).

White solid, m.p. = 229–230 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.42 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H_{Ar}), 7.26-7.24 (m, 1H, H_{Ar}), 7.04-7.02 (m, 2H, H_{Ar}), 6.45 (dd, $^3J_{HH}$ = 3.1, 0.9 Hz, 1H, H_{Ar}), 5.92 (d, $^3J_{HH}$ = 1.4 Hz, 1H, H_{22}), 5.35-5.33 (m, 1H, H_6), 4.58-4.50 (m, 1H, H_3), 3.78 (s, 3H, *Me*N), 3.50 (s, 3H, O*Me*), 2.76 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 2.05-1.84 (m, 6H), 1.84-1.65 (m, 3H), 1.56-1.37 (m, 4H), 1.30-1.12 (m, 5H), 1.02-0.95 (m, 1H, H_1), 0.92 (s, 3H, Me_{19}), 0.84-0.73 (m, 2H, H_9+H_{12}), 0.68-0.58 (m, 4H, H_{12}+Me_{18}).

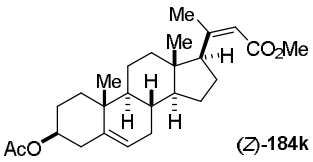
[18] (*E*)-**184j** was obtained in 63% purity. The contaminated unknown byproducts were easily removed by chromatography after DIBAL reduction (*vide infra*).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.5 (*C*O_2Me), 160.9 (C_{20}), 139.7 (C_5), 136.4 (C_{Ar}), 132.7 (C_{Ar}), 128.9 (C_{Ar}H), 127.9 (C_{Ar}), 122.4 (C_6H), 122.1 (C_{Ar}H), 119.7 (C_{Ar}H), 116.4 (C_{22}H), 108.2 (C_{Ar}H), 101.3 (C_{Ar}H), 73.9 (C_3H), 59.5 (C_{17}H), 57.0 (C_{14}H), 50.9 (*Me*O), 50.0 (C_9H), 44.1 (C_{13}), 38.1 (C_4H_2), 37.9 ($C_{12}H_2$), 36.9 (C_1H_2), 36.5 (C_{10}), 32.9 (*Me*N), 32.2 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 25.6 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{34}H_{43}NO_4$ $[M+H]^+$: 530.3265, found 530.3270.

IR (neat): ν (cm^{-1}) =.2941, 2892, 2844, 1727, 1620, 1434, 1375, 1282, 1239, 1183, 1140, 1029, 800, 725.

$[\alpha]^{25}_D$ = +61.9 (*c* 0.10, CH_2Cl_2).



(*Z*)-**184k**

Following general procedure A using methyl magnesium bromide (3.0 M in Et_2O, 0.51 mL, 1.5 mmol), an anhydrous zinc chloride solution (1.8 mL, 1.8 mmol), enoate **172** (400 mg, 0.70 mmol) and bis(triphenylphosphine)palladium chloride (14.7 mg, 3.0 mol%) in THF (7.0 mL, 0.1 M). Purification by flash chromatography (Pentane/ Ethyl acetate = 12/1) gave (*Z*)-**184k** (170 mg, 59%).

White solid, m.p. = 168–170 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.55).

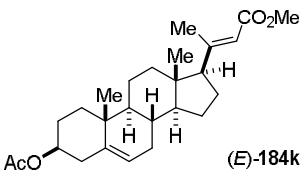
^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.79-5.78 (m, 1H, H_{22}), 5.39-5.37 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 3.88 (t, $^3J_{HH}$ = 9.4 Hz, 1H, H_{17}), 3.65 (s, 3H, O*Me*), 2.36-2.26 (m, 2H, H_4), 2.03 (s, 3H, *Me*CO), 1.99-1.96 (m, 1H, H_7), 1.90 (d, $^3J_{HH}$ = 1.3 Hz, 3H, Me_{21}), 1.89-1.69 (m, 4H), 1.62-1.36 (m, 7H), 1.31-1.21 (m, 2H), 1.12 (td, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 13.0, 4.1 Hz, 1H, H_1), 1.04-0.97 (m, 4H, H_9+Me_{19}), 0.68 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.0 (*C*O_2Me), 160.2 (C_{20}), 139.7 (C_5), 122.5 (C_6H), 118.5 (C_{22}H), 73.9 (C_3H), 55.8 (C_{14}H), 50.7 (*Me*O), 50.1 (C_9H), 49.8 (C_{17}H), 46.9 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.7 (C_{10}), 36.6 (C_1H_2), 31.9 (C_8H), 31.9 (C_7H_2), 27.8(C_2H_2), 24.9 ($C_{16}H_2$), 24.7 ($C_{15}H_2$), 24.0 (Me_{21}), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{26}H_{39}O_4$ $[M+H]^+$: 485.2843, found 485.2836.

IR (neat): ν (cm^{-1}) =.2945, 2908, 1729, 1715, 1620, 1436, 1367, 1246, 1211, 1154, 1032, 954, 918, 863, 798, 736, 665.

$[\alpha]^{25}_D$ = –153.5 (*c* 0.10, CH_2Cl_2).



(*E*)-**184k**

Following general procedure A using methyl magnesium bromide (3.0 M in Et_2O, 0.33 mL, 1.0 mmol), an anhydrous zinc chloride solution (1.1 mL, 1.1 mmol), enoate **173** (250 mg, 0.46 mmol) and tertakis(triphenylphosphine)palladium (15.8 mg, 3.0 mol%) in THF (5.0 mL, 0.1 M). Purification by flash chromatography (Eluent: Pentane/Ethyl acetate = 20/1) gave (*E*)-**184k** (240 mg, 86%).

White solid, m.p. = 144−146 °C (Pentane/Ethyl acetate = 8/1, R_f = 0.45).

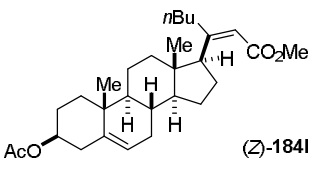
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.71-5.70 (m, 1H, H_{22}), 5.38-5.37 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 3.69 (s, 3H, O*Me*), 2.37-2.26 (m, 2H, H_4), 2.22-2.17 (m, 4H), 2.03 (s, 3H, *Me*CO), 1.99-1.96 (m, 1H, H_7), 1.89-1.82 (m, 3H), 1.76-1.38 (m, 6H), 1.30-1.10 (m, 4H), 1.03-0.96 (m, 4H, H_9+Me_{19}), 0.60 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.4 (*C*O_2Me), 160.4 (C_{20}), 139.7 (C_5), 122.4 (C_6H), 115.6 (C_{22}H), 73.9 (C_3H), 60.3 (C_{17}H), 56.5 (C_{14}H), 50.8 (*Me*O), 50.1 (C_9H), 44.5 (C_{13}), 38.5 (C_4H_2), 38.1 ($C_{12}H_2$), 37.0 (C_1H_2), 36.6 (C_{10}), 32.1 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 24.9 ($C_{16}H_2$), 24.3 ($C_{15}H_2$), 21.4 (*Me*CO), 21.0 ($C_{11}H_2$), 20.7 (Me_{21}), 19.3 ($C_{19}H_3$), 12.9 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{26}H_{39}O_4$ $[M+H]^+$: 485.2843, found 485.2837.

IR (neat): ν (cm^{-1}) =.2949, 2909, 1731, 1716, 1626, 1470, 1429, 1377, 1363, 1234, 1151, 1021, 980, 854, 899, 873, 837, 824, 800, 756, 738.

$[\alpha]^{25}_D$ = −35.0 (*c* 0.14, CH_2Cl_2).



(*Z*)-**184l**

Following general procedure A using *n*-butylmagnesium chloride (1.7 M in THF/Toluene, 0.95 mL, 1.6 mmol), an anhydrous zinc chloride solution (1.8 mL, 1.8 mmol), enoate **172** (420 mg, 0.74 mmol) and bis(triphenylphosphine)palladium chloride (15.7 mg, 3.0 mol%) in THF (7.0 mL, 0.1 M). Purification by flash chromatography (Pentane/Ethyl acetate = 12/1) gave (*Z*)-**184l** (155 mg, 46%).

Colorless foam (Pentane /Ethyl acetate = 4/1, R_f = 0.45).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.75 (s, 1H, H_{22}), 5.38-5.36 (m, 1H, H_6), 4.64-4.56 (m, 1H, H_3), 3.93 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 3.65 (s, 3H, O*Me*), 2.36-2.25 (m, 2H, H_4), 2.19-2.06 (m, 2H, H_{21}), 2.03 (s, 3H, *Me*CO), 1.98-1.95 (m, 1H, H_7), 1.90 (d, $^3J_{HH}$ = 1.3 Hz, 3H, Me_{21}), 1.88-1.69 (m, 4H), 1.62-1.24 (m, 14H), 1.11 (td, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 12.9, 4.1 Hz, 1H, H_1), 1.02-0.98 (m, 4H, H_9+Me_{19}), 0.90 (t, $^3J_{HH}$ = 7.0 Hz, 3H, $CH_3CH_2CH_2CH_2$), 0.63 (s, 3H, Me_{18}).

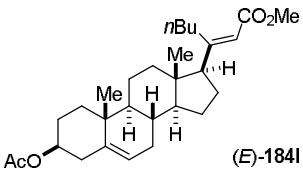
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.5 (*C*O_2Me), 164.5 (C_{20}), 139.7 (C_5), 122.5 (C_6H), 117.4 (C_{22}H), 73.9 (C_3H), 55.7 (C_{14}H), 50.7 (*Me*O), 50.1 (C_9H), 49.9 (C_{17}H), 47.2 (C_{13}), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.7 (C_{10}), 36.3 (C_1H_2), 35.4 ($CH_2CH_2CH_2CH_3$),

32.5 (*C*$H_2CH_2CH_3$), 31.9 (*C*$_8$H), 31.9 (*C*$_7H_2$), 27.7(*C*$_2H_2$), 25.0 (*C*$_{16}H_2$), 24.3 (*C*$_{15}H_2$), 22.7 (*C*H_2CH_3), 21.4 (*Me*CO), 20.7 (*C*$_{11}H_2$), 19.3 (*C*$_{19}H_3$), 14.0 (*C*$_{18}H_3$), 13.7 (*C*$H_3CH_2CH_2CH_2$).

HRMS (+ESI) calculated for $C_{29}H_{44}O_4$ $[M+H]^+$: 457.3312, found 457.3319.

IR (neat): ν (cm^{-1}) =.2946, 1722, 1624, 1434, 1372, 1241, 1214, 1196, 1151, 1096, 1030, 956, 913, 865, 732.

$[\alpha]^{25}_D$ = −131.7 (*c* 0.13, CH_2Cl_2).



(*E*)-**184l**

Following general procedure A using *n*-butylmagnesium chloride (1.7 M in THF/Toluene, 0.47 mL, 0.80 mmol), an anhydrous zinc chloride solution (0.91 mL, 0.91 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (12.6 mg, 3.0 mol%) in THF (3.0 mL, 0.1 M). Purification by flash chromatography (Pentane/Ethyl acetate = 12/1) gave (*E*)-**184l** (126 mg, 76%).

Colorless foam (Pentane /Ethyl acetate = 4/1, R_f = 0.50).

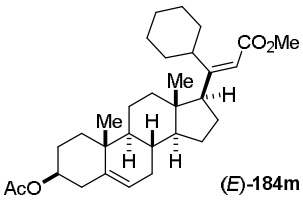
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.67 (d, $^3J_{HH}$ = 0.9 Hz, 1H, *H*$_{22}$), 5.38-5.36 (m, 1H, *H*$_6$), 4.64-4.56 (m, 1H, *H*$_3$), 3.68 (s, 3H, O*Me*), 2.99-2.92 (m, 1H, *H*$_{21}$), 2.35-2.16 (m, 4H), 2.03 (s, 3H, *Me*CO), 1.99-1.96 (m, 1H, *H*$_7$), 1.88-1.70 (m, 6H), 1.62-1.10 (m, 14H), 1.02-0.95 (m, 4H, *H*$_9$+*Me*$_{19}$), 0.91 (t, $^3J_{HH}$ = 7.0 Hz, 3H, C*H*$_3$CH$_2$CH$_2$CH$_2$), 0.60 (s, 3H, *Me*$_{18}$).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.0 (*C*O_2Me), 165.4 (*C*$_{20}$), 139.7 (*C*$_5$), 122.4 (*C*$_6$H), 115.1 (*C*$_{22}$H), 73.9 (*C*$_3$H), 58.3 (*C*$_{17}$H), 56.7 (*C*$_{14}$H), 50.8 (*Me*O), 50.1 (*C*$_9$H), 44.7 (*C*$_{13}$), 38.3 (*C*$_4H_2$), 38.1 (*C*$_{12}H_2$), 37.0 (*C*$_1H_2$), 36.6 (*C*$_{10}$), 33.6 (*C*$H_2CH_2CH_2CH_3$), 32.2 (*C*$_8$H), 31.8 (*C*$_7H_2$), 31.6 (*C*$H_2CH_2CH_3$), 27.7(*C*$_2H_2$), 25.9 (*C*$_{16}H_2$), 24.4 (*C*$_{15}H_2$), 23.2 (*C*H_2CH_3), 21.4 (*Me*CO), 21.0 (*C*$_{11}H_2$), 19.3 (*C*$_{19}H_3$), 14.0 (*C*$H_3CH_2CH_2CH_2$), 13.0 (*C*$_{18}H_3$).

HRMS (+ESI) calculated for $C_{29}H_{44}O_4$ $[M+H]^+$: 457.3312, found 457.3318.

IR (neat): ν (cm^{-1}) =.2946, 1719, 1633, 1435, 1373, 1317, 1239, 1194, 1148, 1030, 958, 911, 870, 731, 648, 610.

$[\alpha]^{25}_D$ = −15.0 (*c* 0.50, CH_2Cl_2).



(*E*)-**184m**

Following general procedure A using cyclohexylmagnesium chloride (1.3 M in THF/Toluene, 1.2 mL, 1.6 mmol), an anhydrous zinc chloride solution (1.8 mL, 1.8 mmol), enoate **173** (400 mg, 0.72 mmol), palladium acetate (5.0 mg, 3.0 mol%) and CPhos (19 mg, 6.0 mol%) in THF (15 mL, 0.05 M).[19] The reaction was

[19] C. Han, S. L. Buchwald, *J. Am. Chem. Soc*. **2009**, **131**, 7532–7533.

performed first at 40 °C for 4 h followed by additional 2 h at 60 °C before quenching. Purification by flash chromatography (Pentane/Ethyl acetate = 30/1) gave (*E*)-**184m** (170 mg, 48%).

Colorless foam (Pentane /Ethyl acetate = 8/1, R_f = 0.50).

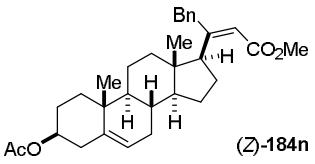
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.74 (s, 1H, H_{22}), 5.39-5.37 (m, 1H, H_6), 4.62-4.59 (m, 1H, H_3), 3.68 (s, 3H, O*Me*), 3.58-3.53 (m, 1H, H_{21}), 2.33-2.31 (m, 3H, H_4+Me_{17}), 2.03 (s, 3H, *Me*CO), 2.02-1.11 (m, 28H), 1.03 (s, 3H, Me_{19}), 1.01-0.94 (m, 1H, H_9), 0.76 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 169.6 (C_{20}), 167.2 (CO_2Me), 139.7 (C_5), 122.4 (C_6H), 115.9 (C_{22}H), 73.9 (C_3H), 57.1 (C_{14}H), 52.9 (C_{17}H), 50.8 (*Me*O), 50.0 (C_9H), 44.8 (C_{13}), 41.9 (C_{21}H), 38.6 ($C_{12}H_2$), 38.1 (C_4H_2), 37.0 (C_1H_2), 36.6 (C_{10}), 32.2 (C_8H), 32.1 (CH_{2cy}), 31.8 (C_7H_2), 31.1 (CH_{2cy}), 30.2 (CH_{2cy}), 27.8(C_2H_2), 26.5 (CH_{2cy}), 26.3 (CH_{2cy}), 26.1 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 21.4 (*Me*CO), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 13.6 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{31}H_{47}O_4$ $[M+H]^+$: 483.3469, found 483.3486.

IR (neat): ν (cm^{-1}) =.2929, 2852, 1731, 1717, 1626, 1436, 1367, 1240, 1199, 1146, 1030, 942, 895, 875.

$[\alpha]^{25}_D$ = +3.8 (*c* 0.10, THF).



(*Z*)-**184n**

Following general procedure A using benzylicmagnesium chloride (1.0 M in Et_2O, freshly prepared, 1.0 mL, 1.0 mmol),[20] an anhydrous zinc chloride solution (1.1 mL, 1.1 mmol), enoate **172** (260 mg, 0.46 mmol) and bis(triphenylphosphine)palladium chloride (9.7 mg, 3.0 mol%) in THF (9.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 20/1) gave (*Z*)-**184n** (145 mg, 65%).

Colorless foam (Pentane /Ethyl acetate = 8/1, R_f = 0.45).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.32-7.28 (m, 2H, 2$H_{meta\text{-}Ph}$), 7.23-7.18 (m, 1H, $H_{para\text{-}Ph}$), 7.15-7.12 (m, 2H, $H_{ortho\text{-}Ph}$), 5.52 (s, 1H, H_{22}), 5.39-5.37 (m, 1H, H_6), 4.64-4.58 (m, 1H, H_3), 4.00 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 3.63 (s, 3H, O*Me*), 3.54 (s, 2H, H_{21}), 2.38-2.29 (m, 2H, H_4), 2.03 (s, 3H, *Me*CO), 1.99-1.09 (m, 16H), 1.13 (td, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 13.5, 4.2 Hz, 1H, H_1), 1.03 (s, 3H, Me_{19}), 0.81 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.4 (CO_2Me), 161.9 (C_{20}), 139.0 (C_{Ph}), 139.7 (C_5), 129.3 ($C_{ortho\text{-}Ph}$), 128.5 ($C_{meta\text{-}Ph}$), 126.3 ($C_{para\text{-}Ph}$), 122.5 (C_6H), 120.4 (C_{22}H), 73.9 (C_3H), 55.8 (C_{14}H), 50.8 (*Me*O), 50.1 (C_9H), 49.9 (C_{17}H), 47.4 (C_{13}), 41.9 ($C_{21}H_2$), 38.1 (C_4H_2), 37.0 ($C_{12}H_2$), 36.7 (C_{10}), 36.4 (C_1H_2), 31.9 (C_8H), 31.9 (C_7H_2),

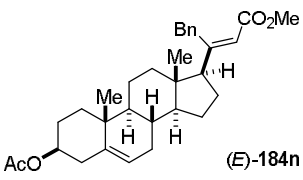
[20] Benzylicmagnesium chloride can also be used right after the preparation. Commercially available reagent shows low concentration due to decomposition. For the preparation, see: A. Shokri, J. Schmidt, X.-B. Wang, S. R. Kass, *J. Am. Chem. Soc*. **2012**, **134**, 2094–2099.

27.7(C_2H_2), 24.9 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 21.4 (*Me*CO), 20.7 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.1 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{32}H_{42}O_4$ $[M]^+$: 490.3, found $[M+H]^+$: 491.6.

IR (neat): ν (cm^{-1}) = 2945, 1724, 1627, 1495, 1434, 1373, 1243, 1197, 1175, 1152, 1032, 956, 737, 701.

$[\alpha]^{25}_D$ = −115.2 (*c* 0.10, THF).



(*E*)-**184n**

Following general procedure A using benzylicmagnesium chloride (1.0 M in Et_2O, freshly prepared, 0.8 mL, 0.8 mmol),[22] an anhydrous zinc chloride solution (0.91 mL, 0.91 mmol), enoate **173** (200 mg, 0.36 mmol) and tertakis(triphenylphosphine)palladium (12.6 mg, 3.0 mol%) in THF (7.0 mL, 0.05 M). Purification by flash chromatography (Pentane/Ethyl acetate = 15/1) gave (*E*)-**184n** (170 mg, 95%).

Colorless foam (Pentane /Ethyl acetate = 8/1, R_f = 0.40).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.28-7.24 (m, 2H, 2$H_{meta\text{-}Ph}$), 7.20-7.16 (m, 3H, 2$H_{ortho\text{-}Ph}$+$H_{para\text{-}Ph}$), 5.93 (s, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.80 (d, $^2J_{HH}$ = 13.9 Hz, 1H, H_{21}), 4.64-4.56 (m, 1H, H_3), 3.72 (s, 3H, O*Me*), 3.37 (d, $^2J_{HH}$ = 13.9 Hz, 1H, H_{21}), 2.32-2.30 (m, 2H, H_4), 2.25-2.20 (m, 1H, H_{17}), 2.03 (s, 3H, *Me*CO), 1.99-1.06 (m, 16H), 1.02 (s, 3H, Me_{19}), 0.99-0.94 (m, 1H, H_9), 0.68 (s, 3H, Me_{18}).

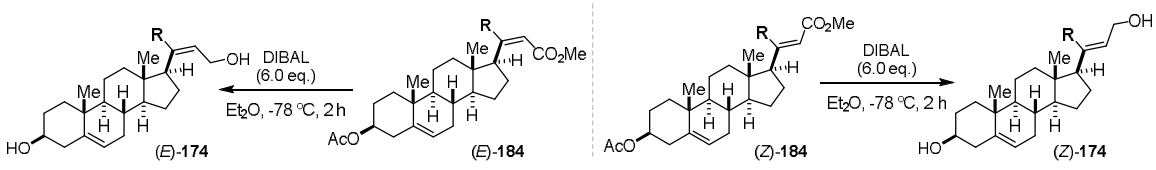
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.2 (*C*O_2Me), 161.2 (C_{20}), 139.7 (C_5), 139.1 (C_{Ph}), 128.8 ($C_{ortho\text{-}Ph}$), 128.3 ($C_{meta\text{-}Ph}$), 126.0 ($C_{para\text{-}Ph}$), 122.3 (C_6H), 117.0 (C_{22}H), 73.8 (C_3H), 56.7 (C_{17}H), 56.7 (C_{14}H), 51.0 (*Me*O), 50.0 (C_9H), 44.5 (C_{13}), 38.9 ($C_{21}H_2$), 38.6 (C_4H_2), 38.1 ($C_{12}H_2$), 37.0 (C_1H_2), 36.6 (C_{10}), 32.2 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 26.6 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.4 (*Me*CO), 21.1 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 13.2 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{32}H_{42}O_4$ $[M]^+$: 490.3, found $[M+H]^+$: 491.8.

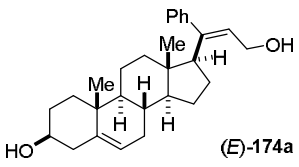
IR (neat): ν (cm^{-1}) = 2943, 1723, 1640, 1436, 1373, 1242, 1167, 1031, 874, 700.

$[\alpha]^{25}_D$ = +41.7 (*c* 0.10, THF).

*7.3.1.4. General procedure for the syntheses of (E) and (Z)-allylic alcohols (**174**)*



To a solution of either (*E*)- or (*Z*)-Enoate **184** (0.32 mmol) in anhydrous diethyl ether (10 mL, 0.03 M) was added dropwise diisobutylaluminium hydride (1.9 mmol, 6.0 eq., 1.0 M in hexanes) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution (25 mL). The resulting white suspension was stirred at ambient temperature for 2 h before extraction with Et_2O/THF (5:1 v/v, 3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash chromatography.



(*E*)-**174a**

Following the general procedure using enoate (*E*)-**184a** (150 mg, 0.32 mmol) and diisobutylaluminium hydride (1.9 mL, 1.9 mmol) in anhydrous diethyl ether (10 mL, 0.03 M). Purification by flash chromatography ($CHCl_3$/Acetone = 3/1) gave (*E*)-**174a** (115 mg, 90%).

White solid, m.p. = 181−184 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.27-7.20 (m, 3H, $2H_{ortho\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.15-7.13 (m, 2H, $H_{meta\text{-}Ph}$), 5.61 (dd, $^3J_{HH}$ = 7.8, 5.4 Hz, 1H, H_{22}), 5.35-5.34 (m, 1H, H_6), 4.45 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 7.8 Hz, H_{23}), 4.29 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.5 Hz, H_{23}), 3.55-3.49 (m, 1H, H_3), 2.70 (dd, $^3J_{HH}$ = 8.5 Hz, 1H, H_{17}), 2.31-2.19 (m, 2H, H_4), 2.00-1.92 (m, 2H, H_7+H_{16}), 1.89-1.80 (m, 3H, H_1+H_2+H_{16}), 1.74-1.69 (m, 1H, H_{15}), 1.66-1.63 (m, 1H, H_{12}), 1.59-1.34 (m, 5H, H_2+H_7+H_8+$2H_{11}$), 1.15-1.01 (m, 4H, H_1+H_{12}+H_{14}+H_{15}), 0.98-0.92 (m, 4H, H_9+Me_{19}), 0.44 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 144.7 (C_{Ph}), 144.5 (C_{20}), 140.8 (C_5), 132.5 (C_{22}H), 129.4 ($C_{meta\text{-}Ph}$), 127.3 ($C_{ortho\text{-}Ph}$), 126.2 ($C_{para\text{-}Ph}$), 121.5 (C_6H), 71.7 (C_3H), 59.7 ($C_{23}H_2$), 55.9 (C_{14}H), 52.2 (C_{17}H), 50.3 (C_9H), 46.2 (C_{13}), 42.2 (C_4H_2), 38.1 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 26.0 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 14.1 ($C_{18}H_3$).

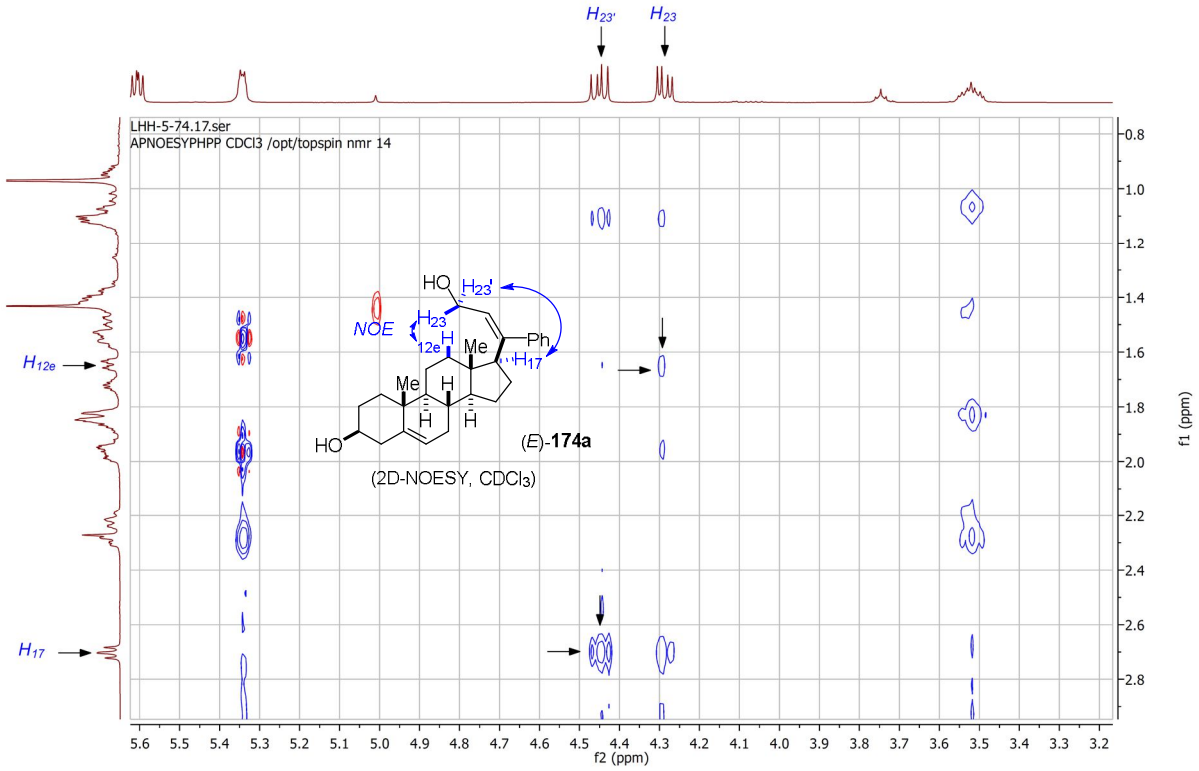
HRMS (MALDI−TOF) calculated for $C_{28}H_{38}O_2Na$ $[M+Na]^+$: 429.2764, found 429.2741.

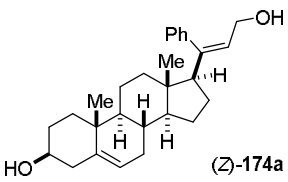
IR (neat): ν (cm^{-1}) = 3262, 2933, 1437, 1359, 1221, 1124, 1112, 1043, 1024, 1007, 952, 837, 808, 768, 704.

$[\alpha]^{25}_D$ = −85.4 (*c* 0.12, THF).

The locked confirmation of (*E*)-**174a** was determined by 2D−NOESY and confirmed by single crystal X-ray diffraction analysis.

The original 2D-NOESY spectrum of (*E*)-**174a** were shown as below:





Following the general procedure using enoate (*Z*)-**184a** (131 mg, 0.28 mmol) and diisobutylaluminium hydride (1.7 mL, 1.7 mmol) in anhydrous diethyl ether (10 mL, 0.03 M). Purification by flash chromatography ($CHCl_3$/Acetone = 3/1) gave (*Z*)-**174a** (114 mg, >99%).

White solid, m.p. = 174−176 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.31-7.22 (m, 3H, $2H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.11-7.09 (m, 2H, $H_{ortho\text{-}Ph}$), 5.69 (ddd, $^3J_{HH}$ = 7.6, 6.0, 1.6 Hz, 1H, H_{22}), 5.34-5.32 (m, 1H, H_6), 4.11-4.01 (m, 2H, H_{23}), 3.52-3.44 (m, 1H, H_3), 2.54 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 2.30-2.17 (m, 2H, H_4), 2.02-1.91 (m, 2H, H_7+H_{16}), 1.86-1.67 (m, 4H, H_1+H_2+H_{15}+H_{16}), 1.56-1.36 (m, 3H, H_2+H_7+H_8), 1.31-1.05 (m, 3H, $2H_{11}$+H_{14}), 1.02-0.93 (m, 4H, H_1+Me_{19}), 0.86-0.77 (m, 2H, H_9+H_{12}), 0.69-0.60 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 144.4 (C_{Ph}), 141.8 (C_{20}), 140.8 (C_5), 128.5 ($C_{ortho\text{-}Ph}$), 127.8 ($C_{meta\text{-}Ph}$), 126.8 ($C_{para\text{-}Ph}$), 125.8 (C_{22}H), 121.5 (C_6H), 71.7 (C_3H), 60.5 ($C_{23}H_2$), 57.2 (C_{17}H), 56.7 (C_{14}H), 50.2 (C_9H), 43.3 (C_{13}), 42.2 (C_4H_2), 38.2 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 32.2 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 25.1 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.6 ($C_{18}H_3$).

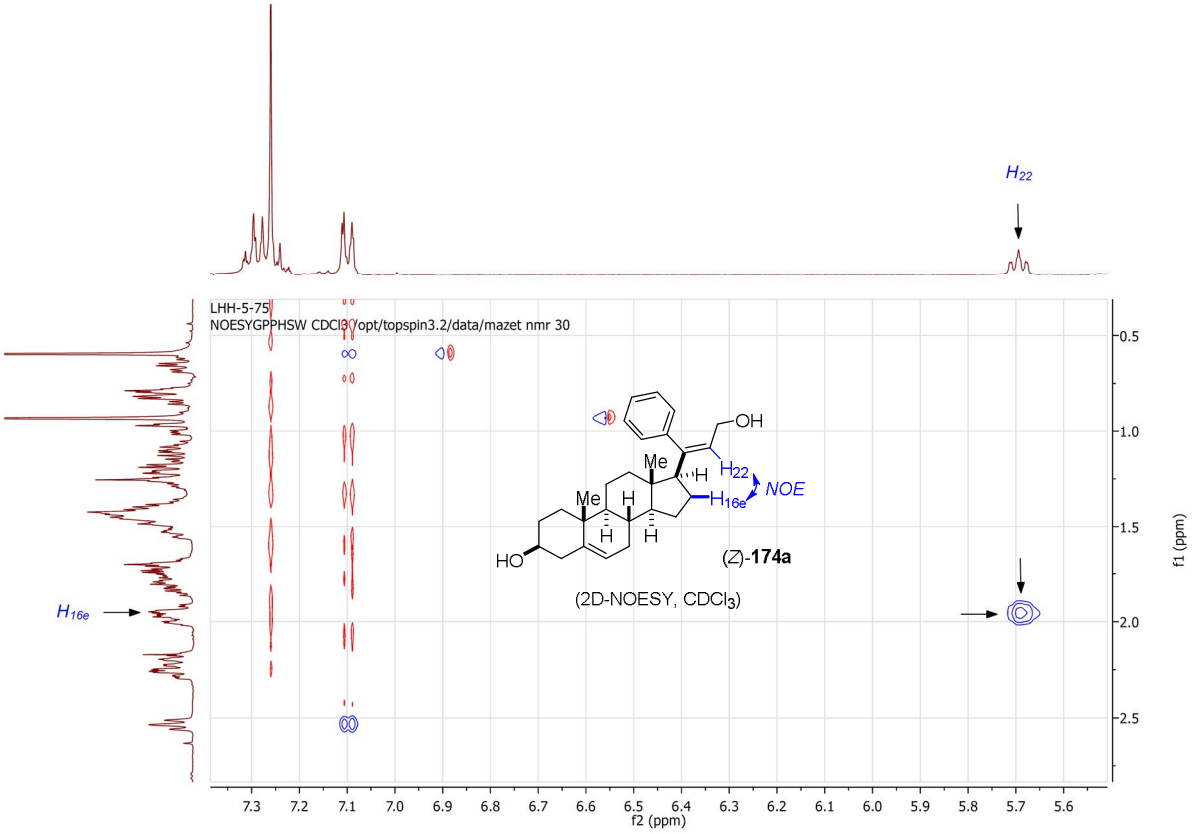
HRMS (+ESI) calculated for $C_{28}H_{38}O_2$ $[M-OH]^+$: 389.2839, found 389.2824.

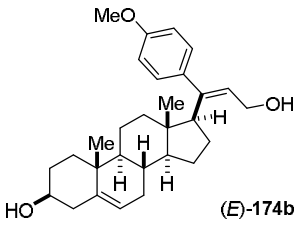
IR (neat): ν (cm^{-1}) = 3286, 2930, 2888, 1490, 1454, 1438, 1379, 1355, 1059, 1045, 1023, 1005, 950, 845, 802.

$[\alpha]^{25}_D$ = +32.0 (*c* 0.12, THF).

The locked confirmation of (*Z*)-**174a** was determined by 2D–NOESY and confirmed by single crystal X-ray diffraction analysis.

The original 2D-NOESY spectrum of (*Z*)-**174a** were shown as below:





Following the general procedure using enoate (*E*)-**184b** (119 mg, 0.24 mmol) and diisobutylaluminium hydride (1.4 mL, 1.4 mmol) in anhydrous diethyl ether (10 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 3/1) gave (*E*)-**174b** (63 mg, 61%).

White solid, m.p. = 158–160 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.06 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{ortho\text{-}Ph}$), 6.79 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{meta\text{-}Ph}$), 5.59 (dd, $^3J_{HH}$ = 7.9, 5.5, 0.7 Hz, 1H, H_{22}), 5.36-5.33 (m, 1H, H_6), 4.43 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, H_{23}), 4.27 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, H_{23}), 3.80

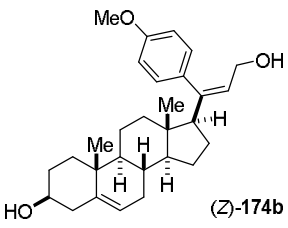
(s, 3H, *Me*OC$_6$H$_4$), 3.56-3.48 (m, 1H, H_3), 2.68 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 2.31-2.20 (m, 2H, H_4), 1.99-1.36 (m, 17H), 1.15-1.06 (m, 4H), 0.98-0.91 (m, 4H, H_9+Me_{19}), 0.44 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 158.0 (C_{Ar}), 144.1 (C_{20}), 140.8 (C_5), 137.2 (C_{Ar}), 132.3 (C_{22}H), 130.4 (C_{Ar}H), 121.5 (C_6H), 112.7 (C_{Ar}H), 71.7 (C_3H), 59.8 (C_{23}H$_2$), 55.9 (C_{14}H), 55.2 (*Me*OC$_6$H$_4$), 52.3 (C_{17}H), 50.3 (C_9H), 46.1 (C_{13}), 42.3 (C_4H$_2$), 38.1 (C_{12}H$_2$), 37.3 (C_1H$_2$), 36.6 (C_{10}), 31.9 (C_8H), 31.8 (C_7H$_2$), 31.6 (C_2H$_2$), 26.0 (C_{16}H$_2$), 24.6 (C_{15}H$_2$), 20.8 (C_{11}H$_2$), 19.4 (C_{19}H$_3$), 14.1 (C_{18}H$_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2942.

IR (neat): ν (cm^{-1}) = 3339, 2934, 2901, 1608, 1509, 1462, 1438, 1284, 1243, 1176, 1040, 834, 810, 738.

$[\alpha]^{25}_D$ = –66.0 (*c* 0.09, THF).



(*Z*)-**174b**

Following the general procedure using enoate (*Z*)-**184b** (184 mg, 0.36 mmol) and diisobutylaluminium hydride (2.2 mL, 2.2 mmol) in anhydrous diethyl ether (12 mL, 0.03 M). Purification by flash chromatography ($CHCl_3$/Acetone = 3/1) gave (*Z*)-**174b** (100 mg, 63%).

White solid, m.p. = 164–167 °C (Pentane/Ethyl acetate = 1/1, R_f = 0.2).

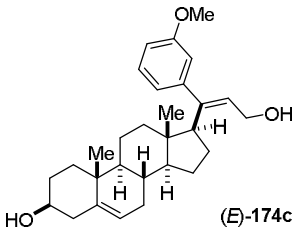
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.02 (d, $^3J_{HH}$ = 8.6 Hz, 2H, $H_{ortho\text{-}Ph}$), 6.83 (d, $^3J_{HH}$ = 8.6 Hz, 2H, $H_{meta\text{-}Ph}$), 5.66 (ddd, $^3J_{HH}$ = 7.6, 6.1, 1.6 Hz, 1H, H_{22}), 5.34-5.32 (m, 1H, H_6), 4.09-4.06 (m, 2H, H_{23}), 3.81 (s, 3H, *Me*OC$_6$H$_4$), 3.52-3.44 (m, 1H, H_3), 2.51 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 2.30-2.16 (m, 2H, H_4), 2.02-1.90 (m, 2H), 1.86-1.67 (m, 4H), 1.56-1.05 (m, 9H), 1.01-0.94 (m, 4H, H_1+Me_{19}), 0.86-0.80 (m, 2H), 0.67 (td, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 12.9, 4.5 Hz, 1H, H_{12}), 0.58 (m, 4H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 158.5 (C_{Ar}), 143.9 (C_{20}), 140.8 (C_5), 134.1 (C_{Ar}), 129.5 (C_{Ar}H), 125.4 (C_{22}H), 121.5 (C_6H), 113.1 (C_{Ar}H), 71.7 (C_3H), 60.6 (C_{23}H$_2$), 57.3 (C_{17}H), 56.7 (C_{14}H), 55.2 (*Me*OC$_6$H$_4$), 50.2 (C_9H), 43.3 (C_{13}), 42.3 (C_4H$_2$), 38.3 (C_{12}H$_2$), 37.2 (C_1H$_2$), 36.4 (C_{10}), 32.3 (C_8H), 31.7 (C_7H$_2$), 31.6 (C_2H$_2$), 25.1 (C_{16}H$_2$), 23.9 (C_{15}H$_2$), 21.0 (C_{11}H$_2$), 19.4 (C_{19}H$_3$), 12.6 (C_{18}H$_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2942.

IR (neat): ν (cm^{-1}) = 3336, 2935, 1608, 1510, 1438, 1375, 1288, 1245, 1178, 1108, 1032, 834, 737.

$[\alpha]^{25}_D$ = +51.5 (*c* 0.11, THF).



(*E*)-**174c**

Following the general procedure using enoate (*E*)-**184c** (120 mg, 0.24 mmol) and diisobutylaluminium hydride (1.4 mL, 1.4 mmol) in anhydrous diethyl ether (20 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*E*)-**174c** (89 mg, 86%).

White solid, m.p. = 180–182 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

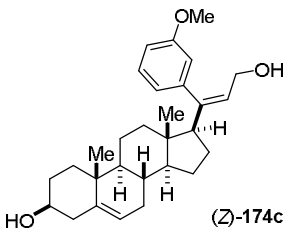
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.17 (t, $^3J_{HH}$ = 7.9 Hz, 1H, $H_{meta\text{-}Ph}$), 6.78-6.69 (m, 3H, H_{Ar}), 5.62 (dd, $^3J_{HH}$ = 7.7, 5.6 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.44 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, H_{23}), 4.28 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, H_{23}), 3.80 (s, 3H, *Me*OC_6H_4), 3.56-3.45 (m, 1H, H_3), 2.69 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.32-2.18 (m, 2H, H_4), 2.01-1.81 (m, 5H), 1.74-1.33 (m, 12H), 1.14-1.03 (m, 4H), 0.97-0.91 (m, 4H, H_9+Me_{19}), 0.46 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 158.6 (C_{Ar}), 146.2 (C_{Ar}), 144.3 (C_{20}), 140.8 (C_5), 132.4 (C_{22}H), 128.3 (C_{Ar}H), 122.0 (C_{Ar}H), 121.5 (C_6H), 115.4 (C_{Ar}H), 111.4 (C_{Ar}H), 71.7 (C_3H), 59.7 ($C_{23}H_2$), 55.9 (C_{14}H), 55.2 (*Me*OC_6H_4), 52.3 (C_{17}H), 50.3 (C_9H), 46.1 (C_{13}), 42.3 (C_4H_2), 38.1 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 32.0 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 26.1 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 14.1 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2942.

IR (neat): ν (cm^{-1}) = 3325, 2934, 1599, 1576, 1482, 1460, 1432, 1284, 1199, 1170, 1049, 1009, 784, 737, 712.

$[\alpha]^{25}_D$ = –66.4 (*c* 0.07, THF).



(*Z*)-**174c**

Following the general procedure using enoate (*Z*)-**184c** (140 mg, 0.28 mmol) and diisobutylaluminium hydride (1.7 mL, 1.7 mmol) in anhydrous diethyl ether (20 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 15/1 to 10/1) gave (*Z*)-**174c** (111 mg, 93%).

White solid, m.p. = 184–186 °C (Pentane/Ethyl acetate = 1/1, R_f = 0.2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.21 (7, $^3J_{HH}$ = 7.6 Hz, 1H, $H_{meta\text{-}Ph}$), 6.78-6.65 (m, 3H, H_{Ar}), 5.68 (ddd, $^3J_{HH}$ = 7.5, 5.9, 1.6 Hz, 1H, H_{22}), 5.34-5.32 (m, 1H, H_6), 4.12-4.02 (m, 2H, H_{23}), 3.80 (s, 3H, *Me*OC_6H_4), 3.52-3.44 (m, 1H, H_3), 2.52 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 2.30-2.16 (m, 2H, H_4), 2.02-1.68 (m, 6H), 1.56-1.07 (m, 6H), 1.01-0.80 (m, 4H), 0.70 (td, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.6 Hz, 1H, H_{12}), 0.60 (s, 3H, Me_{18}).

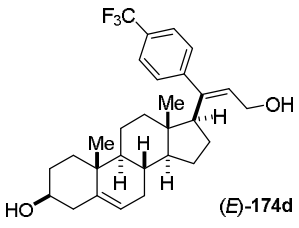
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 159.1 (C_{Ar}), 143.3 (C_{Ar}), 144.1 (C_{20}), 140.8 (C_5), 128.7 (C_{Ar}H), 125.9 (C_{22}H), 121.5 (C_6H), 121.1 (C_{Ar}H), 114.4 (C_{Ar}H), 111.9 (C_{Ar}H), 71.7 (C_3H), 60.5 ($C_{23}H_2$), 57.1 (C_{17}H), 56.7 (C_{14}H), 55.2 (*Me*OC_6H_4), 50.2 (C_9H), 43.3 (C_{13}), 42.3

(C_4H_2), 38.1 ($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 32.3 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 25.2 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 12.6 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2873.

IR (neat): ν (cm^{-1}) = 3344, 2935, 1597, 1577, 1484, 1464, 1432, 1377, 1316, 1284, 1253, 1233, 1170, 1047, 954, 790, 736, 715.

$[\alpha]^{25}_D$ = +31.4 (*c* 0.14, THF).



(*E*)-**174d**

Following the general procedure using enoate (*E*)-**184d** (127 mg, 0.23 mmol) and diisobutylaluminium hydride (1.4 mL, 1.4 mmol) in anhydrous diethyl ether (10 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 15/1) gave (*E*)-**174d** (96 mg, 87%).

White solid, m.p. = 118–120 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.51 (d, $^3J_{HH}$ = 7.9 Hz, 2H, $H_{meta\text{-}Ph}$), 7.25 (d, $^3J_{HH}$ = 8.0 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.60 (dd, $^3J_{HH}$ = 7.7, 5.5 Hz, 1H, H_{22}), 5.35-5.33 (m, 1H, H_6), 4.46 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, H_{23}), 4.30 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, H_{23}), 3.56-3.48 (m, 1H, H_3), 2.71 (t, $^3J_{HH}$ = 9.7 Hz, 1H, H_{17}), 2.32-2.17 (m, 2H, H_4), 2.01-1.33 (m, 12H), 1.15-1.01 (m, 4H), 0.98-0.91 (m, 4H, H_9+Me_{19}), 0.43 (s, 3H, Me_{18}).

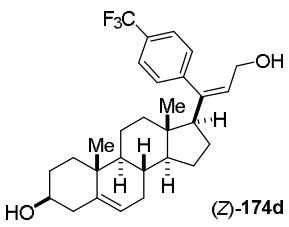
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 148.4 (C_{Ph}), 143.1 (C_{20}), 140.8 (C_5), 133.6 ($C_{22}H$), 129.7 ($C_{ortho\text{-}Ph}$), 128.4 (q, $^2J_{CF}$ = 32.5 Hz, $C_{para\text{-}Ph}CF_3$), 124.3 (q, $^1J_{CF}$ = 272 Hz, CF_3), 124.3 (q, $^3J_{CF}$ = 3.8 Hz, $C_{meta\text{-}Ph}$), 121.4 (C_6H), 71.7 (C_3H), 59.6 ($C_{23}H_2$), 55.8 ($C_{14}H$), 52.1 ($C_{17}H$), 50.3 (C_9H), 46.4 (C_{13}), 42.2 (C_4H_2), 38.1 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 31.9 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 26.0 ($C_{16}H_2$), 24.5 ($C_{15}H_2$), 20.7 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = –62.3.

HRMS (MALDI–TOF) calculated for $C_{29}H_{36}F_3O$ $[M–OH]^+$: 457.2713, found 457.2700.

IR (neat): ν (cm^{-1}) = 3339, 2935, 1436, 1325, 1276, 1164, 1124, 1067, 1019, 844, 738.

$[\alpha]^{25}_D$ = –32.9 (*c* 0.13, CH_2Cl_2).



(*Z*)-**174d**

Following the general procedure using enoate (*Z*)-**184d** (217 mg, 0.40 mmol) and diisobutylaluminium hydride (2.4 mL, 2.4 mmol) in anhydrous diethyl ether (15 mL, 0.03 M). Purification by flash chromatography ($CHCl_3$/Acetone = 3/1) gave (*Z*)-**174d** (189 mg, >99%).

Colorless foam (Pentane/Ethyl acetate = 1/1, R_f = 0.2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.56 (d, $^3J_{HH}$ = 8.0 Hz, 2H, $H_{meta\text{-}Ph}$), 7.24 (d, $^3J_{HH}$ = 5.9 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.76 (ddd, $^3J_{HH}$ = 7.6, 6.0, 1.6 Hz, 1H, H_{22}), 5.34-5.32 (m, 1H, H_6), 4.03

(ddd, $^{2}J_{HH}$ = 18.2 Hz, $^{3}J_{HH}$ = 6.7, 1.1 Hz, 2H, *H*$_{23}$), 4.30 (dd, $^{2}J_{HH}$ = 13.2 Hz, $^{3}J_{HH}$ = 5.3 Hz, *H*$_{23}$), 3.53-3.45 (m, 1H, *H*$_{3}$), 2.53 (t, $^{3}J_{HH}$ = 9.4 Hz, 1H, *H*$_{17}$), 2.30-2.17 (m, 2H, *H*$_{4}$), 2.01-1.69 (m, 6H), 1.57-1.06 (m, 6H), 1.02-0.94 (m, 4H, *H*$_{1}$+*Me*$_{19}$), 0.87-0.77 (m, 2H, *H*$_{9}$+*H*$_{12}$), 0.70-0.60 (m, 4H, *H*$_{12}$+*Me*$_{18}$).

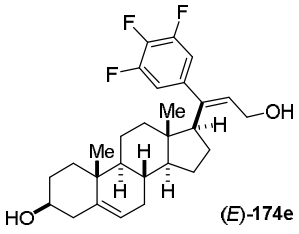
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 145.7 (*C*$_{Ph}$), 143.1 (*C*$_{20}$), 140.8 (*C*$_{5}$), 129.1 (q, $^{2}J_{CF}$ = 32.5 Hz, *C*$_{para\text{-}Ph}CF_3$), 128.8 (*C*$_{ortho\text{-}Ph}$), 127.0 (*C*$_{22}$H), 124.8 (q, $^{3}J_{CF}$ = 3.8 Hz, *C*$_{meta\text{-}Ph}$), 124.2 (q, $^{1}J_{CF}$ = 272 Hz, *C*F_3), 121.4 (*C*$_{6}$H), 71.7 (*C*$_{3}$H), 60.2 (*C*$_{23}H_2$), 57.1 (*C*$_{17}$H), 56.7 (*C*$_{14}$H), 50.1 (*C*$_{9}$H), 43.4 (*C*$_{13}$), 42.2 (*C*$_{4}H_2$), 38.4 (*C*$_{12}H_2$), 37.1 (*C*$_{1}H_2$), 36.4 (*C*$_{10}$), 32.2 (*C*$_{8}$H), 31.7 (*C*$_{7}H_2$), 31.6 (*C*$_{2}H_2$), 25.2 (*C*$_{16}H_2$), 23.8 (*C*$_{15}H_2$), 20.9 (*C*$_{11}H_2$), 19.4 (*C*$_{19}H_3$), 12.7 (*C*$_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −61.6.

HRMS (MALDI−TOF) calculated for $C_{29}H_{36}F_3O$ [M−OH]$^+$: 457.2713, found 457.2700.

IR (neat): ν (cm^{-1}) = 3331, 2935, 1616, 1324, 1278, 1164, 1124, 1064, 1016, 952, 848, 738, 615.

$[\alpha]^{25}_{D}$ = +17.4 (*c* 0.12, CH_2Cl_2).



(*E*)-**174e**

Following the general procedure using enoate (*E*)-**184e** (98 mg, 0.19 mmol) and diisobutylaluminium hydride (1.1 mL, 1.1 mmol) in anhydrous diethyl ether (20 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1 to 6/1) gave (*E*)-**174e** (79 mg, 92%).

White solid, m.p. = 139−140 °C (Pentane/Acetone = 3/1, R_f = 0.2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.77 (dd, $^{3}J_{HH}$ = 8.7, 6.6 Hz, 2H, *H*$_{ortho\text{-}Ph}$), 5.61 (dd, $^{3}J_{HH}$ = 7.6, 5.4 Hz, 1H, *H*$_{22}$), 5.35-5.33 (m, 1H, *H*$_{6}$), 4.42 (dd, $^{2}J_{HH}$ = 13.3 Hz, $^{3}J_{HH}$ = 7.7 Hz, *H*$_{23}$), 4.27 (dd, $^{2}J_{HH}$ = 13.3 Hz, $^{3}J_{HH}$ = 5.3 Hz, *H*$_{23}$), 3.56-3.48 (m, 1H, *H*$_{3}$), 2.63 (t, $^{3}J_{HH}$ = 9.6 Hz, 1H, *H*$_{17}$), 2.32-2.17 (m, 2H, *H*$_{4}$), 2.01-1.94 (m, 1H, *H*$_{7}$), 1.86-1.81 (m, 4H), 1.78-1.72 (m, 1H, *H*$_{15}$), 1.61-0.98 (m, 10H), 0.98-0.86 (m, 4H, *H*$_{9}$+*Me*$_{19}$), 0.46 (s, 3H, *Me*$_{18}$).

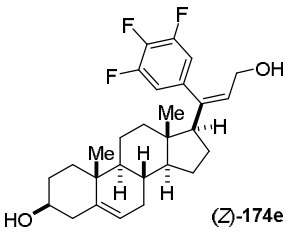
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 150.2 (ddd, $^{1}J_{CF}$ = 249 Hz, $^{2}J_{CF}$ = 10 Hz, $^{3}J_{CF}$ = 4.2 Hz, *C*$_{meta\text{-}Ph}$F), 141.7 (*C*$_{20}$), 140.8 (*C*$_{5}$), 140.7 (m, *C*$_{Ph}$), 138.5 (dt, $^{1}J_{CF}$ = 250Hz, $^{2}J_{CF}$ = 15 Hz, *C*$_{para\text{-}Ph}$F), 134.2 (*C*$_{22}$H), 121.4 (*C*$_{6}$H), 113.4 (dd, $^{2}J_{CF}$ = 16.0 Hz, $^{3}J_{CF}$ = 6.2 Hz, *C*$_{ortho\text{-}Ph}$), 71.7 (*C*$_{3}$H), 59.5 (*C*$_{23}H_2$), 55.8 (*C*$_{14}$H), 52.2 (*C*$_{17}$H), 50.2 (*C*$_{9}$H), 46.3 (*C*$_{13}$), 42.2 (*C*$_{4}H_2$), 38.1 (*C*$_{12}H_2$), 37.2 (*C*$_{1}H_2$), 36.6 (*C*$_{10}$), 31.9 (*C*$_{8}$H), 31.7 (*C*$_{7}H_2$), 31.6 (*C*$_{2}H_2$), 25.9 (*C*$_{16}H_2$), 24.5 (*C*$_{15}H_2$), 20.7 (*C*$_{11}H_2$), 19.3 (*C*$_{19}H_3$), 14.2 (*C*$_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −134.9 (d, $^{3}J_{FF}$ = 20.6 Hz), −163.0 (t, $^{3}J_{FF}$ = 20.7 Hz).

HRMS (MALDI−TOF) calculated for $C_{28}H_{34}F_3O$ [M−OH]$^+$: 443.2556, found 443.2533.

IR (neat): ν (cm^{-1}) = 3302, 2941, 1612, 1524, 1429, 1359, 1233, 1041, 1017, 865, 837, 796, 778, 709.

$[\alpha]^{25}_{D}$ = –67.4 (*c* 0.18, CH_2Cl_2).



(*Z*)-**174e**

Following the general procedure using enoate (*Z*)-**184e** (204 mg, 0.38 mmol) and diisobutylaluminium hydride (2.3 mL, 2.3 mmol) in anhydrous diethyl ether (20 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*Z*)-**174e** (166 mg, 94%).

Colorless foam (Pentane/Ethyl acetate = 1/1, R_f = 0.2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.76 (dd, $^3J_{HH}$ = 8.3, 6.5 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.72 (ddd, $^3J_{HH}$ = 7.7, 6.0, 1.6 Hz, 1H, H_{22}), 5.34-5.32 (m, 1H, H_6), 4.10-3.98 (m, 2H, H_{23}), 3.53-3.45 (m, 1H, H_3), 2.41 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.30-2.17 (m, 2H, H_4), 2.02-1.68 (m, 6H), 1.56-0.99 (m, 12H), 0.95 (s, 3H, Me_{19}), 0.90-0.82 (m, 2H, H_9+H_{12}), 0.74 (td, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, H_{12}), 0.58 (s, 3H, Me_{18}).

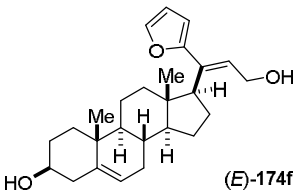
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 150.6 (ddd, $^1J_{CF}$ = 250 Hz, $^2J_{CF}$ = 10 Hz, $^3J_{CF}$ = 4.1 Hz, $C_{meta\text{-}Ph}$F), 141.4 (C_{20}), 140.8 (C_5), 138.7 (dt, $^1J_{CF}$ = 251.5Hz, $^2J_{CF}$ = 15.5 Hz, $C_{para\text{-}Ph}$F), 137.8 (m, C_{Ph}), 127.5 (C_{22}H), 121.4 (C_6H), 112.6 (dd, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 6.2 Hz, $C_{ortho\text{-}Ph}$), 71.7 (C_3H), 60.0 ($C_{23}H_2$), 57.0 (C_{17}H), 56.6 (C_{14}H), 50.1 (C_9H), 43.4 (C_{13}), 42.2 (C_4H_2), 38.4 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 32.2 (C_8H), 31.6 (C_7H_2), 31.6 (C_2H_2), 25.1 ($C_{16}H_2$), 23.7 ($C_{15}H_2$), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.7 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = –134.6 (d, $^3J_{FF}$ = 20.6 Hz), –162.2 (t, $^3J_{FF}$ = 20.7 Hz).

HRMS (MALDI–TOF) calculated for $C_{28}H_{34}F_3O$ [M–OH]$^+$: 443.2556, found 443.2532.

IR (neat): ν (cm^{-1}) = 3324, 2935, 1613, 1526, 1424, 1380, 1346, 1265, 1232, 1040, 954, 867, 805, 781, 736, 704, 638.

$[\alpha]^{25}_{D}$ = +30.9 (*c* 0.26, CH_2Cl_2).



(*E*)-**174f**

Following the general procedure using enoate (*E*)-**184f** (100 mg, 0.21 mmol) and diisobutylaluminium hydride (1.3 mL, 1.3 mmol) in anhydrous diethyl ether (20 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 15/1) gave (*E*)-**174f** (75 mg, 88%).

White solid, m.p. = 211–213 °C (Pentane/Acetone = 3/1, R_f = 0.2).

^{1}H NMR (THF–d_8, 400 MHz): δ (ppm) = 7.36 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H_{Ar}), 6.30 (dd, $^3J_{HH}$ = 3.3, 1.8 Hz, 1H, H_{Ar}), 6.23 (d, $^3J_{HH}$ = 3.2, 1H, H_{Ar}), 6.12 (dd, $^3J_{HH}$ = 7.3, 5.3 Hz, 1H, H_{22}), 5.31-

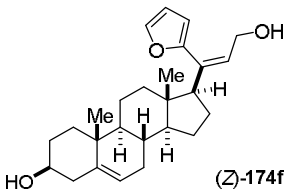
5.29 (m, 1H, H_6), 4.34-4.14 (m, 2H, H_{23}), 3.34-3.28 (m, 1H, H_3), 2.72 (t, $^3J_{HH}$ = 9.5 Hz, 1H, H_{17}), 2.46-2.10 (m, 3H), 2.04-1.97 (m, 1H, H_7), 1.64-1.29 (m, 6H), 1.31-1.05 (m, 3H, $2H_{11}$+H_{14}), 1.09-0.95 (m, 6H), 0.60 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR (THF–d_8, 126 MHz): δ (ppm) = 158.1(C_{Ar}), 142.5 (C_5), 141.5 (C_{Ar}H), 134.9 (C_{22}H), 130.8 (C_{20}), 121.1 (C_6H), 111.1 (C_{Ar}H), 107.3 (C_{Ar}H), 71.4 (C_3H), 59.7 ($C_{23}H_2$), 56.7 (C_{14}H), 52.1 (C_{17}H), 51.5 (C_9H), 46.0 (C_{13}), 43.5 (C_4H_2), 38.9 ($C_{12}H_2$), 38.3 (C_1H_2), 37.4 (C_{10}), 32.9 (C_8H), 32.8 (C_7H_2), 32.6 (C_2H_2), 26.1 ($C_{16}H_2$), 25.5 ($C_{15}H_2$), 21.6 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 13.7 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2540.

IR (neat): ν (cm^{-1}) = 3274, 2941, 2896, 1454, 1434, 1359, 1344, 1156, 1043, 1027, 954, 806, 732, 659, 620.

$[\alpha]^{25}_D$ = –67.2 (*c* 0.06, THF).



(*Z*)-**174f**

Following the general procedure using enoate (*Z*)-**184f** (120 mg, 0.26 mmol) and diisobutylaluminium hydride (1.5 mL, 1.5 mmol) in anhydrous diethyl ether (15 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 15/1 to 10/1) gave (*Z*)-**174f** (96 mg, 94%).

White solid, m.p. = 189–191 °C (Pentane/Acetone = 3/1, R_f = 0.2).

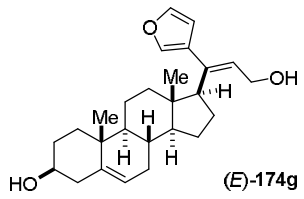
^1H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 7.40 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H_{Ar}), 6.39 (dd, $^3J_{HH}$ = 3.3, 1.8 Hz, 1H, H_{Ar}), 6.21 (d, $^3J_{HH}$ = 3.3, 1H, H_{Ar}), 5.73 (t, $^3J_{HH}$ = 6.3 Hz, 1H, H_{22}), 5.35-5.34 (m, 1H, H_6), 4.38-4.25 (m, 2H, H_{23}), 3.48-3.41 (m, 1H, H_3), 2.73 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.28-2.14 (m, 2H, H_4), 2.07-1.70 (m, 5H), 1.60-1.15 (m, 7H), 1.07-0.89 (m, 7H), 0.55 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 154.0 (C_{Ar}), 141.6 (C_{Ar}H), 141.4 (C_{20}), 131.7 (C_5), 128.7 (C_{22}H), 121.7 (C_6H), 111.0 (C_{Ar}H), 109.5 (C_{Ar}H), 72.0 (C_3H), 60.9 ($C_{23}H_2$), 57.0 (C_{14}H), 54.1 (C_{17}H), 50.8 (C_9H), 43.7 (C_{13}), 42.8 (C_4H_2), 37.9 ($C_{12}H_2$), 37.7 (C_1H_2), 36.9 (C_{10}), 32.8 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 25.3 ($C_{16}H_2$), 24.5 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 12.6 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2486.

IR (neat): ν (cm^{-1}) = 3322, 2936, 1454, 1436, 1375, 1245, 1227, 1195, 1156, 1053, 1027, 1013, 954, 918, 885, 806, 736.

$[\alpha]^{25}_D$ = +22.0 (*c* 0.06, THF).



(*E*)-**174g**

Following the general procedure using enoate (*E*)-**184g** (95 mg, 0.20 mmol) and diisobutylaluminium hydride (1.2 mL, 1.2 mmol) in anhydrous diethyl ether (20 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 15/1) gave (*E*)-**174g** (61 mg, 76%).

White solid, m.p. = 213–215 °C (Pentane/Acetone = 3/1, R_f = 0.2).

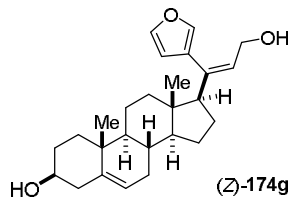
^{1}H NMR (THF–d_8, 500 MHz): δ (ppm) = 7.36-7.32 (m, 2H, H_{Ar}), 6.35 (dd, $^3J_{HH}$ = 1.8, 0.8 Hz, 1H, H_{Ar}), 5.75 (dd, $^3J_{HH}$ = 7.7, 4.9 Hz, 1H, H_{22}), 5.30-5.28 (m, 1H, H_6), 4.33-4.06 (m, 2H, H_{23}), 3.35-3.26 (m, 1H, H_3), 2.67 (dd, $^3J_{HH}$ = 10.1, 8.6 Hz, 1H, H_{17}), 2.21-2.10 (m, 2H, H_4), 2.07-1.65 (m, 5H), 1.60-1.12 (m, 8H), 1.09-0.94 (m, 5H), 0.58 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR (THF–d_8, 126 MHz): δ (ppm) = 142.5 (C_5), 142.5 (C_{Ar}H), 140.2 (C_{Ar}H), 135.3 (C_{22}H), 132.6 (C_{20}), 129.6 (C_{Ar}), 121.1 (C_6H), 112.6 (C_{Ar}H), 71.4 (C_3H), 59.6 ($C_{23}H_2$), 56.7 (C_{14}H), 52.5 (C_{17}H), 51.5 (C_9H), 46.6 (C_{13}), 43.4 (C_4H_2), 38.9 ($C_{12}H_2$), 38.3 (C_1H_2), 37.4 (C_{10}), 32.8 (C_8H), 32.7 (C_7H_2), 32.6 (C_2H_2), 26.3 ($C_{16}H_2$), 25.4 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 14.3 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2557.

IR (neat): ν (cm^{-1}) = 3331, 2932, 1668, 1454, 1436, 1377, 1158, 1108, 1049, 1023, 1009, 954, 871, 786, 734, 681.

$[\alpha]^{25}_D$ = –87.6 (*c* 0.08, THF).



(*Z*)-**174g**

Following the general procedure using enoate (*Z*)-**184g** (140 mg, 0.30 mmol) and diisobutylaluminium hydride (1.8 mL, 1.8 mmol) in anhydrous diethyl ether (20 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 15/1) gave **174g** (110 mg, 92%).
White solid, m.p. = 196–198 °C (Pentane/Acetone = 3/1, R_f = 0.2).

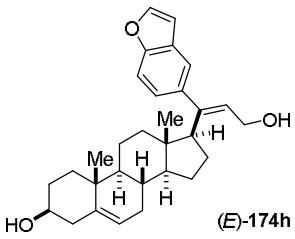
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.38 (d, $^3J_{HH}$ = 1.5 Hz, 1H, H_{Ar}), 7.26-7.25 (m, 1H, H_{Ar}), 6.32-6.31 (m, 1H, H_{Ar}), 5.72 (t, $^3J_{HH}$ = 6.6 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.26 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 7.5 Hz, H_{23}), 4.15 (dd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 5.8 Hz, H_{23}), 3.54-3.47 (m, 1H, H_3), 2.40 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 2.31-2.17 (m, 2H, H_4), 2.02-1.69 (m, 5H), 1.58-1.12 (m, 7H), 1.05-0.86 (m, 7H), 0.55 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR (THF–d_8, 126 MHz): δ (ppm) = 142.9 (C_{Ar}H), 142.5 (C_5), 140.9 (C_{Ar}H), 132.4 (C_{20}), 129.4 (C_{22}H), 126.2 (C_{Ar}), 121.1 (C_6H), 111.9 (C_{Ar}H), 71.4 (C_3H), 60.1 ($C_{23}H_2$), 57.6 (C_{14}H), 57.1 (C_{17}H), 51.4 (C_9H), 44.1 (C_{13}), 43.5 (C_4H_2), 39.5 ($C_{12}H_2$), 38.2 (C_1H_2), 37.3 (C_{10}), 33.2 (C_8H), 32.6 (C_7H_2), 32.6 (C_2H_2), 25.6 ($C_{16}H_2$), 24.7 ($C_{15}H_2$), 21.7 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2523.

IR (neat): ν (cm^{-1}) = 3331, 2935, 1666, 1448, 1436, 1377, 1160, 1057, 1022, 952, 871, 798, 734.

$[\alpha]^{25}_D$ = +19.6 (*c* 0.09, THF).



(*E*)-**174h**

Following the general procedure using enoate (*E*)-**184h** (112 mg, 0.22 mmol) and diisobutylaluminium hydride (1.3 mL, 1.3 mmol) in anhydrous diethyl ether (10 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*E*)-**174h** (78 mg, 80%).

White solid, m.p. = 193–195 °C (Pentane/Acetone = 3/1, R_f = 0.2).

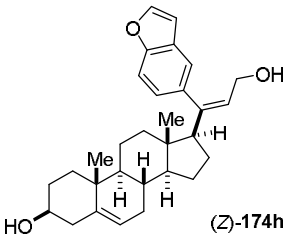
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.60 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H_{Ar}), 7.39-7.35 (m, 2H, H_{Ar}), 7.08 (dd, $^3J_{HH}$ = 8.5, 1.8 Hz, 1H, H_{Ar}), 6.72 (dd, $^3J_{HH}$ = 2.2, 1.0 Hz, 1H, H_{Ar}), 5.64 (ddd, $^3J_{HH}$ = 7.9, 5.4, 0.7 Hz, 1H, H_{22}), 5.35-5.33 (m, 1H, H_6), 4.45 (dd, $^3J_{HH}$ = 7.9 Hz, H_{23}), 4.30 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.5 Hz, H_{23}), 3.56-3.48 (m, 1H, H_3), 2.74 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 2.31-2.17 (m, 2H, H_4), 2.05-1.34 (m, 17H), 1.16-1.02 (m, 4H), 0.99-0.88 (m, 4H, H_9+Me_{19}), 0.45 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 153.6 (C_{Ar}), 145.1 (C_{Ar}H), 144.6 (C_{20}), 140.8 (C_5), 139.5 (C_{Ar}), 132.9 (C_{22}H), 126.6 (C_{Ar}), 126.1 (C_{Ar}H), 121.7 (C_{Ar}H), 121.5 (C_6H), 110.0 (C_{Ar}H), 106.6 (C_{Ar}H), 71.7 (C_3H), 59.8 ($C_{23}H_2$), 56.0 (C_{14}H), 52.5 (C_{17}H), 50.3 (C_9H), 46.2 (C_{13}), 42.2 (C_4H_2), 38.1 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 26.2 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{30}H_{38}O_3Na$ $[M+Na]^+$: 469.2713, found 469.2725.

IR (neat): ν (cm^{-1}) = 3318, 2934, 1464, 1436, 1377, 1262, 1130, 1110, 1029, 1007, 954, 883, 810, 768, 740.

$[\alpha]^{25}_D$ = –49.2 (*c* 0.14, THF).



(*Z*)-**174h**

Following the general procedure using enoate (*Z*)-**184h** (157 mg, 0.30 mmol) and diisobutylaluminium hydride (1.8 mL, 1.8 mmol) in anhydrous diethyl ether (10 mL, 0.03 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*Z*)-**174h** (141 mg, >99%).

White solid, m.p. = 145–148 °C (Pentane/Acetone = 3/1, R_f = 0.2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.62 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H_{Ar}), 7.44-7.31 (m, 2H, H_{Ar}), 7.04 (dd, $^3J_{HH}$ = 8.4, 1.7 Hz, 1H, H_{Ar}), 6.74 (dd, $^3J_{HH}$ = 2.2, 1.0 Hz, 1H, H_{Ar}), 5.73 (ddd, $^3J_{HH}$ = 7.6, 5.9, 1.6 Hz, 1H, H_{22}), 5.34-5.31 (m, 1H, H_6), 4.12-4.01 (m, 2H, H_{23}), 3.51-3.43 (m, 1H, H_3), 2.59 (t, $^3J_{HH}$ = 9.4 Hz, 1H, H_{17}), 2.19-2.16 (m, 2H, H_4), 2.02-1.66 (m, 6H), 1.56-1.02

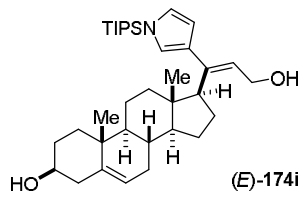
(m, 10H), 0.98-0.90 (m, 4H, H_1+Me_{19}), 0.84-0.74 (m, 2H, H_9+H_{12}), 0.66-0.57 (m, 4H, H_{12}+Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 154.0 (C_{Ar}), 145.2 ($C_{Ar}H$), 144.4 (C_{20}), 140.8 (C_5), 136.5 (C_{Ar}), 127.0 (C_{Ar}), 125.9 ($C_{22}H$), 125.0 ($C_{Ar}H$), 121.5 ($C_{Ar}H$), 120.8 (C_6H), 110.6 ($C_{Ar}H$), 106.6 ($C_{Ar}H$), 71.7 (C_3H), 60.6 ($C_{22}H_2$), 57.7 ($C_{17}H$), 56.7 ($C_{14}H$), 50.2 (C_9H), 43.3 (C_{13}), 42.2 (C_4H_2), 38.3 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 32.3 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 25.2 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.7 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{30}H_{38}O_3Na$ $[M+Na]^+$: 469.2713, found 469.2699.

IR (neat): ν (cm^{-1}) = 3335, 2937, 1466, 1436, 1377, 1328, 1260, 1132, 1110, 1055, 1029, 1003, 818, 766, 740.

$[\alpha]^{25}_D$ = +21.7 (*c* 0.10, THF).



(*E*)-**174i**

Following the general procedure using enoate (*E*)-**184i** (195 mg, 0.31 mmol) and diisobutylaluminium hydride (1.9 mL, 1.9 mmol) in anhydrous diethyl ether (30 mL, 0.01 M). Purification by flash chromatography (Pentane/Diethyl ether/Dichloromethane = 1/1/1, buffered with 0.1% triethylamine) gave (*E*)-**174i** (141 mg, 82%).

White solid, m.p. = 175–176 °C (Pentane/Diethyl ether = 1/1, R_f = 0.1).

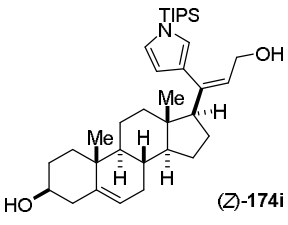
^1H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 6.66 (t, $^3J_{HH}$ = 2.4 Hz, 1H, H_{Ar}), 6.61 (dd, $^3J_{HH}$ = 2.2, 1.4 Hz, 1H, H_{Ar}), 6.21 (dd, $^3J_{HH}$ = 2.7, 1.4 Hz, 1H, H_{Ar}), 5.74 (dd, $^3J_{HH}$ = 7.9, 5.7 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 4.39-4.16 (m, 2H, H_{23}), 3.50-3.41 (m, 1H, H_3), 2.68 (t, $^3J_{HH}$ = 9.4 Hz, 1H, H_{17}), 2.28-2.13 (m, 2H, H_4), 2.03-1.96 (m, 1H, H_7), 1.85-1.21 (m, 12H), 1.16-1.04 (m, 22H), 1.00-0.93 (m, 5H), 0.52 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR (CD_2Cl_2,101 MHz): δ (ppm) = 141.5 (C_5), 138.4 (C_{20}), 130.1 (C_{Ar}), 129.8 ($C_{22}H$), 123.6 ($C_{Ar}H$), 122.8 ($C_{Ar}H$), 121.8 (C_6H), 112.1 ($C_{Ar}H$), 72.1 (C_3H), 60.2 ($C_{23}H_2$), 56.4 ($C_{14}H$), 52.5 ($C_{17}H$), 50.9 (C_9H), 46.0 (C_{13}), 42.8 (C_4H_2), 38.7 ($C_{12}H_2$), 37.7 (C_1H_2), 37.0 (C_{10}), 32.4 (C_8H), 32.4 (C_7H_2), 32.1 (C_2H_2), 26.2 ($C_{16}H_2$), 25.2 ($C_{15}H_2$), 21.3 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 18.0 (Me_2CHSi), 18.0 (Me_2CHSi), 14.2 ($C_{18}H_3$), 12.0 (*C*HSi).

HRMS (MALDI–TOF) calculated for $C_{35}H_{57}NO_2SiNa$ $[M+Na]^+$: 574.4051, found 574.4070.

IR (neat): ν (cm^{-1}) = 3335, 2937, 2868, 1462, 1373, 1318, 1258, 1227, 1148, 1094, 1043, 1015, 992, 881, 786, 691, 659.

$[\alpha]^{25}_D$ = –55.4 (*c* 0.09, CH_2Cl_2).



(*Z*)-**174i**

Following the general procedure using enoate (*Z*)-**184i** (200 mg, 0.32 mmol) and diisobutylaluminium hydride (1.9 mL, 1.9 mmol) in anhydrous diethyl ether (30 mL, 0.01 M). Purification by flash chromatography (Pentane/Diethyl ether = 1/1, buffered with 0.1% triethylamine) gave (*Z*)-**174i** (169 mg, 95%).

White solid, m.p. = 74–77 °C (Pentane/Diethyl ether = 1/1, R_f = 0.1).

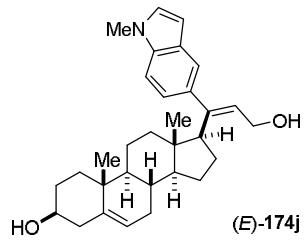
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 6.71 (t, $^3J_{HH}$ = 2.4 Hz, 1H, H_{Ar}), 6.55 (dd, $^3J_{HH}$ = 2.1, 1.4 Hz, 1H, H_{Ar}), 6.15 (dd, $^3J_{HH}$ = 2.7, 1.4 Hz, 1H, H_{Ar}), 5.55 (ddd, $^3J_{HH}$ = 7.3, 5.5, 1.5 Hz, 1H, H_{22}), 5.34-5.32 (m, 1H, H_6), 4.30-4.11 (m, 2H, H_{23}), 3.46-3.40 (m, 1H, H_3), 2.51 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.26-2.13 (m, 2H, H_4), 2.03-1.92 (m, 2H), 1.79-1.68 (m, 4H), 1.55-1.18 (m, 16H), 1.16-1.00 (m, 22H), 0.95 (s, 3H, Me_{19}), 0.91-0.84 (m, 2H), 0.54 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR (CD_2Cl_2,101 MHz): δ (ppm) = 141.5 (C_5), 138.4 (C_{20}), 126.4 (C_{Ar}), 124.2 (C_{22}H), 123.8 (C_{Ar}H), 123.0 (C_{Ar}H), 121.8 (C_6H), 111.8 (C_{Ar}H), 72.1 (C_3H), 61.0 ($C_{23}H_2$), 57.4 (C_{17}H), 57.2 (C_{14}H), 50.8 (C_9H), 43.8 (C_{13}), 42.8 (C_4H_2), 39.1 ($C_{12}H_2$), 37.7 (C_1H_2), 36.9 (C_{10}), 32.8 (C_8H), 32.3 (C_7H_2), 32.1 (C_2H_2), 25.3 ($C_{16}H_2$), 24.5 ($C_{15}H_2$), 21.3 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 18.0 (Me_2CHSi), 12.6 ($C_{18}H_3$), 12.0 (*C*HSi).

HRMS (+ESI) calculated for $C_{35}H_{58}NO_2Si$ $[M-OH]^+$: 534.4126, found 534.4127.

IR (neat): ν (cm^{-1}) =.3302, 2938, 2896, 2868, 1462, 1379, 1264, 1225, 1132, 1086, 1006, 996, 956, 922, 884, 843, 798, 691.

$[\alpha]^{25}_D$ = +63.8 (*c* 0.10, CH_2Cl_2).



(*E*)-**174j**

Following the general procedure using enoate (*E*)-**184j**[19] (140 mg, 0.26 mmol) and diisobutylaluminium hydride (2.0 mL, 2.0 mmol) in a 2:1 mixture of anhydrous Et_2O and THF (2:1 v/v, 30 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*E*)-**174j** (83 mg, 43% *over 2 steps*).

White solid, m.p. = 200–201 °C (Pentane/Acetone = 3/1, R_f = 0.1).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 7.36-7.35 (m, 1H, H_{Ar}), 7.23-7.21 (m, 1H, H_{Ar}), 7.06-7.01 (m, 2H, H_{Ar}), 6.41 (d, $^3J_{HH}$ = 3.0 Hz, 1H, H_{Ar}), 5.59 (dd, $^3J_{HH}$ = 7.8, 5.4 Hz, 1H, H_{Ar}), 5.34-5.32 (m, 1H, H_6), 4.42 (d, $^3J_{HH}$ = 7.9 Hz, H_{23}), 4.28 (d, $^3J_{HH}$ = 5.5 Hz, H_{23}), 3.77 (*Me*N), 3.49-3.41 (m, 1H, H_3), 2.76 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 2.27-2.12 (m, 2H, H_4), 2.04-1.01 (m, 18H), 0.99-0.91 (m, 4H, H_9+Me_{19}), 0.45 (s, 3H, Me_{18}).

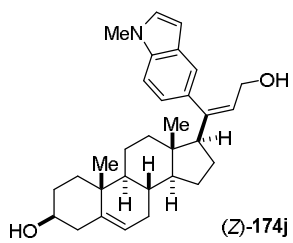
^{13}C{^{1}H} NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 145.4 (C_{20}), 141.5 (C_5), 136.7 (C_{Ar}), 135.8 (C_{Ar}), 133.0 (C_{22}H), 129.5 (C_{Ar}H), 128.2 (C_{Ar}), 125.8 (C_{Ar}H), 124.0 (C_{Ar}H), 121.7 (C_6H), 121.5 (C_{Ar}H), 108.2 (C_{Ar}H), 101.0 (C_{Ar}H), 72.0 (C_3H), 60.1 ($C_{23}H_2$), 56.4 (C_{14}H), 53.1 (C_{17}H), 50.9

(C_9H), 46.5 (C_{13}), 42.7 (C_4H_2), 38.6 ($C_{12}H_2$), 37.7 (C_1H_2), 37.0 (C_{10}), 33.1 (*Me*N), 32.4 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 26.6 ($C_{16}H_2$), 25.0 ($C_{15}H_2$), 21.2 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 14.3 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{31}H_{40}NO$ $[M–OH]^+$: 442.3104, found 442.3096.

IR (neat): ν (cm^{-1}) = 3323, 2938, 1510, 1436, 1361, 1330, 1243, 1038, 1029, 802, 722.

$[\alpha]^{25}_D$ = –44.4 (*c* 0.16, CH_2Cl_2).



(*Z*)-**174j**

Following the general procedure using enoate (*Z*)-**184j** (126 mg, 0.24 mmol) and diisobutylaluminium hydride (1.8 mL, 1.8 mmol) in a 2:1 mixture of anhydrous Et_2O and THF (2:1 v/v, 30 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*Z*)-**174j** (113 mg, >99%).

White solid, m.p. = 114–117 °C (Pentane/Acetone = 3/1, R_f = 0.1).

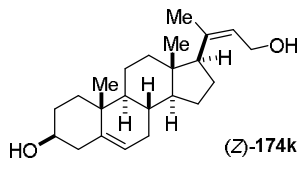
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.33-7.32 (m, 1H, H_{Ar}), 7.25-7.23 (m, 1H, H_{Ar}), 7.05 (d, $^3J_{HH}$ = 3.1 Hz, 1H, H_{Ar}), 6.98 (dd, $^3J_{HH}$ = 8.4, 1.6 Hz, 1H, H_{Ar}), 6.45 (dd, $^3J_{HH}$ = 3.1, 0.8 Hz, 1H, H_{Ar}), 5.71 (ddd, $^3J_{HH}$ = 7.5, 5.9, 1.6 Hz, 1H, H_{Ar}), 5.73 (ddd, $^3J_{HH}$ = 7.6, 5.9, 1.6 Hz, 1H, H_{22}), 5.34-5.31 (m, 1H, H_6), 4.13-4.04 (m, 2H, H_{23}), 3.80 (*Me*N), 3.51-3.43 (m, 1H, H_3), 2.63 (t, $^3J_{HH}$ = 9.8 Hz, 1H, H_{17}), 2.29-2.15 (m, 2H, H_4), 2.02-1.65 (m, 6H), 1.56-1.06 (m, 11H), 0.97-0.88 (m, 4H, H_1+Me_{19}), 0.83-0.76 (m, 2H, H_9+H_{12}), 0.66-0.58 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 145.3 (C_{20}), 140.8 (C_5), 135.8 (C_{Ar}), 132.9 (C_{Ar}), 129.0 (C_{Ar}H), 127.9 (C_{Ar}), 125.2 (C_{22}H), 122.6 (C_{Ar}H), 121.6 (C_6H), 120.5 (C_{Ar}H), 108.4 (C_{Ar}H), 100.9 (C_{Ar}H), 71.7 (C_3H), 60.8 ($C_{23}H_2$), 57.7 (C_{17}H), 56.8 (C_{14}H), 50.2 (C_9H), 43.3 (C_{13}), 42.3 (C_4H_2), 38.2 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 32.9 (*Me*N), 32.3 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 25.2 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.7 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{31}H_{40}NO$ $[M–OH]^+$: 442.3104, found 442.3146.

IR (neat): ν (cm^{-1}) = 3346, 2935, 1512, 1486, 1440, 1330, 1280, 1243, 1057, 1007, 806, 730.

$[\alpha]^{25}_D$ = +33.8 (*c* 0.18, CH_2Cl_2).



(*Z*)-**174k**

Following the general procedure using enoate (*Z*)-**184k** (160 mg, 0.39 mmol) and diisobutylaluminium hydride (2.3 mL, 2.3 mmol) in anhydrous diethyl ether (20 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 3/1) gave (*Z*)-**174k** (115 mg, 86%).

White solid, m.p. = 196–197 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 5.57 (t, $^3J_{HH}$ = 7.0 Hz, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.29 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 8.3 Hz, 1H, H_{23}), 4.06-4.03 (m, 1H, H_{23}), 3.56-3.50 (m, 1H, H_3), 2.49 (t, $^3J_{HH}$ = 9.5 Hz, 1H, H_{17}), 2.32-2.20 (m, 2H, H_4), 2.03-1.98 (m, 1H, H_7), 1.92-1.81

(m, 3H, H_1+H_2+H_{16}), 1.77 (s, 3H, Me_{21}), 1.74-1.41 (m, 8H, H_2+H_7+H_8+2H_{11}+H_{12}+H_{15}+H_{16}), 1.31-1.22 (m, 1H, H_{15}), 1.12-1.06 (m, 3H, H_1+H_{12}+H_{14}), 1.01 (s, 3H, Me_{19}), 0.99-0.92 (m, 1H, H_9), 0.66 (s, 3H, Me_{18}).

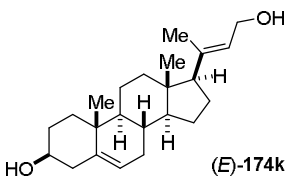
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 140.8 (C_5), 138.8 (C_{20}), 127.7 (C_{22}H), 121.6 (C_6H), 71.7 (C_3H), 59.3 ($C_{23}H_2$), 55.8 (C_{14}H), 51.2 (C_{17}H), 50.4 (C_9H), 45.6 (C_{13}), 42.2 (C_4H_2), 37.7 ($C_{12}H_2$), 37.2 (C_1H_2), 36.6 (C_{10}), 31.9 (C_7H_2), 31.9 (C_8H), 31.6 (C_2H_2), 24.8 ($C_{15}H_2$), 24.6 ($C_{16}H_2$), 23.2 ($C_{21}H_3$), 20.7 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 13.9 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{23}H_{37}O_2$ $[M+H]^+$: 367.2608, found 367.2620.

IR (neat): ν (cm^{-1}) = 3347, 2917, 2868, 1436, 1375, 1316, 1189, 1106, 1047, 983, 956, 833, 800.

$[\alpha]^{25}_D$ = −103.9 (*c* 0.12, THF).

The structure of (*Z*)-**174k** was confirmed by single crystal X-ray diffraction analysis.



(*E*)-**174k**

Following the general procedure using enoate (*E*)-**184k** (220 mg, 0.53 mmol) and diisobutylaluminium hydride (3.2 mL, 3.2 mmol) in anhydrous diethyl ether (27 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*E*)-**174k** (183 mg, >99%).

White solid, m.p. = 188−189 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

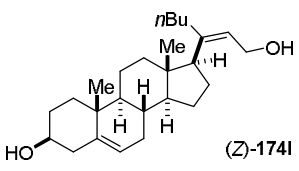
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.45-5.44 (m, 1H, H_{22}), 5.36-5.35 (m, 1H, H_6), 4.26-4.18 (m, 2H, H_{23}), 3.56-3.50 (m, 1H, H_3), 2.32-2.21 (m, 2H, H_4), 2.06-1.97 (m, 2H, H_7+H_{17}), 1.86-1.80 (m, 4H, H_1+H_2+H_{12}+H_{16}), 1.72-1.62 (m, 5H, H_{15}+H_{16}+Me_{21}), 1.62-1.40 (m, 5H, H_2+H_7+H_8+2H_{11}), 1.25-1.05 (m, 4H, H_1+H_{12}+H_{14}+H_{15}), 1.02-0.94 (m, 4H, H_9+Me_{19}), 0.57 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 140.8 (C_5), 139.0 (C_{20}), 124.4 (C_{22}H), 121.6 (C_6H), 71.8 (C_3H), 59.6 ($C_{23}H_2$), 58.7 (C_{17}H), 56.4 (C_{14}H), 50.3 (C_9H), 43.5 (C_{13}), 42.3 (C_4H_2), 38.6 ($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 24.7 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 18.1 ($C_{21}H_3$), 12.9 ($C_{18}H_3$).

HRMS (+ESI) calculated for $C_{23}H_{37}O_2$ $[M+H]^+$: 367.2608, found 367.2606.

IR (neat): ν (cm^{-1}) = 3278, 2933, 2852, 1434, 1379, 1132, 1102, 1063, 998, 841, 800, 774.

$[\alpha]^{25}_D$ = −55.7 (*c* 0.12, THF).



(*Z*)-**174l**

Following the general procedure using enoate (*Z*)-**184l** (143 mg, 0.31 mmol) and diisobutylaluminium hydride (1.9 mL, 1.9 mmol) in anhydrous diethyl ether (10 mL, 0.03 M). Purification by flash chromatography ($CHCl_3$/Acetone = 3/1) gave (*Z*)-**174l** (103 mg, 85%).

White solid, m.p. = 193–195 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

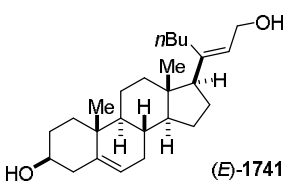
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.54-5.51 (m, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.31 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 8.2 Hz, 1H, H_{23}), 4.10-4.06 (m, 1H, H_{23}), 3.57-3.49 (m, 1H, H_3), 2.51 (t, $^3J_{HH}$ = 9.5 Hz, 1H, H_{17}), 2.33-2.20 (m, 2H, H_4), 2.05-1.92 (m, 3H), 1.92-1.82 (m, 3H), 1.75-1.61 (m, 2H, H_{15}+H_{16}), 1.62-1.26 (m, 12H), 1.13-1.03 (m, 3H), 1.01 (s, 3H, Me_{19}), 1.01-0.95 (m, 1H, H_9), 0.90 (t, $^3J_{HH}$ = 7.2 Hz, 1H, CH_2CH_3), 0.62 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 143.0 (C_{20}), 140.8 (C_5), 126.8 ($C_{22}H$), 121.6 (C_6H), 71.7 (C_3H), 59.5 ($C_{23}H_2$), 55.8 ($C_{14}H$), 51.4 ($C_{17}H$), 50.4 (C_9H), 45.8 (C_{13}), 42.3 (C_4H_2), 37.7 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 34.4 ($C_{21}H_2$), 33.0 ($CH_2CH_2CH_3$), 31.9 (C_7H_2), 31.9 (C_8H), 31.6 (C_2H_2), 24.9 ($C_{15}H_2$), 24.6 ($C_{16}H_2$), 22.8 (CH_2CH_3), 20.7 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 14.1 (CH_2CH_3), 13.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{41}O$ $[M–OH]^+$: 369.3152, found 369.3151.

IR (neat): ν (cm^{-1}) = 3286, 2934, 1464, 1375, 1344, 1332, 1053, 1009, 954, 802, 736, 671, 614.

$[\alpha]^{25}_D$ = –33.3 (*c* 0.28, THF).



(*E*)-**1741**

Following the general procedure using enoate (*E*)-**184l** (113 mg, 0.25 mmol) and diisobutylaluminium hydride (1.5 mL, 1.5 mmol) in anhydrous diethyl ether (10 mL, 0.02 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*E*)-**174l** (82 mg, 86%).

White solid, m.p. = 164–165 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.43 (t, $^3J_{HH}$ = 6.8 Hz, 1H, H_{22}), 5.37-5.34 (m, 1H, H_6), 4.21 (dd, $^2J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 2.2 Hz, 2H, H_{23}), 3.56-3.50 (m, 1H, H_3), 2.33-2.15 (m, 3H), 2.11 (t, $^3J_{HH}$ = 9.6 Hz, 1H, H_{17}), 2.04-1.96 (m, 1H, H_7), 1.93-1.64 (m, 8H), 1.58-1.42 (m, 5H), 1.38-1.16 (m, 5H), 1.16-1.04 (m, 2H), 1.01 (s, 3H, Me_{19}), 0.98-0.94 (m, 1H, H_9), 0.90 (t, $^3J_{HH}$ = 6.8 Hz, 1H, CH_2CH_3), 0.58 (s, 3H, Me_{18}).

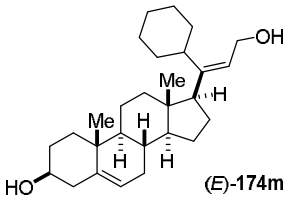
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 143.5 (C_{20}), 140.8 (C_5), 124.4 ($C_{22}H$), 121.6 (C_6H), 71.8 (C_3H), 59.6 ($C_{23}H_2$), 56.6 ($C_{14}H$), 56.2 ($C_{17}H$), 50.3 (C_9H), 43.6 (C_{13}), 42.3 (C_4H_2), 38.5 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 32.2 (C_8H), 32.2 ($CH_2CH_2CH_3$), 31.9 (C_7H_2), 31.8

($C_{21}H_2$), 31.6 (C_2H_2), 25.8 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 22.9 (CH_2CH_3), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 14.0 (CH_2CH_3), 12.9 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{41}O$ $[M-OH]^+$: 369.3152, found 369.3151.

IR (neat): ν (cm^{-1}) = 3262, 2930, 2872, 1454, 1436, 1379, 1241, 1193, 1106, 1050, 1002, 952, 841, 800, 692.

$[\alpha]^{25}_D$ = –7.7 (*c* 0.42, THF).



(*E*)-**174m**

Following the general procedure using enoate (*E*)-**184m** (158 mg, 0.33 mmol) and diisobutylaluminium hydride (2.0 mL, 2.0 mmol) in anhydrous diethyl ether (35 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 10/1) gave (*E*)-**174m** (120 mg, 89%).

White solid, m.p. = 200–202 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

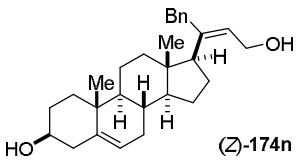
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 5.44 (t, $^3J_{HH}$ = 6.8 Hz, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 4.29 (dd, $^2J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 1.3 Hz, 2H, H_{23}), 3.56-3.50 (m, 1H, H_3), 2.32-2.16 (m, 3H, H_4+H_{21}), 2.09-2.05 (m, 1H, H_{17}), 2.03-1.97 (m, 1H, H_7), 1.86-1.07 (m, 28H), 1.02 (s, 3H, Me_{19}), 0.97-0.92 (m, 1H, H_9), 0.68 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 148.1 (C_{20}), 140.8 (C_5), 125.0 ($C_{22}H$), 121.6 (C_6H), 71.8 (C_3H), 59.5 ($C_{23}H_2$), 56.9 ($C_{14}H$), 54.3 ($C_{17}H$), 50.2 (C_9H), 43.5 (C_{13}), 43.0 ($C_{21}H$), 42.3 (C_4H_2), 38.5 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 32.3 (C_8H), 32.0 (CH_{2cy}), 31.8 (C_7H_2), 31.7 ($C_{21}H_2$), 31.6 (C_2H_2), 29.9 (CH_{2cy}), 27.0 (CH_{2cy}), 26.9 (CH_{2cy}), 26.2 ($C_{16}H_2$), 24.3 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 13.3 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{28}H_{44}O_2$ $[M]^+$: 412.3, found $[M+H]^+$: 413.4.

IR (neat): ν (cm^{-1}) = 3343, 2927, 2852, 1446, 1373, 1060, 1025, 1009, 952, 891, 802, 738, 667, 620.

$[\alpha]^{25}_D$ = –11.8 (*c* 0.10, THF).



(*Z*)-**174n**

Following the general procedure using enoate (*Z*)-**184n** (146 mg, 0.30 mmol) and diisobutylaluminium hydride (1.8 mL, 1.8 mmol) in anhydrous diethyl ether (30 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 5/1) gave (*Z*)-**174n** (103 mg, 82%).

White solid, m.p. = 206–208 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.30-7.26 (m, 2H, $2H_{meta\text{-}Ph}$), 7.20-7.16 (m, 3H, $H_{para\text{-}Ph}$+$2H_{ortho\text{-}Ph}$), 5.37-5.34 (m, 2H, H_{22}+H_6), 4.35 (dd, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, H_{23}), 4.11 (dd, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, H_{23}), 3.57-3.49 (m, 1H, H_3), 3.42 (d, $^2J_{HH}$ = 4.0

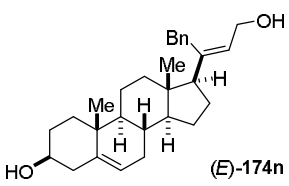
Hz, H_{21}), 2.59 (t, $^3J_{HH}$ = 9.7 Hz, 1H, H_{17}), 2.34-2.20 (m, 2H, H_4), 2.03-1.06 (m, 23H), 1.03 (s, 3H, Me_{19}), 1.01-0.94 (m, 1H, H_9), 0.78 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 141.2 (C_5), 140.8 (C_{20}), 140.8 (C_{Ph}), 130.3 ($C_{22}H$), 129.1 ($C_{ortho\text{-}Ph}$), 128.2 ($C_{meta\text{-}Ph}$), 125.9 ($C_{para\text{-}Ph}$), 121.5 (C_6H), 71.7 (C_3H), 59.6 ($C_{23}H_2$), 55.8 ($C_{14}H$), 51.6 ($C_{17}H$), 50.4 (C_9H), 46.1 (C_{13}), 42.2 (C_4H_2), 41.5 ($C_{21}H_2$), 37.7 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 34.4 ($C_{21}H_2$), 33.0 ($CH_2CH_2CH_3$), 31.9 (C_7H_2), 31.9 (C_8H), 31.6 (C_2H_2), 24.9 ($C_{15}H_2$), 24.8 ($C_{16}H_2$), 20.8 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 13.8 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{29}H_{40}O_2$ $[M]^+$: 420.3, found $[M+Na]^+$: 443.9.

IR (neat): ν (cm^{-1}) = 3297, 2930, 1492, 1452, 1432, 1373, 1053, 1009, 954, 839, 748, 701, 669.

$[\alpha]^{25}_D$ = −106.6 (*c* 0.10, THF).



(*E*)-**174n**

Following the general procedure using enoate (*E*)-**184n** (186 mg, 0.38 mmol) and diisobutylaluminium hydride (2.3 mL, 2.3 mmol) in anhydrous diethyl ether (40 mL, 0.01 M). Purification by flash chromatography ($CHCl_3$/Acetone = 5/1) gave (*E*)-**174n** (152 mg, 96%).

White solid, m.p. = 157−159 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.1).

^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.29-7.26 (m, 2H, $2H_{meta\text{-}Ph}$), 7.20-7.13 (m, 3H, $H_{ortho\text{-}Ph}$+$H_{para\text{-}Ph}$), 5.72 (t, $^3J_{HH}$ = 6.7 Hz, 1H, H_{22}), 5.34-5.32 (m, 1H, H_6), 4.27 (d, $^2J_{HH}$ = 6.7 Hz, 2H, H_{23}), 3.70 (d, $^2J_{HH}$ = 15.5 Hz, 1H, H_{21}), 3.56-3.48 (m, 1H, H_3), 3.26 (d, $^2J_{HH}$ = 15.5 Hz, 1H, H_{21}), 2.28-2.22 (m, 2H, H_4), 2.10-2.05 (m, 1H, H_{17}), 2.00-1.92 (m, 1H, H_7), 1.87-1.04 (m, 18H), 1.01 (s, 3H, Me_{19}), 0.93 (ddd, $^3J_{HH}$ = 12.2, 10.4, 4.9 Hz, 1H, H_9), 0.66 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 170.5 (Me*C*O), 167.2 (*C*O_2Me), 161.2 (C_{20}), 139.7 (C_5), 139.1 (C_{Ph}), 128.8 ($C_{ortho\text{-}Ph}$), 128.3 ($C_{meta\text{-}Ph}$), 126.0 ($C_{para\text{-}Ph}$), 122.3 (C_6H), 117.0 ($C_{22}H$), 73.8 (C_3H), 56.7 ($C_{17}H$), 56.7 ($C_{14}H$), 51.0 (*Me*O), 50.0 (C_9H), 44.5 (C_{13}), 38.9 ($C_{21}H_2$), 38.6 (C_4H_2), 38.1 ($C_{12}H_2$), 37.0 (C_1H_2), 36.6 (C_{10}), 32.2 (C_8H), 31.7 (C_7H_2), 27.7(C_2H_2), 26.6 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.4 (*Me*CO), 21.1 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 13.2 ($C_{18}H_3$).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 140.8 (C_{20}), 140.7 (C_5), 128.4 ($C_{ortho\text{-}Ph}$), 128.3 ($C_{meta\text{-}Ph}$), 126.5 ($C_{22}H$), 125.9 ($C_{para\text{-}Ph}$), 121.5 (C_6H), 71.7 (C_3H), 59.8 ($C_{23}H_2$), 56.5 ($C_{14}H$), 55.8 ($C_{17}H$), 50.2 (C_9H), 43.6 (C_{13}), 42.3 (C_4H_2), 38.6 ($C_{12}H_2$), 37.7 ($C_{21}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 32.2 (C_8H), 31.7 (C_7H_2), 31.6 ($C_{21}H_2$), 31.6 (C_2H_2), 26.1 ($C_{16}H_2$), 24.1 ($C_{15}H_2$), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 13.1 ($C_{18}H_3$).

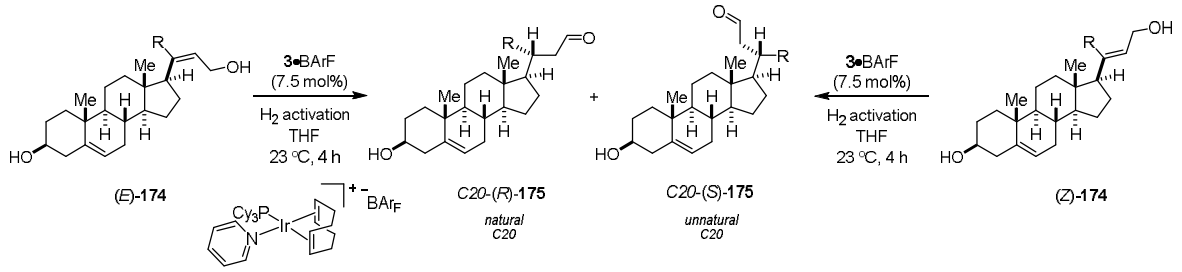
LRMS (ESI) calculated for $C_{29}H_{40}O_2$ $[M]^+$: 420.3, found $[M+Na]^+$: 443.9.

IR (neat): ν (cm^{-1}) = 3323, 2933, 1660, 1601, 1492, 1452, 1436, 1375, 1057, 1027, 954, 835, 800, 736, 699.

$[\alpha]^{25}_{D}$ = –9.8 (*c* 0.10, THF).

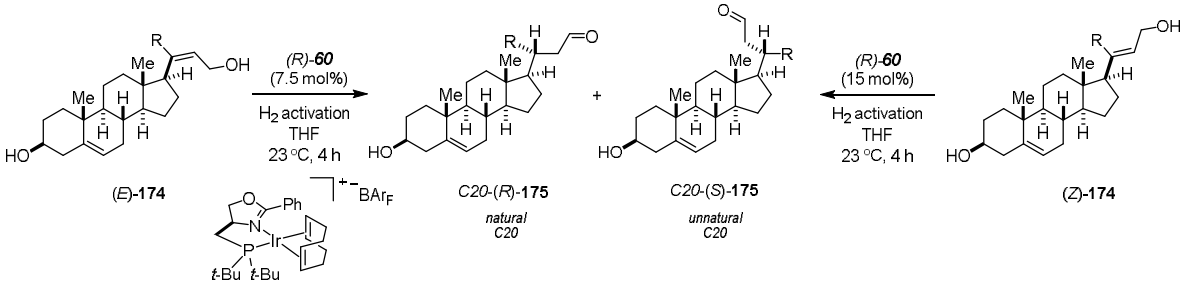
*7.3.2. General procedures for the isomerization of (E) and (Z)-allylic alcohols (**174**)*

General Procedure A: Crabtree (3•BAr_F)–catalyzed isomerization



A 10 mL Schlenk containing Crabtree catalyst **3**•BAr_F (5.7 mg, 7.5 mol%) was purged by three successive vacuum/nitrogen sequences and refilled with nitrogen. Degassed anhydrous tetrahydrofuran (1.5 mL) was added next and hydrogen gas was gently bubbled directly through the solution (2-3 bubbles per second) via a stainless-steel needle at room temperature. The orange solution rapidly discolored. After 1 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol **174** (0.05 mmol) was added immediately to the cold solution in one portion. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 4 h. The reaction was then stopped, quenched with 2 drops of triethylamine, and concentrated under vaccum. The C20-(*R*)/C-20-(*S*) diastereomeric ratio was assessed by ^{1}H NMR of the crude reaction mixture. Purification by flash chromatography afforded the analytically pure aldehyde.

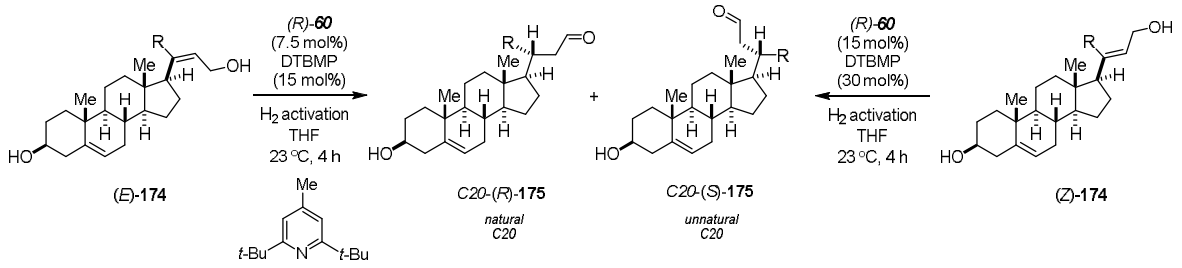
General Procedure B: (*R*)-60–catalyzed isomerization



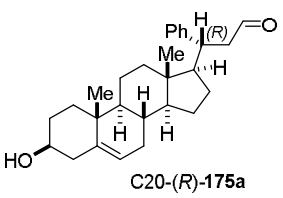
A 10 mL Schlenk containing (*R*)-**60** (5.5 mg (7.5 mol%) for (*E*)-**174** and 11 mg (15 mol%) for (*Z*)-**174**) was purged by three successive vacuum/nitrogen sequences and refilled with nitrogen. Degassed anhydrous tetrahydrofuran (1.5 mL) was added next and hydrogen gas

was gently bubbled directly through the solution (2-3 bubbles per second) via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minutes, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol **174** (0.05 mmol) was added immediately to the cold solution in one portion. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h. The reaction was then stopped, quenched with 2 drops of triethylamine, and concentrated under vaccum. The C20-(*R*)/C20-(*S*) diastereomeric ratio was assessed by ^{1}H NMR of the crude reaction mixture. Purification by flash chromatography afforded the analytically pure aldehyde.

General Procedure C: (*R*)-60–catalyzed isomerization in the presence of DTBMP



A 10 mL Schlenk containing (*R*)-**60** (5.5 mg (7.5 mol%) for (*E*)-**174** and 11 mg (15 mol%) for (*Z*)-**174**) was purged by three successive vacuum/nitrogen sequences and refilled with nitrogen. Degassed anhydrous tetrahydrofuran (1.5 mL) was added next and hydrogen gas was gently bubbled directly through the solution (2-3 bubbles per second) via a stainless-steel needle at room temperature. The orange solution gradually discolored. After 5 minutes, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol **174** (0.05 mmol) and 2,6-di*t*-butyl-4-methylpyridine (15 mol% for (*E*)-**174** and 30 mol% for (*Z*)-**174**) were added immediately to the cold solution in one portion. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 24 h. The reaction was then stopped, quenched with 2 drops of triethylamine, and concentrated under vaccum. The C20-(*R*)/C20-(*S*) diastereomeric ratio was assessed by ^{1}H NMR of the crude reaction mixture. Purification by flash chromatography afforded the analytically pure aldehyde.



Following general procedure B using (*R*)-**60** (7.5 mol%) and *(E)*-**174a** (20 mg, 0.05 mmol). Purification by flash chromatography (Cyclohexane/Ethyl acetate = 2/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175a** (14 mg, 70%, dr >50/1).

Colorless oil (Pentane/Ethyl acetate = 2/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.52 (t, $^{3}J_{HH}$ = 2.2 Hz, 1H, C*H*O), 7.28-7.20 (m, 4H, 2$H_{ortho\text{-}Ph}$+2$H_{meta\text{-}Ph}$), 7.20-7.16 (m, 1H, $H_{para\text{-}Ph}$), 5.33-5.31 (m, 1H, H_6), 3.51-3.43 (m, 1H, H_3), 3.11 (td, $^{3}J_{HH}$ = 10.7, 4.4 Hz, 1H, H_{20}), 2.74-2.60 (m, 2H, H_{22}), 2.29-2.15 (m, 2H, H_4), 2.00-1.90 (m, 2H, H_7+H_{16}), 1.83-1.62 (m, 4H, H_1+H_2+H_{15}+H_{17}), 1.54-1.37 (m, 4H, H_2+H_7+H_8+H_{16}), 1.28-1.06 (m, 3H, 2H_{11}+H_{15}), 1.06-0.91 (m, 5H, H_1+H_{14}+Me_{19}), 0.79 (td, $^{3}J_{HH}$ = 11.6, 5.2 Hz, 1H, H_9), 0.72 (s, 3H, Me_{18}), 0.58 (td, $^{2}J_{HH}$ = 12.9 Hz, $^{3}J_{HH}$ = 4.7 Hz, 1H, H_{12e}), 0.38 (dt, $^{2}J_{HH}$ = 12.9 Hz, $^{3}J_{HH}$ = 3.6 Hz, 1H, H_{12a}).

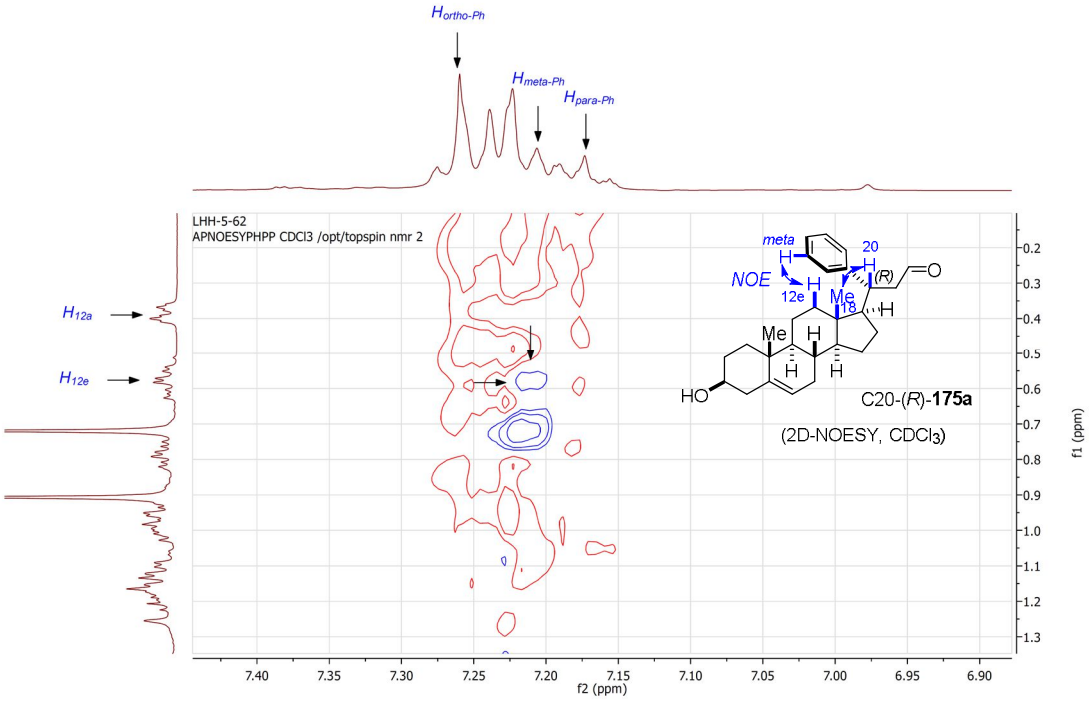
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 202.6 (*C*HO), 143.5 (C_{Ph}), 140.8 (C_5), 128.3 ($C_{ortho\text{-}Ph}$), 128.2 ($C_{meta\text{-}Ph}$), 126.6 ($C_{para\text{-}Ph}$), 121.4 (C_6H), 71.7 (C_3H), 56.5 (C_{14}H), 55.3 (C_{17}H), 50.3 ($C_{22}H_2$), 50.0 (C_9H), 42.9 (C_{20}H), 42.5 (C_{13}), 42.2 (C_4H_2), 38.4 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 28.2 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

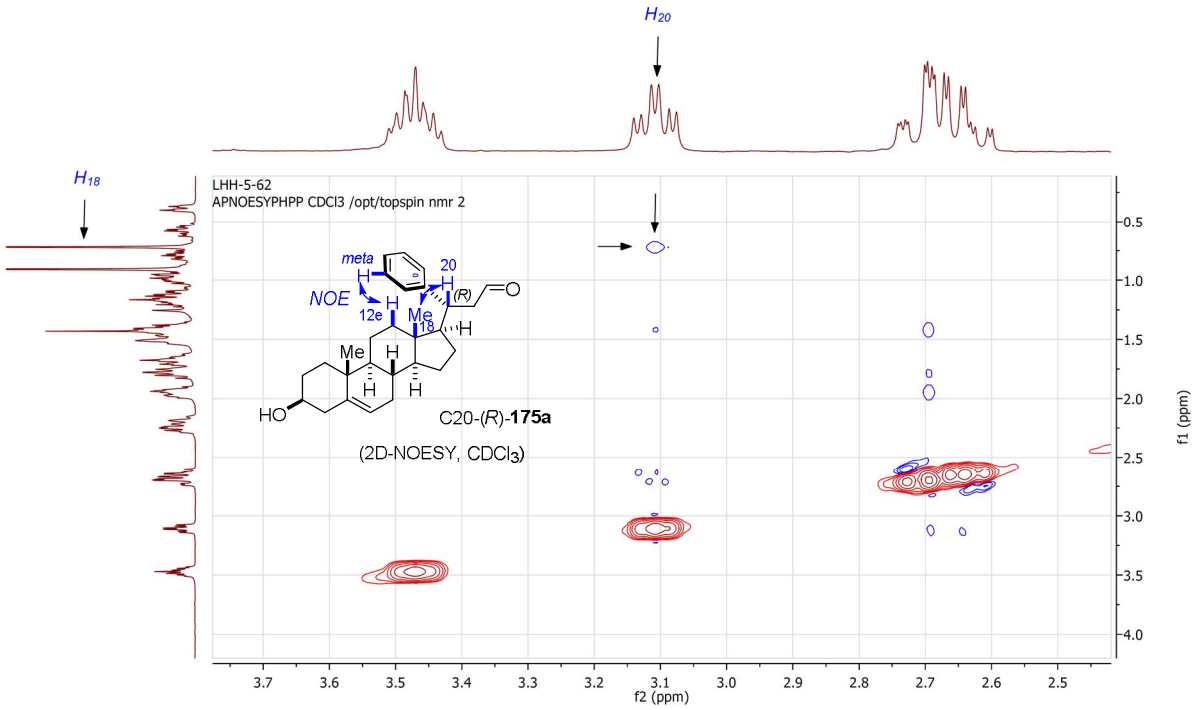
HRMS (MALDI–TOF) calculated for $C_{28}H_{38}O_2Na$ $[M+Na]^+$: 429.2764, found 429.2731.

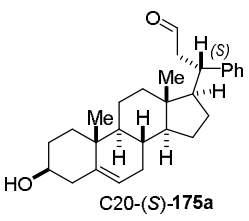
IR (neat): ν (cm^{-1}) = 3400, 2936, 2864, 1722, 1668, 1454, 1436, 1377, 1058, 1023, 954, 910, 843, 802, 754, 732, 702.

$[\alpha]^{25}_D$ = –17.0 (*c* 1.30, CH_2Cl_2).

The C20 stereochemistry of C20-(*R*)-**175a** was determined by 2D–NOESY (shown as below)







Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174a** (37 mg, 0.09 mmol). Purification by flash chromatography (Pentane/Ethyl acetate = 4/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175a** (18 mg, 49%, dr 1/50).

Colorless oil (Pentane/Ethyl acetate = 2/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.47 (dd, $^3J_{HH}$ = 3.1, 1.6 Hz, 1H, C*H*O), 7.29-7.25 (m, 2H, $H_{ortho\text{-}Ph}$), 7.20-7.16 (m, 3H, $H_{para\text{-}Ph}$+2$H_{meta\text{-}Ph}$), 5.36-5.34 (m, 1H, H_6), 3.57-3.48 (m, 1H, H_3), 3.09 (td, $^3J_{HH}$ = 11.1, 4.0 Hz, 1H, H_{20}), 2.95 (ddd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 4.0, 1.7 Hz, 1H, H_{22}), 2.73 (ddd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 11.3, 3.1 Hz, 1H, H_{22}), 2.33-2.21 (m, 2H, H_4), 2.02 (dt, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, H_{12}), 1.98-1.94 (m, 1H, H_7), 1.90-1.84 (m, 2H, H_1+H_2), 1.74 (dt, $^3J_{HH}$ = 10.8, 9.2 Hz, 1H, H_{17}), 1.62-1.43 (m, 6H, H_2+H_7+H_8+2H_{11}+H_{15}), 1.36 (td, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, H_{12}), 1.29-1.22 (m, 1H, H_{16}), 1.19-0.94 (m, 8H, H_1+H_9+H_{14}+H_{15}+H_{16}+Me_{19}), 0.84 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 202.5 (*C*HO), 143.8 (C_{Ph}), 140.7 (C_5), 128.5 ($C_{ortho\text{-}Ph}$), 127.9 ($C_{meta\text{-}Ph}$), 126.5 ($C_{para\text{-}Ph}$), 121.5 (C_6H), 71.7 (C_3H), 56.7 (C_{14}H), 55.3 (C_{17}H), 50.0 (C_9H), 49.1 ($C_{22}H_2$), 43.1 (C_{20}H), 42.4 (C_{13}), 42.2 (C_4H_2), 39.9 ($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 28.5 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

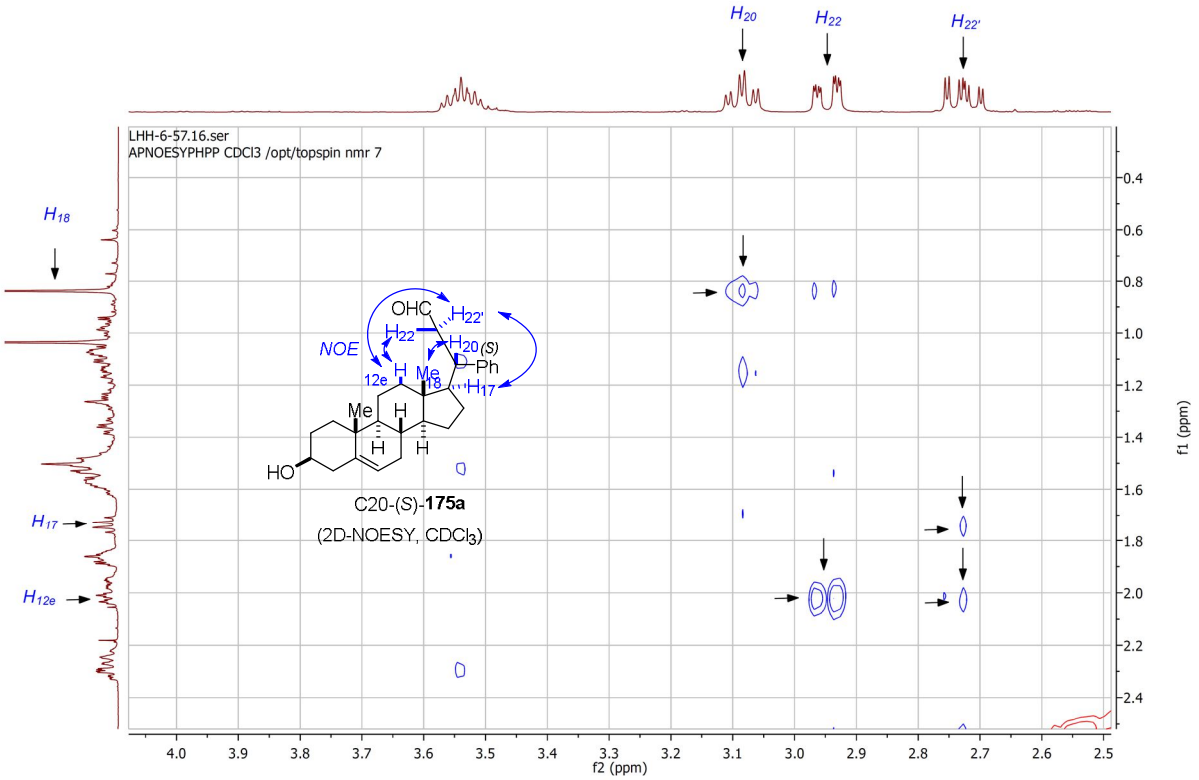
HRMS (MALDI–TOF) calculated for $C_{28}H_{38}O_2Na$ $[M+Na]^+$: 429.2764, found 429.2752.

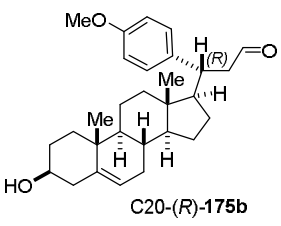
IR (neat): ν (cm^{-1}) = 3383, 2932, 1721, 1666, 1452, 1379, 1266, 1052, 955, 843, 803, 774, 735, 701.

$[\alpha]^{25}_{D}$ = –49.6 (*c* 0.43, CH_2Cl_2).

The C20 stereochemistry of C20-(*S*)-**175a** was determined by 2D–NOESY and confirmed by single crystal X-ray diffraction analysis of carbonate derivative C20-(*S*)-**177**.

The original 2D-NOESY spectrum of C20-(*S*)-**175a** were shown as below:





Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**174b** (20 mg, 0.046 mmol). Purification by flash chromatography (Chloroform/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175b** (11 mg, 55%, dr >50/1).

Colorless oil (Pentane/Ethyl acetate = 2/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.51 (dd, $^3J_{HH}$ = 2.9, 1.8 Hz, 1H, C*H*O), 7.12 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{ortho\text{-}Ph}$), 6.80 (d, $^3J_{HH}$ = 8.7 Hz, 2H, $H_{meta\text{-}Ph}$), 5.33-5.31 (m, 1H, H_6), 3.78 (s, 3H, *Me*O), 3.52-3.44 (m, 1H, H_3), 3.06 (td, $^3J_{HH}$ = 10.9, 4.2 Hz, 1H, H_{20}), 2.71-2.55 (m, 2H, H_{22}), 2.29-2.16 (m, 2H, H_4), 1.98-1.10 (m, 14H), 1.28-1.06 (m, 3H, $2H_{11}$+H_{15}), 1.02-0.91 (m, 5H, H_1+H_{14}+Me_{19}), 0.79 (td, $^3J_{HH}$ = 11.9, 5.0 Hz, 1H, H_9), 0.71 (s, 3H, Me_{18}), 0.63-0.55 (m, 1H, H_{12e}), 0.47 (dt, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, H_{12a}).

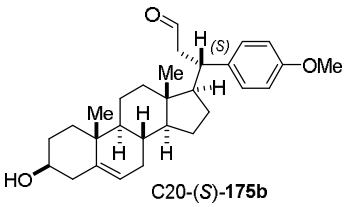
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 202.9 (*C*HO), 158.1 ($C_{para\text{-}Ph}$OMe), 140.8 (C_5), 135.5 (C_{Ar}), 129.1 (C_{Ar}H), 121.5 (C_6H), 113.7 (C_{Ar}H), 71.7 (C_3H), 56.5 (C_{14}H), 55.5 (C_{17}H), 55.2 (*Me*O), 50.4 ($C_{22}H_2$), 50.0 (C_9H), 42.5 (C_{13}), 42.2 (C_4H_2), 42.2 (C_{20}H), 38.5 ($C_{12}H_2$), 37.1

(C_1H_2), 36.4 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 28.3 ($C_{16}H_2$), 24.1 ($C_{15}H_2$), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2860.

IR (neat): ν (cm^{-1}) = 3405, 2936, 1721, 1610, 1510, 1420, 1276, 1246, 1211, 1175, 1139, 1037, 954, 887, 832, 808, 755, 732.

$[\alpha]^{25}_D$ = –14.9 (*c* 1.0, CH_2Cl_2).



C20-(*S*)-**175b**

Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174b** (40 mg, 0.093 mmol). Purification by flash chromatography (Chloroform/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175b** (16 mg, 40%, dr 1/50).

Colorless oil (Pentane/Ethyl acetate = 2/1, R_f = 0.20).

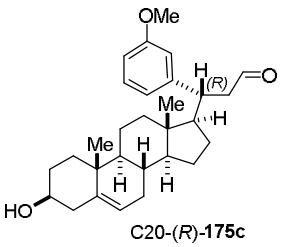
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.45 (dd, $^3J_{HH}$ = 3.3, 1.6 Hz, 1H, C*H*O), 7.09 (d, $^3J_{HH}$ = 8.6 Hz, 2H, $H_{ortho\text{-}Ph}$), 6.80 (d, $^3J_{HH}$ = 8.6 Hz, 2H, $H_{meta\text{-}Ph}$),, 5.35-5.33 (m, 1H, H_6), 3.77 (s, 3H, *Me*O), 3.56-3.49 (m, 1H, H_3), 3.03 (td, $^3J_{HH}$ = 11.1, 4.0 Hz, 1H, H_{20}), 2.91 (ddd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 4.1, 1.7 Hz, 1H, H_{22}), 2.66 (ddd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 11.4, 3.4 Hz, 1H, H_{22}), 2.32-2.17 (m, 2H, H_4), 2.01-1.22 (m, 17H), 1.13-0.92 (m, 6H), 0.82 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 202.7 (*C*HO), 158.0 ($C_{para\text{-}Ph}$OMe), 140.7 (C_5), 135.9 (C_{Ar}), 128.8 ($C_{Ar}H$), 121.5 (C_6H), 113.8 ($C_{Ar}H$), 71.7 (C_3H), 56.7 ($C_{14}H$), 55.5 ($C_{17}H$), 55.2 (*Me*O), 50.0 (C_9H), 49.2 ($C_{22}H_2$), 42.3 (C_{13}), 42.3 ($C_{20}H$), 42.2 (C_4H_2), 39.9 ($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 28.6 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2881.

IR (neat): ν (cm^{-1}) = 3416, 2934, 1720, 1610, 1511, 1461, 1378, 1247, 1178, 1110, 1037, 954, 831, 735, 703.

$[\alpha]^{25}_D$ = –27.9 (*c* 1.0, CH_2Cl_2).



C20-(*R*)-**175c**

Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**174c** (19 mg, 0.044 mol). Purification by flash chromatography (Pentane/Acetone = 3/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175c** (13 mg, 69%, dr >50/1).

Colorless oil (Pentane/Acetone = 3/1, R_f = 0.20).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.50 (dd, $^3J_{HH}$ = 3.0, 1.7 Hz, 1H, C*H*O), 7.18 (t, $^3J_{HH}$ = 7.9 Hz, 1H, H_{Ar}), 6.84-6.71 (m, 3H, H_{Ar}), 5.33-5.31 (m, 1H, H_6), 3.78 (s, 3H, *Me*O), 3.45-3.36 (m, 1H, H_3), 3.08 (td, $^3J_{HH}$ = 10.8, 4.2 Hz, 1H, H_{20}), 2.71-2.52 (m, 2H, H_{22}), 2.25-2.12 (m, 2H, H_4), 1.99-1.35 (m, 13H), 1.19-0.96 (m, 4H), 0.94-0.77 (m,

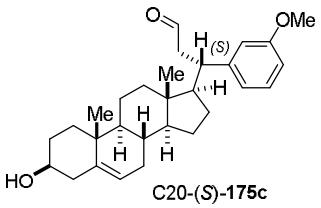
6H), 0.73 (s, 3H, Me_{18}), 0.62 (dt, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 6.4 Hz, 1H, H_{12e}), 0.48 (dt, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, H_{12a}).

$^{13}C\{^1H\}$ NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 202.7 (*C*HO), 160.0 (C_{Ar}), 145.8 (C_{Ar}), 141.4 (C_5), 129.6 ($C_{Ar}H$), 121.6 (C_6H), 121.2 ($C_{Ar}H$), 114.7 ($C_{Ar}H$), 111.8 ($C_{Ar}H$), 72.0 (C_3H), 56.9 ($C_{14}H$), 55.6 ($C_{17}H$), 55.5 (*Me*O), 50.6 ($C_{22}H_2$), 50.5 (C_9H), 43.3 (C_4H_2), 42.9 (C_{13}), 42.7 ($C_{20}H$), 38.9 ($C_{12}H_2$), 37.6 (C_1H_2), 36.8 (C_{10}), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 28.6 ($C_{16}H_2$), 24.4 ($C_{15}H_2$), 21.3 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2859.

IR (neat): ν (cm^{-1}) = 3408, 2936, 1723, 1600, 1488, 1458, 1436, 1377, 1286, 1258, 1154, 1050, 784, 705.

$[\alpha]^{25}_D$ = –16.0 (*c* 0.63, CH_2Cl_2).



C20-(*S*)-**175c**

Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174c** (20 mg, 0.046 mmol). Purification by flash chromatography (Dichloromethane/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175c** (8.3 mg, 42%, dr 1/50).

White solid, m.p. = 118–119 °C (Pentane/Ethyl acetate = 2/1, R_f = 0.20).

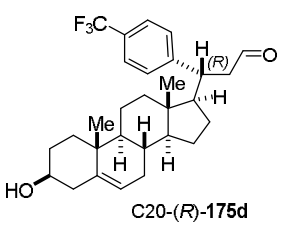
^1H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.44 (dd, $^3J_{HH}$ = 3.3, 1.4 Hz, 1H, C*H*O), 7.18 (t, $^3J_{HH}$ = 7.5, 1.1 Hz, 1H, H_{Ar}), 6.79-6.70 (m, 3H, H_{Ar}), 5.34-5.32 (m, 1H, H_6), 3.77 (s, 3H, *Me*O), 3.49-3.42 (m, 1H, H_3), 3.05 (td, $^3J_{HH}$ = 10.1, 4.0 Hz, 1H, H_{20}), 2.92 (ddd, $^3J_{HH}$ = 16.0, 4.0, 1.5 Hz, 1H, H_{22}), 2.66 (ddd, $^3J_{HH}$ = 16.0, 11.4, 3.4 Hz, 1H, H_{22}), 2.28-2.14 (m, 2H, H_4), 2.03-1.05 (m, 16H), 1.02 (s, 3H, Me_{18}), 1.01-0.88 (m, 1H, H_9), 0.83 (s, 3H, Me_{19}).

$^{13}C\{^1H\}$ NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 202.5 (*C*HO), 160.2 (C_{Ar}), 146.2 (C_{Ar}), 141.4 (C_5), 129.7 ($C_{Ar}H$), 121.7 (C_6H), 120.8 ($C_{Ar}H$), 114.4 ($C_{Ar}H$), 111.6 ($C_{Ar}H$), 72.0 (C_3H), 57.1 ($C_{14}H$), 55.5 ($C_{17}H$), 55.5 (*Me*O), 50.5 (C_9H), 49.4 ($C_{22}H_2$), 43.6 (C_4H_2), 42.8 (C_{13}), 42.7 ($C_{20}H$), 40.3 ($C_{12}H_2$), 37.7 (C_1H_2), 36.9 (C_{10}), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 28.8 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{40}O_3Na$ $[M+Na]^+$: 459.2870, found 459.2869.

IR (neat): ν (cm^{-1}) = 2935, 1722, 1597, 1488, 1461, 1436, 1377, 1320, 1259, 1162, 1055, 954, 786, 734, 701.

$[\alpha]^{25}_D$ = –22.3 (*c* 0.59, CH_2Cl_2).



C20-(*R*)-**175d**

Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**174d** (15 mg, 0.032 mmol). Purification by flash chromatography (Chloroform/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175d** (7.1 mg, 51%, dr >50/1).

Colorless oil (Pentane/Ethyl acetate = 2/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.54 (dd, $^3J_{HH}$ = 2.3, 1.4 Hz, 1H, C*H*O), 7.52 (d, $^3J_{HH}$ = 8.1 Hz, 2H, $H_{meta\text{-}Ph}$), 7.36 (d, $^3J_{HH}$ = 8.0 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.33-5.30 (m, 1H, H_6), 3.52-3.44 (m, 1H, H_3), 3.22 (td, $^3J_{HH}$ = 10.7, 4.1 Hz, 1H, H_{20}), 2.80-2.64 (m, 2H, H_{22}), 2.29-2.16 (m, 2H, H_4), 1.99-0.96 (m, 15H), 0.91 (s, 3H, Me_{19}), 0.79 (dt, $^3J_{HH}$ = 11.9, 5.9 Hz, 1H, H_9), 0.72 (s, 3H, Me_{18}), 0.58 (td, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 4.6 Hz, 1H, H_{12e}), 0.34 (dt, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, H_{12a}).

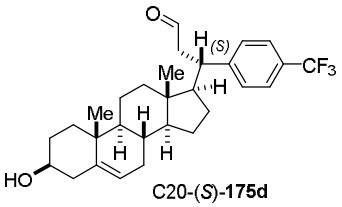
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 201.4 (*C*HO), 148.0 (C_{Ar}), 140.8 (C_5), 128.6 ($C_{ortho\text{-}Ph}$H), 125.3 (q, $^3J_{CF}$ = 3.7 Hz, $C_{meta\text{-}Ph}$H), 121.4 (C_6H), 71.7 (C_3H), 56.5 (C_{14}H), 55.0 (C_{17}H), 50.3 ($C_{22}H_2$), 49.9 (C_9H), 42.5 (C_{13}), 42.4 (C_{20}H), 42.2 (C_4H_2), 38.6 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 31.9 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 28.2 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −58.2.

HRMS (MALDI−TOF) calculated for $C_{29}H_{37}F_3O_2Na$ $[M+Na]^+$: 497.2638, found 497.2657.

IR (neat): ν (cm^{-1}) = 2936, 1723, 1618, 1325, 1163, 1122, 1068, 1017, 841, 756.

$[\alpha]^{25}_D$ = −11.9 (*c* 0.73, CH_2Cl_2).



C20-(*S*)-**175d**

Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174d** (20 mg, 0.042 mmol). Purification by flash chromatography (Pentane/Acetone = 6/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175d** (8.0 mg, 40%, dr 1/50).[21]

Colorless oil (Pentane/Ethyl acetate = 2/1, R_f = 0.20).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.51 (dd, $^3J_{HH}$ = 2.9, 1.1 Hz, 1H, C*H*O), 7.58 (d, $^3J_{HH}$ = 8.0 Hz, 2H, $H_{meta\text{-}Ph}$), 7.38 (d, $^3J_{HH}$ = 8.0 Hz, 2H, $H_{ortho\text{-}Ph}$),, 5.38-5.36 (m, 1H, H_6), 3.53-3.46 (m, 1H, H_3), 3.23 (td, $^3J_{HH}$ = 11.1, 3.8 Hz, 1H, H_{20}), 3.06 (ddd, $^2J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 3.7, 1.2 Hz, 1H, H_{22}), 2.83-2.75 (m, 1H, H_{22}), 2.32-2.18 (m, 2H, H_4), 2.08-1.11 (m, 18H), 1.06 (s, 3H, Me_{19}), 0.88 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 201.6 (*C*HO), 149.1 (C_{Ar}), 141.4 (C_5), 128.9 ($C_{ortho\text{-}Ph}$H), 125.7 (q, $^3J_{CF}$ = 3.7 Hz, $C_{meta\text{-}Ph}$H), 121.7 (C_6H), 72.0 (C_3H), 57.1 (C_{14}H), 55.2 (C_{17}H), 50.5 (C_9H), 49.4 ($C_{22}H_2$), 43.1 (C_{20}H), 43.0 (C_{13}), 42.7 (C_4H_2), 40.4 ($C_{12}H_2$), 37.7

[21] C20-(*S*)-**175d** was contaminated with the corresponding (*Z*)-α,β-unsaturated aldehyde (ratio: 4/1).

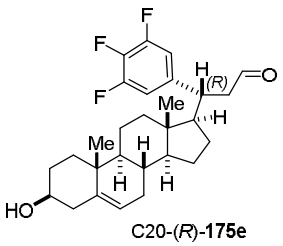
(C_1H_2), 36.9 (C_{10}), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 28.9 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, 282 MHz): δ (ppm) = –60.0.

HRMS (MALDI–TOF) calculated for $C_{29}H_{37}F_3O_2Na$ $[M+Na]^+$: 497.2638, found 497.2657.

IR (neat): ν (cm^{-1}) = 3396, 2930, 1723, 1670, 1618, 1458, 1324, 1265, 1164, 1120, 1067, 1016, 955, 838, 803, 736, 702.

$[\alpha]^{25}_D$ = –16.5 (*c* 0.87, CH_2Cl_2).



C20-(*R*)-**175e**

Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**174e** (20 mg, 0.043 mmol). Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175e** (8.0 mg, 40%, dr >50/1).

Colorless oil (Pentane/Acetone = 3/1, R_f = 0.30).

^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.56 (dd, $^3J_{HH}$ = 2.2, 1.1 Hz, 1H, C*H*O), 6.86 (dd, $^3J_{HH}$ = 8.5, 6.4 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.35-5.31 (m, 1H, H_6), 3.54-3.45 (m, 1H, H_3), 3.09 (td, $^3J_{HH}$ = 10.9, 3.8 Hz, 1H, H_{20}), 2.75 (ddd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 3.8, 1.2 Hz, 1H, H_{22}), 2.64-2.57 (m, 1H, H_{22}), 2.30-2.16 (m, 2H, H_4), 1.94-0.96 (m, 15H), 0.93 (s, 3H, Me_{19}), 0.90-0.77 (m, 1H, H_9), 0.71 (s, 3H, Me_{18}), 0.67-0.62 (m, 1H, H_{12e}), 0.49 (dt, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, H_{12a}).

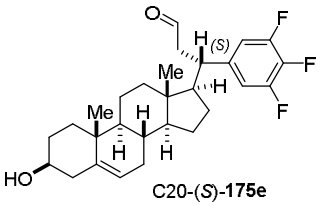
$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 200.7 (*C*HO), 151.0 (ddd, $^1J_{CF}$ = 250 Hz, $^2J_{CF}$ = 9.9 Hz, $^3J_{CF}$ = 4.2 Hz, $C_{meta\text{-}Ph}F$), 140.8 (C_5), 140.3 (m, C_{Ph}), 138.3 (dt, $^1J_{CF}$ = 250Hz, $^2J_{CF}$ = 15 Hz, $C_{para\text{-}Ph}F$), 121.3 (C_6H), 112.2 (dd, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 6.2 Hz, $C_{ortho\text{-}Ph}$), 71.7 (C_3H), 56.4 ($C_{14}H$), 55.0 ($C_{17}H$), 50.2 ($C_{22}H_2$), 49.9 (C_9H), 42.5 (C_{13}), 42.2 (C_4H_2), 41.7 ($C_{20}H$), 38.6 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 31.9 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 28.1 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, 282 MHz): δ (ppm) = –133.4 (d, $^3J_{FF}$ = 20.5 Hz), –162.1 (t, $^3J_{FF}$ = 20.5 Hz).

HRMS (MALDI–TOF) calculated for $C_{28}H_{34}F_3O$ $[M–OH]^+$: 443.2556, found 443.2559.

IR (neat): ν (cm^{-1}) = 3404, 2936, 1723, 1617, 1527, 1448, 1349, 1236, 1041, 909, 857, 732.

$[\alpha]^{25}_D$ = –11.4 (*c* 1.10, CH_2Cl_2).



C20-(*S*)-**175e**

Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174e** (20 mg, 0.043 mmol). Purification by flash chromatography (Pentane/Acetone = 6/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175e** (5.0 mg, 25%, dr 1/50).[22]

Colorless oil (Pentane/Acetone = 3/1, R_f = 0.30).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.52 (dd, $^3J_{HH}$ = 2.6, 1.0 Hz, 1H, C*H*O), 6.81 (dd, $^3J_{HH}$ = 8.6, 6.4 Hz, 2H, $H_{ortho\text{-}Ph}$), 5.35-5.33 (m, 1H, H_6), 3.54-3.45 (m, 1H, H_3), 3.07-2.95 (m, 1H, H_{20}), 2.72-2.58 (m, 2H, H_{22}), 2.32-2.17 (m, 2H, H_4), 1.98-1.06 (m, 15H), 1.02 (s, 3H, Me_{19}), 0.79 (s, 3H, Me_{18}).

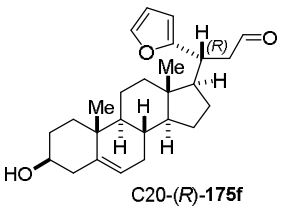
^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 200.6 (*C*HO), 140.7 (C_5), 121.4 (C_6H), 111.8 (dd, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 6.2 Hz, $C_{ortho\text{-}Ph}$), 71.7 (C_3H), 56.6 (C_{14}H), 54.8 (C_{17}H), 49.9 (C_9H), 49.0 ($C_{22}H_2$), 42.5 (C_{13}), 42.2 (C_4H_2), 39.9 (C_{20}H), 38.2 ($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 31.9 (C_8H), 31.7 (C_7H_2), 31.6 (C_2H_2), 28.5 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −133.5 (d, $^3J_{FF}$ = 20.5 Hz), −162.4 (t, $^3J_{FF}$ = 20.5 Hz).

HRMS (MALDI−TOF) calculated for $C_{28}H_{34}F_3O$ $[M-OH]^+$: 443.2556, found 443.2569.

IR (neat): ν (cm^{-1}) = 3363, 2933, 1724, 1673, 1618, 1528, 1448, 1348, 1236, 1046, 864.

$[\alpha]^{25}_D$ = −9.7 (*c* 0.71, CH_2Cl_2).



C20-(*R*)-**175f**

Following general procedure C using (*R*)-**60** (7.5 mol%), (*E*)-**174f** (18 mg, 0.045 mmol) and 2,6-di*t*-butyl-4-methylpyridine (1.6 mg, 15 mol%). Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175f** (4.0 mg, 22%, dr >50/1).

Colorless oil (Pentane/Ethyl acetate = 1/1, R_f = 0.40).

^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) = 9.57 (dd, $^3J_{HH}$ = 2.7, 1.8 Hz, 1H, C*H*O), 7.32-7.32 (m, 1H, H_{Ar}), 6.26 (dd, $^3J_{HH}$ = 3.2, 1.9 Hz, 1H, H_{Ar}), 6.05 (dd, $^3J_{HH}$ = 3.2, 0.9 Hz, 1H, H_{Ar}), 5.33-5.31 (m, 1H, H_6), 3.46-3.40 (m, 1H, H_3), 3.18 (td, $^3J_{HH}$ = 11.0, 4.5 Hz, 1H, H_{20}), 2.68-2.57 (m, 2H, H_{22}), 2.26-2.12 (m, 2H, H_4), 1.79-1.14 (m, 13H), 1.03-0.95 (m, 5H), 0.90-0.84 (m, 1H, H_9), 0.79-0.72 (m, 4H, H_{12e}+Me_{18}), 0.56 (dt, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, H_{12a}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 202.2 (*C*HO), 157.6 (C_{Ar}), 141.4 (C_5), 141.0 (C_{Ar}H), 121.7 (C_6H), 110.3 (C_{Ar}H), 106.6 (C_{Ar}H), 72.0 (C_3H), 56.7 (C_{14}H), 53.9 (C_{17}H), 50.5 (C_9H), 47.8 ($C_{22}H_2$), 42.7 (C_4H_2), 42.5 (C_{13}), 37.6 ($C_{12}H_2$), 37.1 (C_1H_2), 36.8 (C_{10}), 36.0

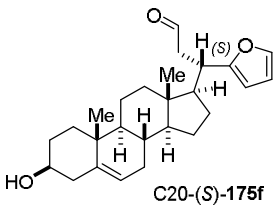
[22] C20-(*S*)-**175e** was contaminated with the corresponding (*Z*)-α,β-unsaturated aldehyde (ratio: 1.9/1).

(C_{20}H), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 28.3 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 21.3 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 11.7 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2559.

IR (neat): ν (cm^{-1}) = 2938, 1724, 1506, 1454, 1436, 1379, 1355, 1278, 1129, 1057, 1011, 802, 734.

$[\alpha]^{25}_D$ = –24.8 (*c* 0.62, CH_2Cl_2).



C20-(*S*)-**175f**

Following general procedure C using (*R*)-**60** (15 mol%), (*Z*)-**174f** (19 mg, 0.048 mmol) and 2,6-di*t*-butyl-4-methylpyridine (3.2 mg, 30 mol%). Purification by flash chromatography (Dichloromethane/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175f** (10 mg, 55%, dr 1/50).

Colorless oil (Pentane/Ethyl acetate = 1/1, R_f = 0.40).

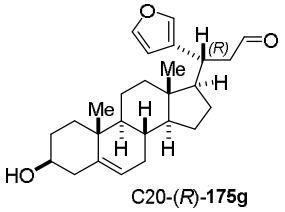
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.54 (dd, $^3J_{HH}$ = 2.9, 1.6 Hz, 1H, C*H*O), 7.30 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H_{Ar}), 6.26 (dd, $^3J_{HH}$ = 3.2, 1.8 Hz, 1H, H_{Ar}), 6.02 (d, $^3J_{HH}$ = 3.1 Hz, 1H, H_{Ar}), 5.35-5.32 (m, 1H, H_6), 3.49-3.42 (m, 1H, H_3), 3.23 (td, $^3J_{HH}$ = 10.4, 4.4 Hz, 1H, H_{20}), 2.83-2.67 (m, 2H, H_{22}), 2.25-1.05 (m, 16H), 1.02 (s, 3H, Me_{19}), 0.98-0.86 (m, 1H, H_9), 0.76 (m, 3H, Me_{18}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 202.0 (*C*HO), 157.6 (C_{Ar}), 141.4 (C_5), 141.3 (C_{Ar}H), 121.7 (C_6H), 110.2 (C_{Ar}H), 106.1 (C_{Ar}H), 72.0 (C_3H), 57.0 (C_{14}H), 53.8 (C_{17}H), 50.5 (C_9H), 47.3 ($C_{22}H_2$), 42.7 (C_4H_2), 42.6 (C_{13}), 40.0 ($C_{12}H_2$), 37.7 (C_1H_2), 37.2 (C_1H_2), 36.9 (C_{10}), 36.4 (C_{20}H), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 28.0 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2537.

IR (neat): ν (cm^{-1}) = 3379, 2934, 1723, 1466, 1436, 1379, 1148, 1112, 1053, 1014, 802, 735.

$[\alpha]^{25}_D$ = –25.7 (*c* 0.83, CH_2Cl_2).



C20-(*R*)-**175g**

Following general procedure C using (*R*)-**60** (7.5 mol%), (*E*)-**174g** (19 mg, 0.048 mmol) and 2,6-di*t*-butyl-4-methylpyridine (1.6 mg, 15 mol%). Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175g** (9.0 mg, 47%, dr >50/1).

White solid, m.p. = 173–175 °C (Pentane/Ethyl acetate = 1/1, R_f = 0.40).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.53 (dd, $^3J_{HH}$ = 3.2, 1.5 Hz, 1H, C*H*O), 7.36-7.35 (m, 1H, H_{Ar}), 7.25-7.25 (m, 1H, H_{Ar}), 6.32-6.32 (m, 1H, H_{Ar}), 5.34-5.32 (m, 1H, H_6), 3.46-3.40 (m,

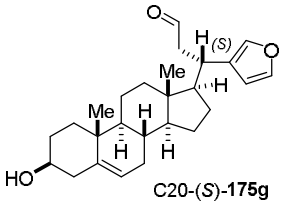
1H, H_3), 3.09 (td, $^3J_{HH}$ = 10.9, 3.8 Hz, 1H, H_{20}), 2.63-2.40 (m, 2H, H_{22}), 2.26-2.12 (m, 2H, H_4), 1.99-1.09 (m, 11H), 1.03-0.94 (m, 5H), 0.89-0.77 (m, 2H), 0.72 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 202.8 (*C*HO), 143.4 ($C_{Ar}H$), 141.4 (C_5), 139.4 ($C_{Ar}H$), 127.6 (C_{Ar}), 121.6 (C_6H), 110.2 ($C_{Ar}H$), 72.0 (C_3H), 57.0 ($C_{14}H$), 54.8 ($C_{17}H$), 50.5 (C_9H), 49.7 ($C_{22}H_2$), 42.9 (C_{13}), 42.7 (C_4H_2), 39.1 ($C_{12}H_2$), 37.6 (C_1H_2), 36.8 (C_{10}), 33.1 ($C_{20}H$), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 28.6 ($C_{16}H_2$), 24.4 ($C_{15}H_2$), 21.2 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 12.1 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2556.

IR (neat): ν (cm^{-1}) = 2942, 2864, 1724, 1434, 1365, 1233, 1156, 1055, 1025, 871, 784.

$[\alpha]^{25}_D$ = –6.1 (*c* 0.83, CH_2Cl_2).



C20-(*S*)-**175g**

Following general procedure C using (*R*)-**60** (15 mol%), (*Z*)-**174g** (17 mg, 0.044 mol) and 2,6-di*t*-butyl-4-methylpyridine (2.8 mg, 30 mol%). Purification by flash chromatography (Dichloromethane/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175g** (8.2 mg, 47%, dr 1/50).

Colorless oil (Pentane/Ethyl acetate = 1/1, R_f = 0.40).

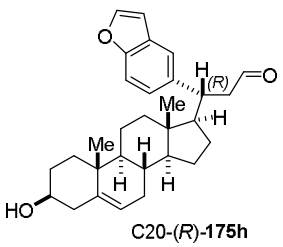
^1H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.51 (dd, $^3J_{HH}$ = 3.5, 1.3 Hz, 1H, C*H*O), 7.35-7.34 (m, 1H, H_{Ar}), 7.23-7.22 (m, 1H, H_{Ar}), 6.31 (dd, $^3J_{HH}$ = 1.9, 0.9 Hz, 1H, H_{Ar}), 5.35-5.33 (m, 1H, H_6), 3.50-3.42 (m, 1H, H_3), 3.07 (td, $^3J_{HH}$ = 10.9, 3.9 Hz, 1H, H_{20}), 2.83 (ddd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 3.9, 1.4 Hz, 1H, H_{22}), 2.62-2.48 (m, 1H, H_{22}), 2.28-2.14 (m, 2H, H_4), 2.00-1.18 (m, 11H), 1.17-0.94 (m, 8H), 0.79 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 202.6 (*C*HO), 143.6 ($C_{Ar}H$), 141.4 (C_5), 139.4 ($C_{Ar}H$), 128.0 (C_{Ar}), 121.7 (C_6H), 109.8 ($C_{Ar}H$), 72.0 (C_3H), 57.3 ($C_{14}H$), 54.8 ($C_{17}H$), 50.5 (C_9H), 48.8 ($C_{22}H_2$), 42.7 (C_4H_2), 42.6 (C_{13}), 40.2 ($C_{12}H_2$), 37.7 (C_1H_2), 36.9 (C_{10}), 33.5 ($C_{20}H$), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 29.0 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{36}O_3Na$ $[M+Na]^+$: 419.2557, found 419.2573.

IR (neat): ν (cm^{-1}) = 3386, 2932, 1721, 1664, 1502, 1457, 1355, 1277, 1159, 1127, 1056, 1023, 954, 873, 842, 791, 734, 671, 601.

$[\alpha]^{25}_D$ = –20.7 (*c* 0.82, CH_2Cl_2).



C20-(*R*)-**175h**

Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**174h** (20 mg, 0.045 mmol). Purification by flash chromatography (Chloroform/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175h** (10.4 mg, 52%, dr >50/1).

Colorless oil (Pentane/Ethyl acetate = 1/1, R_f = 0.40).

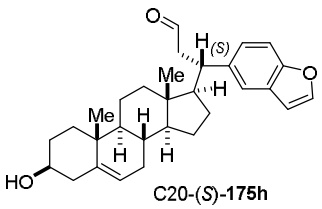
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.52 (dd, $^3J_{HH}$ = 2.8, 1.8 Hz, 1H, C*H*O), 7.59 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H_{Ar}), 7.43-7.39 (m, 2H, H_{Ar}), 7.16 (dd, $^3J_{HH}$ = 8.5, 1.8 Hz, 1H, H_{Ar}), 6.71 (dd, $^3J_{HH}$ = 2.2, 1.0 Hz, 1H, H_{Ar}), 5.32-5.31 (m, 1H, H_6), 3.49-3.44 (m, 1H, H_3), 3.22 (td, $^3J_{HH}$ = 10.7, 4.4 Hz, 1H, H_{20}), 2.78-2.63 (m, 2H, H_{22}), 2.28-2.14 (m, 2H, H_4), 1.99-0.92 (m, 13H), 0.89 (s, 3H, Me_{19}), 0.80-0.71 (m, 4H, H_9+Me_{18}), 0.56 (td, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 11.4, 4.4 Hz, 1H, H_{12e}), 0.31 (dt, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, H_{12a}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 202.8 (*C*HO), 153.8 (C_{Ar}), 145.2 (C_{Ar}H), 140.8 (C_5), 138.0 (C_{Ar}), 127.4 (C_{Ar}), 124.4 (C_{Ar}H), 121.4 (C_6H), 120.6 (C_{Ar}H), 112.2 (C_{Ar}H), 106.6 (C_{Ar}H), 71.7 (C_3H), 56.5 (C_{14}H), 55.7 (C_{17}H), 50.7 ($C_{22}H_2$), 49.9 (C_9H), 42.9 (C_{20}H), 42.6 (C_{13}), 42.2 (C_4H_2), 38.4 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 28.3 ($C_{16}H_2$), 24.1 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.3 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{30}H_{38}O_3Na$ $[M+Na]^+$: 469.2713, found 469.2724.

IR (neat): ν (cm^{-1}) = 3432, 2936, 1722, 1467, 1376, 1263, 1194, 1128, 1053, 952, 882, 812, 739.

$[\alpha]^{25}_D$ = –14.4 (*c* 0.87, CH_2Cl_2).



C20-(*S*)-**175h**

Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174h** (40 mg, 0.09 mmol). Purification by flash chromatography (Chloroform/Acetone = 20/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175h** (16.5 mg, 41%, dr 1/50).

Colorless oil (Pentane/Ethyl acetate = 1/1, R_f = 0.40).

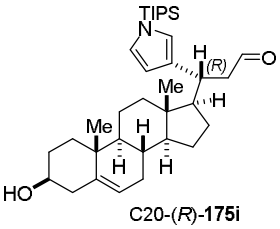
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.46 (dd, $^3J_{HH}$ = 3.3, 1.6 Hz, 1H, C*H*O), 7.58 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H_{Ar}), 7.41-7.39 (m, 2H, H_{Ar}), 7.12 (dd, $^3J_{HH}$ = 8.6, 1.8 Hz, 1H, H_{Ar}), 6.69 (dd, $^3J_{HH}$ = 2.2, 1.0 Hz, 1H, H_{Ar}), 5.35-5.33 (m, 1H, H_6), 3.57-3.49 (m, 1H, H_3), 3.18 (td, $^3J_{HH}$ = 11.1, 4.0 Hz, 1H, H_{20}), 2.95 (dd, $^3J_{HH}$ = 4.0, 1.7 Hz, 1H, H_{22}), 2.79-2.71 (m, 1H, H_{22}), 2.32-2.17 (m, 2H, H_4), 2.04-1.05 (m, 15H), 1.04-0.92 (m, 4H, H_9+Me_{19}), 0.85 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 202.6 (*C*HO), 153.7 (C_{Ar}), 145.3 (C_{Ar}H), 140.7 (C_5), 138.4 (C_{Ar}), 127.5 (C_{Ar}), 124.1 (C_{Ar}H), 121.5 (C_6H), 120.3 (C_{Ar}H), 111.3 (C_{Ar}H), 106.5 (C_{Ar}H), 71.7 (C_3H), 56.8 (C_{14}H), 55.8 (C_{17}H), 50.0 (C_9H), 49.5 ($C_{22}H_2$), 43.1 (C_{20}H), 42.4 (C_{13}), 42.2 (C_4H_2), 39.9 ($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 28.6 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{30}H_{38}O_3Na$ [M+Na]$^+$: 469.2713, found 469.2702.

IR (neat): ν (cm^{-1}) = 3390, 2933, 1720, 1466, 1379, 1263, 1194, 1128, 1110, 1053, 955, 882, 811, 770, 737, 701.

$[\alpha]^{25}_D$ = –31.8 (*c* 1.10, CH_2Cl_2).



C20-(*R*)-**175i**

Following general procedure C using (*R*)-**60** (7.5 mol%), (*E*)-**174i** (20 mg, 0.036 mmol) and 2,6-di*t*-butyl-4-methylpyridine (8.5 mg, 100 mol%). Purification by flash chromatography (Pentane/Diethyl ether = 1/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175i** (10.8 mg, 54%, dr >50/1).

Colorless oil (Pentane/Diethyl ether = 1/1, R_f = 0.20).

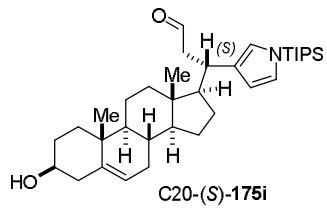
^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) = 9.49 (dd, $^3J_{HH}$ = 3.4, 2.1 Hz, 1H, C*H*O), 6.67 (t, $^3J_{HH}$ = 2.4 Hz, 1H, H_{Ar}), 6.53 (t, $^3J_{HH}$ = 1.7 Hz, 1H, H_{Ar}), 6.13 (dd, $^3J_{HH}$ = 2.7, 1.4 Hz, 1H, H_{Ar}), 5.33-5.31 (m, 1H, H_6), 3.46-3.39 (m, 1H, H_3), 3.02 (td, $^3J_{HH}$ = 11.0, 4.1 Hz, 1H, H_{20}), 2.53 (dd, $^3J_{HH}$ = 4.1, 2.1 Hz, 1H, H_{22}), 2.46-2.40 (m, 1H, H_{22}), 2.25-2.13 (m, 2H, H_4), 1.98-0.95 (m, 37H), 1.02-0.92 (m, 5H), 0.88-0.77 (m, 2H), 0.72-0.65 (m, 4H, H_{12a}+Me_{18}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 204.4 (*C*HO), 141.4 (C_5), 128.1 (C_{Ar}), 124.4 (C_{Ar}H), 121.7 (C_6H), 121.6 (C_{Ar}H), 110.1 (C_{Ar}H), 72.0 (C_3H), 57.0 (C_{14}H), 56.1 (C_{17}H), 50.6 (C_9H), 50.3 ($C_{22}H_2$), 42.9 (C_{13}), 42.7 (C_4H_2), 39.0 ($C_{12}H_2$), 37.6 (C_1H_2), 36.8 (C_{10}), 35.9 (C_{20}H), 32.3 (C_8H), 32.3 (C_7H_2), 32.1 (C_2H_2), 28.7 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 17.9 (Me_2CHSi), 12.0 ($C_{18}H_3$), 11.9 (*C*HSi).

HRMS (MALDI–TOF) calculated for $C_{35}H_{57}NO_2SiNa$ [M+Na]$^+$: 574.4051, found 574.4043.

IR (neat): ν (cm^{-1}) = 3387, 2937, 2867, 1722, 1464, 1378, 1249, 1103, 1017, 884, 784, 690, 658.

$[\alpha]^{25}_D$ = –6.7 (*c* 0.86, CH_2Cl_2).



C20-(*S*)-**175i**

Following general procedure C using (*R*)-**60** (15 mol%), (*Z*)-**174i** (20 mg, 0.036 mmol) and 2,6-di*t*-butyl-4-methylpyridine (8.5 mg, 100 mol%). Purification by flash chromatography (Pentane/Diethyl ether = 1/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175i** (5.0 mg, 25%, dr 1/50).

Colorless oil (Pentane/Diethyl ether = 1/1, R_f = 0.20).

^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) = 9.45 (dd, $^3J_{HH}$ = 3.8, 1.7 Hz, 1H, C*H*O), 6.68 (t, $^3J_{HH}$ = 2.4 Hz, 1H, H_{Ar}), 6.50 (t, $^3J_{HH}$ = 1.8 Hz, 1H, H_{Ar}), 6.11 (dd, $^3J_{HH}$ = 2.7, 1.4 Hz, 1H, H_{Ar}), 5.34-5.32 (m, 1H, H_6), 3.49-3.43 (m, 1H, H_3), 3.04 (td, $^3J_{HH}$ = 11.0, 4.2 Hz, 1H, H_{20}), 2.76 (ddd,

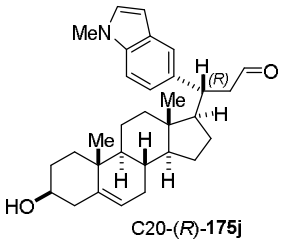
$^{2}J_{HH}$ = 15.3 Hz, $^{3}J_{HH}$ = 4.2, 1.8 Hz, 1H, H_{22}), 2.52-2.46 (m, 1H, H_{22}), 2.27-1.97 (m, 2H, H_4), 2.00-1.04 (m, 37H), 1.02 (s, 3H, Me_{19}), 1.00-0.88 (m, 1H, H_9), 0.79 (s, 3H, Me_{18}).

$^{13}C\{^{1}H\}$ NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 204.1 (*C*HO), 141.4 (C_5), 128.7 (C_{Ar}), 124.7 (C_{Ar}H), 121.8 (C_6H), 121.6 (C_{Ar}H), 109.5 (C_{Ar}H), 72.0 (C_3H), 57.3 (C_{14}H), 56.2 (C_{17}H), 50.6 (C_9H), 49.4 ($C_{22}H_2$), 42.7 (C_4H_2), 42.5 (C_{13}), 40.0 ($C_{12}H_2$), 37.7 (C_1H_2), 36.9 (C_{10}), 36.0 (C_{20}H), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 29.0 ($C_{16}H_2$), 24.3 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 18.0 (Me_2CHSi), 12.2 ($C_{18}H_3$), 12.0 (*C*HSi).

HRMS (MALDI–TOF) calculated for $C_{35}H_{57}NO_2SiNa$ $[M+Na]^+$: 574.4051, found 574.4043.

IR (neat): ν (cm^{-1}) = 3396, 2938, 2867, 1722, 1465, 1382, 1106, 1090, 1017, 884, 784, 691, 658.

$[\alpha]^{25}_D$ = –19.9 (*c* 0.47, CH_2Cl_2).



C20-(*R*)-**175j**

Following general procedure C using (*R*)-**60** (7.5 mol%), (*E*)-**174j** (14 mg, 0.031 mmol) and 2,6-di*t*-butyl-4-methylpyridine (2.0 mg, 30 mol%). Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175j** (7.1 mg, 51%, dr >50/1).

Colorless oil (Pentane/Ethyl acetate = 1/1, R_f = 0.30).

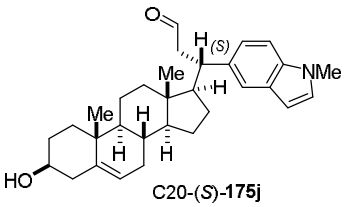
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.47 (dd, $^{3}J_{HH}$ = 3.4, 1.7 Hz, 1H, C*H*O), 7.43-7.42 (m, 1H, H_{Ar}), 7.25-7.24 (m, 1H, H_{Ar}), 7.10-7.04 (m, 2H, H_{Ar}), 6.39 (dd, $^{3}J_{HH}$ = 3.2, 0.9 Hz, 1H, H_{Ar}), 5.33-5.31 (m, 1H, H_6), 3.76 (s, 3H, *Me*N), 3.43-3.35 (m, 1H, H_3), 3.20 (td, $^{3}J_{HH}$ = 10.9, 4.2 Hz, 1H, H_{20}), 2.74-2.58 (m, 2H, H_{22}), 2.24-2.12 (m, 2H, H_4), 2.00-0.95 (m, 14H), 0.88 (s, 3H, Me_{19}), 0.79-0.74 (m, ^{4}H, H_9+Me_{18}), 0.61-0.53 (m, 1H, H_{12e}), 0.31 (dt, $^{2}J_{HH}$ = 12.9 Hz, $^{3}J_{HH}$ = 3.6 Hz, 1H, H_{12a}).

$^{13}C\{^{1}H\}$ NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 203.5 (*C*HO), 141.4 (C_5), 136.2 (C_{Ar}), 134.7 (C_{Ar}), 129.5 (C_{Ar}H), 128.8 (C_{Ar}), 122.3 (C_{Ar}H), 121.7 (C_6H), 120.6 (C_{Ar}H), 109.4 (C_{Ar}H), 100.8 (C_{Ar}H), 72.0 (C_3H), 57.0 (C_{14}H), 56.1 (C_{17}H), 51.1 ($C_{22}H_2$), 50.5 (C_9H), 43.6 (C_{20}H), 43.0 (C_{13}), 42.7 (C_4H_2), 38.9 ($C_{12}H_2$), 37.6 (C_1H_2), 36.8 (C_{10}), 33.1 (*Me*N), 32.3 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 28.7 ($C_{16}H_2$), 24.5 ($C_{15}H_2$), 21.2 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{31}H_{41}NO_2Na$ $[M+Na]^+$: 482.3030, found 482.3035.

IR (neat): ν (cm^{-1}) = 2931, 1720, 1513, 1491, 1448, 1265, 1052, 954, 881, 802, 732.

$[\alpha]^{25}_D$ = –14.6 (*c* 0.62, CH_2Cl_2).



C20-(*S*)-**175j**

Following general procedure C using (*R*)-**60** (15 mol%), (*Z*)-**174j** (23 mg, 0.05 mmol) and 2,6-di*t*-butyl-4-methylpyridine (3.2 mg, 30 mol%). Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175j** (14.2 mg, 62%, dr 1/50).

White solid, m.p. = 196−199 °C (Pentane/Ethyl acetate = 1/1, R_f = 0.30).

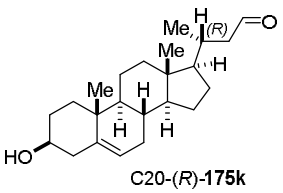
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.42 (dd, $^3J_{HH}$ = 3.8, 1.4 Hz, 1H, C*H*O), 7.39-7.38 (m, 1H, H_{Ar}), 7.26-7.24 (m, 1H, H_{Ar}), 7.06-7.04 (m, 2H, H_{Ar}), 6.38 (dd, $^3J_{HH}$ = 3.1, 0.9 Hz, 1H, H_{Ar}), 5.35-5.32 (m, 1H, H_6), 3.75 (s, 3H, *Me*N), 3.50-3.43 (m, 1H, H_3), 3.17 (td, $^3J_{HH}$ = 11.2, 4.1 Hz, 1H, H_{20}), 2.95 (ddd, $^2J_{HH}$ = 15.6 Hz, $^3J_{HH}$ = 4.2, 1.5 Hz, 1H, H_{22}), 2.70 (ddd, $^2J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 11.5, 3.8 Hz, 1H, H_{22}), 2.29-2.16 (m, 2H, H_4), 2.08-1.06 (m, 17H), 1.05-0.96 (m, 4H, H_9+Me_{19}), 0.87 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 203.2 (*C*HO), 141.4 (C_5), 136.0 (C_{Ar}), 135.1 (C_{Ar}), 129.6 (C_{Ar}H), 128.9 (C_{Ar}), 121.9 (C_{Ar}H), 121.7 (C_6H), 120.2 (C_{Ar}H), 109.6 (C_{Ar}H), 100.8 (C_{Ar}H), 72.1 (C_3H), 57.3 (C_{14}H), 56.3 (C_{17}H), 50.6 (C_9H), 50.0 ($C_{22}H_2$), 43.7 (C_{20}H), 42.7 (C_{13}), 42.7 (C_4H_2), 40.4 ($C_{12}H_2$), 37.7 (C_1H_2), 36.9 (C_{10}), 33.1 (*Me*N), 32.4 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 29.0 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.6 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

HRMS (MALDI−TOF) calculated for $C_{31}H_{41}NO_2Na$ $[M+Na]^+$: 482.3030, found 482.3042.

IR (neat): ν (cm^{-1}) = 3396, 2934, 1720, 1510, 1491, 1447, 1354, 1278, 1245, 1128, 1054, 954, 881, 841, 802, 732.

$[\alpha]^{25}_D$ = −32.7 (*c* 1.10, CH_2Cl_2).



C20-(*R*)-**175k**

Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174k** (17 mg, 0.049 mmol). Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**175k** (5.0 mg, 29%, dr >50/1).

Colorless oil (Pentane/Acetone = 4/1, R_f = 0.40).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.76 (dd, $^3J_{HH}$ = 3.4, 1.4 Hz, 1H, C*H*O), 5.36-5.34 (m, 1H, H_6), 3.56-3.45 (m, 1H, H_3), 2.46 (ddd, $^2J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 3.3, 1.4 Hz, 1H, H_{22}), 2.32-2.22 (m, 2H, H_4), 2.20-2.13 (m, 1H, H_{22}), 2.08-1.94 (m, 3H, H_7+H_{12}+H_{20}), 1.87-1.76 (m, 3H, H_1+H_2+H_{16}), 1.65-1.41 (m, 5H, H_2+H_7+H_8+2H_{11}), 1.29-1.06 (m, 6H, H_1+H_{12}+H_{14}+H_{15}+H_{16}+H_{17}), 1.02 (d, $^3J_{HH}$ = 6.4 Hz, 3H, Me_{21}), 1.01 (s, 3H, Me_{19}), 0.94 (td, $^3J_{HH}$ = 11.3, 5.3 Hz, 1H, H_9), 0.73 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 203.5 (*C*HO), 140.8 (C_5), 121.6 (C_6H), 71.8 (C_3H), 56.7 (C_{14}H), 55.8 (C_{17}H), 50.9 ($C_{22}H_2$), 50.0 (C_9H), 42.5 (C_{13}), 42.2 (C_4H_2), 39.6

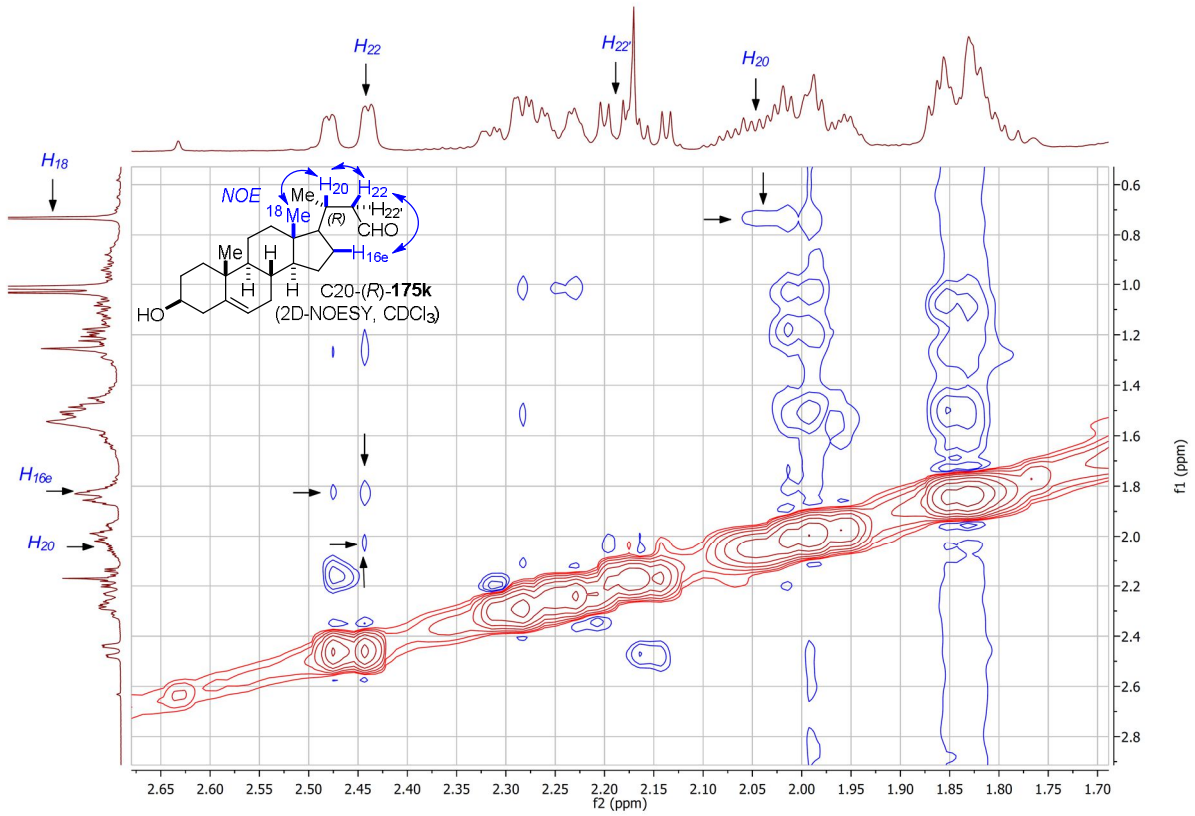
($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 31.6 ($C_{20}H$), 28.4 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 20.0 ($C_{21}H_3$), 19.4 ($C_{19}H_3$), 11.8 ($C_{18}H_3$).

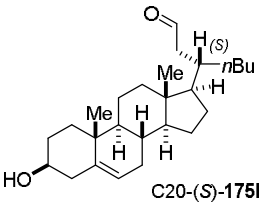
HRMS (MALDI–TOF) calculated for $C_{23}H_{36}O_2Na$ $[M+Na]^+$: 367.2608, found 367.2613.

IR (neat): ν (cm^{-1}) = 3391, 2933, 1722, 1458, 1377, 1056, 956, 840, 801, 732.

$[\alpha]^{25}_D$ = –31.9 (*c* 0.20, CH_2Cl_2).

The C20 stereochemistry of C20-(*R*)-**175k** was determined by 2D–NOESY (shown as below)





Following general procedure B using (*R*)-**60** (15 mol%) and (*E*)-**174l** (19 mg, 0.049 mmol). Purification by flash chromatography (Chloroform/Acetone = 15/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**175l** (12.7 mg, 67%, dr 1/50).

Colorless oil (Pentane/Ethyl acetate = 1/1, R_f = 0.50).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.78 (dd, $^3J_{HH}$ = 3.1, 1.7 Hz, 1H, C*H*O), 5.36-5.33 (m, 1H, H_6), 3.56-3.48 (m, 1H, H_3), 2.59 (ddd, $^2J_{HH}$ = 16.5 Hz, $^3J_{HH}$ = 4.3, 1.8 Hz, 1H, H_{22}), 2.42 (ddd, $^2J_{HH}$ = 16.5 Hz, $^3J_{HH}$ = 7.7, 3.1 Hz, 1H, H_{22}), 2.32-2.18 (m, 2H, H_4), 2.00-1.94 (m, 2H, H_7+H_{20}), 1.90-1.80 (m, 4H, H_1+H_2+H_{12}+H_{16}), 1.60-1.38 (m, 8H, H_2+H_7+H_8+2H_{11}+H_{15}+H_{17}+H_{21}), 1.35-1.03 (m, 10H), 1.00 (s, 3H, Me_{19}), 0.96-0.90 (m, 1H, H_9), 0.87 (d, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 0.71 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 203.5 (CHO), 140.7 (C_5), 121.5 (C_6H), 71.7 (C_3H), 56.5 ($C_{14}H$), 53.0 ($C_{17}H$), 50.0 (C_9H), 46.5 ($C_{22}H_2$), 42.4 (C_{13}), 42.2 (C_4H_2), 39.6

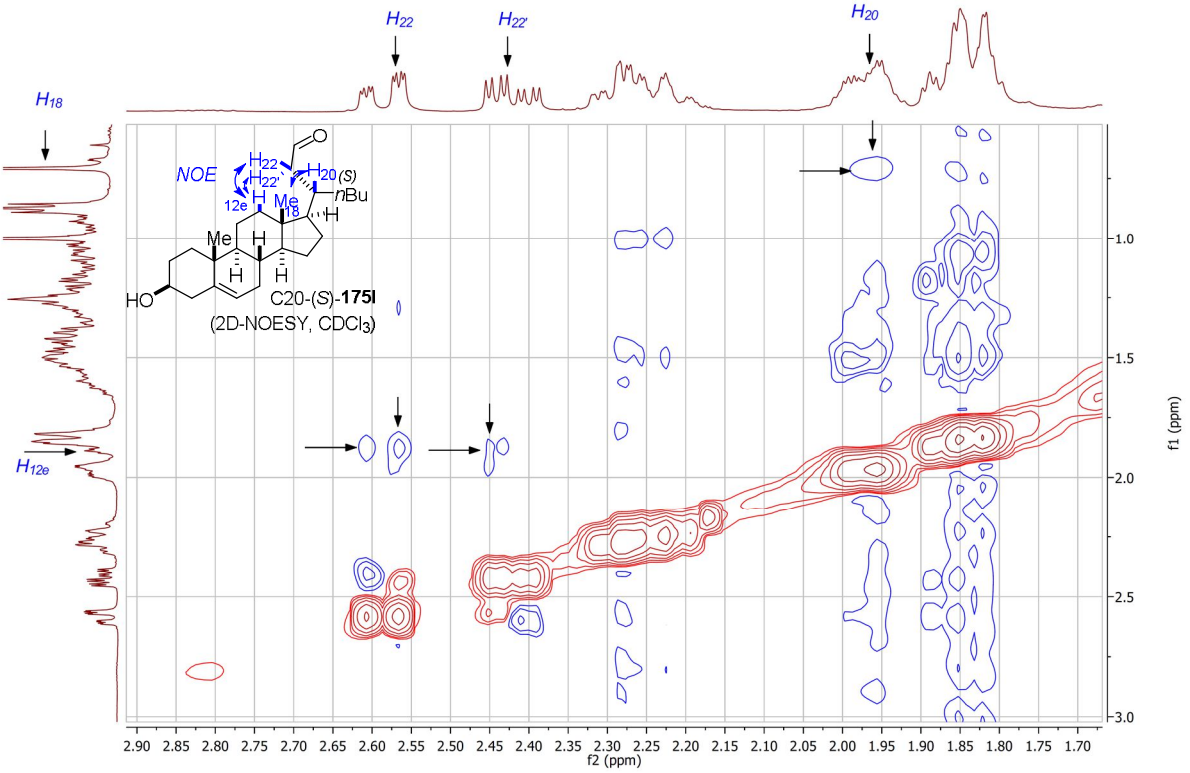
($C_{12}H_2$), 37.2 (C_1H_2), 36.4 (C_{10}), 35.1 ($C_{20}H$), 32.4 ($C_{21}H_2$), 31.8 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 27.7 ($C_{16}H_2$), 27.6 ($CH_2CH_2CH_3$), 24.0 ($C_{15}H_2$), 23.1 (CH_2CH_3), 21.0 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 14.0 (CH_2CH_3), 11.8 ($C_{18}H_3$).

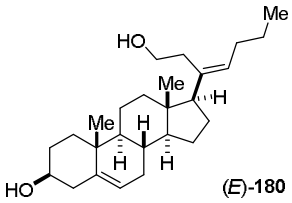
HRMS (MALDI–TOF) calculated for $C_{26}H_{42}O_2Na$ $[M+Na]^+$: 409.3077, found 409.3061.

IR (neat): ν (cm^{-1}) = 3378, 2932, 2866, 1720, 1461, 1377, 1277, 1129, 1054, 955, 841, 802, 754.

$[\alpha]^{25}_D$ = –25.8 (*c* 0.84, CH_2Cl_2).

The C20 stereochemistry of C20-(*S*)-**175l** was determined by 2D–NOESY (shown as below).





Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174l** (19 mg, 0.05 mmol). Purification by flash chromatography (Chloroform/Acetone = 10/1, buffered with 0.1% triethylamine) gave (*E*)-**180** (13 mg, 69%).

Colorless foam (Pentane/Ethyl acetate = 1/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.39-5.30 (m, 2H, H_6+H_{21}), 3.60-3.50 (m, 3H, H_3+CH_2OH), 2.56-2.49 (m, 1H, CH_2CH_2OH), 2.33-2.15 (m, 3H, 2H_4+CH_2CH_2OH), 2.11-1.96 (m, 4H, H_7+H_{17}+$CH_2CH_2CH_3$), 1.86-1.54 (m, 6H, H_1+H_2+H_{12}+2H_{15}+H_{16}), 1.58-1.35 (m, 7H, H_2+H_7+H_8+2H_{11}+CH_2CH_3), 1.25-1.04 (m, 4H, H_1+H_{12}+H_{14}+H_{15}), 1.01 (s, 3H, Me_{19}), 1.01-0.95 (m, 1H, H_9), 0.91 (t, $^3J_{HH}$ = 7.2 Hz, 1H, CH_2CH_3), 0.57 (s, 3H, Me_{18}).

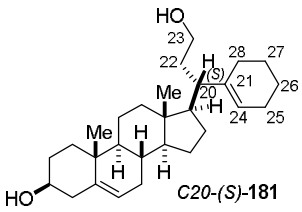
$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 140.8 (C_5), 133.9 (C_{20}), 129.0 ($C_{21}H$), 121.6 (C_6H), 71.8 (C_3H), 61.4 (CH_2OH), 56.4 ($C_{14}H$), 56.4 ($C_{17}H$), 50.3 (C_9H), 43.6 (C_{13}), 42.3 (C_4H_2), 38.5 ($C_{12}H_2$), 37.2 (C_1H_2), 36.6 (C_{10}), 35.0 (CH_2CH_2OH), 32.2 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 30.2 ($CH_2CH_2CH_3$), 25.7 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 23.4 (CH_2CH_3), 21.0 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 13.9 (CH_2CH_3), 12.8 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{26}H_{42}O_2Na$ $[M+Na]^+$: 409.3077, found 409.3089.

IR (neat): ν (cm^{-1}) = 3282, 2939, 1434, 1355, 1277, 1160, 1127, 1067, 1044, 885, 713, 678.

$[\alpha]^{25}_D$ = –29.4 (*c* 0.41, THF).

The structure of (*E*)-**180** was confirmed by single crystal X-ray diffraction analysis.



C20-(S)-**181**

Following general procedure A using **3**•BAr_F (7.5 mol%) and (*E*)-**174m** (20 mg, 0.05 mmol). Purification by flash chromatography (Chloroform/Acetone = 10/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**181** (18 mg, 90%).

White solid, m.p. = 226–228 °C (Pentane/Ethyl acetate = 1/1, R_f = 0.20).

^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 5.43-5.41 (m, 1H, H_{24}), 5.35-5.34 (m, 2H, H_6), 3.54-3.49 (m, 3H, H_3+2H_{23}), 2.29-2.23 (m, 2H, H_4), 2.05-1.03 (m, 35H), 1.01 (s, 3H, Me_{19}), 0.93 (ddd, $^3J_{HH}$ = 12.0, 10.6, 5.1 Hz, 1H, H_9), 0.71 (s, 3H, Me_{18}).

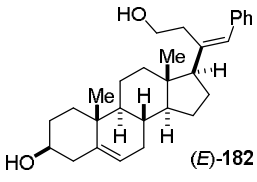
$^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ (ppm) = 140.8 (C_5), 139.6 (C_{21}), 123.0 ($C_{24}H$), 121.6 (C_6H), 71.8 (C_3H), 62.0 ($C_{23}H_2$), 57.1 ($C_{14}H$), 52.0 ($C_{17}H$), 50.1 (C_9H), 47.8 ($C_{20}H$), 42.3 (C_4H_2), 42.0 (C_{13}), 40.1 ($C_{12}H_2$), 37.2 (C_1H_2), 36.5 (C_{10}), 33.9 ($C_{22}H_2$), 31.9 (C_8H), 31.9 (C_7H_2), 31.6 (C_2H_2), 27.8 (CH_{2cy}), 25.3 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 24.0 (CH_{2cy}), 23.0 (CH_{2cy}), 22.9 (CH_{2cy}), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 12.0 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{28}H_{44}O_2$ $[M]^+$: 412.3, found $[M+NH_4]^+$: 430.5.

IR (neat): ν (cm^{-1}) = 3233, 2927, 2901, 2868, 1448, 1381, 1278, 1132, 1110, 1088, 1050, 956, 920, 841, 798, 756, 681, 657, 622.

$[\alpha]^{25}_D$ = –47.9 (*c* 0.10, THF).

The structure of C20-(*S*)-**181** was confirmed by single crystal X-ray diffraction analysis.



(*E*)-**182**

Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**174n** (20 mg, 0.05 mmol). Purification by flash chromatography (Chloroform/Acetone = 4/1, buffered with 0.1% triethylamine) gave (*E*)-**182** (19 mg, 95%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.20).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.34-7.18 (m, 5H, H_{Ar}), 6.53 (s, 1H, H_{21}), 5.38-5.36 (m, 1H, H_6), 3.66 (t, $^3J_{HH}$ = 7.1 Hz, 1H, $2H_{23}$), 3.56-3.50 (m, 1H, H_3), 2.83-2.76 (m, 1H, H_{22}), 2.37-2.17 (m, 4H, $2H_4$+H_{22}+H_{17}), 2.05-0.96 (m, 17H), 1.01-0.95 (m, 1H, H_9), 0.70 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 140.8 (C_5), 138.4 (C_{Ph}), 138.3 (C_{20}), 128.7 ($C_{ortho\text{-}Ph}$), 128.5 (C_{21}H), 128.2 ($C_{meta\text{-}Ph}$), 126.2 ($C_{para\text{-}Ph}$), 121.5 (C_6H), 71.7 (C_3H), 61.4 ($C_{23}H_2$), 56.6 (C_{14}H), 56.3 (C_{17}H), 50.3 (C_9H), 44.2 (C_{13}), 42.3 (C_4H_2), 38.7 ($C_{12}H_2$), 37.3 (C_1H_2), 36.6 (C_{10}), 35.5 ($C_{22}H_2$), 32.3 (C_8H), 31.8 (C_7H_2), 31.6 (C_2H_2), 26.0 ($C_{16}H_2$), 24.3 ($C_{15}H_2$), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 13.0 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{29}H_{40}O_2$ $[M]^+$: 420.3, found $[M+Na]^+$: 443.8.

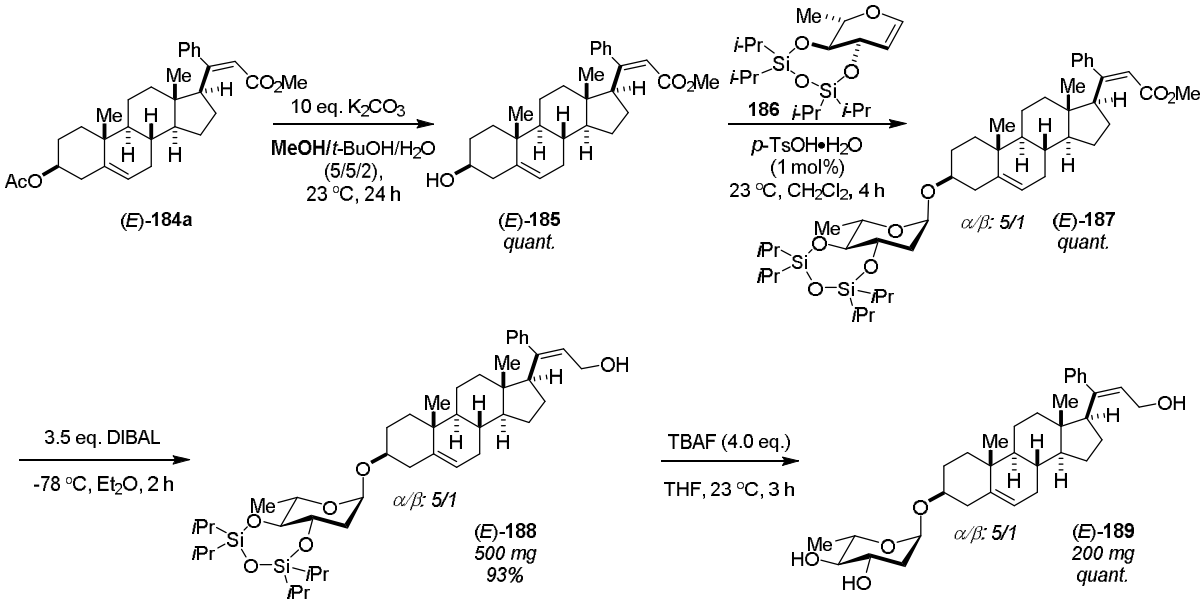
IR (neat): ν (cm^{-1}) = 3270, 2928, 2860, 1448, 1373, 1229, 1061, 1040, 954, 863, 800, 750, 697.

$[\alpha]^{25}_D$ = +16.0 (*c* 0.10, THF).

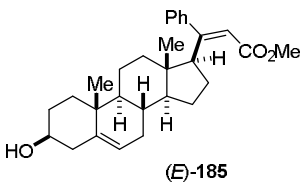
The structure of (*E*)-**182** was confirmed by single crystal X-ray diffraction analysis.

7.3.3. Preparation of advanced steroidal allylic alcohols

*7.3.3.1. Preparation of (E)-(**188**) and (E)-(**189**)*[23]



[23] E. I. Balmond, D. Benito-Alifonso, D. M. Coe, R. W. Alder, E. M. McGarrigle, M. C. Galan, *Angew. Chem. Int. Ed.* **2014**, *53*, 8190–8194.



(*E*)-**185**

Enoate (*E*)-**184a** (0.84 g, 1.8 mmol) was dissolved in a 1:1 mixture of methanol and *t*-butanol (1:1 v/v, 140 mL) at ambient temperature, before addition of an aqueous solution of potassium carbonate (30 mL, 8.0 wt%). The reaction mixture was stirred vigorously at ambient temperature for 24 h. After evaporation of the volatiles, the residue was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated to give pure enoate (*E*)-**185** (0.76 g, >99%).

Colorless foam (Pentane/Ethyl acetate = 4/1, R_f = 0.10).

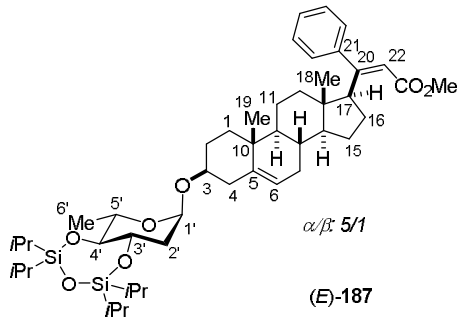
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.31-7.26 (m, 3H, 2$H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.17-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.79 (s, 1H, H_{22}), 5.35-5.32 (m, 1H, H_6), 3.99 (dd, $^3J_{HH}$ = 10.9, 8.5 Hz, 1H, H_{17}), 3.71 (s, 3H, O*Me*), 3.56-3.48 (m, 1H, H_3), 2.31-2.17 (m, 2H, H_4), 2.00-1.06 (m, 16H), 0.95 (s, 3H, Me_{19}), 0.38 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 167.2 (CO_2Me), 162.2 (C_{20}), 143.0 (C_{Ph}), 140.8 (C_5), 128.5 ($C_{ortho\text{-}Ph}$),127.5 ($C_{meta\text{-}Ph}$), 127.1 ($C_{para\text{-}Ph}$), 122.5 (C_{22}H), 121.6 (C_6H), 71.7 (C_3H), 55.9 (C_{14}H), 51.1 (*Me*O), 50.4 (C_{17}H), 50.1 (C_9H), 47.3 (C_{13}), 42.2 (C_4H_2), 37.2 ($C_{12}H_2$), 37.0 (C_1H_2), 36.6 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 31.6(C_2H_2), 25.4 ($C_{16}H_2$), 24.7 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{38}O_3Na$ $[M+Na]^+$: 457.2713, found 457.2713.

IR (neat): ν (cm^{-1}) = 2937, 1716, 1614, 1435, 1357, 1258, 1239, 1191, 1162, 1050, 1025, 1005, 954, 910, 877, 804, 774, 730, 703.

$[\alpha]^{25}_D$ = –114.4 (*c* 0.14, CH_2Cl_2).



(*E*)-**187**

A dichloromethane solution of *p*-toluenesulfonic acid monohydrate (7 mL, 1 mol%, 0.001 M) was added to enoate (*E*)-**185** (0.30 g, 0.69 mmol) and glucal **186** (0.31 g, 0.83 mmol).[24] The resulting mixture was stirred at ambient temperature for 4 h before the reaction was quenched with triethylamine (0.4 mL) and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 50/1, buffered with 0.1% triethylamine) gave (*E*)-**187** (0.56 g, >99%, α/β: 5/1).

Colorless foam (Pentane/Ethyl acetate = 24/1, R_f = 0.30).

[24] 2.2 g of glucal **186** has been synthesized in 2 steps starting from commercial available 3,4-di-*O*-acetyl-L-rhamnal, see ref. 23 for experimental details.

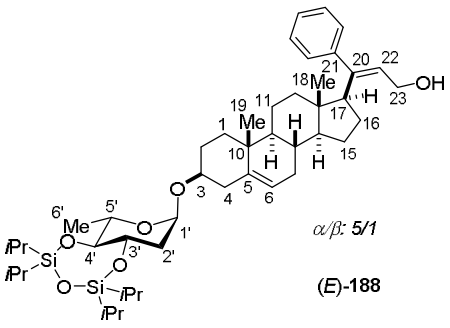
^{1}H NMR ($CDCl_3$, 400 MHz):[25] δ (ppm) = 7.31-7.26 (m, 3H, $2H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.17-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.79 (s, 1H, H_{22}), 5.32-5.30 (m, 1H, H_6), 4.97 (d, $^3J_{HH}$ = 3.6 Hz, 1H, $H_{1'}$), 4.02-3.96 (m, 2H, H_{17}+$H_{3'}$), 3.71 (s, 3H, O*Me*), 3.70-3.66 (m, 1H, $H_{5'}$), 3.45-3.37 (m, 1H, H_3), 3.22 (dd, $^3J_{HH}$ = 9.2, 8.3 Hz, 1H, $H_{4'}$), 2.33-2.12 (m, 2H, H_4), 2.05-0.96 (m, 58H), 0.96 (s, 3H, Me_{19}), 0.38 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz):[25] δ (ppm) = 167.1 (CO_2Me), 162.2 (C_{20}), 143.1 (C_{Ph}), 140.8 (C_5), 128.5 ($C_{ortho\text{-}Ph}$),127.5 ($C_{meta\text{-}Ph}$), 127.1 ($C_{para\text{-}Ph}$), 122.3 (C_{22}H), 121.4 (C_6H), 95.4 ($C_{1'}$), 80.2 ($C_{4'}$), 76.2 (C_3O), 71.5 ($C_{3'}$), 67.8 ($C_{5'}$), 55.9 (C_{14}H), 51.1 (*Me*O), 50.5 (C_{17}H), 50.2 (C_9H), 47.3 (C_{13}), 39.0 ($C_{2'}$), 38.6 (C_4H_2), 37.4 ($C_{12}H_2$), 37.0 (C_1H_2), 36.8 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 29.5 (C_2H_2), 25.4 ($C_{16}H_2$), 24.7 ($C_{15}H_2$), 20.7 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 18.0 ($C_{6'}$), 17.6-17.3 (disiloxane), 14.2 ($C_{18}H_3$), 12.9-12.3 (disiloxane).

HRMS (MALDI–TOF) calculated for $C_{47}H_{74}O_7Si_2Na$ $[M+Na]^+$: 829.4865, found 829.4873.

IR (neat): ν (cm^{-1}) = 2940, 2867, 1722, 1616, 1463, 1383, 1250, 1163, 1104, 1043, 986, 919, 885, 819, 774, 733, 700.

$[\alpha]^{25}_D$ = –182.8 (*c* 0.10, CH_2Cl_2).



To a solution of (*E*)-**187** (0.56 g, 0.69 mmol) in anhydrous diethyl ether (15 mL, 0.05 M) was added dropwise diisobutylaluminium hydride (2.4 mL, 2.4 mmol, 1.0 M in hexanes) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution (30 mL). The white suspension was stirred at ambient temperature for 2 h before extraction with diethyl ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 8/1, buffered with 0.1% triethylamine) gave (*E*)-**188** (0.50 g, 93%, α/β: 5/1).

White solid, m.p. = 88–90 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.50).

^{1}H NMR ($CDCl_3$, 500 MHz):[25] δ (ppm) = 7.28-7.20 (m, 3H, $2H_{ortho\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.15-7.13 (m, 2H, $H_{meta\text{-}Ph}$), 5.60 (dd, $^3J_{HH}$ = 7.8, 5.5 Hz, 1H, H_{22}), 5.36-5.31 (m, 1H, H_6), 4.97 (d, $^3J_{HH}$ = 3.6 Hz, 1H, $H_{1'}$), 4.45 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, H_{23}), 4.29 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, H_{23}), 4.02-3.96 (m, 1H, $H_{3'}$), 3.72-3.65 (m, 1H, $H_{5'}$), 3.45-3.37 (m, 1H, H_3), 3.25-3.20 (m, 1H, $H_{4'}$), 2.70 (dd, $^3J_{HH}$ = 8.5 Hz, 1H, H_{17}), 2.34-2.13 (m, 2H, H_4), 2.05-0.99 (m, 57H), 0.98-0.92 (m, 4H, H_9+Me_{19}), 0.44 (s, 3H, Me_{18}).

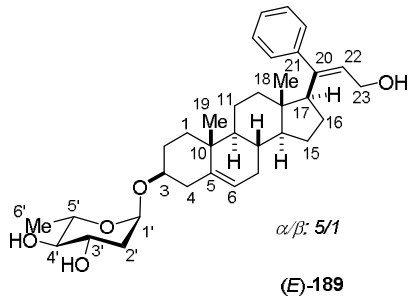
[25] Only the assignement of the major α-isomer of the product is reported.

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz):[25] δ (ppm) = 144.8 (C_{Ph}), 144.5 (C_{20}), 140.9 (C_5), 132.5 ($C_{22}H$), 129.4 ($C_{meta\text{-}Ph}$), 127.3 ($C_{ortho\text{-}Ph}$), 126.1 ($C_{para\text{-}Ph}$), 121.4 (C_6H), 95.4 ($C_{1'}$), 80.2 ($C_{4'}$), 76.2 (C_3O), 71.5 ($C_{3'}$), 67.8 ($C_{5'}$), 59.7 ($C_{23}H_2$), 55.9 ($C_{14}H$), 52.2 ($C_{17}H$), 50.4 (C_9H), 46.2 (C_{13}), 39.0 ($C_{2'}$), 38.5 (C_4H_2), 38.1 ($C_{12}H_2$), 37.4 (C_1H_2), 36.9 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 29.5 (C_2H_2), 26.0 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 20.7 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 18.0 ($C_{6'}$), 17.6-17.4 (disiloxane), 14.1 ($C_{18}H_3$), 12.9-12.3 (disiloxane).

HRMS (MALDI–TOF) calculated for $C_{46}H_{74}O_6Si_2Na$ $[M+Na]^+$: 801.4916, found 801.4912.

IR (neat): ν (cm^{-1}) = 2939, 2867, 1463, 1382, 1253, 1204, 1104, 1042, 985, 919, 886, 863, 819, 738, 700.

$[\alpha]^{25}_D$ = –89.0 (*c* 0.24, CH_2Cl_2).



(*E*)-**189**

To a solution of (*E*)-**188** (0.29 g, 0.37 mmol) in anhydrous THF (10 mL, 0.04 M) was added dropwise tetrabutylammonium fluoride (1.5 mL, 1.5 mmol, 1.0 M in THF) at 0 °C. The resulting reaction mixture was stirred at ambient temperature for 3 h, and then concentrated. Purification by flash chromatography (Dichloromethane/Acetone = 2/1, buffered with 0.1% triethylamine) gave (*E*)-**189** (0.20 g, >99%, α/β: 5/1).

Colorless foam (Pentane/Acetone = 2/1, R_f = 0.10).

^1H NMR (CD_2Cl_2, 400 MHz):[25] δ (ppm) = 7.28-7.18 (m, 3H, $2H_{ortho\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.16-7.14 (m, 2H, $H_{meta\text{-}Ph}$), 5.55 (dd, $^3J_{HH}$ = 7.7, 5.5 Hz, 1H, H_{22}), 5.34-5.31 (m, 1H, H_6), 4.98 (d, $^3J_{HH}$ = 3.6 Hz, 1H, $H_{1'}$), 4.42 (ddd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 7.8, 4.1 Hz, 1H, H_{23}), 4.25 (dt, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, H_{23}), 3.88-3.81 (m, 1H, $H_{3'}$), 3.71-3.64 (m, 1H, $H_{5'}$), 3.44-3.36 (m, 1H, H_3), 3.06-3.01 (m, 1H, $H_{4'}$), 2.71 (dd, $^3J_{HH}$ = 8.5 Hz, 1H, H_{17}), 2.34-2.24 (m, 2H, H_4), 2.16-1.01 (m, 20H), 0.98-0.92 (m, 4H, H_9+Me_{19}), 0.44 (s, 3H, Me_{18}).

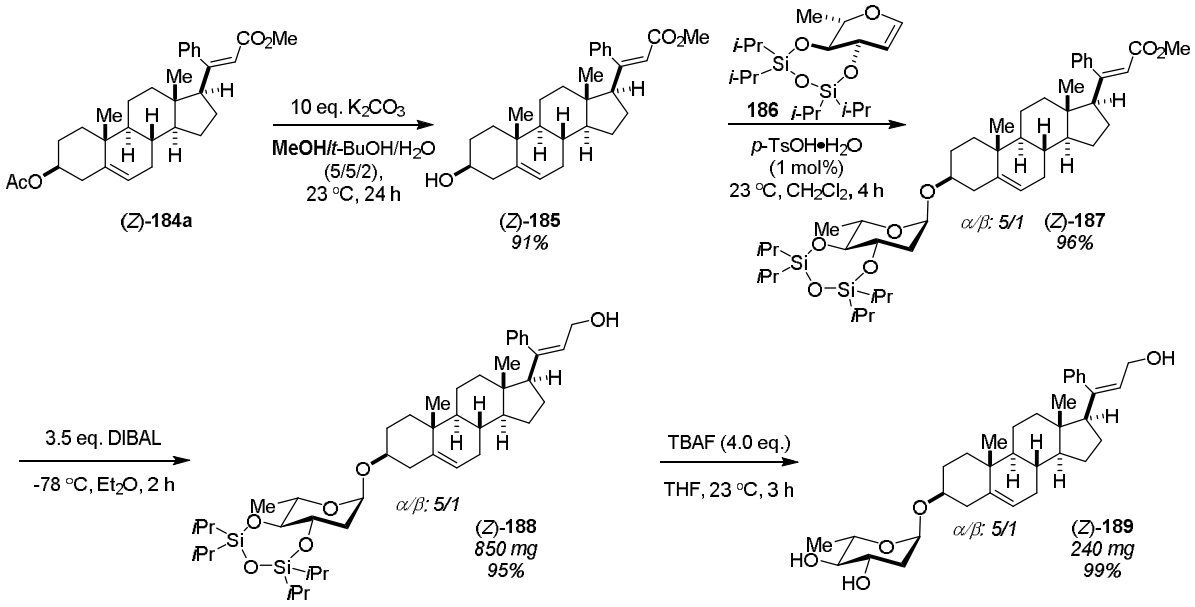
$^{13}C\{^1H\}$ NMR (CD_2Cl_2, 101 MHz):[25] δ (ppm) = 145.5 (C_{Ph}), 144.5 (C_{20}), 141.3 (C_5), 133.4 ($C_{22}H$), 129.8 ($C_{meta\text{-}Ph}$), 127.7 ($C_{ortho\text{-}Ph}$), 126.5 ($C_{para\text{-}Ph}$), 121.8 (C_6H), 95.6 ($C_{1'}$), 78.7 ($C_{4'}$), 76.6 (C_3O), 69.7 ($C_{3'}$), 67.9 ($C_{5'}$), 60.0 ($C_{23}H_2$), 56.3 ($C_{14}H$), 52.7 ($C_{17}H$), 50.9 (C_9H), 46.6 (C_{13}), 38.9 ($C_{2'}$), 38.8 (C_4H_2), 38.5 ($C_{12}H_2$), 37.8 (C_1H_2), 37.2 (C_{10}), 32.3 (C_8H), 32.2 (C_7H_2), 29.9 (C_2H_2), 26.4 ($C_{16}H_2$), 24.9 ($C_{15}H_2$), 21.2 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 17.8 ($C_{6'}$), 14.2 ($C_{18}H_3$).

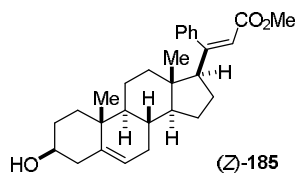
HRMS (MALDI–TOF) calculated for $C_{34}H_{48}O_5Na$ $[M+Na]^+$: 559.3394, found 559.3394.

IR (neat): ν (cm^{-1}) = 3379, 2929, 2905, 1454, 1442, 1379, 1334, 1253, 1122, 1041, 1027, 982, 910, 768, 703.

$[\alpha]^{25}_D$ = –43.1 (*c* 0.91, CH_2Cl_2).

*7.3.3.2. Preparation of (Z)-(**188**) and (Z)-(**189**)*[23]




(Z)-185

Enoate (*Z*)-**184a** (1.7 g, 3.6 mmol) was dissolved in a 1:1 mixture of methanol and *t*-butanol (1:1 v/v, 120 mL) at ambient temperature, before addition of an aqueous solution of potassium carbonate (30 mL, 17 wt%). The reaction mixture was stirred vigorously at ambient temperature for 24 h. After evaporation of the volatiles, the residue was extracted with Et_2O/THF (5:1 v/v, 3 × 60 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Acetone = 4/1) gave (*Z*)-**185** (1.4 g, 91%).

White solid, m.p. = 150−152 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.10).

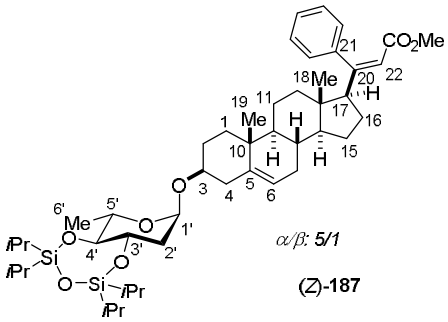
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.33-7.26 (m, 3H, 2$H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.16-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.91 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H_{22}), 5.34-5.31 (m, 1H, H_6), 3.52 (s, 3H, O*Me*), 3.53-3.45 (m, 1H, H_3), 2.62 (t, $^3J_{HH}$ = 8.8 Hz, 1H, H_{17}), 2.30-2.12 (m, 2H, H_4), 1.96-0.96 (m, 14H), 0.94 (s, 3H, Me_{19}), 0.88-0.81 (m, 2H, H_9+H_{12}), 0.71-0.63 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) = 166.9 (CO_2Me), 159.8 (C_{20}), 141.6 (C_{Ph}), 140.8 (C_5), 127.6 ($C_{meta\text{-}Ph}$+$C_{para\text{-}Ph}$), 127.5 ($C_{ortho\text{-}Ph}$), 121.2 (C_6H), 117.2 (C_{22}H), 71.7 (C_3H), 58.9 (C_{17}H), 57.0 (C_{14}H), 51.0 (*Me*O), 50.0 (C_9H), 44.1 (C_{13}), 42.2 (C_4H_2), 38.0 ($C_{12}H_2$), 37.1 (C_1H_2), 36.4 (C_{10}), 32.2 (C_8H), 31.6 (C_7H_2), 31.6(C_2H_2), 25.5 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (MALDI−TOF) calculated for $C_{29}H_{38}O_3Na$ $[M+Na]^+$: 457.2713, found 457.2715.

IR (neat): ν (cm^{-1}) = 3481, 2936, 2896, 2852, 1717, 1625, 1437, 1377, 1230, 1171, 1067, 1025, 776, 704.

$[\alpha]^{25}_D$ = +4.4 (*c* 0.11, CH_2Cl_2).



A dichloromethane solution of *p*-toluenesulfonic acid monohydrate (12 mL, 1 mol%, 0.001 M) was added to enoate (*Z*)-**185** (0.52 g, 1.2 mmol) and glucal **186** (0.54 g, 1.4 mmol).[24] The resulting mixture was stirred at ambient temperature for 4 h before the reaction was quenched with triethylamine (0.7 mL) and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 40/1 to 30/1, buffered with 0.1% triethylamine) gave (*Z*)-**187** (0.93 g, 96%, α/β: 5/1).

Colorless foam (Pentane/Ethyl acetate = 24/1, R_f = 0.30).

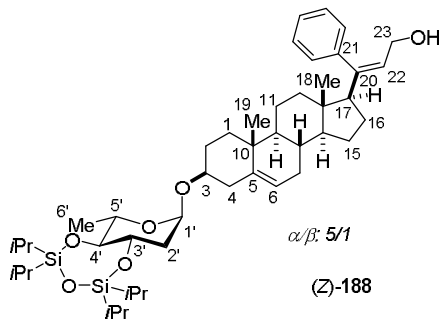
^{1}H NMR ($CDCl_3$, 400 MHz):[25] δ (ppm) = 7.33-7.28 (m, 3H, 2$H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.21-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.91 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H_{22}), 5.34-5.29 (m, 1H, H_6), 4.96 (d, $^3J_{HH}$ = 3.6 Hz, 1H, $H_{1'}$), 4.01-3.95 (m, 1H, $H_{3'}$), 3.70-3.63 (m, 1H, $H_{5'}$), 3.53 (s, 3H, O*Me*), 3.42-3.34 (m, 1H, H_3), 3.24-3.19 (m, 1H, $H_{4'}$), 2.62 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.32-2.11 (m, 2H, H_4), 2.04-1.00 (m, 54H), 0.94 (s, 3H, Me_{19}), 0.88-0.81 (m, 2H, H_9+H_{12}), 0.71-0.63 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz):[25] δ (ppm) = 166.9 (CO_2Me), 159.8 (C_{20}), 141.6 (C_{Ph}), 140.8 (C_5), 127.6 ($C_{meta\text{-}Ph}$+$C_{para\text{-}Ph}$), 127.5 ($C_{ortho\text{-}Ph}$), 121.4 (C_6H), 117.2 (C_{22}H), 95.3 ($C_{1'}$), 80.2 ($C_{4'}$), 76.1 (C_3O), 71.5 ($C_{3'}$), 67.8 ($C_{5'}$), 59.0 (C_{17}H), 57.0 (C_{14}H), 51.0 (*Me*O), 50.1 (C_9H), 44.1 (C_{13}), 39.0 ($C_{2'}$), 38.5 (C_4H_2), 38.0 ($C_{12}H_2$), 37.3 (C_1H_2), 36.7 (C_{10}), 32.2 (C_8H), 31.7 (C_7H_2), 29.5 (C_2H_2), 25.5 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 20.9 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 18.0 ($C_{6'}$), 17.6-17.2 (disiloxane), 12.8 ($C_{18}H_3$), 12.9-12.3 (disiloxane).

HRMS (MALDI–TOF) calculated for $C_{47}H_{74}O_7Si_2Na$ $[M+Na]^+$: 829.4865, found 829.4871.

IR (neat): ν (cm^{-1}) = 2940, 2867, 1730, 1630, 1463, 1381, 1221, 1160, 1105, 1045, 985, 915, 885, 819, 731, 697.

$[\alpha]^{25}_D$ = –33.1 (*c* 0.35, CH_2Cl_2).



To a solution of (*Z*)-**187** (0.93 g, 1.2 mmol) in anhydrous diethyl ether (25 mL, 0.05 M) was added dropwise diisobutylaluminium hydride (4.0 mL, 4.0 mmol, 1.0 M in hexanes) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution (50 mL). The white suspension was stirred at ambient temperature for 2 h before extraction with diethyl ether (3 × 50 mL). The combined organic layers were dried

over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 6/1, buffered with 0.1% triethylamine) gave (*Z*)-**188** (0.85 g, 95%, α/β: 5/1).

White solid, m.p. = 162–164 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

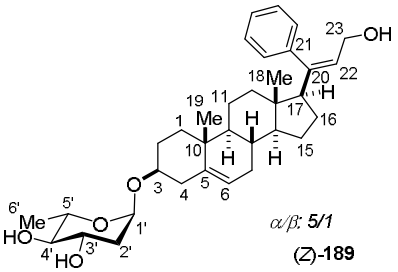
^{1}H NMR ($CDCl_3$, 500 MHz):[25] δ (ppm) = 7.31-7.22 (m, 3H, $2H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.11-7.09 (m, 2H, $H_{ortho\text{-}Ph}$), 5.69 (ddd, $^3J_{HH}$ = 7.6, 6.0, 1.6 Hz, 1H, H_{22}), 5.34-5.29 (m, 1H, H_6), 4.95 (d, $^3J_{HH}$ = 3.5 Hz, 1H, $H_{1'}$), 4.11-4.01 (m, 2H, H_{23}), 4.00-3.95 (m, 1H, $H_{3'}$), 3.70-3.63 (m, 1H, $H_{5'}$), 3.40-3.34 (m, 1H, H_3), 3.24-3.19 (m, 1H, $H_{4'}$), 2.54 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 2.31-2.12 (m, 2H, H_4), 2.03-0.99 (m, 49H), 0.96-0.93 (m, 4H, H_1+Me_{19}), 0.86-0.77 (m, 2H, H_9+H_{12}), 0.69-0.60 (m, 4H, H_{12}+Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz):[25] δ (ppm) = 144.3 (C_{Ph}), 141.8 (C_{20}), 140.8 (C_5), 128.5 ($C_{ortho\text{-}Ph}$), 127.8 ($C_{meta\text{-}Ph}$), 126.8 ($C_{para\text{-}Ph}$), 125.8 (C_{22}H), 121.4 (C_6H), 95.3 ($C_{1'}$), 80.2 ($C_{4'}$), 76.2 (C_3O), 71.5 ($C_{3'}$), 67.8 ($C_{5'}$), 60.5 ($C_{23}H_2$), 57.2 (C_{17}H), 56.7 (C_{14}H), 50.2 (C_9H), 43.3 (C_{13}), 39.0 ($C_{2'}$), 38.5 (C_4H_2), 38.2 ($C_{12}H_2$), 37.3 (C_1H_2), 36.7 (C_{10}), 32.3 (C_8H), 31.7 (C_7H_2), 29.5 (C_2H_2), 25.1 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 18.0 ($C_{6'}$), 17.6-17.3 (disiloxane), 12.9-12.3 (disiloxane), 12.6 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{46}H_{74}O_6Si_2Na$ $[M+Na]^+$: 801.4916, found 801.4916.

IR (neat): ν (cm^{-1}) = 2939, 2867, 1463, 1382, 1251, 1106, 1045, 987, 919, 886, 863, 819, 701.

$[\alpha]^{25}_D$ = –19.7 (*c* 0.25, CH_2Cl_2).



To a solution of (*Z*)-**188** (0.35 g, 0.45 mmol) in anhydrous THF (10 mL, 0.04 M) was added dropwise tetrabutylammonium fluoride (1.8 mL, 1.8 mmol, 1.0 M in THF) at 0 °C. The resulting reaction mixture was stirred at ambient temperature for 3 h, and then concentrated. Purification by flash chromatography (Dichloromethane/Acetone = 2/1, buffered with 0.1% triethylamine) gave (*Z*)-**189** (0.24 g, 99%, α/β: 5/1).

Colorless foam (Pentane/Acetone = 2/1, R_f = 0.10).

^{1}H NMR (CD_2Cl_2, 400 MHz):[25] δ (ppm) = 7.31-7.22 (m, 3H, $2H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.11-7.09 (m, 2H, $H_{ortho\text{-}Ph}$), 5.67 (ddd, $^3J_{HH}$ = 7.6, 6.0, 1.6 Hz, 1H, H_{22}), 5.33-5.29 (m, 1H, H_6), 4.95 (d, $^3J_{HH}$ = 3.5 Hz, 1H, $H_{1'}$), 4.07-3.94 (m, 2H, H_{23}), 3.87-3.80 (m, 1H, $H_{3'}$), 3.68-3.59 (m, 1H, $H_{5'}$), 3.41-3.32 (m, 1H, H_3), 3.05-3.00 (m, 1H, $H_{4'}$), 2.55 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 2.32-2.20 (m, 2H, H_4), 2.08-0.97 (m, 21H), 0.98-0.92 (m, 4H, H_1+Me_{19}), 0.86-0.77 (m, 2H, H_9+H_{12}), 0.69-0.60 (m, 4H, H_{12}+Me_{18}).

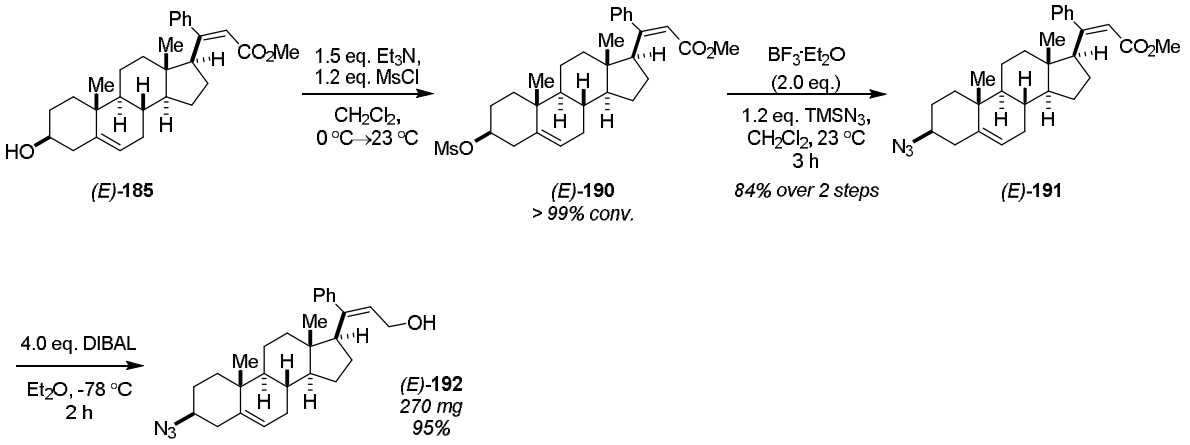
$^{13}C\{^1H\}$ NMR (CD_2Cl_2, 101 MHz):[25] δ (ppm) = 144.4 (C_{Ph}), 142.4 (C_{20}), 141.2 (C_5), 129.0 ($C_{ortho\text{-}Ph}$), 128.1 ($C_{meta\text{-}Ph}$), 127.1 ($C_{para\text{-}Ph}$), 126.5 ($C_{22}H$), 121.8 (C_6H), 95.6 ($C_{1'}$), 78.7 ($C_{4'}$), 76.6 (C_3O), 69.7 ($C_{3'}$), 67.9 ($C_{5'}$), 60.7 ($C_{23}H_2$), 57.6 ($C_{17}H$), 57.1 ($C_{14}H$), 50.7 (C_9H), 43.7 (C_{13}), 38.9 ($C_{2'}$), 38.8 (C_4H_2), 38.7 ($C_{12}H_2$), 37.7 (C_1H_2), 37.1 (C_{10}), 32.7 (C_8H), 32.2 (C_7H_2), 29.9 (C_2H_2), 25.6 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.4 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 17.8 ($C_{6'}$), 12.8 ($C_{18}H_3$).

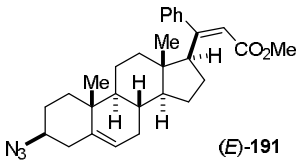
HRMS (MALDI–TOF) calculated for $C_{34}H_{48}O_5Na$ $[M+Na]^+$: 559.3394, found 559.3397.

IR (neat): ν (cm^{-1}) = 3365, 2936, 1443, 1378, 1265, 1196, 1120, 1023, 983, 910, 769, 735, 703.

$[\alpha]^{25}_D$ = –9.1 (*c* 0.16, CH_2Cl_2).

*7.3.3.3. Preparation of (E)-(**192**)*[26]



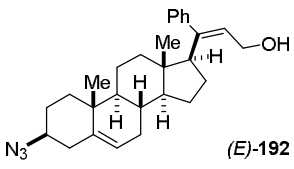


To a solution of (*E*)-**185** (370 mg, 0.85 mmol) in anhydrous dichloromethane (20 mL, 0.05 M) were successively added dropwise triethylamine (178 μL, 1.3 mmol) and methanesulfonyl chloride (79 μL, 1.0 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 22 h, and then quenched with ice before extraction with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mesylate (*E*)-**190** (>99% conversion based on crude ^1H NMR) was engaged directly into the next step without further purification.

To a solution of the crude mesylate (0.85 mmol) in anhydrous dichloromethane (20 mL, 0.05 M) was added trimethylsilyl azide (138 μL, 1.0 mmol) followed by dropwise addition of boron trifluoride diethyl etherate (216 μL, 1.7 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 3 h, and then quenched with ice. The resulting mixture was extracted with dichloromethane (3 × 30 mL). The combined organic

[26]. Q. Sun, S. Cai, B. R. Peterson, *Org. Lett.* **2009**, *11*, 567–570.

layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 25/1) gave (*E*)-**191** (330 mg, 84% over 2 steps).
White solid, m.p. = 149–151 °C (Pentane/Ethyl acetate = 5/1, R_f = 0.60).
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.31-7.26 (m, 3H, $2H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.17-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.79 (s, 1H, H_{22}), 5.38-5.36 (m, 1H, H_6), 4.00 (dd, $^3J_{HH}$ = 10.9, 8.5 Hz, 1H, H_{17}), 3.72 (s, 3H, O*Me*), 3.24-3.18 (m, 1H, H_3), 2.31-2.23 (m, 2H, H_4), 2.00-.99 (m, 16H), 1.01-0.95 (m, 4H, H_9+Me_{19}), 0.38 (s, 3H, Me_{18}).
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 167.1 (CO_2Me), 162.2 (C_{20}), 143.0 (C_{Ph}), 139.9 (C_5), 128.5 ($C_{ortho\text{-}Ph}$),127.5 ($C_{meta\text{-}Ph}$), 127.1 ($C_{para\text{-}Ph}$), 122.4 (C_{22}H), 122.4 (C_6H), 61.1 (C_3H), 55.9 (C_{14}H), 51.1 (*Me*O), 50.4 (C_{17}H), 50.1 (C_9H), 47.3 (C_{13}), 38.1 (C_4H_2), 37.6 ($C_{12}H_2$), 36.9 (C_1H_2), 36.7 (C_{10}), 31.8 (C_8H), 31.7 (C_7H_2), 27.9 (C_2H_2), 25.4 ($C_{16}H_2$), 24.6 ($C_{15}H_2$), 20.7 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 14.2 ($C_{18}H_3$).
HRMS (MALDI–TOF) calculated for $C_{29}H_{37}N_3O_2Na$ $[M+Na]^+$: 482.2778, found 482.2791.
IR (neat): ν (cm^{-1}) = 2940, 2092 (N_3), 1716, 1613, 1435, 1358, 1254, 1191, 1162, 1091, 1013, 879, 804, 775, 736, 704, 631.
$[\alpha]^{25}_D$ = –120.0 (*c* 0.13, CH_2Cl_2).

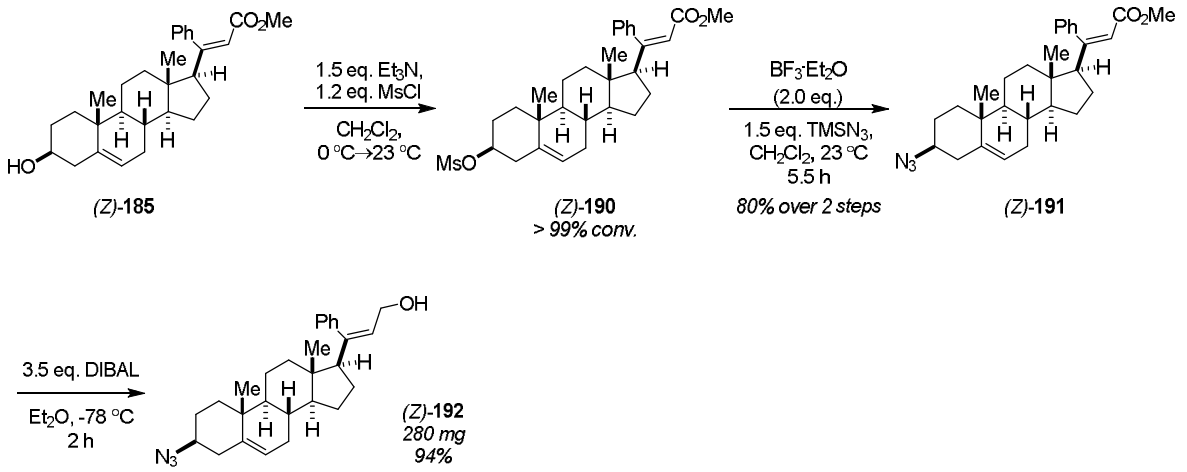


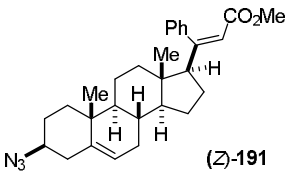
(E)-**192**

To a solution of (*E*)-**191** (302 mg, 0.66 mmol) in anhydrous diethyl ether (65 mL, 0.01 M) was added dropwise diisobutylaluminium hydride (2.6 mL, 2.6 mmol, 1.0 M in hexanes) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution (30 mL). The white suspension was stirred at ambient temperature for 2 h before extraction with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 5/1) gave (*E*)-**192** (270 mg, 95%).
Colorless foam (Pentane/Ethyl acetate = 5/1, R_f = 0.10).
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.27-7.20 (m, 3H, $2H_{ortho\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.15-7.13 (m, 2H, $H_{meta\text{-}Ph}$), 5.61 (dd, $^3J_{HH}$ = 7.9, 5.6 Hz, 1H, H_{22}), 5.39-5.37 (m, 1H, H_6), 4.45 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 7.8 Hz, H_{23}), 4.29 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.5 Hz, H_{23}), 3.24-3.18 (m, 1H, H_3), 2.70 (dd, $^3J_{HH}$ = 8.5 Hz, 1H, H_{17}), 2.32-2.23 (m, 2H, H_4), 2.00-1.06 (m, 16H), 0.98-0.92 (m, 4H, H_9+Me_{19}), 0.44 (s, 3H, Me_{18}).
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 144.7 (C_{Ph}), 144.5 (C_{20}), 139.9 (C_5), 132.6 (C_{22}H), 129.4 ($C_{meta\text{-}Ph}$), 127.3 ($C_{ortho\text{-}Ph}$), 126.2 ($C_{para\text{-}Ph}$), 122.3 (C_6H), 61.1 (C_3H), 59.7 ($C_{23}H_2$), 55.9 (C_{14}H), 52.2 (C_{17}H), 50.3 (C_9H), 46.1 (C_{13}), 38.1 (C_4H_2), 38.0 ($C_{12}H_2$), 37.6 (C_1H_2), 36.7 (C_{10}), 31.8 (C_8H), 31.7 (C_7H_2), 27.9 (C_2H_2), 26.0 ($C_{16}H_2$), 24.5 ($C_{15}H_2$), 20.7 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 14.1 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{28}H_{37}N_3ONa$ [M+Na]$^+$: 454.2829, found 454.2822.
IR (neat): ν (cm^{-1}) = 3318, 2938, 2094 (N_3), 1464, 1438, 1379, 1250, 1015, 767, 705.
$[\alpha]^{25}_D$ = –68.3 (*c* 0.17, CH_2Cl_2).

*7.3.3.4. Preparation of (Z)-(**192**)*[26]





To a solution of (*Z*)-**185** (400 mg, 0.92 mmol) in anhydrous dichloromethane (20 mL, 0.05 M) were successively added dropwise triethylamine (193 μL, 1.4 mmol) and methanesulfonyl chloride (86 μL, 1.1 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 22 h, and then quenched with ice before extraction with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mesylate (*Z*)-**190** (>99% conversion based on crude ^{1}H NMR) was engaged directly into the next step without further purification.

To a solution of crude mesylate (0.92 mmol) in anhydrous dichloromethane (20 mL, 0.05 M) trimethylsilyl azide (187 μL, 1.4 mmol) was added followed by dropwise addition of boron trifluoride diethyl etherate (233 μL, 1.8 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 3 h, and then quenched with ice. The resulting mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 25/1) gave (*Z*)-**191** (340 mg, 80% over 2 steps).

White solid, m.p. = 126–128 °C (Pentane/Ethyl acetate = 5/1, R_f = 0.60).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.33-7.28 (m, 3H, 2$H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.16-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.91 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H_{22}), 5.37-5.35 (m, 1H, H_6), 3.53 (s, 3H, O*Me*), 3.20-3.12

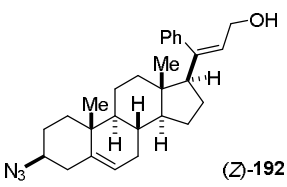
(m, 1H, H_3), 2.62 (t, $^3J_{HH}$ = 9.1 Hz, 1H, H_{17}), 2.30-2.20 (m, 2H, H_4), 2.03-1.12 (m, 15H), 1.05-0.93 (m, 4H), 0.88-0.81 (m, 2H, H_9+H_{12}), 0.71-0.63 (m, 4H, H_{12}+Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 166.9 (CO_2Me), 159.7 (C_{20}), 141.6 (C_{Ph}), 139.9 (C_5), 127.6 ($C_{meta\text{-}Ph}$+$C_{para\text{-}Ph}$), 127.5 ($C_{ortho\text{-}Ph}$), 122.2 (C_6H), 117.3 ($C_{22}H$), 61.0 (C_3H), 58.9 ($C_{17}H$), 56.9 ($C_{14}H$), 51.0 (MeO), 50.0 (C_9H), 44.1 (C_{13}), 38.1 (C_4H_2), 37.9 ($C_{12}H_2$), 37.4 (C_1H_2), 36.5 (C_{10}), 32.1 (C_8H), 31.6 (C_7H_2), 27.9 (C_2H_2), 25.5 ($C_{16}H_2$), 23.8 ($C_{15}H_2$), 20.9 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 12.8 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{29}H_{37}N_3O_2Na$ $[M+Na]^+$: 482.2778, found 482.2791.

IR (neat): ν (cm^{-1}) = 2940, 2091 (N_3), 1728, 1630, 1434, 1379, 1222, 1158, 1067, 1028, 936, 841, 808, 772, 736, 700.

$[\alpha]^{25}_D$ = +21.3 (*c* 0.12, CH_2Cl_2).



(*Z*)-**192**

To a solution of (*Z*)-**191** (315 mg, 0.68 mmol) in anhydrous diethyl ether (35 mL, 0.02 M) was added dropwise diisobutylaluminium hydride (2.4 mL, 2.4 mmol, 1.0 M in hexanes) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution (30 mL). The white suspension was stirred at ambient temperature for 2 h before extraction with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Eluent: Pentane/Ethyl acetate = 5/1) gave (*Z*)-**192** (279 mg, 94%).

Colorless foam (Pentane/Ethyl acetate = 5/1, R_f = 0.10).

^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.31-7.22 (m, 3H, 2$H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.11-7.09 (m, 2H, $H_{ortho\text{-}Ph}$), 5.69 (ddd, $^3J_{HH}$ = 7.6, 6.0, 1.6 Hz, 1H, H_{22}), 5.37-5.36 (m, 1H, H_6), 4.11-4.01 (m, 2H, H_{23}), 3.20-3.12 (m, 1H, H_3), 2.54 (t, $^3J_{HH}$ = 9.3 Hz, 1H, H_{17}), 2.29-2.20 (m, 2H, H_4), 2.02-1.08 (m, 12H), 1.02-0.93 (m, 4H, H_1+Me_{19}), 0.86-0.77 (m, 2H, H_9+H_{12}), 0.69-0.60 (m, 4H, H_{12}+Me_{18}).

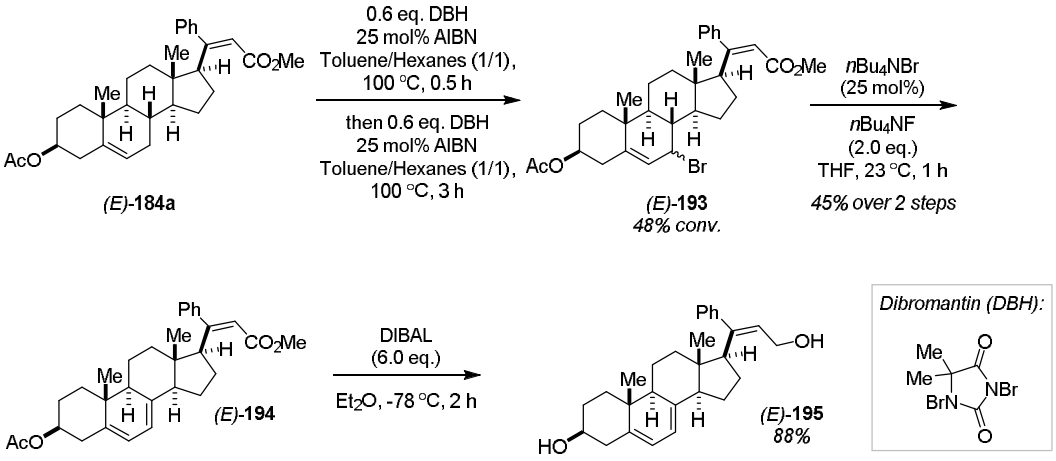
$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 144.3 (C_{Ph}), 141.8 (C_{20}), 139.9 (C_5), 128.5 ($C_{ortho\text{-}Ph}$), 127.8 ($C_{meta\text{-}Ph}$), 126.9 ($C_{para\text{-}Ph}$), 125.8 ($C_{22}H$), 122.3 (C_6H), 61.1 (C_3H), 60.5 ($C_{23}H_2$), 57.2 ($C_{17}H$), 56.7 ($C_{14}H$), 50.1 (C_9H), 43.3 (C_{13}), 38.2 (C_4H_2), 38.1 ($C_{12}H_2$), 37.5 (C_1H_2), 36.6 (C_{10}), 32.2 (C_8H), 31.7 (C_7H_2), 27.9 (C_2H_2), 25.1 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 20.9 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 12.6 ($C_{18}H_3$).

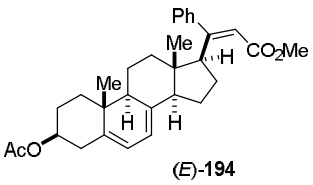
HRMS (MALDI–TOF) calculated for $C_{28}H_{37}N_3ONa$ $[M+Na]^+$: 454.2829, found 454.2811.

IR (neat): ν (cm^{-1}) = 3323, 2937, 2092 (N_3), 1439, 1378, 1249, 1063, 1009, 807, 769, 738, 704, 665.

$[\alpha]^{25}_D$ = +46.4 (*c* 0.15, CH_2Cl_2).

*7.3.3.5. Preparation of (E)-(**195**)*[27]





Enoate (*E*)-**184a** (190 mg, 0.40 mmol), dibromantin (70 mg, 0.24 mmol) and azobisisobutyronitrile (17 mg, 0.10 mmol) were dissolved in a 1:1 mixture of anhydrous toluene and hexanes (1:1 v/v, 20 mL, 0.02 M) at ambient temperature. The reaction mixture was degassed by two successive freeze–pump–thaw cycles and refilled with nitrogen. The second portion of dibromantin (70 mg, 0.24 mmol) and azobisisobutyronitrile (17 mg, 0.10 mmol) were added to the reaction mixture after refluxing for 0.5 h. The resulting mixture was degassed by another two successive freeze–pump–thaw cycles and refilled with nitrogen. The reaction was stirred under reflux for 2.5 h before extraction with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude bromides (*E*)-**193** (48% conversion based on crude ^{1}H NMR) were engaged directly into the next step without further purification.

To a solution of crude bromides (*E*)-**193** (0.20 mmol, based on crude ^{1}H NMR from the previous step) in tetrahydrofuran (10 mL, 0.02 M) was added tetrabutylammonium bromide (32 mg, 0.10 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 75 minutes, before dropwise addition of tetrabutylammonium fluoride (0.8 mL, 0.80 mmol, 1.0 M in THF). The resulting mixture was stirred for 1 h. Water (5 mL) was added and the reaction mixture was extracted by diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Ethyl acetate = 30/1) gave (*E*)-**194** (85 mg, 45% over 2 steps) and recovered (*E*)-**184a** (68 mg).

(*E*)-**194**, colorless foam (Pentane/Ethyl acetate = 18/1, R_f = 0.10).

[27] W. Li, J. Chen, Z. Janjetovic, T. Kim, T. Sweatman, Y. Lu, J. Zjawiony, R. C. Tuckey, D. Miller, A. Slominski, *Steroids* **2010**, *75*, 926–935.

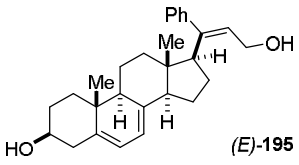
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.32-7.26 (m, 3H, $2H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.16-7.14 (m, 2H, $H_{ortho\text{-}Ph}$), 5.80 (s, 1H, H_{22}), 5.55-5.53 (m,1H, H_6), 5.36-5.33 (m, 1H, H_7), 4.73-4.65 (m, 1H, H_3), 4.15-4.08 (m, 1H, H_{17}), 3.72 (s, 3H, O*Me*), 2.51-2.29 (m, 2H, H_4), 2.12-1.24 (m, 19H), 0.87 (s, 3H, Me_{19}), 0.28 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 170.5 (Me*C*O), 167.0 (*C*O_2Me), 162.1 (C_{20}), 142.6 (C_{Ph}), 141.0 (C_5), 138.8 (C_8), 128.6 ($C_{ortho\text{-}Ph}$),127.5 ($C_{meta\text{-}Ph}$), 127.1 ($C_{para\text{-}Ph}$), 122.3 (C_{22}H), 120.1 (C_6H), 116.7 (C_7H), 72.7 (C_3H), 53.8 (C_{14}H), 51.1 (*Me*O), 50.2 (C_{17}H), 47.5 (C_{13}), 46.1 (C_9H), 37.9 ($C_{12}H_2$), 37.1 (C_{10}), 36.6 (C_4H_2), 36.5 (C_1H_2), 28.1 (C_2H_2), 25.3 ($C_{16}H_2$), 23.3 ($C_{15}H_2$), 21.4 (*Me*CO), 20.8 ($C_{11}H_2$), 16.1 ($C_{19}H_3$), 14.3 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{31}H_{38}O_4Na$ $[M+Na]^+$: 497.2662, found 497.2635.

IR (neat): ν (cm^{-1}) = 2945, 1723, 1616, 1436, 1368, 1241, 1163, 1029, 906, 877, 825, 775, 735, 706.

$[\alpha]^{25}_D$ = –126.9 (*c* 0.14, CH_2Cl_2).



(E)-**195**

To a solution of (*E*)-**194** (80 mg, 0.17 mmol) in anhydrous diethyl ether (17 mL, 0.01 M) was added dropwise diisobutylaluminium hydride (1.0 mL, 1.0 mmol, 1.0 M in hexanes) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution (15 mL). The white suspension was stirred at ambient temperature for 2 h before extraction with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Chloroform/Acetone = 10/1) gave (*E*)-**195** (60 mg, 88%).

Colorless foam (Pentane/Ethyl acetate = 2/1, R_f = 0.10).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.27-7.20 (m, 3H, $2H_{ortho\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.15-7.13 (m, 2H, $H_{meta\text{-}Ph}$), 5.61 (ddd, $^3J_{HH}$ = 7.7, 5.6, 0.7 Hz, 1H, H_{22}), 5.56-5.55 (m, 1H, H_6), 5.37-5.35 (m, 1H, H_7), 4.46 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 7.8 Hz, H_{23}), 4.30 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.6 Hz, H_{23}), 3.66-3.60 (m, 1H, H_3), 2.80 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H_{17}), 2.48-2.22 (m, 2H, H_4), 2.02-1.19 (m, 19H), 0.88 (s, 3H, Me_{19}), 0.34 (s, 3H, Me_{18}).

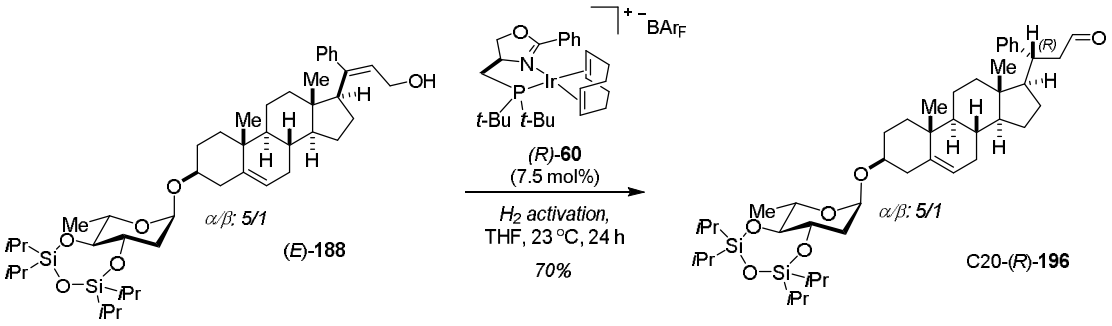
^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 144.5 (C_{Ph}), 144.3 (C_{20}), 140.7 (C_5), 140.1 (C_8), 132.4 (C_{22}H), 129.5 ($C_{meta\text{-}Ph}$), 127.3 ($C_{ortho\text{-}Ph}$), 126.2 ($C_{para\text{-}Ph}$), 119.5 (C_6H), 116.7 (C_7H), 71.4 (C_3H), 59.6 ($C_{23}H_2$), 53.7 (C_{14}H), 51.9 (C_{17}H), 46.5 (C_{13}), 46.3 (C_9H), 40.7 (C_4H_2), 38.3 ($C_{12}H_2$), 37.5 (C_1H_2), 37.1 (C_{10}), 31.9 (C_2H_2), 25.9 ($C_{16}H_2$), 23.2 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 16.1 ($C_{19}H_3$), 14.1 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{28}H_{36}O_2Na$ $[M+Na]^+$: 427.2608, found 427.2579.

IR (neat): ν (cm^{-1}) = 3331, 2934, 2872, 1458, 1441, 1363, 1324, 1130, 1059, 1033, 824, 766, 705.

$[\alpha]^{25}_D$ = –147.1 (*c* 0.10, CH_2Cl_2).

7.3.4. Isomerization of advanced steroidal allylic alcohols



Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**188** (30 mg, 0.038 mmol). Purification by flash chromatography (Pentane/Ethyl acetate = 25/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**196** (21 mg, 70%, dr >50/1, α/β: 5/1).

Colorless oil (Pentane/Ethyl acetate = 9/1, R_f = 0.50).

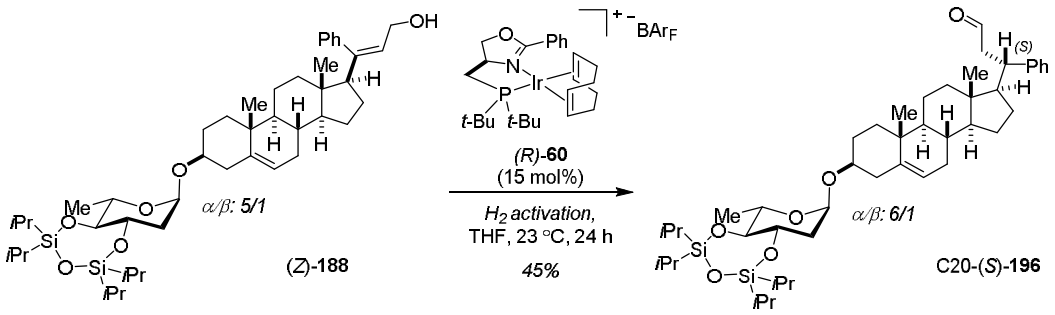
^{1}H NMR ($CDCl_3$, 400 MHz):[26] δ (ppm) = 9.52 (t, $^3J_{HH}$ = 2.2 Hz, 1H, C*H*O), 7.28-7.15 (m, 5H, H_{Ar}), 5.33-5.28 (m, 1H, H_6), 4.95 (d, $^3J_{HH}$ = 3.6 Hz, 1H, $H_{1'}$), 4.00-3.93 (m, 1H, $H_{3'}$), 3.70-3.62 (m, 1H, $H_{5'}$), 3.41-3.33 (m, 1H, H_3), 3.24-3.18 (m, 1H, $H_{4'}$), 3.11 (td, $^3J_{HH}$ = 10.7, 4.4 Hz, 1H, H_{20}), 2.74-2.60 (m, 2H, H_{22}), 2.31-2.10 (m, 2H, H_4), 2.04-0.98 (m, 48H), 0.91 (s, 3H, Me_{19}), 0.72 (s, 3H, Me_{18}), 0.58 (td, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, H_{12e}), 0.38 (dt, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, H_{12a}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz):[11] δ (ppm) = 202.7 (*C*HO), 143.5 (C_{Ph}), 140.8 (C_5), 128.4 ($C_{ortho\text{-}Ph}$), 128.3 ($C_{meta\text{-}Ph}$), 126.6 ($C_{para\text{-}Ph}$), 121.3 (C_6H), 95.3 ($C_{1'}$), 80.2 ($C_{4'}$), 76.2 (C_3O), 71.5 ($C_{3'}$), 67.8 ($C_{5'}$), 56.5 (C_{14}H), 55.3 (C_{17}H), 50.3 ($C_{22}H_2$), 50.0 (C_9H), 42.9 (C_{20}H), 42.5 (C_{13}), 39.0 ($C_{2'}$), 38.5 (C_4H_2), 38.4 ($C_{12}H_2$), 37.3 (C_1H_2), 36.7 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 29.5 (C_2H_2), 28.2 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 18.0 ($C_{6'}$), 17.6-17.3 (disiloxane), 12.9-12.2 (disiloxane), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{46}H_{74}O_6Si_2Na$ $[M+Na]^+$: 801.4916, found 801.4922.

IR (neat): ν (cm^{-1}) = 2939, 2867, 1725, 1462, 1382, 1250, 1203, 1104, 1043, 986, 911, 886, 863, 819, 732, 700.

$[\alpha]^{25}_D$ = –43.9 (*c* 1.70, CH_2Cl_2).



Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**188** (38 mg, 0.049 mmol). Purification by flash chromatography (Pentane/Ethyl acetate = 50/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**196** (17 mg, 45%, dr 1/50, α/β: 6/1).

Colorless oil (Pentane/Ethyl acetate = 24/1, R_f = 0.40).

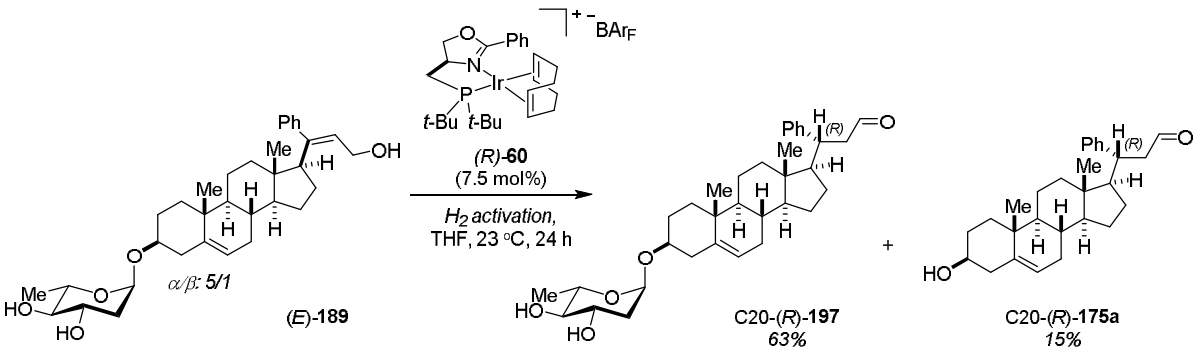
^{1}H NMR ($CDCl_3$, 400 MHz):[26] δ (ppm) = 9.46 (dd, $^3J_{HH}$ = 3.1, 1.6 Hz, 1H, C*H*O), 7.28-7.15 (m, 5H, H_{Ar}), 5.35-5.29 (m, 1H, H_6), 4.98 (d, $^3J_{HH}$ = 3.6 Hz, 1H, $H_{1'}$), 4.02-3.97 (m, 1H, $H_{3'}$), 3.72-3.64 (m, 1H, $H_{5'}$), 3.45-3.35 (m, 1H, H_3), 3.27-3.19 (m, 1H, $H_{4'}$), 3.07 (td, $^3J_{HH}$ = 11.1, 4.0 Hz, 1H, H_{20}), 2.94 (ddd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 4.0, 1.7 Hz, 1H, H_{22}), 2.72 (ddd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 11.3, 3.1 Hz, 1H, H_{22}), 2.34-2.16 (m, 2H, H_4), 2.03-0.92 (m, 60H), 0.82 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz):[11] δ (ppm) = 202.5 (*C*HO), 143.8 (C_{Ph}), 140.8 (C_5), 128.5 ($C_{ortho\text{-}Ph}$), 127.9 ($C_{meta\text{-}Ph}$), 126.5 ($C_{para\text{-}Ph}$), 121.4 (C_6H), 95.4 ($C_{1'}$), 80.2 ($C_{4'}$), 76.2 (C_3O), 71.5 ($C_{3'}$), 67.8 ($C_{5'}$), 56.7 (C_{14}H), 55.3 (C_{17}H), 50.1 (C_9H), 49.1 ($C_{22}H_2$), 43.1 (C_{20}H), 42.4 (C_{13}), 39.9 ($C_{12}H_2$), 39.0 ($C_{2'}$), 38.6 (C_4H_2), 37.4 (C_1H_2), 36.8 (C_{10}), 31.9 (C_8H), 31.8 (C_7H_2), 29.5 (C_2H_2), 28.5 ($C_{16}H_2$), 23.9 ($C_{15}H_2$), 21.1 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 18.0 ($C_{6'}$), 17.6-17.3 (disiloxane), 12.9-12.2 (disiloxane), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{46}H_{74}O_6Si_2Na$ $[M+Na]^+$: 801.4916, found 801.4912.

IR (neat): ν (cm^{-1}) = 2936, 2867, 1725, 1463, 1382, 1250, 1105, 1044, 986, 914, 886, 863, 820, 733, 699.

$[\alpha]^{25}_D$ = –37.6 (*c* 1.20, CH_2Cl_2).



Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**189** (27 mg, 0.05 mmol). Purification by flash chromatography (Pentane/Acetone = 3/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**18** (17 mg, 63%, dr >50/1, α only) and C20-(*R*)-**175a** (3 mg, 15%, dr >50/1).

C20-(*R*)-**197**, colorless oil (Pentane/Acetone = 2/1, R_f = 0.30).

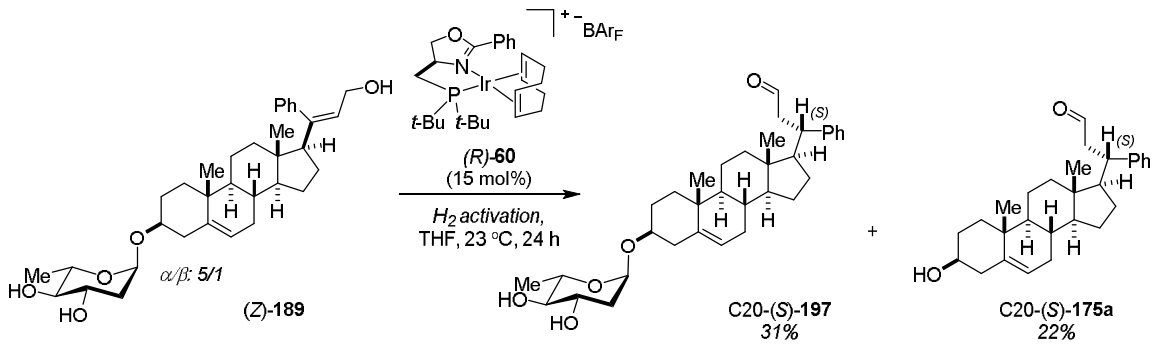
^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) = 9.50 (dd, $^3J_{HH}$ = 3.0, 1.6 Hz, 1H, C*H*O), 7.28-7.16 (m, 5H, H_{Ar}), 5.32-5.30 (m, 1H, H_6), 4.96 (d, $^3J_{HH}$ = 3.2 Hz, 1H, $H_{1'}$), 3.86-3.80 (m, 1H, $H_{3'}$), 3.67-3.62 (m, 1H, $H_{5'}$), 3.41-3.33 (m, 1H, H_3), 3.11 (td, $^3J_{HH}$ = 10.8, 4.1 Hz, 1H, H_{20}), 3.02 (t, $^3J_{HH}$ = 9.1 Hz, 1H, $H_{4'}$), 2.74-2.60 (m, 2H, H_{22}), 2.31-2.26 (m, 2H, H_4), 2.15-0.96 (m, 22H), 0.91 (s, 3H, Me_{19}), 0.83-0.76 (m, 1H, H_9), 0.72 (s, 3H, Me_{18}), 0.58 (td, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 5.1 Hz, 1H, H_{12e}), 0.36 (dt, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, H_{12a}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 202.8 (*C*HO), 144.2 (C_{Ph}), 141.2 (C_5), 128.8 ($C_{ortho\text{-}Ph}$), 128.6 ($C_{meta\text{-}Ph}$), 126.8 ($C_{para\text{-}Ph}$), 121.8 (C_6H), 95.6 ($C_{1'}$), 78.7 ($C_{4'}$), 76.5 (C_3O), 69.7 ($C_{3'}$), 67.9 ($C_{5'}$), 56.9 (C_{14}H), 55.7 (C_{17}H), 50.7 (C_9H), 50.5 ($C_{22}H_2$), 43.2 (C_{20}H), 42.9 (C_{13}), 38.9 ($C_{2'}$), 38.9 (C_4H_2), 38.7 ($C_{12}H_2$), 37.7 (C_1H_2), 37.0 (C_{10}), 32.3 (C_8H), 32.2 (C_7H_2), 29.9 (C_2H_2), 28.6 ($C_{16}H_2$), 24.4 ($C_{15}H_2$), 21.2 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 17.8 ($C_{6'}$), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{34}H_{48}O_5Na$ $[M+Na]^+$: 559.3394, found 559.3392.

IR (neat): ν (cm^{-1}) = 3390, 2936, 1722, 1452, 1356, 1272, 1121, 1035, 983, 910, 735, 702.

$[\alpha]^{25}_D$ = –45.4 (*c* 1.30, CH_2Cl_2).



Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**189** (49 mg, 0.091 mmol). Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**18** (15 mg, 31%, dr 1/50, α only) and C20-(*S*)-**175a** (8 mg, 22%, dr 1/50).

C20-(*S*)-**197**, colorless oil (Pentane/Acetone = 2/1, R_f = 0.30).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.44 (d, $^3J_{HH}$ = 3.2 Hz, 1H, C*H*O), 7.32-7.11 (m, 5H, H_{Ar}), 5.34-5.32 (m, 1H, H_6), 4.99 (d, $^3J_{HH}$ = 3.6 Hz, 1H, $H_{1'}$), 3.91-3.80 (m, 1H, $H_{3'}$), 3.72-3.60 (m, 1H, $H_{5'}$), 3.47-3.33 (m, 1H, H_3), 3.12-3.02 (m, 2H, $H_{4'}$+H_{20}), 2.93 (ddd, $^2J_{HH}$ = 16.2, $^3J_{HH}$ =

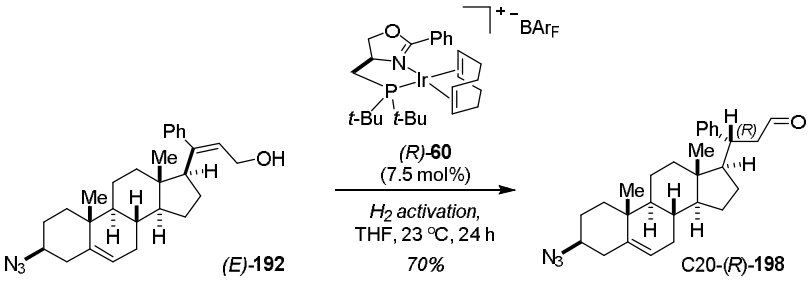
4.0, 1.5 Hz, 1H, H_{22}), 2.69 (ddd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 11.4, 3.4 Hz, 1H, H_{22}), 2.34-1.06 (m, 34H), 1.02 (s, 3H, Me_{19}), 0.84 (s, 3H, Me_{18}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 202.5 (*C*HO), 144.6 (C_{Ph}), 141.2 (C_5), 128.8 ($C_{ortho\text{-}Ph}$), 128.5 ($C_{meta\text{-}Ph}$), 126.7 ($C_{para\text{-}Ph}$), 121.8 (C_6H), 95.7 ($C_{1'}$), 78.8 ($C_{4'}$), 76.6 (C_3O), 69.7 ($C_{3'}$), 67.9 ($C_{5'}$), 57.1 (C_{14}H), 55.6 (C_{17}H), 50.6 (C_9H), 49.5 ($C_{22}H_2$), 43.5 (C_{20}H), 42.8 (C_{13}), 40.3 ($C_{12}H_2$), 38.9 ($C_{2'}$), 38.8 (C_4H_2), 37.8 (C_1H_2), 37.1 (C_{10}), 32.3 (C_8H), 32.2 (C_7H_2), 30.1 (C_2H_2), 28.9 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.4 ($C_{19}H_3$), 17.9 ($C_{6'}$), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{34}H_{48}O_5Na$ $[M+Na]^+$: 559.3394, found 559.3395.

IR (neat): ν (cm^{-1}) = 3382, 2930, 1723, 1668, 1452, 1379, 1258, 1197, 1121, 1044, 1029, 984, 912, 703.

$[\alpha]^{25}_D$ = –44.8 (*c* 0.33, CH_2Cl_2).



Following general procedure B using (*R*)-**60** (7.5 mol%) and (*E*)-**192** (22 mg, 0.05 mmol). Purification by flash chromatography (Pentane/Ethyl acetate = 10/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**198** (15 mg, 70%, dr >50/1).

Colorless oil (Pentane/Ethyl acetate = 5/1, R_f = 0.60).

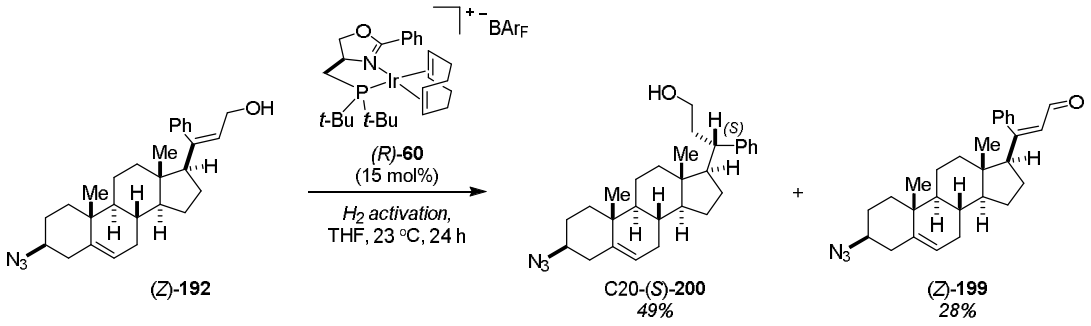
^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.52 (t, $^3J_{HH}$ = 2.2 Hz, 1H, C*H*O), 7.28-7.15 (m, 5H, H_{Ar}), 5.38-5.34 (m, 1H, H_6), 3.20-3.08 (m, 2H, H_3+H_{20}), 2.74-2.60 (m, 2H, H_{22}), 2.30-2.19 (m, 2H, H_4), 2.04-0.93 (m, 16H), 0.90 (s, 3H, Me_{19}), 0.80 (td, $^3J_{HH}$ = 11.6, 5.2 Hz, 1H, H_9), 0.72 (s, 3H, Me_{18}), 0.58 (td, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, H_{12e}), 0.39 (dt, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, H_{12a}).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) = 202.5 (*C*HO), 143.5 (C_{Ph}), 139.9 (C_5), 128.4 ($C_{ortho\text{-}Ph}$), 128.2 ($C_{meta\text{-}Ph}$), 126.6 ($C_{para\text{-}Ph}$), 122.3 (C_6H), 61.1 (C_3H), 56.4 (C_{14}H), 55.3 (C_{17}H), 50.3 ($C_{22}H_2$), 49.9 (C_9H), 42.9 (C_{20}H), 42.5 (C_{13}), 38.3 (C_4H_2), 38.1 ($C_{12}H_2$), 37.4 (C_1H_2), 36.5 (C_{10}), 31.8 (C_8H), 31.7 (C_7H_2), 28.2 (C_2H_2), 27.9 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 20.7 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 12.2 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{28}H_{37}N_3ONa$ $[M+Na]^+$: 454.2829, found 454.2850.

IR (neat): ν (cm^{-1}) = 2938, 2093 (N_3), 1724, 1454, 1379, 1251, 1027, 845, 804, 770, 702.

$[\alpha]^{25}_D$ = –17.7 (*c* 1.10, CH_2Cl_2).



Following general procedure B using (*R*)-**60** (15 mol%) and (*Z*)-**192** (20 mg, 0.046 mmol). Purification by flash chromatography (Pentane/Ethyl acetate = 5/1, buffered with 0.1% triethylamine) gave C20-(*S*)-**200** (9.8 mg, 49%, dr 1/50) and (*Z*)-α,β-unsaturated aldehyde **199** (5.7 mg, 28%).

C20-(*S*)-**200**, white solid, m.p. = 139–141 °C (Pentane/Ethyl acetate = 5/1, R_f = 0.10).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.28-7.24 (m, 2H, $H_{ortho\text{-}Ph}$), 7.19-7.14 (m, 3H, $H_{para\text{-}Ph}$+2$H_{meta\text{-}Ph}$), 5.38-5.37 (m, 1H, H_6), 3.39-3.25 (m, 2H, H_{23}), 3.24-3.17 (m, 1H, H_3), 2.64 (td, $^3J_{HH}$ = 11.3, 3.7 Hz, 1H, H_{20}), 2.30-2.23 (m, 2H, H_4), 2.17 (dt, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, H_{12}), 1.99-1.05 (m, 17H), 1.02 (s, 3H, Me_{19}), 0.82 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 144.9 (C_{Ar}), 139.8 (C_5), 128.3 (C_{Ar}H), 126.0 (C_{Ar}H), 122.4 (C_6H), 61.3 ($C_{23}H_2$), 61.1 (C_3H), 56.8 (C_{14}H), 55.6 (C_{17}H), 50.1 (C_9H), 45.6 (C_{20}H), 42.4 (C_{13}), 40.0 ($C_{22}H_2$), 38.1 (C_4H_2), 37.6 ($C_{12}H_2$), 37.5 (C_1H_2), 36.6 (C_{10}), 31.8 (C_8H), 31.8 (C_7H_2), 28.9 (C_2H_2), 27.9 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 21.0 ($C_{11}H_2$), 19.3 ($C_{19}H_3$), 12.1 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{28}H_{39}N_3ONa$ $[M+Na]^+$: 456.2985, found 456.2956.

IR (neat): ν (cm^{-1}) = 3359, 2937, 2093, 1490, 1453, 1381, 1251, 1049, 1024, 841, 802, 774, 702.

$[\alpha]^{25}_D$ = –35.2 (*c* 0.17, CH_2Cl_2).

(*Z*)-**199**, white solid, m.p. = 135–137 °C (Pentane/Ethyl acetate = 5/1, R_f = 0.10).

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 9.41 (d, $^3J_{HH}$ = 7.9 Hz, C*H*O), 7.39-7.36 (m, 3H, 2$H_{meta\text{-}Ph}$+$H_{para\text{-}Ph}$), 7.26-7.24 (m, 2H, $H_{ortho\text{-}Ph}$), 6.16 (dd, $^3J_{HH}$ = 7.9, 1.4 Hz, 1H, H_{22}), 5.38-5.36 (m, 1H, H_6), 4.11-4.01 (m, 2H, H_{23}), 3.20-3.13 (m, 1H, H_3), 2.74 (t, $^3J_{HH}$ = 9.2 Hz, 1H, H_{17}), 2.30-2.21 (m, 2H, H_4), 2.04-1.17 (m, 15H), 1.02-0.99 (m, 1H, H_1), 0.93 (s, 3H, Me_{19}), 0.89-0.79 (m, 2H, H_9+H_{12}), 0.72 (td, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, H_{12}), 0.63 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ (ppm) = 194.1 (*C*HO), 166.6 (C_{20}), 139.9 (C_5), 139.3 (C_{Ar}), 128.8 (C_{Ar}H), 128.6 (C_{22}H), 128.1 (C_{Ar}H), 126.9 (C_{Ar}H), 122.1 (C_6H), 61.0 (C_3H), 58.7 (C_{17}H),

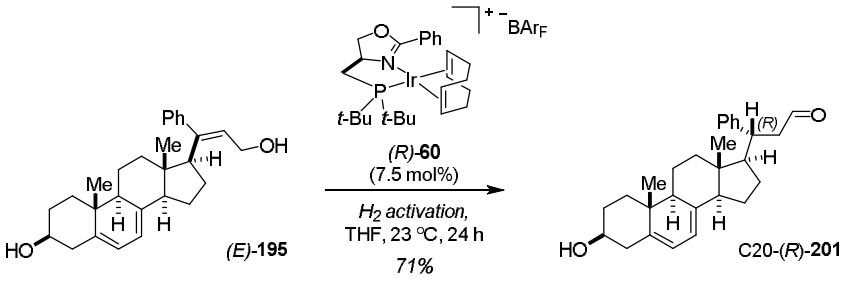
57.1 (C_{14}H), 50.0 (C_9H), 44.7 (C_{13}), 38.1 (C_4H_2), 38.0 ($C_{12}H_2$), 37.4 (C_1H_2), 36.5 (C_{10}), 32.1 (C_8H), 31.6 (C_7H_2), 27.9 (C_2H_2), 25.2 ($C_{16}H_2$), 24.0 ($C_{15}H_2$), 20.8 ($C_{11}H_2$), 19.2 ($C_{19}H_3$), 13.0 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{28}H_{35}N_3ONa$ $[M+Na]^+$: 452.2672, found 452.2678.

IR (neat): ν (cm^{-1}) = 2936, 2092 (N_3), 1725, 1670, 1604, 1450, 1382, 1251, 1199, 1127, 1019, 777, 705.

$[\alpha]^{25}_D$ = +9.8 (*c* 0.25, CH_2Cl_2).

The structure of (*Z*)-**199** was confirmed by single crystal X-ray diffraction analysis.



Following general procedure B using (*R*)-**2** (7.5 mol%) and (*E*)-**16** (14 mg, 0.035 mmol). Purification by flash chromatography (Pentane/Acetone = 5/1 to 3/1, buffered with 0.1% triethylamine) gave C20-(*R*)-**201** (10 mg, 71%, dr >50/1).

Colorless oil (Pentane/Acetone = 3/1, R_f = 0.20).

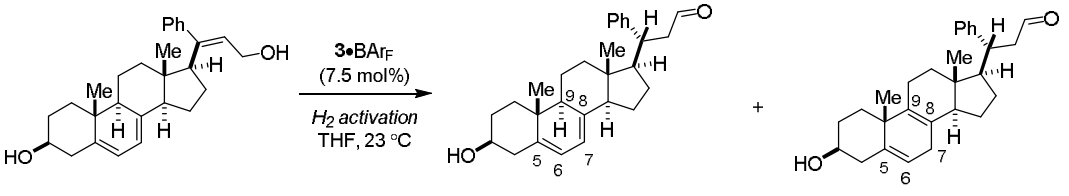
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 9.51 (dd, $^3J_{HH}$ = 2.9,1.6 Hz, 1H, C*H*O), 7.30-7.17 (m, 5H, H_{Ar}), 5.53 (dd, $^3J_{HH}$ = 5.8, 2.6 Hz, 1H, H_6), 5.38-5.36 (m, 1H, H_7), 3.58-3.49 (m, 1H, H_3), 3.12 (td, $^3J_{HH}$ = 10.8, 4.2 Hz, 1H, H_{20}), 2.76-2.60 (m, 2H, H_{22}), 2.42-2.14 (m, 2H, H_4), 2.09-1.98 (m, 1H, H_{16}), 1.91-1.15 (m, 12H), 0.84 (s, 3H, Me_{19}), 0.73-0.64 (m, 4H, H_{12}+Me_{18}), 0.42 (ddd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 5.0, 2.6 Hz, 1H, H_{12a}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 202.6 (*C*HO), 144.2 (C_{Ph}), 141.1 (C_5), 140.7 (C_8), 128.8 ($C_{ortho\text{-}Ph}$), 128.7 ($C_{meta\text{-}Ph}$), 126.9 ($C_{para\text{-}Ph}$), 119.7 (C_6H), 116.9 (C_7H), 70.6 (C_3H), 55.5 (C_{14}H), 54.4 (C_{17}H), 50.6 ($C_{22}H_2$), 46.5 (C_9H), 43.4 (C_{20}H), 43.4 (C_{13}), 41.2 (C_4H_2), 38.6 (C_1H_2), 38.2 ($C_{12}H_2$), 37.3 (C_{10}), 32.4 (C_2H_2), 28.4 ($C_{16}H_2$), 23.1 ($C_{15}H_2$), 21.2 ($C_{11}H_2$), 16.3 ($C_{19}H_3$), 12.3 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{28}H_{36}O_2Na$ $[M+Na]^+$: 427.2608, found 427.2598.

IR (neat): ν (cm^{-1}) = 3390, 2934, 1722, 1667, 1455, 1379, 1061, 837, 734, 703.

$[\alpha]^{25}_D$ = –73.6 (*c* 0.64, CH_2Cl_2).



(*E*)-**195** — *C20-(R)*-**201** — *66%, 27/1 dr* **201/202** = 1/1 — *C20-(R)*-**202**

δ (ppm)	**201**	**202**
6-C(H)	*119.7 (5.53)*	*119.5 (5.38)*
7-C(H)	*116.9 (5.37)*	*29.1 (2.58-2.43)*
18-C(H)	*12.4 (0.65)*	*11.7 (0.70)*
19-C(H)	*16.4 (0.84)*	*23.0 (1.09)*

Following general procedure A using **3**•BAr_F (7.5 mol%) and (*E*)-**195** (15 mg, 0.037 mmol). Purification by flash chromatography (Pentane/Acetone = 5/1 to 3/1, buffered with 0.1% triethylamine) gave an inseparable mixture of C20-(*R*)-**201** and C20-(*R*)-**202** (10 mg, 67%, **201**/**202**: 1/1, dr = 27/1).[28]

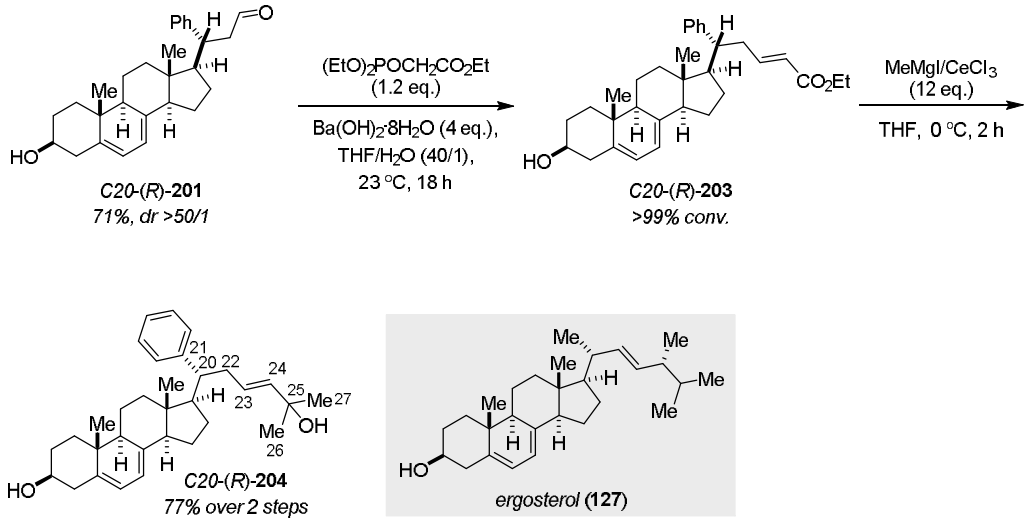
Colorless oil (Pentane/Acetone = 3/1, R_f = 0.20).

^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) = 9.51 (dd, $^3J_{HH}$ = 3.0,1.6 Hz, 1H, C*H*O), 7.29-7.17 (m, 5H, H_{Ar}), 5.53 (dd, $^3J_{HH}$ = 5.7, 2.6 Hz, 1H, H_6(**201**)), 5.40-5.35 (m, 2H, H_6(**202**)+H_7(**201**)), 3.58-3.49 (m, 1H, H_3(**201**)), 3.46-3.39 (m, 1H, H_3(**202**)), 3.16-3.09 (m, 2H, H_{20}(**202**)+H_{20}(**201**)), 2.76-2.60 (m, 4H, H_{22}(**202**)+H_{22}(**201**)), 2.58-2.43 (m, 2H, H_7(**202**)), 2.42-2.37 (m, 1H, H_4(**201**)), 2.29-2.17 (m, 3H, 2H_4(**202**)+H_4(**201**)), 2.15-1.96 (m, 2H, H_{16}(**202**)+H_{16}(**201**)), 1.91-1.15 (m, 12H), 1.09 (s, 3H, Me_{19}(**202**)), 0.84 (s, 3H, Me_{19}(**201**)), 0.70 (s, 3H, Me_{18}(**202**)), 0.65 (s, 3H, Me_{18}(**201**)), 0.43-0.35 (m, 1H, H_{12a}(**202**)+H_{12a}(**201**)).

^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 202.7(*C*HO(**202**)), 202.6 (*C*HO(**201**)), 144.2 (C_{Ar}), 141.1 (C_5(**201**)), 140.7 (C_8(**201**)), 139.4 (C_5(**202**)), 132.6 (C_9(**202**)), 128.8 (C_{Ar}H), 128.7 (C_{Ar}H), 128.6 (C_{Ar}H), 126.9 (C_{Ar}H(**201**)), 126.8 (C_{Ar}H(**202**)), 126.1 (C_8(**202**)), 119.7 (C_6H(**201**)), 119.5 (C_6H(**202**)), 116.9 (C_7H(**201**)), 71.7 (C_3H(**202**)), 70.6 (C_3H(**201**)), 55.5 (C_{14}H(**201**)), 54.4 (C_{17}H), 52.0 (C_{14}H(**202**)), 50.6 ($C_{22}H_2$), 46.5 (C_9H(**201**)), 43.5 (C_{20}H(**202**)), 43.4 (C_{20}H(**201**)), 43.4 (C_{13}(**201**)), 42.6 (C_4H_2(**202**)), 42.4 (C_{13}(**202**)), 41.2 (C_4H_2(**201**)), 38.6 (C_1H_2(**201**)), 38.2 ($C_{12}H_2$(**201**)), 37.7 (C_{10}(**202**)), 37.3 (C_{10}(**201**)), 36.0 (C_1H_2(**202**)), 35.8 ($C_{12}H_2$(**202**)), 32.4 (C_2H_2), 29.3 ($C_{16}H_2$(**202**)), 29.1 (C_7H_2(**202**)), 28.4 ($C_{16}H_2$(**201**)), 23.2 ($C_{15}H_2$(**202**)), 23.1 ($C_{15}H_2$(**201**)), 23.0 ($C_{19}H_3$(**202**)), 22.4 ($C_{11}H_2$(**202**)), 21.2 ($C_{11}H_2$(**201**)), 16.3 ($C_{19}H_3$(**201**)), 12.3 ($C_{18}H_3$(**201**)), 11.7 ($C_{18}H_3$(**202**)).

[28] L. Xu, N. A. Porter, *J. Am. Chem. Soc.* **2014**, *136*, 5443–5450.

*7.3.5. Synthesis of C20-(R)-**204***[29,30]



To a solution of triethyl phosphonoacetate (5.0 μL, 0.024 mmol) in tetrahydrofuran (1.5 mL) was added barium hydroxide octahydrate (28 mg, 0.09 mmol). The solution was stirred at ambient temperature for 45 minutes, before dropwise addition of a solution of C20-(*R*)-**201** (8.0 mg, 0.02 mmol) in THF/H_2O (40:1 v/v, 1 mL) at 0 °C. The resulting solution was stirred at ambient temperature for 18 h, and then quenched with ice. The resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude enoate C20-(*R*)-**203** (>99% conversion based on crude ^{1}H NMR) was engaged directly into the next step without further purification.

Anhydrous cerium chloride (74 mg, 0.30 mmol) was weighed into a 10 mL shlenk and dried at 160 °C under vacum for 4 h. Anhydrous tetrahydrofuran (2 mL) was then added to the same schlenk at ambient temperature. The resulting white suspension was stirred at ambient temperature for 18 h, before dropwise addition of methyl magnesium iodide (80 μL, 0.24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, followed by dropwise addition of a solution of crude enoate C20-(*R*)-**203** (0.02 mmol) in THF (2 mL). The resulting mixture was stirred at 0 °C for 1.5 h, and then quenched with ice before extraction with dichloromethane (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Acetone = 3/1) gave (*E*)-C20-(*R*)-**204** (7.0 mg, 77% over 2 steps, dr >50/1).

Colorless foam (Pentane/Acetone = 3/1, R_f = 0.10).

^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) = 7.25-7.12 (m, 5H, H_{Ar}), 5.52 (dd, $^3J_{HH}$ = 5.8, 2.6 Hz, 1H, H_6), 5.38-5.36 (m, 1H, H_7), 5.35-5.31 (m, 1H, H_{24}), 5.28-5.22 (m, 1H, H_{23}), 3.55-3.51 (m,

[29] C. R. Reddy, B. Latha, N. N. Rao, *Tetrahedron* **2012**, *68*, 145–151.
[30] T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, Y. Kamiya, *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

1H, H_3), 2.53-2.37 (m, 3H, H_4+H_{20}+H_{22}), 2.22-2.07 (m, 3H, H_4+H_{16}+H_{22}), 1.90-1.13 (m, 12H), 1.08 (Me_{26} *or* Me_{27}), 1.05 (Me_{27} *or* Me_{26}), 0.83 (s, 3H, Me_{19}), 0.69 (td, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, H_{12e}), 0.59 (s, 3H, Me_{18}), 0.47 (ddd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.8, 2.6 Hz, 1H, H_{12a}).

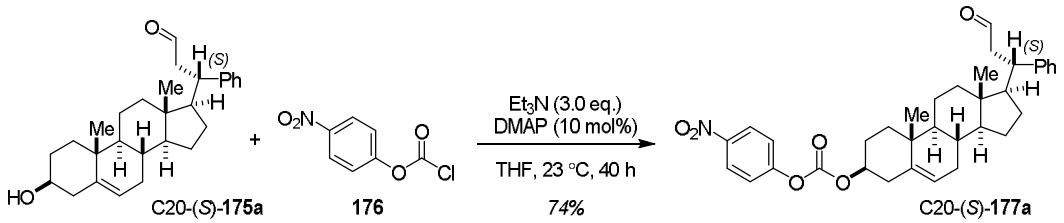
^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 145.2 (C_{Ph}), 141.5 (C_5), 140.6 (C_8), 139.9 (C_{24}H), 129.1 ($C_{ortho\text{-}Ph}$), 128.1 ($C_{meta\text{-}Ph}$), 126.2 ($C_{para\text{-}Ph}$), 125.3 (C_{23}H), 119.7 (C_6H), 116.7 (C_7H), 70.6 (C_3H), 70.5 (C_{25}), 55.4 (C_{14}H), 54.4 (C_{17}H), 49.4 (C_{20}H), 46.5 (C_9H), 43.4 (C_{13}), 41.2 (C_4H_2), 39.0 ($C_{22}H_2$), 38.7 (C_1H_2), 38.4 ($C_{12}H_2$), 37.3 (C_{10}), 32.4 (C_2H_2), 29.8 (Me_{26}), 29.8 (Me_{27}), 28.4 ($C_{16}H_2$), 23.2 ($C_{15}H_2$), 21.3 ($C_{11}H_2$), 16.3 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

HRMS (MALDI–TOF) calculated for $C_{32}H_{44}O_2Na$ $[M+Na]^+$: 483.3234, found 483.3236.

IR (neat): ν (cm^{-1}) = 3347, 2966, 2929, 1456, 1365, 1235, 1148, 1134, 1063, 1031, 984, 833, 798, 756, 699.

$[\alpha]^{25}_D$ = –27.2 (*c* 0.20, CH_2Cl_2).

*7.3.6. Derivatization of aldehyde C20-(S)-**175a***



To a solution of C20-(*S*)-**175a** (9.2 mg, 0.023 mmol) in anhydrous tetrahydrofuran (2.0 mL) were successively added triethylamine (9.5 uL, 0.07 mmol), 4-dimethylaminopyridine (0.5 mg, 10 mol%) and 4-nitrophenyl chloroformate **176** (7.1 mg, 0.03 mmol). The reaction mixture was stirred at ambient temperature for 40 h. The reaction was stopped and concentrated under vacum. Purification by flash chromatography (Pentane/Ethyl acetate = 8/1) gave C20-(*S*)-**177a** (9.6 mg, 74%, dr = 1/50).

White solid, m.p. = 196–198 °C (Pentane/Ethyl acetate = 4/1, R_f = 0.40).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.46 (dd, $^3J_{HH}$ = 3.0, 1.6 Hz, 1H, C*H*O), 8.28 (d, $^3J_{HH}$ = 9.2 Hz, 2H, H_{Ar}), 7.39 (d, $^3J_{HH}$ = 9.2 Hz, 2H, H_{Ar}), 7.30-7.15 (m, 5H, H_{Ar}), 5.43-5.41 (m, 1H, H_6), 4.66-4.58 (m, 1H, H_3), 3.08 (td, $^3J_{HH}$ = 11.0, 4.0 Hz, 1H, H_{20}), 2.94 (ddd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 4.0, 1.7 Hz, 1H, H_{22}), 2.72 (ddd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 11.2, 3.1 Hz, 1H, H_{22}), 2.54-2.44 (m, 2H, H_4), 2.07-1.14 (m, 16H), 1.11-0.97 (m, 5H, H_9+H_{15}+Me_{19}), 0.84 (s, 3H, Me_{18}).

^{13}C{^{1}H} NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 202.5 (*C*HO), 156.2 (CO_2), 152.2 (C_{Ar}), 145.7 (C_{Ar}), 144.5 (C_{Ar}), 139.5 (C_5), 128.8 (C_{Ar}H), 128.5 (C_{Ar}H), 126.7 (C_{Ar}H), 125.6 (C_{Ar}H), 123.6 (C_6H), 122.3 (C_{Ar}H), 80.1 (C_3H), 57.0 (C_{14}H), 55.6 (C_{17}H), 50.4 (C_9H), 49.5 ($C_{22}H_2$), 43.5

(C_{20}H), 42.8 (C_{13}), 40.3 (C_4H_2), 38.2 ($C_{12}H_2$), 37.2 (C_1H_2), 36.9 (C_{10}), 32.3 (C_8H), 32.2 (C_7H_2), 28.9 (C_2H_2), 28.0 ($C_{16}H_2$), 24.2 ($C_{15}H_2$), 21.5 ($C_{11}H_2$), 19.5 ($C_{19}H_3$), 12.4 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{35}H_{41}NO_6$ $[M]^+$: 571.3, found $[M+H]^+$: 572.3.

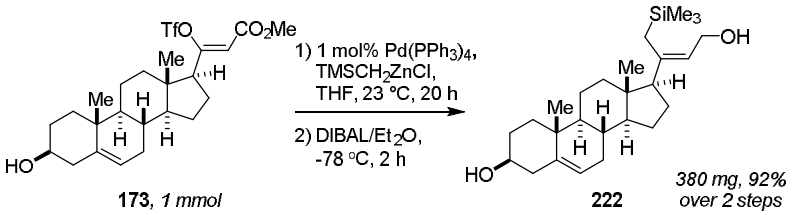
IR (neat): ν (cm^{-1}) = 2936, 1763, 1723, 1616, 1595, 1525, 1493, 1453, 1346, 1257, 1216, 1164, 1043, 1012, 970, 943, 857, 776, 703.

$[\alpha]^{25}_D$ = –20.6 (*c* 0.25, CH_2Cl_2).

The C20 stereochemistry of C20-(*S*)-**177a** was confirmed by single crystal X-ray diffraction analysis.

7.4 Ir-Catalyzed Vinylogous Peterson Elimination of Allylic Alcohols

*7.4.1 Preparation of steroidal allylic alcohol **222***



173, *1 mmol* — **222**, *380 mg, 92% over 2 steps*

(Trimethylsilyl)methylmagnesium chloride (1.3 M in THF, 0.92 mL, 1.2 mmol) was added to an anhydrous zinc chloride solution (1.5 mL, 1.5 mmol, 1.0 M solution in THF) at 0 °C. The resulting white suspension was stirred at the same temperature for 1 h. To this mixture were then successively added enol triflate **173** (550 mg, 1.0 mmol) and tertakis(triphenylphosphine)palladium (11.6 mg, 1.0 mol%) in THF (10 mL, 0.1 M). The reaction mixture was stirred at 23 °C for 17 h. A saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction, which was subsequently extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude enoate (>99% conversion based on crude ^{1}H NMR) was engaged directly into the next step without further purification.

To a solution of crude enoate (1 mmol) in anhydrous diethyl ether (30 mL, 0.03 M) was added dropwise diisobutylaluminium hydride (6.0 mmol, 6.0 eq., 1.0 M in hexanes) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution (25 mL). The resulting white suspension was stirred at ambient temperature for 2 h before extraction with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (Pentane/Acetone = 4/1, buffered with 0.1% triethylamine) gave **222** (385 mg, 92% over 2 steps).

Colorless foam (Pentane/Acetone = 5/1, R_f = 0.1).

^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) = 5.36-5.30 (m, 2H, H_{22}+H_6), 4.20-4.01 (m, 2H, H_{23}), 3.51-3.42 (m, 1H, H_3), 2.29-2.12 (m, 2H, H_4), 2.04-1.94 (m, 2H, H_7+H_{17}), 1.87-1.73 (m, 5H), 1.73-1.07 (m, 12H), 1.04-0.94 (m, 4H, H_9+Me_{19}), 0.60 (s, 3H, Me_{18}), 0.01 (s, 9H, Me_3Si).

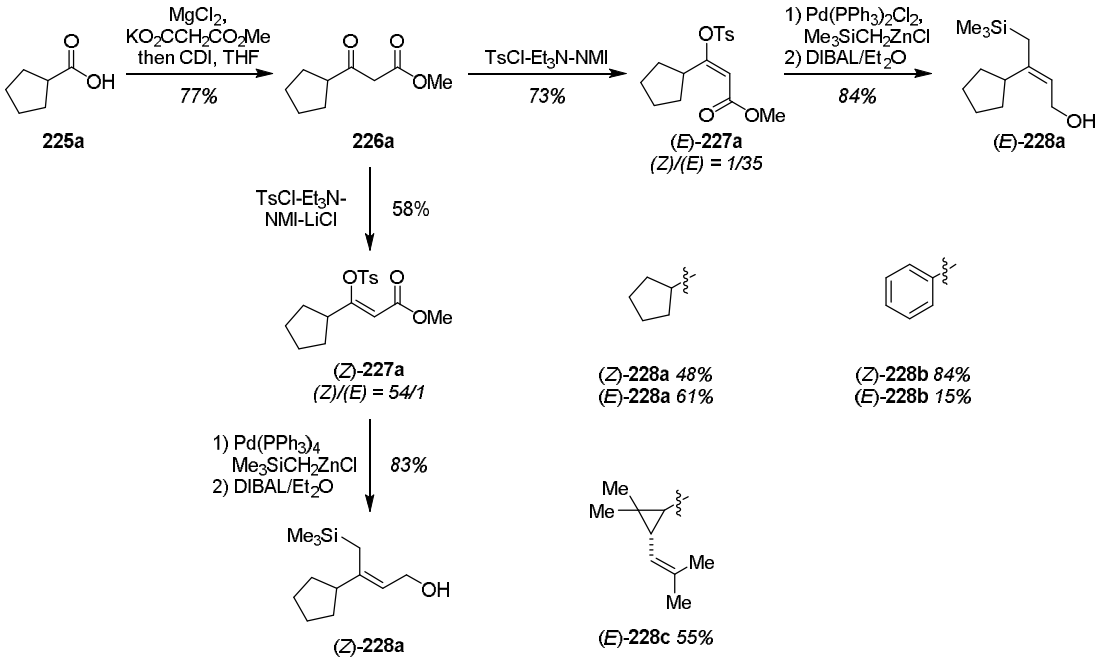
^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz): δ (ppm) = 141.4 (C_5), 140.4 (C_{20}), 121.7 (C_{22}H), 121.2 (C_6H), 72.0 (C_3H), 60.4 ($C_{23}H_2$), 58.5 (C_{17}H), 57.2 (C_{14}H), 50.8 (C_9H), 43.8 (C_{13}), 42.8 (C_4H_2), 39.5 ($C_{12}H_2$), 37.7 (C_1H_2), 36.9 (C_{10}), 32.7 (C_8H), 32.2 (C_7H_2), 32.1 (C_2H_2), 26.1 ($C_{16}H_2$), 24.5 ($C_{15}H_2$), 24.5 ($C_{21}H_2$), 21.6 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 13.2 ($C_{18}H_3$), -0.8 (Me_3Si).

LRMS (ESI) calculated for $C_{26}H_{44}O_2Si$ $[M]^+$: 416.3, found $[M+H]^+$: 417.5.

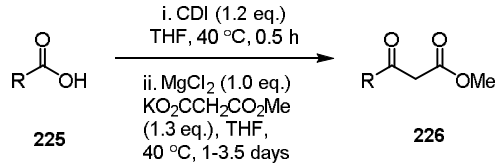
IR (neat): ν (cm^{-1}) = 3288, 2933, 2901, 1647, 1453, 1433, 1376, 1334, 1248, 1191, 1152, 1058, 1003, 852. 847, 836.

$[\alpha]^{25}_D$ = +19.3 (*c* 0.10, THF).

7.4.2 Preparation of allylic alcohols ***228***



Step 1. General procedure for the synthesis of β*-keto ester* ***226a-c***[13]



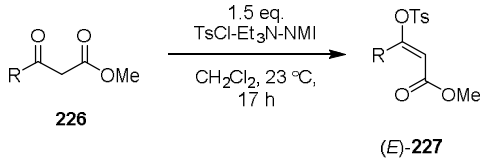
A flame-dried 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with magnesium chloride (1.95 g, 20 mmol, 1.0 equiv) and potassium monomethyl malonate (4.1 g, 26 mmol, 1.3 equiv). A reflux condenser was attached and the flask was subsequently evacuated and back-filled with argon. Tetrahydrofuran (30 mL) was added and the suspension was heated to 65 °C for 3 h.

After the above reaction had proceeded for 2 h, a separate flame-dried 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with the appropriate carboxylic acid (**225**, 20 mmol, 1.0 equiv) and THF (20 mL). To this solution was added

carbonyl diimidazole (3.9 g, 24 mmol, 1.2 equiv) in portions, allowing for effervescence to subside between additions. Warning: vigorous gas evolution. The reaction was stirred at 23 °C until bubbling ceased (30 min), and then heated to 40 °C (at which point bubbling renewed) for an additional 30 min.

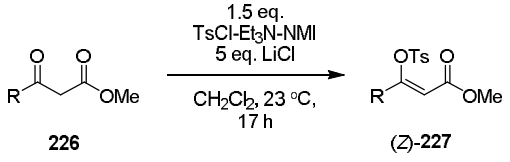
The magnesium malonate suspension was cooled to 30 °C and the acyl-imidazole solution was added dropwise via syringe (NOTE: a white precipitate forms rapidly during this addition; vigorous stirring is necessary to avoid clumping). The resulting milky white suspension was stirred at 40 °C for 1-3.5 days. The reaction was cooled to 0 °C when TLC analysis showed complete consumption of the intermediate acyl imidazole. The reaction was quenched by the addition of 1.0 N HCl (15 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were sequentially washed with water (80 mL), saturated aqueous sodium bicarbonate (80 mL), and brine (80 mL). The organic layer was then dried over MgSO4, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography over silica gel to give β-keto ester **226**.

*Step 2. General procedure for the synthesis of enol tosylate (E)-**227***[14]



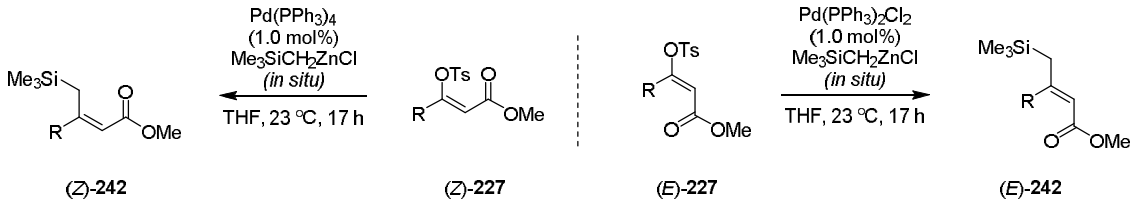
To a solution of **226** (5 mmol) in dichloromethane (25 mL, 0.02 M) were successively added *N*-methylimidazole (7.5 mmol), triethylamine (7.5 mmol) and *p*-toluenesulfonyl chloride (7.5 mmol) at 0 °C. The mixture was stirred at 23 °C for 17 h. Next, 1 M HCl (15 mL) was added at 0 °C, the resulting mixture was extracted twice with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified via flash chromatography over silica gel to give enol tosylate (*E*)-**227**.

*Step 3a. General procedure for the synthesis of enol tosylate (Z)-**227**[14b]*



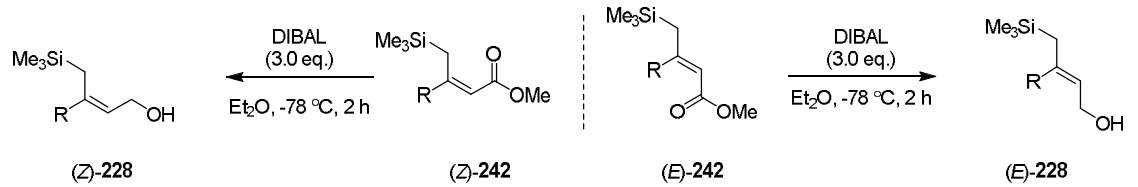
To a solution of **226** (5 mmol) in dichloromethane (25 mL, 0.02 M) were successively added *N*-methylimidazole (7.5 mmol), triethylamine (7.5 mmol), *p*-toluenesulfonyl chloride (7.5 mmol), and anhydrous lithium chloride (25 mmol) at 0 °C. The mixture was stirred at 23 °C for 17 h. Next, 1 M HCl (15 mL) was added at 0 °C, the resulting mixture was extracted twice with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified via flash chromatography over silica gel to give enol tosylate (*Z*)-**227**.

*Step 3b. General procedure for the synthesis of enoate **242**[14a]*



(Trimethylsilyl)methylmagnesium chloride (1.3 M in THF, 1.9 mL, 2.4 mmol) was added to an anhydrous zinc chloride solution (3 mL, 3.0 mmol, 1.0 M solution in THF) at 0 °C. The resulting white suspension was stirred at the same temperature for 1 h. To this mixture were then successively added the appropriate enoate **227** (2.0 mmol) and the palladium catalyst (14 mg of $[(Ph_3P)_2PdCl_2]$ for (*E*)-**227**, or 23 mg of $[(Ph_3P)_4Pd]$ for (*Z*)-**227**, 1 mol%) in anhydrous THF (20 mL, 0.1 M). The reaction mixture was stirred at 23 °C for 17 h. A saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction, which was subsequently extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified via flash chromatography over silica gel to give enoate **242**.

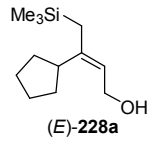
*Step 4. General procedure for the synthesis of silane allylic alcohol **228***



To a solution of either (*E*)- or (*Z*)-Enoate **242** (2 mmol) in anhydrous diethyl ether (20 mL, 0.1 M) was added dropwise diisobutylaluminium hydride (6.0 mmol, 3.0 eq., 1.0 M in hexanes) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 2 h, and then

quenched with a saturated aqueous NH_4Cl solution (25 mL). The resulting white suspension was stirred at ambient temperature for 2 h before extraction with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified via flash chromatography over silica gel give allylic alcohol **228**.

(E)-3-cyclopentyl-4-(trimethylsilyl)but-2-en-1-ol ((*E*)-**228a**)



(*E*)-**228a**

340 mg, 61% over 3 steps from known compound **226a**.

Colorless oil (Pentane/Ethyl acetate = 8/1, R_f = 0.10).

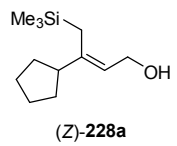
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 5.27 (t, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*CH_2OH), 4.13-4.10 (m, 2H, CH_2OH), 2.90-2.82 (m, 1H, C$H_{c\text{-}pent}$), 1.69-1.35 (m, 8H, C$H_{2c\text{-}pent}$), 1.45 (s, 2H, CH_2SiMe_3), 1.05 (t, $^3J_{HH}$ = 5.4 Hz, 1H, O*H*), 0.04 (s, 9H, *Me*$_3$Si).

^{13}C{^{1}H} NMR (CD_2Cl_2, 100 MHz): δ (ppm) = 145.0 (*C*CH), 123.1 (*C*HCH_2OH), 59.1 (*C*H_2OH), 42.3 (*C*$H_{c\text{-}pent}$), 31.8 (*C*$H_{2c\text{-}pent}$), 26.0 (*C*$H_{2c\text{-}pent}$), 21.8 (*C*H_2SiMe_3), -0.6 (*Me*$_3$Si).

LRMS (ESI) calculated for $C_{12}H_{24}OSi$ $[M]^+$: 212.2, found $[M+NH_4]^+$: 230.4.

IR (neat): ν (cm^{-1}) = 3317, 2952, 2870, 1644, 1452, 1415, 1246, 1162, 1072, 991, 839, 759, 690, 630.

(Z)-3-cyclopentyl-4-(trimethylsilyl)but-2-en-1-ol ((*Z*)-**228a**)



(*Z*)-**228a**

335 mg, 48% over 3 steps from known compound **226a**.

Colorless oil (Pentane/Ethyl acetate = 8/1, R_f = 0.10).

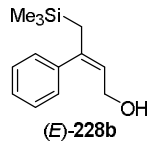
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 5.27 (t, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*CH_2OH), 4.06 (t, $^3J_{HH}$ = 5.9 Hz, 2H, CH_2OH), 2.30-2.25 (m, 1H, C$H_{c\text{-}pent}$), 1.85-1.32 (m, 8H, C$H_{2c\text{-}pent}$), 1.64 (s, 2H, CH_2SiMe_3), 1.11 (t, $^3J_{HH}$ = 5.4 Hz, 1H, O*H*), 0.02 (s, 9H, *Me*$_3$Si).

^{13}C{^{1}H} NMR (CD_2Cl_2, 100 MHz): δ (ppm) = 145.3 (*C*CH), 118.4 (*C*HCH_2OH), 60.2 (*C*H_2OH), 48.3 (*C*$H_{c\text{-}pent}$), 32.2 (*C*$H_{2c\text{-}pent}$), 25.2 (*C*$H_{2c\text{-}pent}$), 22.5 (*C*H_2SiMe_3), -0.7 (*Me*$_3$Si).

LRMS (ESI) calculated for $C_{12}H_{24}OSi$ $[M]^+$: 212.2, found $[M+Na]^+$: 235.4.

IR (neat): ν (cm^{-1}) = 3317, 2953, 2870, 1652, 1418, 1248, 1158, 1007, 849, 764, 692, 631.

(E)-3-phenyl-4-(trimethylsilyl)but-2-en-1-ol ((*E*)-**228b**)



(*E*)-**228b**

270 mg, 15% over 3 steps from commercial available **226b**.

Colorless oil (Pentane/Ethyl acetate = 8/1, R_f = 0.10).

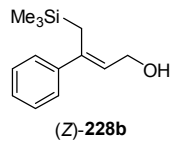
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 7.34-7.16 (H_{Ar}), 5.52 (t, $^3J_{HH}$ = 7.1 Hz, 1H, C*H*CH_2OH), 4.02-4.00 (m, 2H, CH_2OH), 1.94 (s, 2H, CH_2SiMe_3), 0.91-0.86 (m, 1H, O*H*), -0.15 (s, 9H, *Me*$_3$Si).

^{13}C{^{1}H} NMR (CD_2Cl_2, 100 MHz): δ (ppm) = 142.8 (*C*CH), 141.7 (C_{Ar}), 128.8 (*C*H_{Ar}), 128.3 (*C*H_{Ar}), 127.4 (*C*H_{Ar}), , 124.2 (*C*HCH_2OH), 60.6 (*C*H_2OH), 30.0 (*C*H_2SiMe_3), -1.4 (*Me*$_3$Si).

LRMS (ESI) calculated for $C_{13}H_{20}OSi$ $[M]^+$: 220.1, found $[M+Na]^+$: 243.6.

IR (neat): ν (cm^{-1}) = 3320, 2954, 1641, 1493, 1441, 1410, 1247, 1162, 1079, 992, 917, 842, 776, 756, 699, 634.

(Z)-3-phenyl-4-(trimethylsilyl)but-2-en-1-ol ((*Z*)-**228b**)



(*Z*)-**228b**

415 mg, 84% over 3 steps from commercial available **226b**.

Colorless oil (Pentane/Ethyl acetate = 8/1, R_f = 0.10).

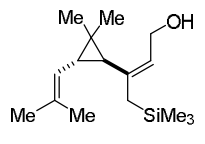
^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 7.38-7.22 (H_{Ar}), 5.69 (t, $^3J_{HH}$ = 6.7 Hz, 1H, C*H*CH_2OH), 4.26-4.23 (m, 2H, CH_2OH), 2.05 (s, 2H, C$H_2$$SiMe_3$), 1.33 (t, $^3J_{HH}$ = 5.6 Hz, 1H, O*H*), -0.15 (s, 9H, *Me*$_3$Si).

^{13}C{^{1}H} NMR (CD_2Cl_2, 100 MHz): δ (ppm) = 144.5 (*C*CH), 141.5 (C_{Ar}), 128.5 (CH_{Ar}), 127.5 (CH_{Ar}), 127.0 (CH_{Ar}), , 124.7 (*C*HCH_2OH), 60.7 (*C*H_2OH), 21.8 (*C*$H_2$$SiMe_3$), -1.1 (*Me*$_3$Si).

LRMS (ESI) calculated for $C_{13}H_{20}OSi$ $[M]^+$: 220.1, found $[M+Na]^+$: 243.6.

IR (neat): ν (cm^{-1}) = 3316, 3026, 2954, 1636, 1493, 1444, 1416, 1319, 1248, 1155, 1106, 1073, 1008, 950, 840, 773, 749, 694, 626.

rac-(E)-3-((1S,3S)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)-4-(trimethylsilyl)but-2-en-1-ol ((*E*)-**228c**)



(E)-**228c**

230 mg, 55% over 3 steps from **226c**.

Colorless oil (Pentane/Ethyl acetate = 14/1, R_f = 0.20).

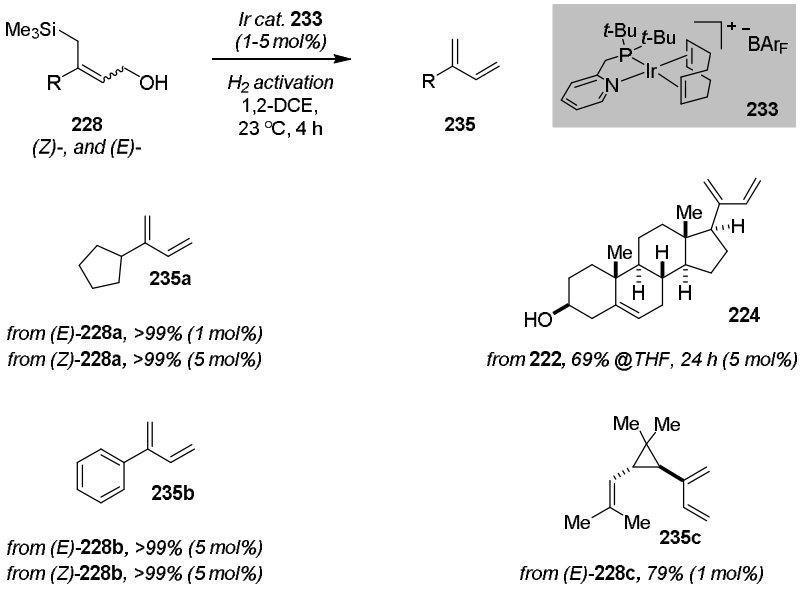
^{1}H NMR (CD_2Cl_2, 400 MHz):[25] δ (ppm) = 5.39-5.35 (m, 1H, C*H*CH_2OH), 4.85-4.82 (C*H*=CMe_2), 4.20-4.03 (m, 2H, CH_2OH), 1.72 (s, 2H, C$H_2$$SiMe_3$), 1.71 (s, 6H, *Me*$_2$C=CH), 1.38-1.34 (m, 1H, C*H*CH=CMe_2), 1.14-1.10 (m, 1H, C*H*C=CH), 1.08 (*Me*$_2$CCH), 0.96 (*Me*$_2$CCH), 0.00 (s, 9H, *Me*$_3$Si).

^{13}C{^{1}H} NMR (CD_2Cl_2, 100 MHz):[25] δ (ppm) = 139.1 (*C*=$CHCH_2$OH), 132.9 (*C*Me_2=CH), 125.7 (*C*HCH_2OH), 124.5 (*C*H=CMe_2), 60.4 (*C*H_2OH), 36.3 (*C*HC=CH), 30.2 (*C*HCH=CMe_2), 28.4 (*C*$H_2$$SiMe_3$), 25.8 (*Me*$_2$C=CH), 24.4 (*C*$Me_2$CH), 22.9 (*Me*$_2$C=CH), 22.3 (*Me*$_2$CCH), 18.4 (*Me*$_2$CCH), -1.2 (*Me*$_3$Si).

LRMS (ESI) calculated for $C_{16}H_{30}OSi$ $[M]^+$: 266.2, found $[M+Na]^+$: 289.8.

IR (neat): ν (cm^{-1}) = 3329, 2940, 1642, 1449, 1412, 1377, 1247, 1157, 1120, 989, 843, 755, 692.

7.4.3 Ir-catalyzed vinylogous Peterson elimination



A 10 mL Schlenk containing **233** (7.0 mg, 5.0 mol% for (*Z*)-**228**, and 1.4 mg, 1.0 mol% for (*E*)-**228**) was purged by three successive vacuum/nitrogen sequences and refilled with nitrogen. Degassed anhydrous 1,2-dichloroethane (1.5 mL) was added next and hydrogen gas was gently bubbled directly through the solution (2-3 bubbles per second) via a stainless-steel needle at room temperature. The orange solution rapidly discolored. After 1 minute, bubbling was ceased and the solution was degassed by two successive freeze–pump–thaw cycles. After the second cycle, the appropriate allylic alcohol **228** (0.1 mmol) was added immediately to the cold solution in one portion. The rubber septum was replaced with a polyethylene stopper and the reaction was stirred at room temperature for 4 h. The reaction was then stopped, quenched with 2-3 drops of triethylamine, and concentrated under vaccum. Purification by flash chromatography (eluent: Pentane) afforded the analytically pure 1,3-diene **235**.

*Note: Both **235a**[31] and **235b**[32] are known compounds and all spectrocopic and spectrometric analyses are consitent with those reported in the literature*.

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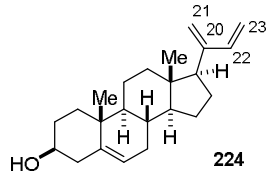


224

Following general procedure using **233** (3.5 mg, 5 mol%) and **222** (20 mg, 0.05 mmol) in anhydrous THF. The reaction was stopped after 24 h at ambient temperature. Purification by flash chromatography (Pentane/Acetone = 6/1, buffered with 0.1% triethylamine) gave **224** (11 mg, 69%).

Colorless foam (Pentane/Acetone = 5/1, R_f = 0.2).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 6.37 (dd, $^3J_{HH}$ = 17.5, 10.9 Hz, 1H, H_{22}), 5.36-5.34 (m, 1H, H_6), 5.30-5.32 (m, 1H, H_{23}), 5.22 (s, 1H, H_{21}), 5.00 (s, 1H, H_{21}), 5.00-4.95 (m, 1H, H_{23}), 3.50-3.42 (m, 1H, H_3), 2.46 (t, $^3J_{HH}$ = 9.4 Hz, 1H, H_{17}), 2.29-2.15 (m, 2H, H_4), 2.05-1.99 (m, 1H, H_7), 1.87-1.04 (m, 18H), 1.01-0.94 (m, 4H, H_9+Me_{19}), 0.58 (s, 3H, Me_{18}).

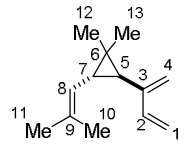
^{13}C{^{1}H} NMR (CD_2Cl_2, 101 MHz): δ (ppm) = 146.7 (C_{20}), 141.5 (C_{22}H), 141.4 (C_5), 121.7 (C_6H), 114.7 ($C_{21}H_2$), 112.9 ($C_{23}H_2$), 72.1 (C_3H), 57.2 (C_{14}H), 51.7 (C_{17}H), 50.8 (C_9H), 43.5 (C_{13}), 42.8 (C_4H_2), 39.3 ($C_{12}H_2$), 37.7 (C_1H_2), 37.0 (C_{10}), 32.9 (C_8H), 32.3 (C_7H_2), 32.1 (C_2H_2), 26.8 ($C_{16}H_2$), 24.7 ($C_{15}H_2$), 21.6 ($C_{11}H_2$), 19.6 ($C_{19}H_3$), 13.1 ($C_{18}H_3$).

LRMS (ESI) calculated for $C_{23}H_{34}O$ $[M]^+$: 326.3, found $[M+NH_4]^+$: 344.8.

IR (neat): ν (cm^{-1}) = 3316, 2934, 1592, 1445, 1376, 1111, 1054, 989, 955, 895, 842, 801.

$[\alpha]^{25}_D$ = –60.5 (*c* 0.10, THF).

rac-2-(buta-1,3-dien-2-yl)-1,1-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane (**235c**)



235c

Following general procedure using **233** (1.4 mg, 1 mol%) and (*E*)-**228c** (25 mg, 0.1 mmol). Purification by flash chromatography (eluent: Pentane) gave **235c** (13 mg, 79%).

Colorless oil (Pentane, R_f = 0.90).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ (ppm) = 6.52 (dd, $^3J_{HH}$ = 17.4, 10.6 Hz, 1H, H_2), 5.29-5.24 (m, 1H, H_1), 5.11-5.07 (m, 2H, H_1+H_4), 5.00-4.95 (m, 2H, H_4+H_8), 1.73 (s, 3H, Me_{10}), 1.73 (s, 3H, Me_{11}), 1.51-1.48 (m, 1H, H_7), 1.24-1.22 (m, 1H, H_8), 1.16 (Me_{12} or Me_{13}), 0.89 (Me_{13} or Me_{12}).

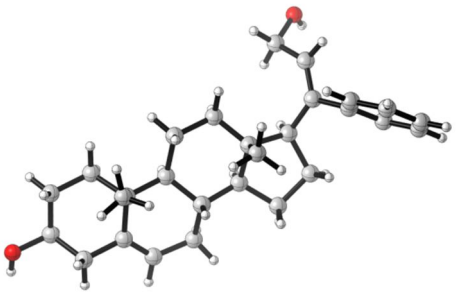
^{13}C{^{1}H} NMR (CD_2Cl_2, 100 MHz): δ (ppm) = 145.7 (C_3), 140.4 (C_2H), 133.7 (C_9), 123.9 (C_8H), 116.0 (C_4H_2), 114.4 (C_1H_2), 35.6 (C_5H), 27.5 (C_7H), 25.7 (Me_{10} or Me_{11}), 23.8 (C_6), 22.3 (Me_{12} or Me_{13}), 20.8 (Me_{12} or Me_{12}), 18.5 (Me_{11} or Me_{10}).

LRMS (ESI) calculated for $C_{13}H_{20}$ $[M]^+$: 176.2, found $[M+H]^+$: 177.6.

IR (neat): ν (cm^{-1}) = 2962, 2923, 1593, 1448, 1378, 1260, 1117, 987, 890.

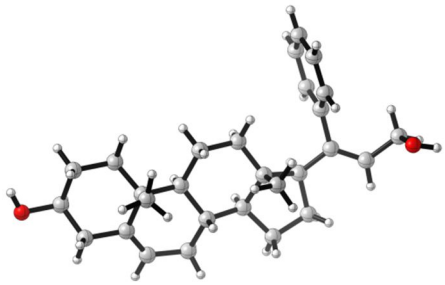
7.5 Tables for X-ray crystallography

*7.5.1. X-ray data and structure refinement for (E)-**174a***



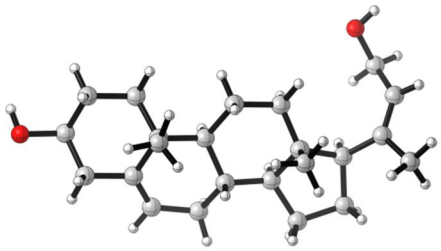
Empirical formula	$C_{28}H_{38}O_2$	
Formula weight	406.58	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.62518(9) Å	α = 90°.
	b = 19.0411(2) Å	β = 90°.
	c = 32.4846(4) Å	γ = 90°.
Volume	4716.50(10) $Å^3$	
Z	8	
Density (calculated)	1.145 Mg/m^3	
Absorption coefficient	0.534 mm^{-1}	
F(000)	1776	
Crystal size	0.3602 x 0.1980 x 0.0954 mm^3	
Theta range for data collection	3.58 to 72.59°.	
Index ranges	-9<=h<=5, -23<=k<=22, -39<=l<=39	
Reflections collected	17662	
Independent reflections	9138 [R(int) = 0.0206]	
Completeness to theta = 67.50°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.956 and 0.888	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9138 / 4 / 558	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0979	
R indices (all data)	R1 = 0.0399, wR2 = 0.1014	
Absolute structure parameter	0.09(17)	
Largest diff. peak and hole	0.172 and -0.165 $e.Å^{-3}$	

*7.5.2. X-ray data and structure refinement for (Z)-**174a***



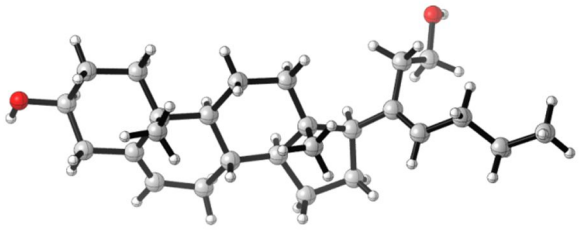
Empirical formula	$C_{28}H_{41}O_{3.50}$	
Formula weight	433.61	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 2	
Unit cell dimensions	a = 31.0988(12) Å	α= 90°.
	b = 9.8634(3) Å	β= 90°.
	c = 7.9792(2) Å	γ = 90°.
Volume	2447.53(14) $Å^3$	
Z	4	
Density (calculated)	1.177 Mg/m^3	
Absorption coefficient	0.590 mm^{-1}	
F(000)	948	
Crystal size	0.4775 x 0.2917 x 0.0164 mm^3	
Theta range for data collection	4.70 to 73.52°.	
Index ranges	-37<=h<=37, -8<=k<=12, -9<=l<=7	
Reflections collected	8300	
Independent reflections	4793 [R(int) = 0.0318]	
Completeness to theta = 67.50°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.990 and 0.846	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4793 / 0 / 299	
Goodness-of-fit on F^2	1.121	
Final R indices [I>2sigma(I)]	R1 = 0.0523, wR2 = 0.1318	
R indices (all data)	R1 = 0.0663, wR2 = 0.1395	
Absolute structure parameter	0.4(3)	
Largest diff. peak and hole	0.207 and -0.201 $e.Å^{-3}$	

*7.5.3. X-ray data and structure refinement for (Z)-**174k***



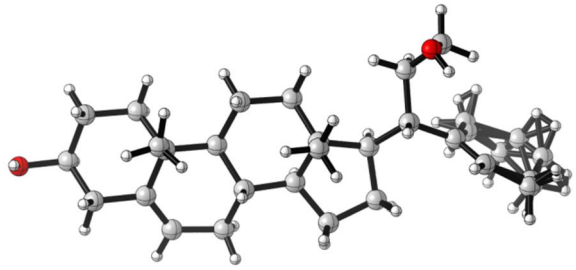
Empirical formula	$C_{23}H_{36}O_2$	
Formula weight	344.52	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 11.4236(8) Å	α= 90°.
	b = 7.3166(4) Å	β= 109.390(8)°.
	c = 12.1844(8) Å	γ = 90°.
Volume	960.62(10) $Å^3$	
Z	2	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	0.562 mm^{-1}	
F(000)	380	
Crystal size	0.4920 x 0.3020 x 0.1054 mm^3	
Theta range for data collection	3.85 to 72.33°.	
Index ranges	-14<=h<=13, -8<=k<=8, -15<=l<=13	
Reflections collected	6254	
Independent reflections	3668 [R(int) = 0.0139]	
Completeness to theta = 67.50°	99.8 %	
Absorption correction	Analytical	
Max. and min. transmission	0.946 and 0.829	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3668 / 3 / 236	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0290, wR2 = 0.0770	
R indices (all data)	R1 = 0.0292, wR2 = 0.0774	
Absolute structure parameter	-0.07(16)	
Largest diff. peak and hole	0.222 and -0.137 $e.Å^{-3}$	

*7.5.4. X-ray data and structure refinement for (E)-**180***



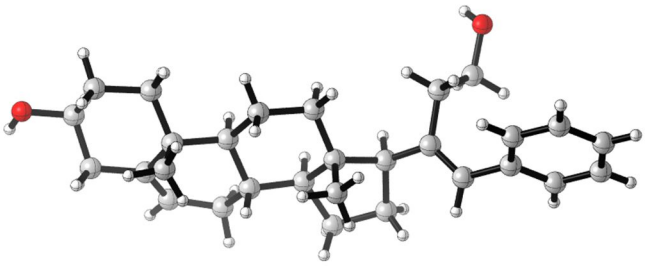
Empirical formula	$C_{26}H_{42}O_2$	
Formula weight	386.60	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P 1	
Unit cell dimensions	a = 7.5739(3) Å	α= 84.447(3)°.
	b = 10.7023(3) Å	β= 87.768(3)°.
	c = 14.5550(4) Å	γ = 89.571(3)°.
Volume	1173.36(6) $Å^3$	
Z	2	
Density (calculated)	1.094 Mg/m^3	
Absorption coefficient	0.507 mm^{-1}	
F(000)	428	
Crystal size	0.4014 x 0.1894 x 0.0975 mm^3	
Theta range for data collection	3.05 to 72.60°.	
Index ranges	-8<=h<=9, -13<=k<=13, -17<=l<=17	
Reflections collected	18064	
Independent reflections	8540 [R(int) = 0.0256]	
Completeness to theta = 67.50°	99.7 %	
Absorption correction	Analytical	
Max. and min. transmission	0.952 and 0.866	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8540 / 7 / 528	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0442, wR2 = 0.1219	
R indices (all data)	R1 = 0.0476, wR2 = 0.1266	
Absolute structure parameter	-0.17(19)	
Largest diff. peak and hole	0.240 and -0.172 e.$Å^{-3}$	

*7.5.5. X-ray data and structure refinement for C20-(S)-**181***



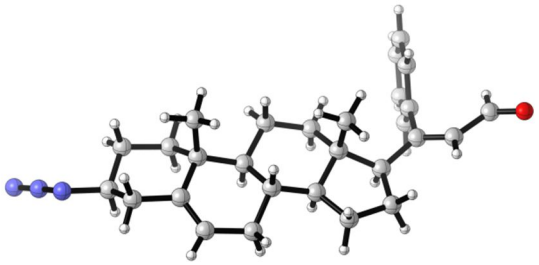
Empirical formula	$C_{28.50}H_{44.50}Cl_{1.50}O_2$	
Formula weight	472.32	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	I 2	
Unit cell dimensions	a = 14.2842(2) Å	α= 90°.
	b = 6.07578(8) Å	β= 92.1970(14)°.
	c = 30.0756(4) Å	γ = 90°.
Volume	2608.27(6) $Å^3$	
Z	4	
Density (calculated)	1.203 Mg/m^3	
Absorption coefficient	1.926 mm^{-1}	
F(000)	1028	
Crystal size	0.4738 x 0.1422 x 0.1279 mm^3	
Theta range for data collection	3.38 to 73.70°.	
Index ranges	-17<=h<=17, -7<=k<=7, -36<=l<=36	
Reflections collected	21351	
Independent reflections	5221 [R(int) = 0.0266]	
Completeness to theta = 67.50°	100.0 %	
Absorption correction	Analytical	
Max. and min. transmission	0.814 and 0.528	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5221 / 1 / 299	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0316, wR2 = 0.0883	
R indices (all data)	R1 = 0.0322, wR2 = 0.0891	
Absolute structure parameter	-0.003(11)	
Largest diff. peak and hole	0.202 and -0.269 $e.Å^{-3}$	

*7.5.6. X-ray data and structure refinement for (E)-**182***



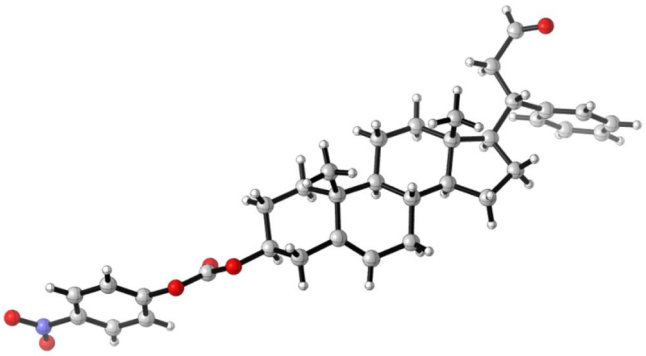
Identification code	shelxl	
Empirical formula	$C_{29}H_{40}O_2$	
Formula weight	420.61	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 12.1279(3) Å	α= 90°.
	b = 7.0339(2) Å	β= 93.725(2)°.
	c = 14.5183(4) Å	γ = 90°.
Volume	1235.89(6) $Å^3$	
Z	2	
Density (calculated)	1.130 Mg/m^3	
Absorption coefficient	0.525 mm^{-1}	
F(000)	460	
Crystal size	0.2803 x 0.1912 x 0.1090 mm^3	
Theta range for data collection	3.05 to 72.57°.	
Index ranges	-14<=h<=13, -8<=k<=8, -17<=l<=17	
Reflections collected	10173	
Independent reflections	4556 [R(int) = 0.0150]	
Completeness to theta = 67.50°	100.0 %	
Absorption correction	Analytical	
Max. and min. transmission	0.948 and 0.906	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4556 / 1 / 289	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0317, wR2 = 0.0842	
R indices (all data)	R1 = 0.0329, wR2 = 0.0855	
Absolute structure parameter	-0.08(18)	
Largest diff. peak and hole	0.149 and -0.151 $e.Å^{-3}$	

*7.5.7. X-ray data and structure refinement for **199***



Empirical formula	$C_{28}H_{35}N_3O$	
Formula weight	429.59	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.28986(16) Å	α= 90°.
	b = 23.9607(5) Å	β= 90°.
	c = 29.1587(5) Å	γ = 90°.
Volume	7189.1(2) $Å^3$	
Z	12	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	0.561 mm^{-1}	
F(000)	2784	
Crystal size	0.3708 x 0.1887 x 0.0820 mm^3	
Theta range for data collection	3.03 to 73.69°.	
Index ranges	-12<=h<=8, -29<=k<=26, -35<=l<=35	
Reflections collected	18753	
Independent reflections	12599 [R(int) = 0.0229]	
Completeness to theta = 67.50°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.957 and 0.874	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12599 / 0 / 872	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.1113	
R indices (all data)	R1 = 0.0529, wR2 = 0.1169	
Absolute structure parameter	0.1(3)	
Largest diff. peak and hole	0.174 and -0.166 $e.Å^{-3}$	

*7.5.8. X-ray data and structure refinement for C20-(S)-**177***



Empirical formula	$C_{35}H_{41}NO_6$
Formula weight	571.69
Temperature/K	180.05(10)
Crystal system	orthorhombic
Space group	P212121
a/Å	10.09180(16)
b/Å	11.48593(15)
c/Å	25.4903(4)
α/°	90
β/°	90
γ/°	90
Volume/Å3	2954.67(7)
Z	4
ρcalcg/cm3	1.285
μ/mm-1	0.700
F(000)	1224.0
Crystal size/mm3	0.2845 × 0.2696 × 0.0804
Radiation	CuKα (λ = 1.5418)
2Θ range for data collection/°	6.936 to 149.302
Index ranges	-11 ≤ h ≤ 12, -14 ≤ k ≤ 9, -31 ≤ l ≤ 30
Reflections collected	23362
Independent reflections	5993 [Rint = 0.0226, Rsigma = 0.0171]
Data/restraints/parameters	5993/0/382
Goodness-of-fit on F2	1.040
Final R indexes [I>=2σ (I)]	R1 = 0.0303, wR2 = 0.0796
Final R indexes [all data]	R1 = 0.0322, wR2 = 0.0816
Largest diff. peak/hole / e Å-3	0.18/-0.14
Flack parameter	0.05(18)

7.6 References

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