Three atoms insertion and addition reactions of α-diazo-β-ketoesters catalyzed by CpRu-complexes

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Three Atoms Insertion and Addition Reactions of α-Diazo-β-Ketoesters Catalyzed by CpRu-Complexes

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In memory of my father

and of his passion for chemistry

Toute la dignité de l'homme consiste donc en la pensée

Balise Pascal, *Pensées*

Réactions d'addition et d'insertion des α-diazo-β-cétoesters catalysées par des complexes de ruthénium(II)

Les complexes de ruthénium sont des alternatives valables à ceux du cuivre et du rhodium pour la décomposition des composés diazoïques.[1] Les α-diazo-β-cétoesters sont caractérisés par une meilleure stabilité et une réactivité modérée par rapport à d'autres types de composés diazoïques.[2] Néanmoins, ces composés sont capables de former, en présence d'un métal de transition, des intermédiaires carbeniques électrophiliques réactifs vis-à-vis des réactions de cyclopropanation, d'insertion, d'addition dipolaire et de réarrangement suite à la formation d'ylure.[3]

Précédemment dans le groupe du Prof. Lacour, le complexe $[CpRu(CH_3CN)_3][PF_6]$ associé à des ligands diimines a été utilisé pour catalyser la décomposition de ce type de ″diazo″ carbonylés. Des réactions d'insertion O-H et de condensation en présence de nitriles, d'aldéhydes et de cétones ont aussi été menées à bien.[4] L'objectif de cette thèse a été d'étendre cette méthodologie à d'autres bases de Lewis, typiquement les éthers cycliques.

Tout d'abord, ce type de réactivité a été étudié en présence de cétones cyclique (**Schéma 1**). Des composés de type ″spiro″ ont été obtenus avec de bon rendements. En améliorant la procédure précédente,[4] les réactions ont pu être menés en utilisant seulement une quantité stœchiométrique de cétone. Une réactivité analogue a été développée pour des lactones et des lactames, menant également à la formation de produits de type ″spiro″ (**Schéma 1**).

---

[1] Che, C. M.; Huang, J. S., *Coord. Chem. Rev.* **2002**, *231* (1-2), 151-164.

[2] Doyle, M. P.; McKervey, M. A.; Ye, T., *Modern catalytic methods for organic synthesis with diazo compounds : from cyclopropanes to ylides*. Wiley: New York, 1998; p xvii, 652 p.

[3] (a) Padwa, A.; Weingarten, M. D., *Chem. Rev.* **1996**, *96* (1), 223-269; (b) Doyle, M. P.; Forbes, D. C., *Chem. Rev.* **1998**, *98* (2), 911-935; (c) Davies, H. M. L.; Beckwith, R. E. J., *Chem. Rev.* **2003**, *103* (8), 2861-2903; (d) Zhang, Z. H.; Wang, J. B., *Tetrahedron* **2008**, *64* (28), 6577-6605; (e) Zeghida, W.; Besnard, C.; Lacour, J., *Angew. Chem. Int. Ed.* **2010**, *49* (40), 7253-7256; (f) Rix, D.; Ballesteros-Garrido, R.; Zeghida, W.; Besnard, C.; Lacour, J., *Angew. Chem. Int. Ed.* **2011**, *50* (32), 7308-7311.

[4] Austeri, M.; Rix, D.; Zeghida, W.; Lacour, J., *Org. Lett.* **2011**, *13* (6), 1394-1397.

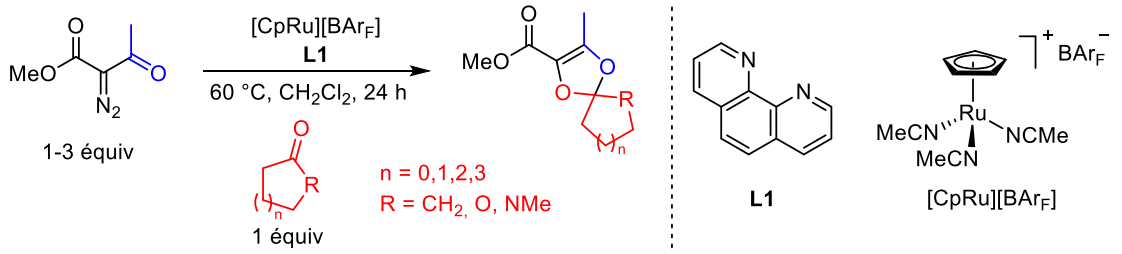

Schéma 1 Réactions de condensation.

Ensuite, il nous a semblé judicieux de tester la réactivité des carbènes de ruthenium, issu de la décomposition des α-diazo-β-cétoesters en présence de THF. Les tetrahydrofuranes substitués sont des structures très répandus dans les produits biologiquement actifs et dans la chimie des produits naturels.[5] Plusieurs exemples de réactions d'insertion C-H catalysées par des complexes de cuivre, d'iridium, de fer, de rhodium et d'argent ont été décrits dans la littérature.[6] Dans chaque cas, la formation d'une nouvelle liaison carbone-carbone a été obtenue, par insertion du carbène dans la liaison C-H en position α de l'atome d'oxygène (**Schéma 2**, chemin b).

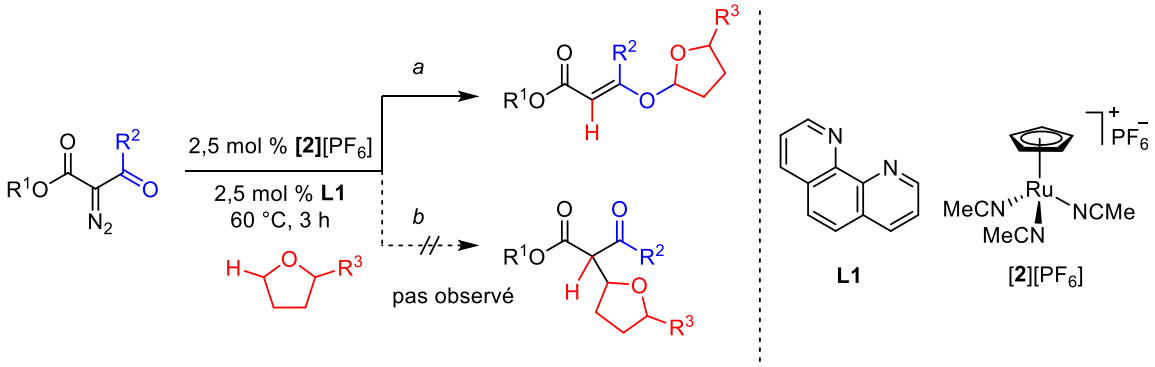

Schéma 2 Réaction d'insertion 1,4-C-H dans le tetrahydrofurane.

[5] (a) Westley, J. W., *Polyether antibiotics : naturally occurring acid ionophores*. M. Dekker: New York, **1982**; (b) Levy, D. E.; Tang, C., *The chemistry of C-glycosides*. 1st ed.; Pergamon: Oxford, OX, U.K. ; Tarrytown, N.Y., U.S.A., **1995**; p xiv, 291 p; (c) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L., *J. Nat. Prod.* **1999**, *62* (3), 504-540; (d) Faul, M. M.; Huff, B. E., *Chem. Rev.* **2000**, *100* (6), 2407-2473; (e) Kang, E. J.; Lee, E., *Chem. Rev.* **2005**, *105* (12), 4348-4378; (f) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S., *Nat. Prod. Rep.* **2005**, *22* (6), 696-716.

[6] (a) Davies, H. M. L.; Hansen, T., *J. Am. Chem. Soc.* **1997**, *119* (38), 9075-9076; (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R., *J. Am. Chem. Soc.* **2000**, *122* (13), 3063-3070; (c) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J., *J. Am. Chem. Soc.* **2002**, *124* (6), 896-897; (d) Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A., *J. Am. Chem. Soc.* **1999**, *121* (27), 6509-6510; (e) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Roldan, M., *Org. Lett.* **2007**, *9* (4), 731-733; (f) Mbuvi, H. M.; Woo, L. K., *Organometallics* **2008**, *27* (4), 637-645; (g) Suematsu, H.; Katsuki, T., *J. Am. Chem. Soc.* **2009**, *131* (40), 14218-14219; (h) Lovely, C. J.; Flores, J. A.; Meng, X. F.; Dias, H. V. R., *Synlett* **2009**, (*1*), 129-132; (i) Fraile, J. M.; Mayoral, J. A.; Ravasio, N.; Roldan, M.; Sordelli, L.; Zaccheria, F., *J. Catal.* **2011**, *281* (2), 273-278.

Ainsi nous avons décrit la formation de nouveaux produits de type énols-acétals, sous contrôle cinétique et en une seule étape (**Schéma 2**, chemin a). A travers ces réactions d'insertion 1,3-C-H, une nouvelle liaison C-O est formée, au lieu d'une liaison C-C, comme largement décrit dans la littérature. La réaction est régiosélective, l'insertion se produisant uniquement au niveau du carbone le moins substitué. D'autre part, elle est aussi stéréosélective, amenant à la formation d'une double liaison avec une configuration *E* exclusivement. Des expériences croisées, en employant un mélange 1:1 entre le THF et le THF-d_8, ont été menées afin de comprendre les aspects mécanistiques de cette transformation. Ces réactions suggèrent un mécanisme concerté pour le transfert d'hydrure. Le réarrangement de ce produit inattendu en adduit classique de réactions d'insertion C-H a été également obtenu à l'aide d'un autre acide de Lewis.

Les époxydes ont ensuite été testés avec une méthodologie analogue. Différents exemples de décompositions de diazo catalysées par des complexes de métaux de transitions en présence d'époxydes ont été décrits dans la littérature et le produit de désoxygénation a été obtenu dans tous les cas comme adduit principal (**Schéma 2**, chemin b).[7]

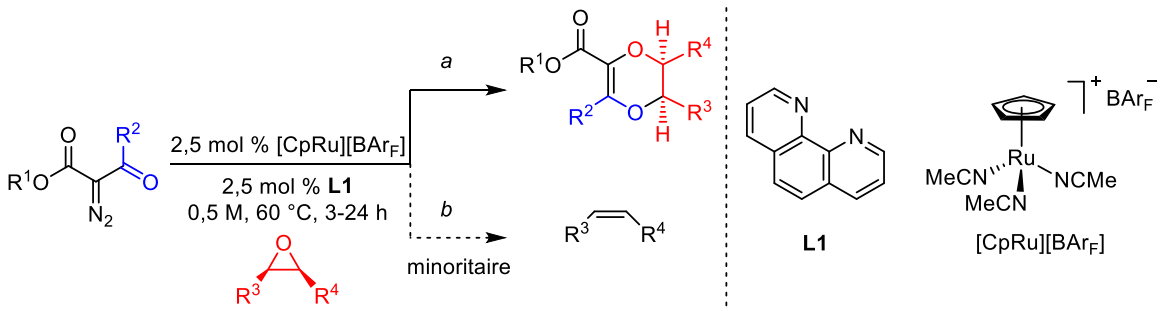

Schéma 3 Réactions d'insertion dans les epoxydes.

Le système catalytique développé au sein du laboratoire nous a permis d'obtenir de nouveaux dioxènes, à travers l'insertion, en une étape, de trois atomes dans une liaison C-O (**Schéma 3**, chemin a). La réaction est parfaitement *syn*-stéréosélective, menant à la formation du produit *cis* en partant de l'époxyde *cis*. D'autre part, elle est aussi régiosélective. De plus, utilisant un époxyde énantioenrichi, l'information chirale est

[7] (a) Nozaki, H.; Takaya, H.; Noyori, R., *Tetrahedron* **1966**, *22* (10), 3393-3401; (b) Martin, M. G.; Ganem, B., *Tetrahedron Lett.* **1984**, *25* (3), 251-254; (c) Quinn, K. J.; Biddick, N. A.; DeChristopher, B. A., *Tetrahedron Lett.* **2006**, *47* (41), 7281-7283; (d) Mack, D. J.; Batory, L. A.; Njardarson, J. T., *Org. Lett.* **2012**, *14* (1), 378-381.

conservée grâce à une rétention de configuration. D'après les observations expérimentales et des études computationnelles, un mécanisme de type S_N1 avec rétention de configuration a été proposé.

Remerciements

Les résultats rapportés dans ce manuscrit ont été obtenus dans le cadre d'un travail de thèse réalisé au sein du laboratoire du Prof. Jérôme Lacour, dans le département de chimie organique de l'Université de Genève, du 1er Mars 2010 au 21 Mars 2014.

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Abbreviations

Ac: acetate

Ar: aryl

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

br(s): broad (singlet)

C: concentration

Cat.: catalyst

conv.: conversion

Cp*: pentamethyl cyclopentadienyl

Cp: cyclopentadienyl

dr: diastereomeric ratio

d: doublet

dd: doublet of doublet

DFT: density functional theory

dt: doublet of triplet

ee: enantiomeric excess

equiv.: equivalent

i-Pr: *iso*-propyl

m: multiplet

Mp: melting point

napht: naphthalene

n-Bu: butyl

NMP:

n-Pr: propyl

Ph: phenyl

phen: 1,10-phenanthroline

ppm: part per million

q: quartet

Rf: retardation factor

s: singlet

t: triplet

t-Bu: *tert*-butyl

Tf: triflate

THF: tetrahydrofuran

TLC: thin layer chromatography

TMSOTf: Trimethylsilyl trifluoromethanesulfonate

TRISPHAT: Tris(tetrachloro-1,2-benzenediolato)phosphate(V)

TRISPHAT-N: bis[3,4,5,6-tetrachlorobenzene-1,2-diolato][5-chloropyridine-2,3-diolato]phosphate anion

VCD: vibrational circular dichroism

Symbols

δ: chemical shift

λ: wave length

J: coupling constant

t_R: retention time

T: temperature

Units

°C: degree Celsius

K: Kelvin

kcal: kilocalorie

g: gram

mg: milligram

µl: microliter

mL: milliliter

µmol: micromole

mmol: millimole

M: molarity

min: minute

h: hour

Hz: Hertz

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1 Introduction

One of the major challenges in synthetic chemistry remains the selective functionalization of heterocycles owing to their prevalence in biological active molecules.[1] Such modifications are not trivial. They often require several steps involving possibly regio-, stereo- and enantioselective controls. As reported in the literature and further detailed in this PhD thesis, this functionalization can be sometimes performed in a single step using metal carbene chemistry.

Transition metal promoted loss of molecular nitrogen from diazo compounds is one of the possible approaches for the formation of metal carbenes.[2] In the last century, this methodology has found numerous applications in a wide range of reactions and it is still nowadays an expanding topic. The versatility of this approach and the high level of selectivity attained in a large number of transformations are the main reasons of its success.

The project of this PhD is the logical extension of the promising results obtained in our group using α-diazo-β-ketoesters and combinations of cationic $[CpRu(CH_3CN)_3]^+$ complexes and diimine ligands as catalysts in classical O-H insertion and condensation reactions.[3] These preliminary results encouraged us to explore the reactivity of ruthenium metal carbenes toward several less basic functional groups such as carbonyl moieties and cyclic ethers. This methodology selectively provided different and original classes of oxygen containing heterocycles in single step processes.

The following introduction will briefly present carbenes structures and their formation from diazo compounds. Then, properties and reactivity of metal carbenes will be considered. Finally, selected examples of reported transformations will be discussed.

---

[1] Heicher, T.; Hauptmann, S., *The chemistry of heterocycles*, Wiley, **2003**.

[2] Doyle, M. P.; McKervey, M. A.; Ye, T., *Modern catalytic methods for organic synthesis with diazo compounds : from cyclopropanes to ylides*, Wiley: New York, **1998**.

[3] Austeri, M.; Rix, D.; Zeghida, W.; Lacour, J., *Org. Lett.* **2011**, *13* (6), 1394-1397.

1.1 Carbene

A carbene is a neutral species containing a carbon atom with only six valence electrons: two associated with the two σ-bonds extending from the central carbon and two nonbonding electrons. In 1855, Geuther and Hermann first proposed the formation of a carbene as reaction intermediate.[4] Since then, a number of theoretical and experimental studies have been carried, trying to validate the existence and to understand the electronic configuration and the geometry around the carbon atom. Considering its electronic structure, a carbene has a two-coordinate carbon atom that can be either linear or bent, each geometry being described by a different hybridization. The linear geometry implies a sp hybridized carbon atom with two nonbonding degenerated p orbitals (**Figure 1.1**).[5]

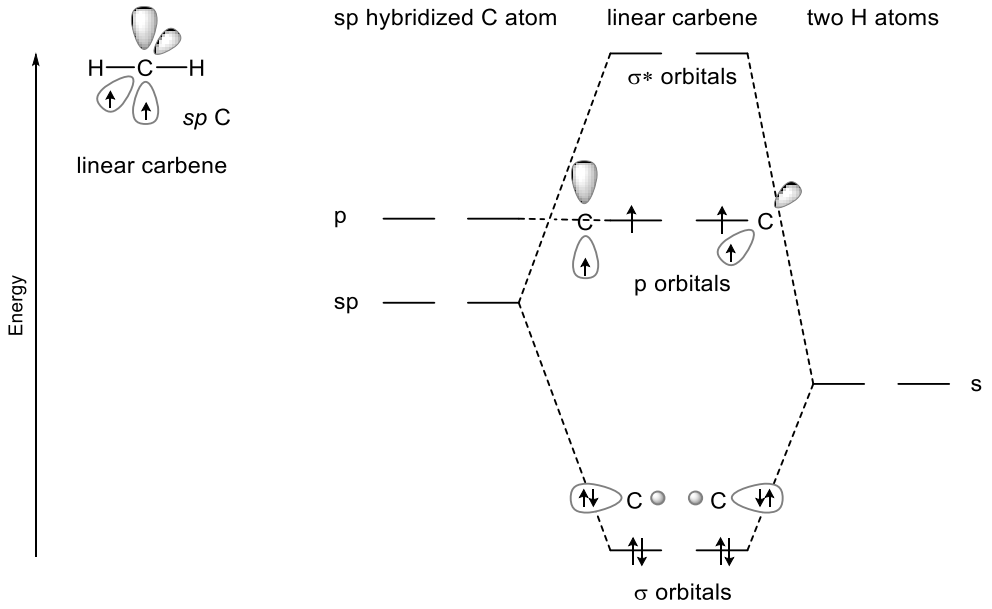


Figure 1.1 Orbital diagram of a linear carbene.

While, for most carbenes a trigonal geometry with a sp^2 hybridization state with three sp^2 orbitals and one p orbital is assumed.[5] Considering the electronic structure of sp^2 hybridized carbenes, they can be divided into two types: singlet and triplet carbenes

[4] Geuther, A.; Hermann, M.; *Liebigs Ann. Chem.* **1855**, *95*, 211.

[5] (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G., *Chem. Rev.* **2000**, *100* (1), 39-91; (b) de Fremont, P.; Marion, N.; Nolan, S. P., *Coord. Chem. Rev.* **2009**, *253* (7-8), 862-892.

(**Figure 1.2**). Singlet carbenes have all the electrons paired in the three sp^2 orbitals and bond angles of 100-110°. In triplet carbenes, on the other hand, two electrons are unpaired with one electron in a sp^2 orbital and the other in a p orbital and bond angles are 130-150°.

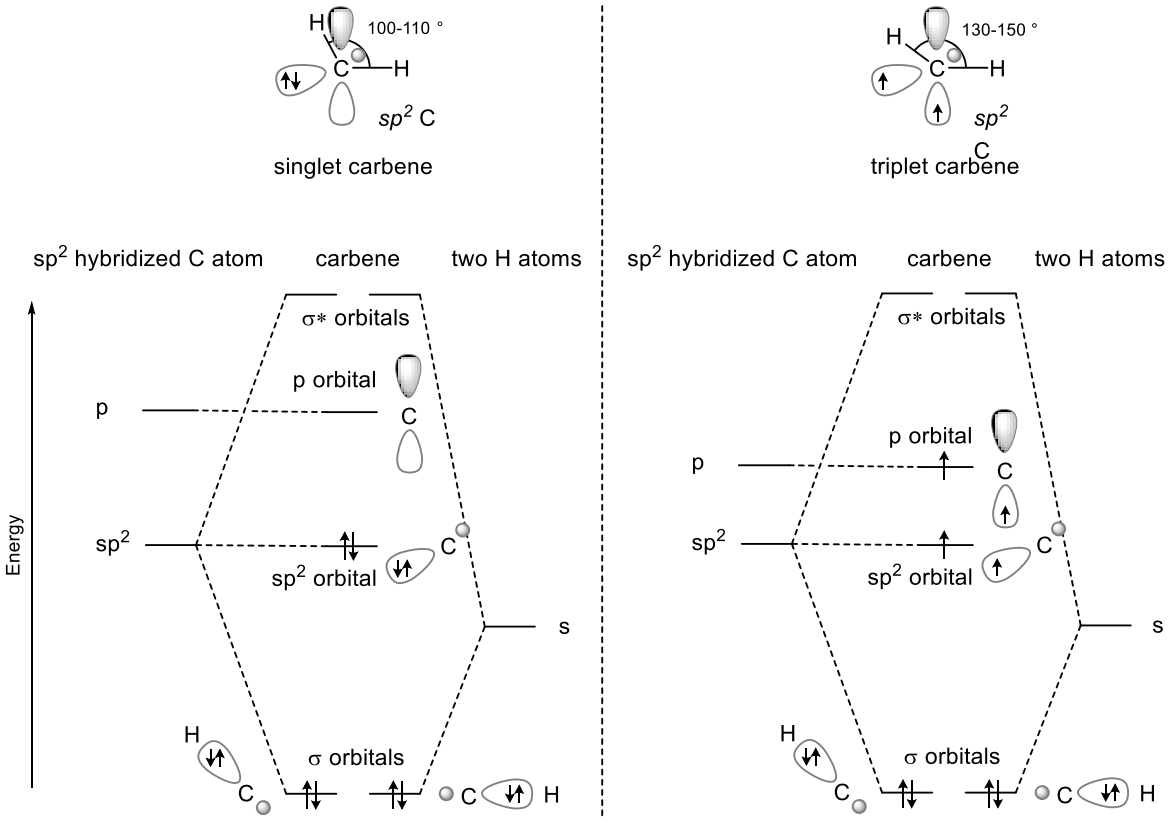


Figure 1.2 Electronic structure of sp^2 singlet and triplet carbenes.

Triplet carbenes are favored when the energy gain bringing the electron in the p orbital down into the sp^2 orbital is not sufficient to overcome the repulsion that exists between two electrons in the same sp^2 orbital (Pauli principle).

Substituents on the carbon atom affect the carbene ground state multiplicity and can determine its nucleophilic or electrophilic character. Their influence can be analysed in terms of electronic and steric effects. Carbenes with two electron-withdrawing substituents are predicted to be linear singlet carbenes (**Figure 1.3a**).[6] σ-Electron-

[6] (a) Schoeller, W. W., *Chem. Commun.* **1980**, (3), 124-125; (b) Pauling, L., *Chem. Commun.* **1980**, (15), 688-689; (c) Irikura, K. K.; Goddard, W. A.; Beauchamp, J. L., *J. Am. Chem. Soc.* **1992**, *114* (1), 48-51.

withdrawing substituents can interact with the partially filled sp orbital of a triplet carbene and inductively stabilize it by increasing its s character and leaving the other p orbital unchanged. The gap between the new σ orbital and the empty p orbital increases and the singlet state is favoured even if the carbenes are linear (**Figure 1.3a**). In contrast, σ-electron-donor substituents induce a small gap which favours the triplet state (**Figure 1.3b**).

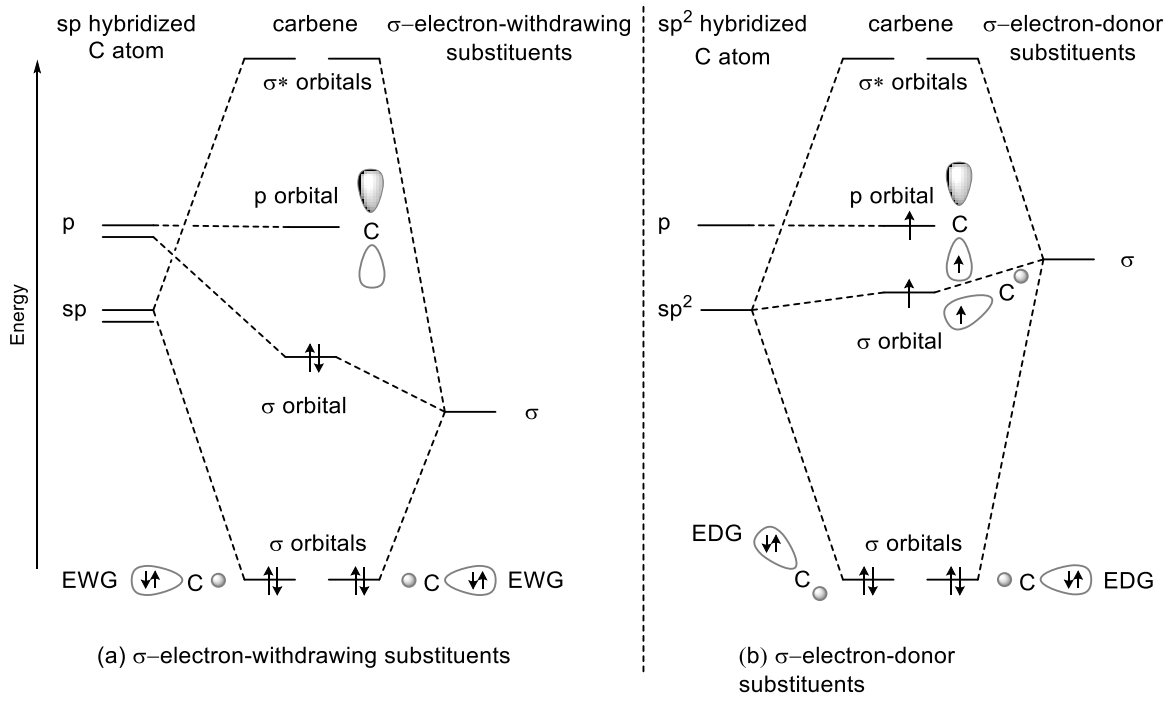


Figure 1.3 Influence of the substituents on carbene ground state multiplicity.

Mesomeric effect can play a significant role as well. π-orbitals of the substituents can interact with the appropriate sp^2 or p orbital of the carbene. The effect of this interaction is described in **Figure 1.4**. The empty π-orbitals of the electron-withdrawing substituents can interact with the p_y orbital of the carbon (the p_x is not on the right orientation and is not affected by this interaction), making it lower in energy. This interaction results in a polarized two-electrons three-centers π-system in which the electron density on the carbon atom decreases and the carbene has an electrophilic character (**Figure 1.4a**). On the contrary, carbenes with two π-electron-donor substituents are predicted to be bent singlet carbenes.[6] The lone pair of electron-donor substituents can interact with the p

orbital of the carbon increasing the gap energy between the full π and the vacant π* orbitals and favouring the singlet state. The relative position of the sp^2 and the π orbital depends on the electronegativity of the substituent atom compared to that one of the carbon. In any case, donation of the electron-donor substituents results in a polarised four-electrons three-centers. The C-EDG bonds acquire a double bond character with a partial negative charge on the carbon and a partial positive charge on the substituents. Consequentially, the carbon atom of the carbene is more electron-rich and its nucleophilicity increases (**Figure 1.4b**).[5a]

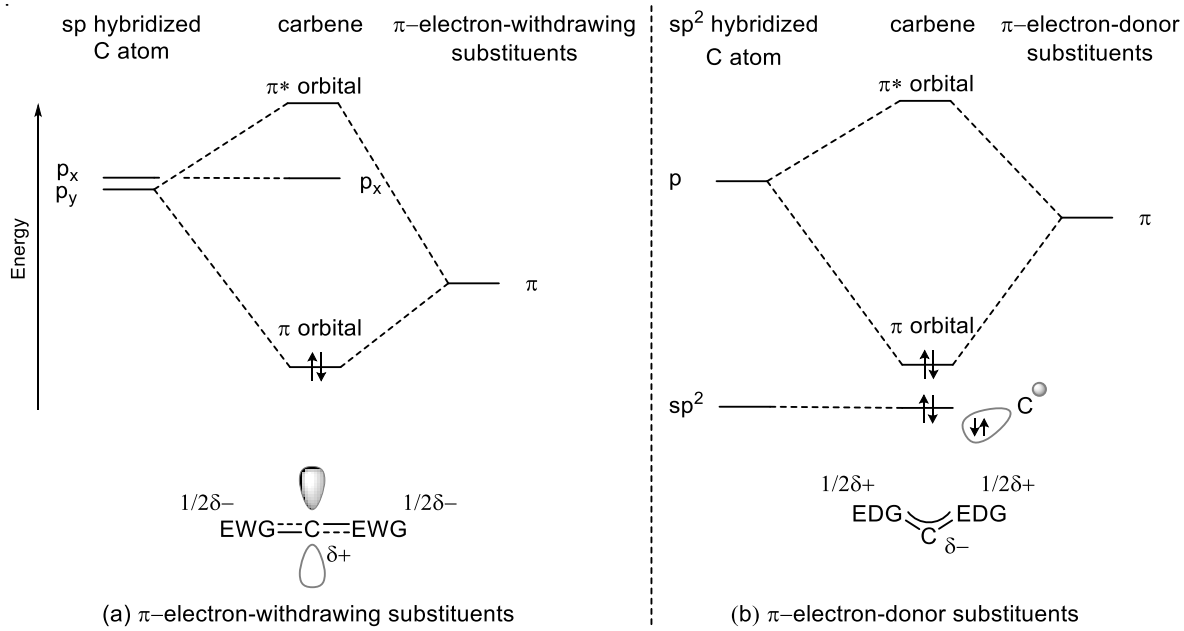


Figure 1.4 Influence of the mesomeric effect. Bonding orbitals are omitted to simplify the scheme.

1.2 Metal carbenes

Carbenes are generally very reactive species and, importantly, they can be stabilized by coordination to a transition metal. When coordinated, these species can act ether as reactive intermediate or serve as supporting ligands.[5b] That is the case, for instance, of N-heterocyclic carbenes. These species are sometimes stable enough to be isolated in their metal free form, as first reported by Bertrand in 1988[7] and Arduengo in 1991.[8] Once

[7] Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G., *J. Am. Chem. Soc.* **1988**, *110* (19), 6463-6466.

coordinated to a metal center, NHCs lead to the formation of well-defined organometallic complexes that can be used for catalysis.[9]

Following the electronic structure classification of the carbene and the nature of the metal, these complexes have been categorized into two types, Schrock complexes[10] and Fischer complexes[11] from the two chemists that first characterized an example of each carbene complex.

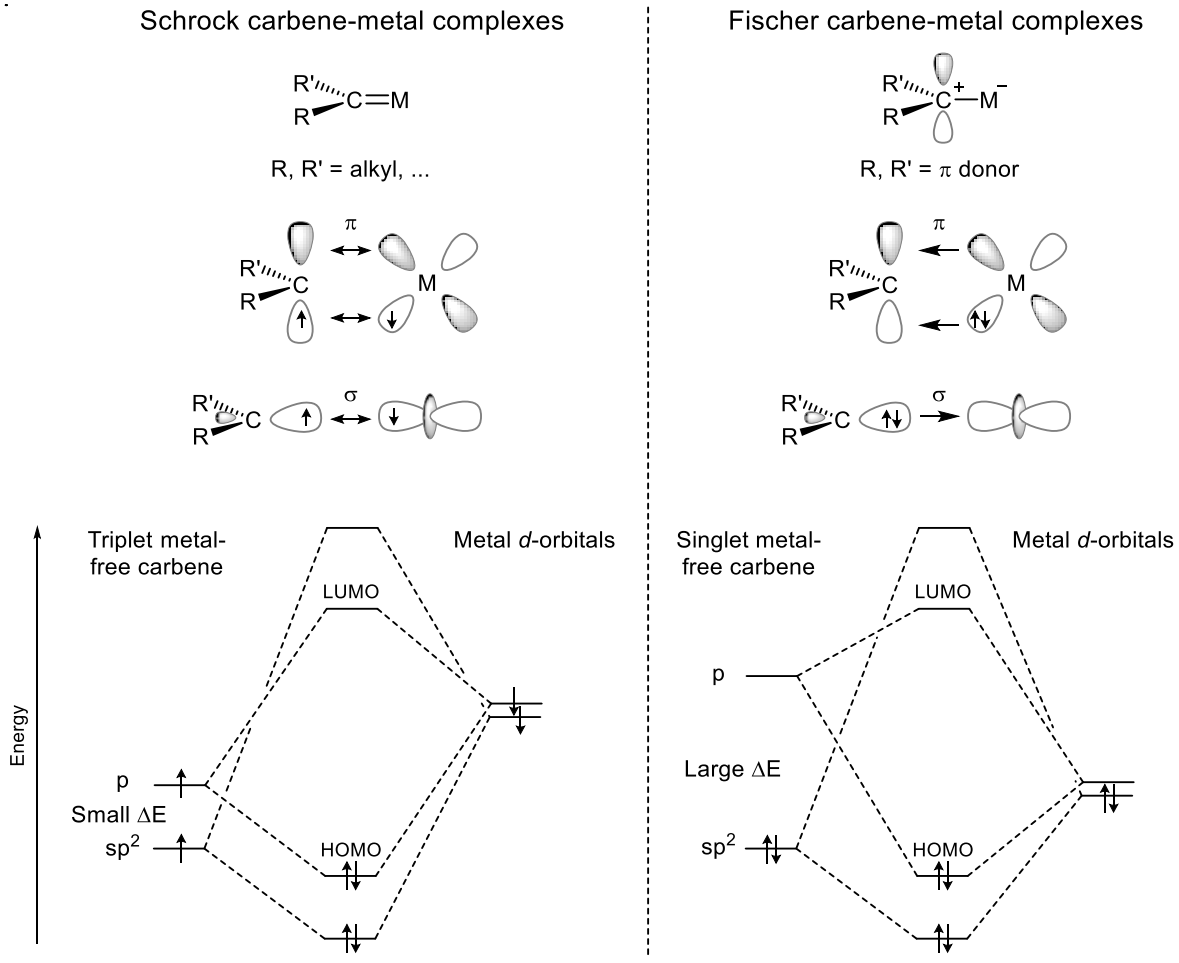


Figure 1.5 Schematic representation of Schrock and Fischer metal-carbene complexes.

[8] Arduengo, A. J.; Harlow, R. L.; Kline, M., *J. Am. Chem. Soc.* **1991**, *113* (1), 361-363.

[9] Bazinet, P.; Ong, T. G.; O'Brien, J. S.; Lavoie, N.; Bell, E.; Yap, G. P. A.; Korobkov, I.; Richeson, D. S., *Organometallics* **2007**, *26* (11), 2885-2895.

[10] Schrock, R. R., *J. Am. Chem. Soc.* **1974**, *96* (21), 6796-6797.

[11] Fischer, E. O.; Maasbol, A., *Angew. Chem. Int. Ed.* **1964**, *3* (8), 580-581.

Schrock metal carbene complexes come from the interaction between a triplet carbene and an early or middle transition metal (groups 3 to 6) with a high oxidation state (**Figure 1.5**).[12] The d orbitals of early transition metals are high in energy compared to the orbitals of late transition metals. The difference in energy between the sp^2 and p orbitals of the carbene is low. The LUMO resulting from the interaction of this two species is closer in energy to the metal orbital and has indeed a metal character. The HOMO is closer in energy to the carbene orbitals so the electron density is more located on the carbene and the carbon has a nucleophilic character. For that reason, Schrock carbenes typically react at the carbene center with electrophiles. The metal-carbon bond has a strong character of double bond and the barrier rotation in these complexes is lower than that of an alkene but still around 19 Kcal/mol.[13]

Fischer metal carbene complexes usually come from the interaction between a singlet carbene and a late transition metal (groups 6 to 8) with a low oxidation state (**Figure 1.5**). The d-orbitals of late transition metals are lower in energy compared to the orbitals of early transition metals. The difference in energy between the sp^2 and p orbitals of the metals-free carbene is high. σ-Donation of the full sp^2 orbital of the carbene toward the empty d orbital of the metal is predominant and the HOMO has a metal character. The π-back-donating contribution of the d full orbital of the metal toward the free p orbital of the carbene is possible but not very extensive. For that reason the carbon center of the carbene has an electrophilic character and the double bond character is not very pronounced with a typical barrier to rotation of 8-10 Kcal/mol.[13] The most famous Fisher carbenes are probably those derived from the interaction of N-Heterocyclic carbenes (NHCs or Arduengo carbenes)[8] with transition metals.[9]

Of particular interest for this work is the specific case of non-heteroatom late-transition metal carbenes, species with two carbon atoms bonded to the carbene center. These species can be considered as a third type of metal carbene complex, electrophilic at the carbon centre and with some borderline characteristics between Fisher and Schrock type carbenes.[5b] Usually those complexes are highly reactive toward nucleophilic attack

[12] Hartwig, J.F., *Organotransition metal chemistry: from bonding to catalysis*; University Science Books **2010**.

[13] Taylor, T. E.; Hall, M. B., *J. Am. Chem. Soc.* **1984**, *106* (6), 1576-1584.

at the carbene carbon atom and they result too reactive to be isolated.[14] In 2013, Davies and co-workers have observed and characterized by different spectroscopic techniques a dirhodium donor-acceptor carbene complex that was found to be stable for 20 hours at 0 °C in chloroform solution.[15]

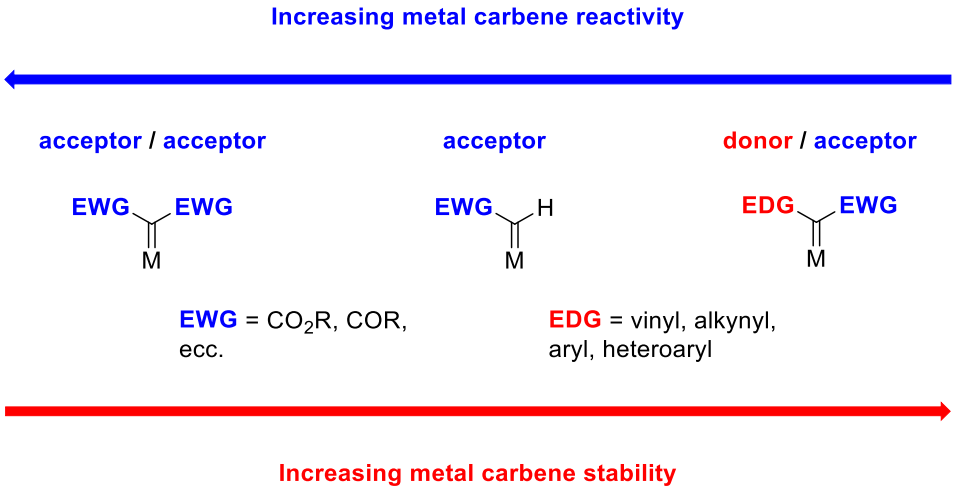


Figure 1.6 Classification, stability and reactivity of electrophilic metal carbene complexes toward nucleophilic attack at the carbene carbon center.

Again, substituents on the carbon atom have a dramatic influence on the nature and the reactivity of the metal carbene-complex. For that reason, electrophilic metal-carbene complexes have also been classified according to the substituents next to the carbon center (**Figure 1.6**).[16] In general, it has been observed that reactivity increases with the electron withdrawing ability of the substituents because it grows the electrophilic character of the carbene carbon atom.[2]

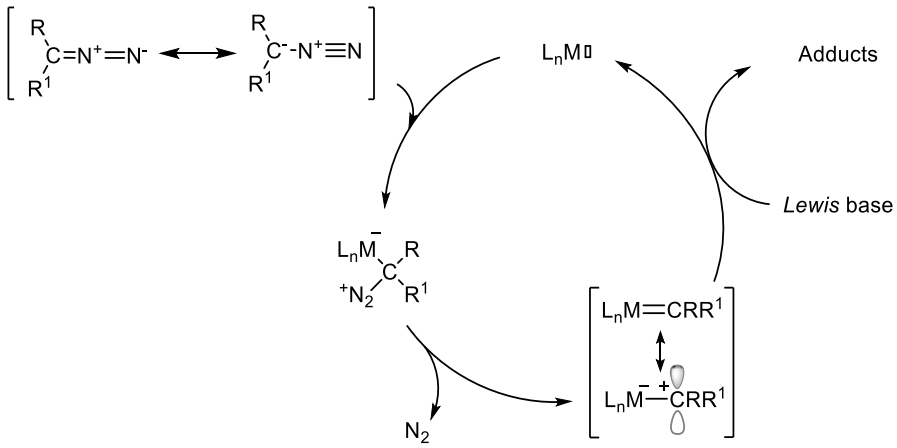
[14] Nakamura, E.; Yoshikai, N.; Yamanaka, M., *J. Am. Chem. Soc.* **2002**, *124* (24), 7181-7192.

[15] Kornecki, K. P.; Briones, J. F.; Boyarskikh, V.; Fullilove, F.; Autschbach, J.; Schrote, K. E.; Lancaster, K. M.; Davies, H. M. L.; Berry, J. F., *Science* **2013**, *342*, 351-354.

[16] Davies, H. M. L.; Beckwith, R. E. J., *Chem. Rev.* **2003**, *103* (8), 2861-2903.

1.3 Synthesis of non-heteroatom metal carbenes from diazo compounds

A large number of different strategies have been developed to prepare non-heteroatom metal carbenes using as starting reagents a variety of moieties such as cyclopropenes,[17] iodine(III) compounds,[18] alkynes[19] and triazoles.[20] In the present manuscript we are particularly interested in the use of diazo decomposition catalyzed by metal complexes.[2] In fact, diazo reagents are important molecules used extensively in organic synthesis due to their readily availability and successful applications in a wide range of metal carbene reactions.[2]



Scheme 1.1 General mechanism for generation of metal-carbene complexes from diazo compounds.

The mechanistic rational described in **Scheme 1.1** is generally accepted for the metal induced decomposition of diazo compounds. Electrophilic coordination of the unsaturated Lewis acid metal catalyst onto the diazo compound generates a zwitterionic intermediate that, after spontaneous loss of molecular nitrogen, forms a highly reactive metal carbene. Transfer of the electrophilic carbene entity to a Lewis base regenerates the catalyst

[17] (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W., *J. Am. Chem. Soc.* **1992**, *114* (10), 3974-3975; (b) Gagne, M. R.; Grubbs, R. H.; Feldman, J.; Ziller, J. W., *Organometallics* **1992**, *11* (12), 3933-3935.

[18] Matveeva, E. D.; Proskurnina, M. V.; Zefirov, N. S., *Heteroatom. Chem.* **2006**, *17* (6), 595-617.

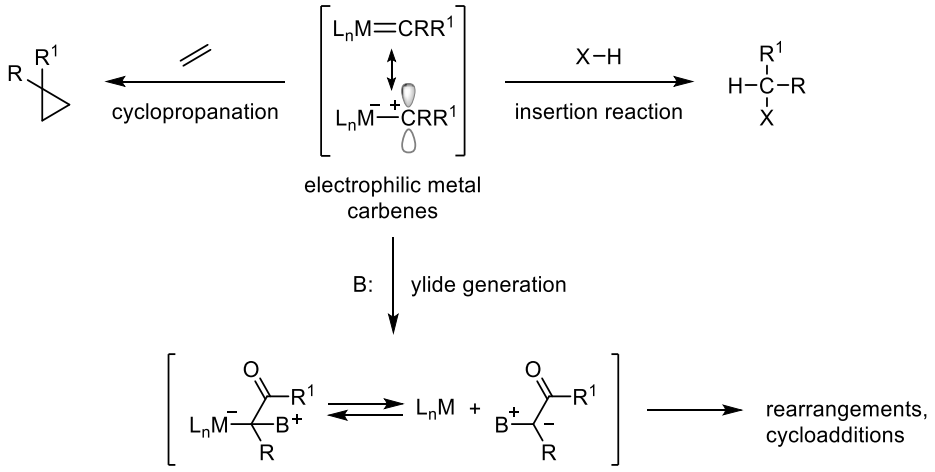
[19] Ye, L. W.; Cui, L.; Zhang, G. Z.; Zhang, L. M., *J. Am. Chem. Soc.* **2010**, *132* (10), 3258-3259.

[20] Gulevich, A. V.; Gevorgyan, V., *Angew. Chem. Int. Ed.* **2013**, *52* (5), 1371-1373.

completing the catalytic cycle. Depending on the nature of the Lewis base, many useful transformations can take place such as dimerization, metathesis, cyclopropanation, cycloaddition, insertion, ylide generation and subsequent rearrangement/macrocyclization reactions.[2,16,21,22]

1.4 Reactivity of metal carbenes

The most important reaction of metal carbene complexes is possibly the olefin metathesis but this field is so vast and, as it is not the object of this thesis, it will not be detailed in this introduction. On the contrary, the mechanism of the main reactions of interest for this manuscript (cyclopropanation, insertion reactions and ylide formation, **Scheme 1.2**) will be briefly discussed before detailing more deeply the reactivity of the main metals complexes.



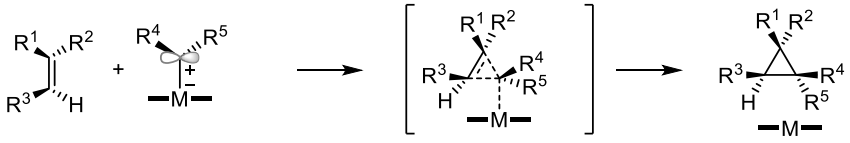
Scheme 1.2 Classical reactivity of electrophilic metal carbenes.

[21] (a) Padwa, A.; Weingarten, M. D., *Chem. Rev.* **1996**, *96* (1), 223-269; (b) Doyle, M. P.; Forbes, D. C., *Chem. Rev.* **1998**, *98* (2), 911-935; (c) Zhang, Z. H.; Wang, J. B., *Tetrahedron* **2008**, *64* (28), 6577-6605; (d) Diaz-Requejo, M. M.; Perez, P. J., *J. Organomet. Chem.* **2005**, *690* (24-25), 5441-5450.

[22] Grubbs, R. H., *Handbook of methatesis*, Wiley-VCH, **2003**.

1.4.1 Cyclopropanations

Non-heteroatom electrophilic metal carbenes react with electron rich alkenes to give cyclopropanes.[23] Only few examples for electron poor olefins have been reported.[24] This is one of the most important reactions of metal carbenes and one of the most significant ways of selectively making cyclopropanes. Due to the widely presence of three-members rings in many biologically active molecules, this transformation has been extensively studied.[25,26] A definitive mechanism for this reaction has not been established but a commonly invoked mechanistic rational is described in **Scheme 1.3**.[2, 25g, 27]



Scheme 1.3 General mechanism of cyclopropanation.

It is generally accepted that with most catalysts (with the exception of copper triflate[28]) the attack of the alkene on the metal carbene occurs without prior coordination of the double bond to the metal. For that reason the respective orientation of the olefin and of the carbene during the approach of the alkene to the metal carbene complex determines the regio and stereochemistry of the cyclopropanation. Due to the steric hindrance of the substituents on the carbon atom of the carbene and of the ligands of the

[23] Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B., *Chem. Rev.* **2003,** *103* (4), 977-1050.

[24] Wang, H.; Guptill, D. M.; Varela-Alvarez, A.; Musaev, D. G.; Davies, H. M. L., Chem. Sci. **2013**, *4*, 2844-2850.

[25] (a) Burgess, K.; Ho, K. K.; Moyesherman, D., *Synlett* **1994**, (8), 575-583; (b) Wessjohann, L. A.; Brandt, W.; Thiemann, T., *Chem. Rev.* **2003**, *103* (4), 1625-1647; (c) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A., *Chem. Rev.* **1997**, *97* (3), 787-828; (d) Brackmann, F.; de Meijere, A., *Chem. Rev.* **2007**, *107* (11), 4538-4583; (e) Reichelt, A.; Martin, S. F., *Acc. Chem. Res.* **2006**, *39* (7), 433-442; (f) Gnad, F.; Reiser, O., *Chem. Rev.* **2003**, *103* (4), 1603-1623; (g) Wasserman, H. H.; Berdahl, D. R.; Lu, T.-J., *The Chemistry of Cyclopropanones. In Cyclopropyl Group and (1987)*, John Wiley & Sons, Ltd**: 2005**; pp 1455-1532; (h) Burke, S. D.; Grieco, P. A., *Intramolecular Reactions of Diazocarbonyl Compounds. In Organic Reactions*, John Wiley & Sons, Inc.: **2004**.

[26] For a review: Rappoport, Z.,*The chemistry of the cyclopropyl group*, Wiley, **1987**, parts 1 and 2.

[27] Davies, H. M. L.; Antoulinakis, E. G., *Intermolecular Metal-Catalyzed Carbenoid Cyclopropanations. In Organic Reactions*, John Wiley & Sons, Inc.: **2004**.

[28] Salomon, R. G.; Kochi, J. K., *J. Am. Chem. Soc.* **1973**, *95* (10), 3300-3310.

metal complex, monosubstituted ethylenes (R^2 = R^3 = H) would have the larger substituent R^1 as far as possible from the metal center, leading to the formation of the *trans*-cyclopropane as main product.

In the specific case of carbonyl diazo compounds (R^4 = COR) steric interactions between the substituents of the olefin and the catalyst are usually much more effective than the interactions with the COR group. The lone pair of the oxygen of the carbonyl group can in contrast stabilize the developing electrophilic carbon of the reacting olefin. The transition-state reported in **Figure 1.7** takes into account all these factors.[2]

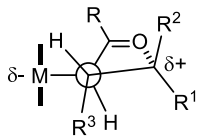
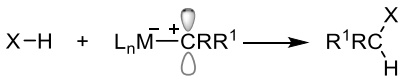


Figure 1.7 Transition state.

In this model proposed by Doyle, the formation of the two new C-C bonds is considered to occur in a concomitant but non-sychronous way.

1.4.2 C-H/C-X insertion reactions

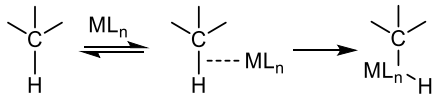
Metal carbenes have proven to be highly useful for insertion into carbon-hydrogen and heteroatom-hydrogen bonds (**Scheme 1.4**).



Scheme 1.4 X-H insertion reactions

C-H bond functionalization is certainly one of the most active fields in chemical research.[29] This effort is justified by the desire to make more useful and complex compounds from cheap and abundant hydrocarbons. One of the big challenges in C-H functionalization is indeed the control of site selectivity, because of the ubiquitous presence of C-H bonds in all organic molecules. Furthermore, this strategy can lead to a completely different approach to the classical organic synthesis that usually consists in several steps modification of pre-existing functional groups. In fact, the activation of

generally unreactive bonds allows the direct introduction of functional groups onto a molecule where none existed before and that in a single step.[29] The classical methods for replacing a C-H with a C-X bond require the presence of an activating group next to the targeted C-H bond or strong reaction conditions that compromise the selectivity. Organometallic chemists have focused much attention on developing C-H activation processes to find a solution in the oxidative addition reactions in which a highly reactive metal complex inserts into a C-H bond.[30,31]This transformation is considered to proceed in two elemental steps (**Scheme 1.5**). The metal coordinates in an equilibrium process to the C-H bond than it is formally oxidized and inserted to form the reactive C-M-H adduct.



Scheme 1.5 General mechanism for oxidative addition.

Metal carbene induced C-H insertions are useful alternative to the oxidative addition strategy.[32] From a mechanistic point of view, in this case the electrophilic carbene is the intermediate that inserts into the C-H bond. The mechanistic rational described in **Scheme 1.6** was first proposed by Doyle[33] and later confirmed by computational studies.[14] In detail, the catalytic cycle consists of three steps: first the metal catalyzed diazo decomposition with extrusion of a molecular nitrogen, then the hydride transfer and finally the C-C bond formation while the metal is dissociating from the carbene. It is commonly accepted that the diazo decomposition is the rate determining step and that the hydride transfer/C-C bond formation occurs in a concerted but nonsynchronous way,

[29] (a) Davies, H. M. L.; Manning, J. R., *Nature* **2008**, *451* (7177), 417-424; (b) Davies, H. M. L.; Morton, D., *Chem. Soc. Rev.* **2011**, *40* (4), 1857-1869; (c) Bergman, R. G., *Nature* **2007**, *446* (7134), 391-3; (d) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L., *Chem. Rev.* **2010**, *110* (2), 704-724; (e) Zhang, S. Y.; Zhang, F. M.; Tu, Y. Q., *Chem. Soc. Rev.* **2011**, *40* (4), 1937-1949.

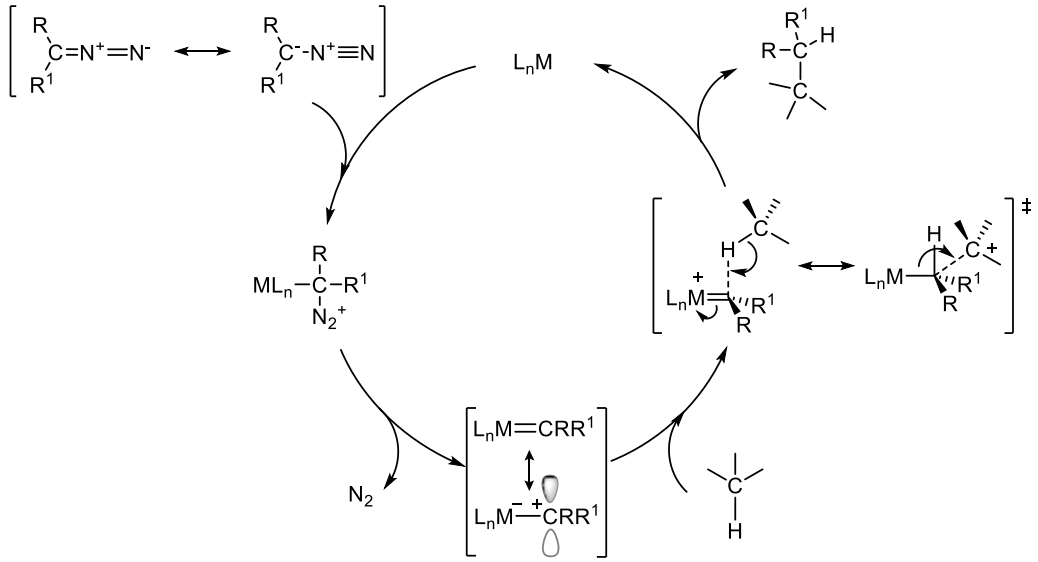
[30] Abel, W.; Gordon F.; Stone, A.; Wilkinson G., *Comprehensive organometallic chemistry: a review of the literature*, 1982-1994 / eds. in chief Edward.

[31] Hegedus, L. S.; Söderberg, B. C. G., *Transition metals in the synthesis of complex organic molecules*, 3rd edition, University science books, **2010**.

[32] Diaz-Requejo, M. M.; Perez, P. J., *Chem. Rev.* **2008**, *108* (8), 3379-3394.

[33] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M., *J. Am. Chem. Soc.* **1993**, *115* (3), 958-964.

through a transition state depicted as two resonance structures.[14] Overlap of the σ orbital of the C-H bond occurs with the empty p orbital of the carbon atom of the carbene.[33]



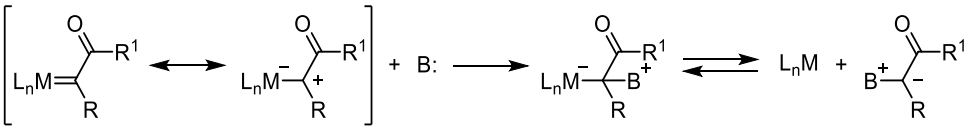
Scheme 1.6 General mechanism for C-H insertion of carbene.

Apart from C-H insertion reactions, metal carbenes can undergo a large array of X-H insertions, where X is a halogen, nitrogen, oxygen, phosphorus, selenium, silicon or sulphur atom.[2,34] This strategy represents one of the most efficient methods to form C-X bonds. The mechanism of these insertion reactions can change with the polarity of the X-H bond. The low polarity of the Si-H bond, comparable to that of the C-H bond, makes those two transformations occur with the same mechanism;[2] on the other hand, other insertion processes into polar X-H bonds are probably better described as stepwise processes.[2] Even if the product is always formally the adduct of insertion of a carbene into a X-H bond, these transformations can be mechanistically different ranging from uncatalyzed electrophilic attack to thermo-, photo- or metal induced ylide formation.[34b]

[34] (a) Zhu, S. F.; Zhou, Q. L., *Acc. Chem. Res.* **2012**, *45* (8), 1365-1377; (b) Gillingham, D.; Fei, N., *Chem. Soc. Rev.* **2013**, *42* (12), 4918-4931.

1.4.3 Ylide generation

As mentioned earlier, electron deficient metal carbenes can interact with a Lewis base (B:) to give free ylide species which can be in equilibrium with metal complexes (**Scheme 1.7**).[21c]



Scheme 1.7 General mechanism for ylide formation.

Commonly, the Lewis bases used for this transformation are alcohols, ethers, amines, imines sulphides and carbonyl compounds. In all this cases, the resulting ylide intermediate is highly reactive and it undergoes a vast range of reactions to give more stable products. The most usual transformations reported are 1,2-shift, 2,3-sigmatropic rearrangements of an allylic or allenic ylide, dipolar cycloadditions and β-hydride eliminations.[2,21a-c,35] Some examples of such important transformations will be detailed in the following paragraphs. The reactivity of carbonyl ylides will be deeper described in the introduction of Chapter 3.

1.5 Classical metal catalysts for diazo decomposition

As evidenced by the mechanism described in **Scheme 1.1**, transition metals used for the decomposition of diazo reagents and the formation of metal carbenes have to be Lewis acidic and coordinatively unsaturated. Late transition metals such as copper, cobalt, iron, palladium, rhodium and ruthenium fit these requirements. In particular, they can be used as salts or as complexes, with ligands coordinated to the metal. Moreover, the nature of the metal center and of the surrounding ligands (electron rich, electron poor,

[35] Padwa, A.; Hornbuckle, S. F., *Chem. Rev.* **1991**, *91* (3), 263-309.

steric hindrance) have a strong influence on the transformations observed.[2] The most commonly used metal complexes will now be briefly examined.[21b,36]

1.5.1 Copper salts and complexes

Copper bronze,[37] copper(II) oxide and copper(II) sulphate[38] have been the first employed as heterogeneous catalysts for diazo decomposition.[39] Only in 1960s some soluble catalysts such as copper(I) chloride,[40] copper(I) triaryl phosphate[41] and copper(II) acetylacetonate[40] were developed. The introduction of copper(I) triflate by Salomon and Kochi in 1973 represented an important breakthrough in the understanding of the mechanism of copper metal carbenes reactions.[28] In fact, it was demonstrated that copper(II) was reduced *in situ* to copper(I) which was able to form the metal carbene. Historically, copper(II) complexes were favoured due to their better stability and easier preparation compared to air-sensitive copper(I) derivatives.

In general, two bidentate ligands are complexed to copper(II) ions and, after reduction to copper(I), it is considered that only one remains coordinated to the metal.[2] This argument has been used later when enantiopure ligands were introduced to perform enantioselective reactions. Among the many ligands used in this field, salycilamines,[42] bis-oxazolines[43] and bis-bipyridines[44] reported in **Figure 1.8** deserve to be highlighted.

[36] Doyle, M. P., *Chem. Rev.* **1986**, *86* (5), 919-939.

[37] (a) Silberrad, O.; Roy, C. S., *J Chem Soc* **1906**, *89*, 179-182; (b) Loose, A., *J Praktische Chemie* **1909**, *79* (11), 505-510.

[38] (a) Lorey, K., *J Praktische Chemie* **1930**, *124* (4/7), 185-190; (b) Grundmann, C., *Justus Liebigs Annalen Der Chemie* **1938**, *536*, 29-36.

[39] Kirmse, W., *Angew. Chem. Int. Ed.* **2003**, *42* (10), 1088-1093.

[40] Moser, W. R., *J. Am. Chem. Soc.* **1969**, *91* (5), 1141-1146.

[41] (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R., *Tetrahedron Lett.* **1966**, (43), 5239-5244; (b) Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R., *Tetrahedron Lett.* **1966**, (1), 59-62.

[42] Aratani, T., *Pure Appl. Chem.* **1985**, *57* (12), 1839-1844.

[43] (a) Lowenthal, R. E.; Masamune, S., *Tetrahedron Lett.* **1991**, *32* (50), 7373-7376; (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M., *J. Am. Chem. Soc.* **1991**, *113* (2), 726-728; (c) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A., *Helv Chim Acta* **1991**, *74* (1), 232-240.

[44] (a) Ito, K.; Katsuki, T., *Tetrahedron Lett.* **1993**, *34* (16), 2661-2664; (b) Ito, K.; Yoshitake, M.; Katsuki, T., *Tetrahedron* **1996**, *52* (11), 3905-3920.

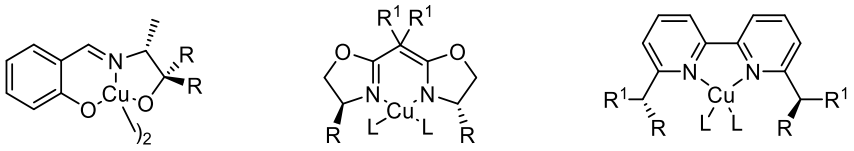
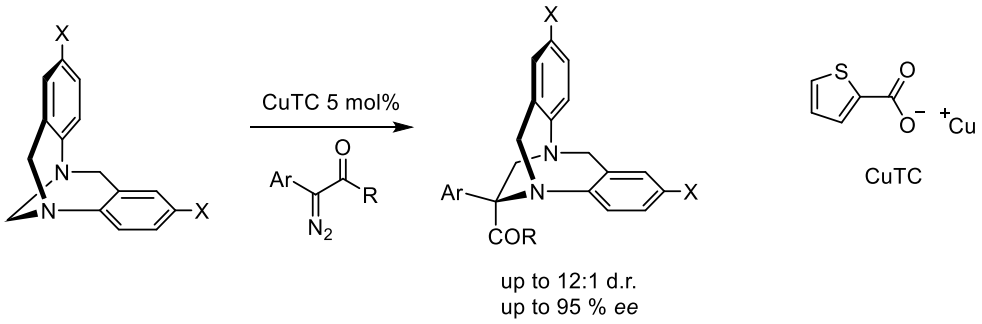


Figure 1.8 Chiral copper catalysts for diazo decomposition.

In fact, copper catalysts have been extensively used for carbene addition,[21d] cyclopropanation[2,45] and insertion reactions.[21d,34a] Recently our group has shown that Copper(I) thiophene-2-carboxylate (CuTC) is particularly effective to generate nitrogen ylide from diazo compounds.[46] It allowed the synthesis of configurationally stable *ethano*-bridged Tröger bases providing good levels of diastereoselectivity (d.r. up to 12:1) and enantiocontrol (*ee* up to 95 %) with aryl diazoketone precursors (**Scheme 1.8**).



Scheme 1.8 Copper catalyzed synthesis of *ethano*-Tröger bases.

1.5.2 Rhodium(II) complexes

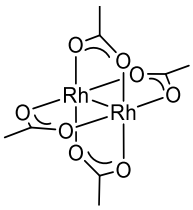


Figure 1.9 Dirhodium(II) tetraacetate.

[45] Doyle, M. P.; Peterson, C. S.; Parker, D. L., *Angew. Chem. Int. Edit.* **1996**, *35* (12), 1334-1336.

[46] Sharma, A.; Besnard, C.; Guenee, L.; Lacour, J., *Org. Biomol. Chem.* **2012**, *10* (5), 966-969.

Dirhodium(II) tetraacetate (**Figure 1.9**) was first reported in 1973 by Teyssie and co-workers for the catalytic decomposition of diazo compounds.[47] Since then, this complex has become the most extensively used catalyst for carbene reactions owning to its general applicability, stability and easily preparation from relatively cheap precursors. It presents a D_{4h} symmetry with four bridging acetate ligands, a vacant site per metal atom and an octahedral geometry; the external part is electron rich while the internal one is electron deficient. Replacing the acetates with other carboxylate ligands provides an easy access for fine tuning of the electronic properties of the metal complexes allowing a modulation of their reactivity. This strategy led in the 1990s to the preparation of chiral dirhodium(II) catalysts. Brunner,[48] McKervey,[49] Ikegami and Hashimoto[50] independently developed complexes possessing chiral carboxylate ligands exploiting the chirality of amino acids or, more generally, α-substituted carboxylic acids (**Figure 1.10**).

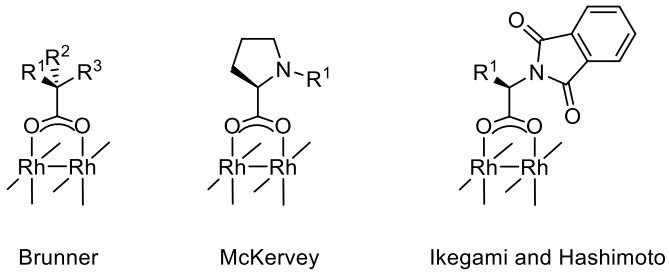


Figure 1.10 Examples of chiral dirhodium(II) carboxylate catalysts.

An example of highly enantio- and diastereoselective cyclopropanation promoted by a dirhodium(II) complex having such chiral carboxylate ligands was reported by Charette and co-workers for instance (**Scheme 1.9**).[51]

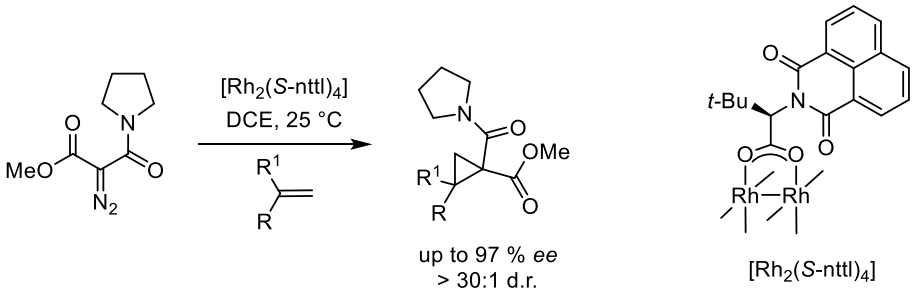
[47] Paulisse.R; Reimling.H; Hayez, E.; Hubert, A. J.; Teyssie, P., *Tetrahedron Lett.* **1973**, (24), 2233-2236.

[48] Brunner, H.; Kluschanzoff, H.; Wutz, K., *B. Soc. Chim. Belg.* **1989**, *98* (1), 63-72.

[49] Kennedy, M.; Mckervey, M. A.; Maguire, A. R.; Roos, G. H. P., *J. Chem. Soc. Chem. Commun.* **1990**, (5), 361-362.

[50] Hashimoto, S.; Watanabe, N.; Ikegami, S., *Tetrahedron Lett.* **1990**, *31* (36), 5173-5174.

[51] Marcoux, D.; Charette, A. B., *Angew. Chem. Int. Ed.* **2008**, *47* (52), 10155-10158.



Scheme 1.9 Asymmetric cyclopropanation of alkenes.

Dirhodium(II) carboxamidates represent another important class of catalysts for diazo decomposition. Excellent enantioselectivities were achieved with chiral variants that have been developed by Doyle, Müller and co-workers.[52] Their structures can be divided into four main families: pyrrolidinone,[53] oxazolidinone,[54] imidazolidinone[55] and azetidinone (**Figure 1.11**).[56] All of them are bonded to the rhodium through an oxygen and a nitrogen atom. Their rigid structure, compared to the carboxylate derivatives, and their different electrophilicity strongly influence reactivity and selectivity in carbene transformations.[57]

[52] (a) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T., *Tetrahedron Lett.* **1990**, *31* (46), 6613-6616; (b) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R., *J. Am. Chem. Soc.* **1993**, *115* (22), 9968-9978.

[53] Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J., *Org. Synth.* **1996**, *73*, 13-24.

[54] (a) Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Muller, P.; Bernardinelli, G.; Ene, D.; Motallebi, S., *Helv. Chim. Acta* **1993**, *76* (6), 2227-2235; (b) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Muller, P., *J. Am. Chem. Soc.* **1991**, *113* (4), 1423-1424.

[55] Doyle, M. P.; Zhou, Q. L.; Raab, C. E.; Roos, G. H. P.; Simonsen, S. H.; Lynch, V., *Inorg Chem* **1996**, *35* (21), 6064-6073.

[56] Doyle, M. P.; Hu, W. H.; Phillips, I. M.; Moody, C. J.; Pepper, A. G.; Slawin, A. M. Z., *Adv. Synth. Catal.* **2001**, *343* (1), 112-117.

[57] (a) Im, C. Y.; Okuyama, T.; Sugimura, T., *Chem. Lett.* **2007**, *36* (2), 314-315; (b) Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, I. C., *Tetrahedron* **1998**, *54* (33), 9689-9700; (c) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P.; Semones, M. A.; Padwa, A.; Richards, I. C., *Tetrahedron* **1996**, *52* (7), 2489-2514; (d) Cox, G. G.; Moody, C. J.; Austin, D. J.; Padwa, A., *Tetrahedron* **1993,** *49* (23), 5109-5126; (e) Padwa, A.; Austin, D. J., *Angew. Chem. Int. Edit.* **1994**, *33* (18), 1797-1815; (f) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N., *J. Am. Chem. Soc.* **1992**, *114* (5), 1874-1876.

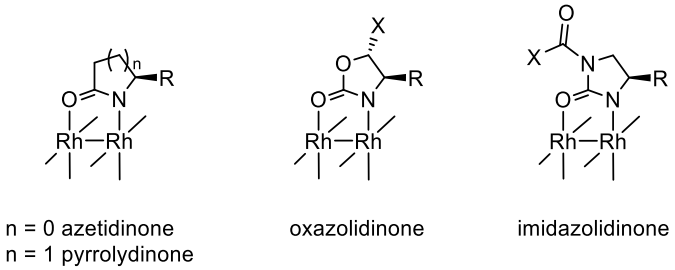
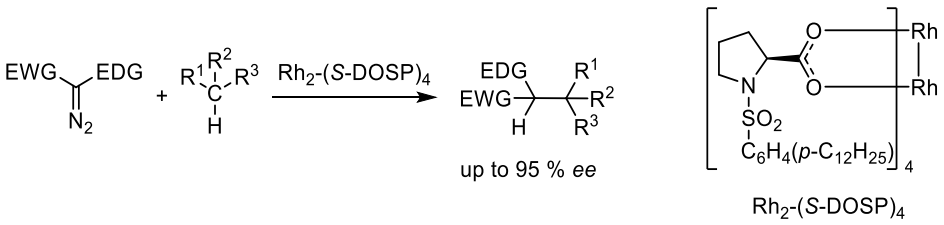


Figure 1.11 Examples of chiral dirhodium(II) carboxamidate catalysts.

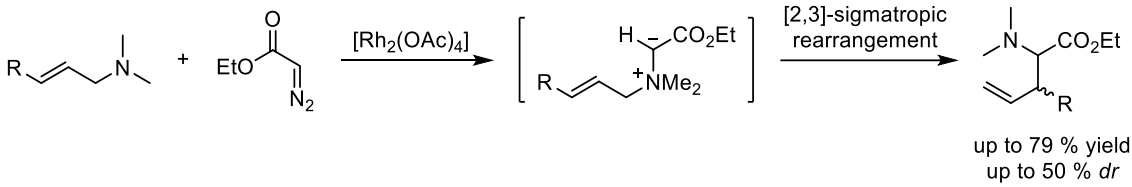
Catalytic asymmetric C-H activation by means of rhodium-carbene induced C-H insertions was recently reported by Davies and co-workers. For instance, the Rh_2(*S*-DOSP)$_4$ complex led to highly site-selective C-H functionalization of alkanes with donor/acceptor carbenes (**Scheme 1.10**) thanks to both steric and electronic factors.[29b]



Scheme 1.10 Rh_2-(*S*-DOSP)$_4$ catalyzed C-H functionalization.

Based on electronic arguments, tertiary C-H bonds are expected to be more reactive than secondary and primary C-H bonds thanks to the better ability of the more substituted center to stabilize the positive transient charge (general mechanism described in **Scheme 1.6**). However, considering the steric hindrance, the reactivity is expected to follow the opposite trend, primary substrates being more reactive than secondary and tertiary. In general, donor/acceptor rhodium carbenes have been found to be more sensitive to steric control.[29b] Insertion at secondary carbon atoms is usually favored due to a good balance between stabilization of the positive charge and avoidance of the steric hindrance.[29b]

Other reactivities have been reported, notably in the field of nitrogen ylide chemistry.[58] Doyle and co-worker showed that $Rh_2(OAc)_4$ catalyzed the formation of nitrogen ylides from amines.[59] These reactive intermediates underwent [2,3]-sigmatropic rearrangements with moderate diastereoselectivity only (up to 50 % *dr*, **Scheme 1.11**).



Scheme 1.11 $Rh_2(OAc)_4$ catalyzed nitrogen ylide formation and subsequent [2,3]-sigmatropic rearrangement.

The study of transition metal catalyzed decomposition of diazo compounds at the University of Geneva was started by Prof. Müller in 90's. In particular, he and his group reported the enantioselective rhodium(II)-catalyzed intramolecular[54b,60] and intermolecular[61] cyclopropanation, the intermolecular cyclopropenation[62] and the intramolecular C-H insertion[63] reactions. One of the most relevant examples is highlighted in **Scheme 1.12**.[54b]

[58] For a review: Bach, R.; Harthong, S.; Lacour, J., in *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G.; Knochel, P. (Eds.); Elsevier **2014**, in press.

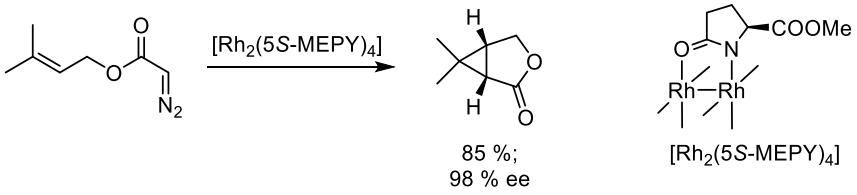
[59] Doyle, M. P.; Tamblyn, W. H.; Bagheri, V., *J. Org. Chem.* **1981**, *46* (25), 5094-5102.

[60] Muller, P.; Allenbach, Y. F.; Grass, S., *Tetrahedron: Asymmetry* **2005**, *16* (11), 2007-2013.

[61] (a) Muller, P.; Baud, C.; Ene, D.; Motallebi, S.; Doyle, M. P.; Brandes, B. D.; Dyatkin, A. B.; See, M. M., *Helv Chim Acta* **1995**, *78* (2), 459-470; (b) Imogai, H.; Bernardinelli, G.; Granicher, C.; Moran, M.; Rossier, J. C.; Muller, P., *Helv. Chim. Acta* **1998**, *81* (10), 1754-1764; (c) Muller, P.; Grass, S.; Shahi, S. P.; Bernardinelli, G., *Tetrahedron* **2004**, *60* (22), 4755-4763; (d) Muller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Flack, H. D., *Org. Lett.* **2004**, *6* (11), 1725-1728; (e) Muller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Grass, S., *Synlett.* **2005**, (9), 1397-1400; (f) Muller, P.; Ghanem, A., *Org. Lett.* **2004**, *6* (23), 4347-4350.

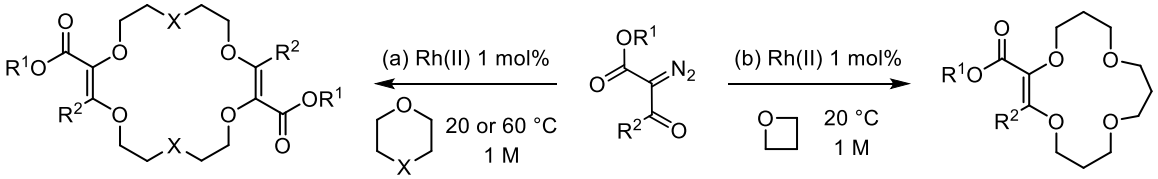
[62] (a) Muller, P.; Milin, D.; Feng, W. G. Q.; Houriet, R.; Della, E. W., *J. Am. Chem. Soc.* **1992**, *114* (15), 6169-6172; (b) Doyle, M. P.; Protopopova, M.; Muller, P.; Ene, D.; Shapiro, E. A., *J. Am. Chem. Soc.* **1994**, *116* (19), 8492-8498.

[63] (a) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; Vanbasten, A.; Muller, P.; Polleux, P., *J. Am. Chem. Soc.* **1994**, *116* (10), 4507-4508; (b) Muller, P.; Polleux, P., *Helv Chim Acta* **1994**, *77* (3), 645-654; (c) Muller, P.; Lacrampe, F.; Bernardinelli, G., *Tetrahedron: Asymmetry* **2003**, *14* (11), 1503-1510.



Scheme 1.12 Rhodium(II)-catalyzed intramolecular cyclopropanation.

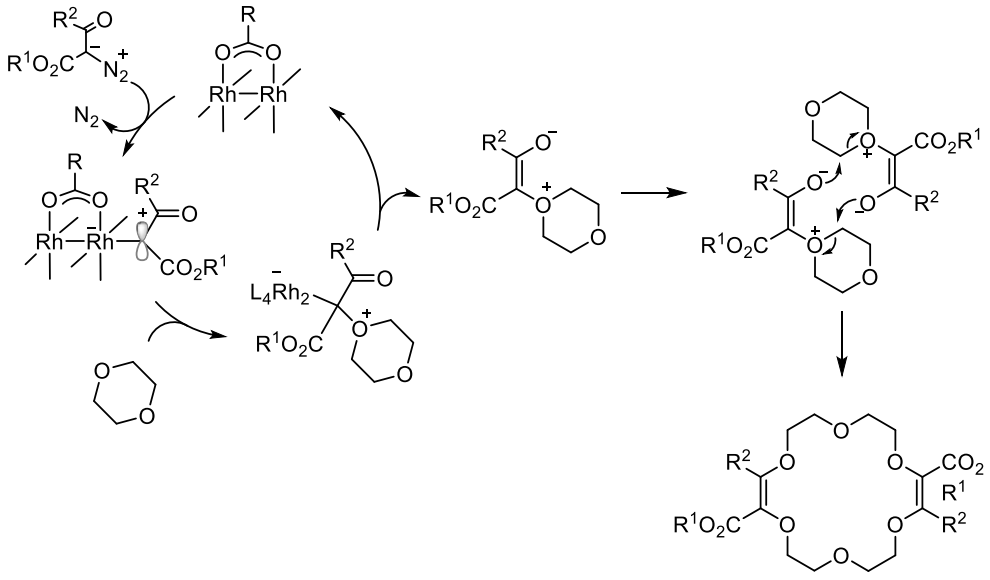
Recently our group has been particularly interested into the rhodium(II) catalyzed formation of original functionalised heterocycles starting from cyclic ethers.[64] Using α-diazo-β-ketoesters in presence of dioxane, tetrahydrofuran or tetrahydropyran, the one-step four-component synthesis of 16- and 18-membered macrocycles was reported (**Scheme 1.13a**).[64a] In view of the actual importance of functionalized crown ether molecules for applications in several fields, this reactivity was recently extended to unsaturated and substituted cyclic ether derivatives.[64b]



Scheme 1.13 Rh(II)-catalyzed synthesis of macrocycles (a) and medium-sized rings (b).

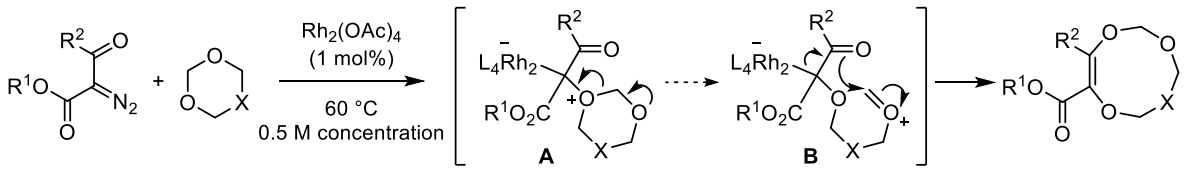
Trying to rationalize all the experimental observations, a mechanistic hypothesis detailed in **Scheme 1.14** was proposed. A metal-free oxonium ylide species is most probably involved and a stepwise dimerization is favoured by the concomitant formation of two oxygen-carbon bonds. Currently, experimental and theoretical studies are conducted confirming globally this hypothesis.

[64] (a) Zeghida, W.; Besnard, C.; Lacour, J., *Angew. Chem. Int. Ed.* **2010**, *49* (40), 7253-7256; (b) Vishe, M.; Hrdina, R.; Guénée, L.; Besnard, C.; Lacour, J., *Adv. Synth. Catal.* **2013**, *355* (16), 3161-3169; (c) Rix, D.; Ballesteros-Garrido, R.; Zeghida, W.; Besnard, C.; Lacour, J., *Angew. Chem. Int. Ed.* **2011**, *50* (32), 7308-7311.



Scheme 1.14 Mechanistic rational.

The synthesis of another rare type of functionalized 15-membered macrocycles was achieved using also $Rh_2(OAc)_4$ for the decomposition of stabilized α-diazocarbonyl compounds (**Scheme 1.13b**).[64c] Interestingly, this one-step synthesis involved the condensation of three molecules of oxetane and one molecule of diazo. The reaction proceeded at high concentration (1 M) under relatively mild reaction conditions (up to 60 °C). Again the formation of an oxonium ylide by reaction of the carbene with an oxetane molecule has been hypothesized.



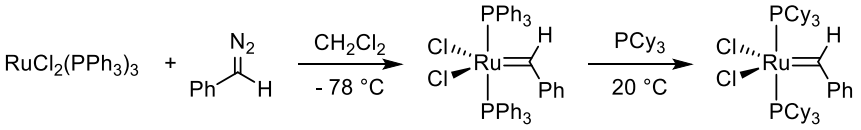
Scheme 1.15 Medium-sized rings synthesis.

Another strategy was applied for the synthesis of 8- and 9-membered rings through the modification of the oxo-nucleophiles (**Scheme 1.15**). Using acetals instead of ethers, an intramolecular nucleophilic attack is preferred in a direct application of the Baldwin's

rules.[65] For instance, the formation of an oxonium ylide intermediate **A** is proposed. At that stage, a ring opening, induced by a lone-pair of the second oxygen atom, would lead to the acyclic intermediate **B** that is suited to undergo the favoured 6-*endo*-*trig* cyclization reaction.

1.5.3 Ruthenium complexes

Only quite recently the interest on ruthenium complexes as catalysts in diazo decomposition has increased.[66] The most famous ruthenium carbene complexes generated from diazo compounds are definitely the Ru complexes developed by Grubbs in 1990s[17a,67] which application in olefin metathesis[22] earned him the Nobel Prize in 2005. This complex, together with the Hoveyda-Grubbs catalysts developed later,[68] will not be discussed in the present introduction as we were looking for other types of reactivity. Just for information, **Scheme 1.16** depicts the reactivity of a diazo reagent with a ruthenium complex for the preparation of the first generation Grubbs catalyst.



Scheme 1.16 Synthesis of the first generation Grubbs catalyst.

In 1993, a polymeric dicarbonyl ruthenium(I) acetate complex and its bis-acetonitrile analogue have been found to be efficient for cyclopropanation of alkenes with diazoacetates.[69] Later, Nishiyama and co-workers reported the development of chiral ruthenium complexes with pybox ligands. This catalytic combination efficiently catalyzed

[65] Ballesteros-Garrido, R.; Rix, D.; Besnard, C.; Lacour, J., *Chem. Eur. J.* **2012**, *18* (21), 6626-6631.

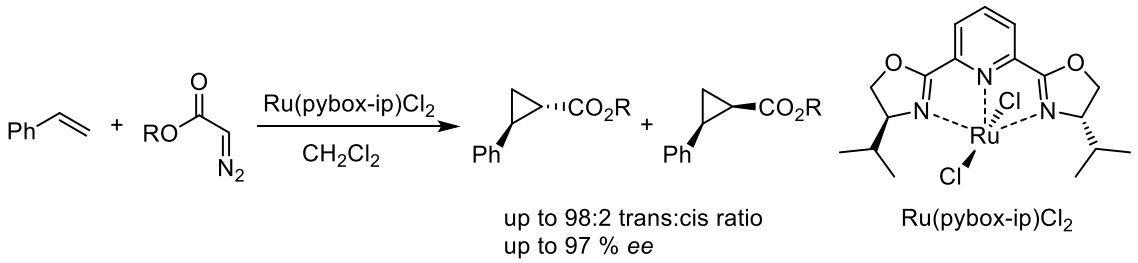
[66] Maas, G., *Chem. Soc. Rev.* **2004**, *33* (3), 183-190.

[67] (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W., *J. Am. Chem. Soc.* **1993**, *115* (21), 9858-9859; (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H., *Angew. Chem. Int. Edit.* **1995**, *34* (18), 2039-2041; (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W., *J. Am. Chem. Soc.* **1996**, *118* (1), 100-110; (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H., *Org. Lett.* **1999**, *1* (6), 953-956.

[68] (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H., *J. Am. Chem. Soc.* **1999**, *121* (4), 791-799; (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2000**, *122* (34), 8168-8179; (c) Gessler, S.; Randl, S.; Blechert, S., *Tetrahedron Lett.* **2000**, *41* (51), 9973-9976.

[69] Maas, G.; Werle, T.; Alt, M.; Mayer, D., *Tetrahedron* **1993**, *49* (4), 881-888.

the reaction of diazoacetates with styrene leading to highly enantioenriched cyclopropanes with excellent stereoselectivity (**Scheme 1.17**).[70,71]



Scheme 1.17 Enantioselective Ru(II) catalyzed cyclopropanation.

Ruthenium-porphyrin complexes[72] have been also developed and successfully used for the diazo decomposition and following carbenes transfer reactions.[73] Their versatility, together with the unusual and high selectivity rendered these complexes a valid alternative to the use of rhodium carboxylates as catalysts for cyclopropanation, C-H, N-H and S-H insertion, olefination, coupling and ylide formation reactions.[74] An example of azomethine ylide formation followed by 1,3-dipolar cycloaddition reaction is depicted in **Scheme 1.18**.[75] This stereoselective three component coupling reaction led to the stereoselective synthesis of functionalized pyrrolidines.

[70] (a) Park, S. B.; Nishiyama, H.; Itoh, Y.; Itoh, K., *J Chem Soc Chem Comm* **1994**, (*11*), 1315-1316; (b) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S. B.; Itoh, K., *J. Am. Chem. Soc.* **1994**, *116* (5), 2223-2224; (c) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K., *B Chem Soc Jpn* **1995**, *68* (5), 1247-1262.

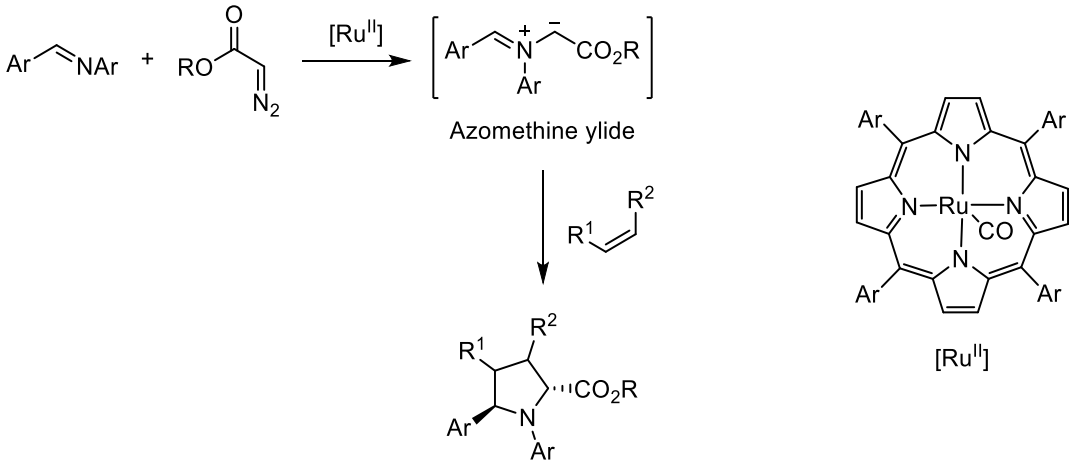
[71] Nishiyama, H. In *Ruthenium in Organic Synthesis* Murahashi, S.-I. Ed.; Wiley-VCH: Weinheim, **2004**, 179.

[72] Park, S. B.; Sakata, N.; Nishiyama, H., *Chem. Eur. J.* **1996**, *2* (3), 303-306.

[73] (a) Galardon, E.; LeMaux, P.; Simonneaux, G., *Chem. Commun.* **1997**, (10), 927-928; (b) Galardon, E.; Roue, S.; Le Maux, P.; Simonneaux, G., *Tetrahedron Lett.* **1998**, *39* (16), 2333-2334; (c) Lo, W. C.; Che, C. M.; Cheng, K. F.; Mak, T. C. W., *Chem. Commun.* **1997**, (*13*), 1205-1206. (d) Chan, K.-H.; Guan, X.; Lo, V. K.-Y; Che, C.-M. *Angew.Chem.Int.Ed.* **2014**, *53*, 2982-2987.

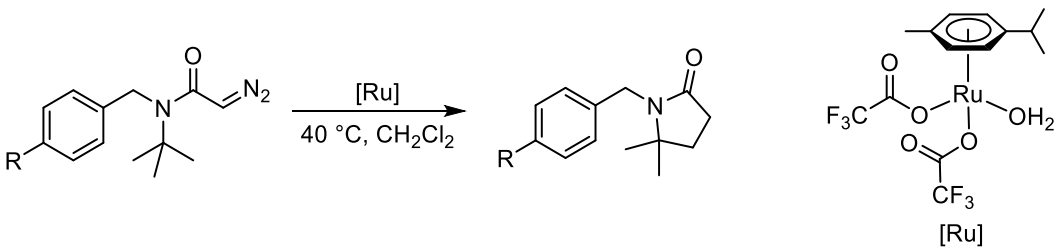
[74] Zhou, C. Y.; Huang, J. S.; Che, C. M., *Synlett* **2010**, (18), 2681-2700.

[75] Li, G. Y.; Chen, J.; Yu, W. Y.; Hong, W.; Che, C. M., *Org. Lett.* **2003**, *5* (12), 2153-2156.



Scheme 1.18 Example of a Ru-porphyrin catalyzed decomposition of α-diazo esters.

It has also been reported that $[RuCl_2(p\text{-cymene})]_2$ complex can decompose diazo compounds to give sulfonium[76] and nitrogen[77] ylides and subsequent functionalization reactions.[78] Recently Che and co-workers reported that a (*p*-cymene)ruthenium(II) carboxylate complex catalyzes the selective intramolecular carbene insertion into primary C-H bond using α-diazoacetamides (**Scheme 1.19**).[79]



Scheme 1.19 (*p*-cymene)Ru(II) carboxylate mediated carbene insertion.

The first CpRu (Cp = Cyclopentadiene) catalyzed decomposition of diazo compounds was reported by Rigo and co-workers in 1997.[80] $[CpRuCl(PPh_3)_2]$ complex was shown to

[76] Xiao, Q.; Wang, J. B., *Acta Chim Sinica* **2007**, *65* (16), 1733-1735.

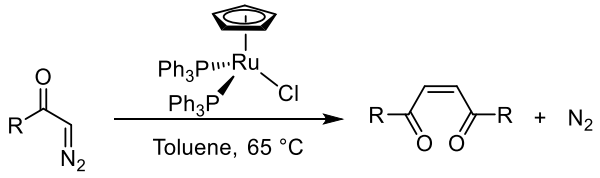
[77] Jiang, J.; Ma, X.; Ji, C.; Guo, Z.; Shi, T.; Liu, S.; Hu, W., *Chem. Eur. J.* **2014**, *20* (6), 1505-1509.

[78] Chan, W. W.; Yeung, S. H.; Zhou, Z. Y.; Chan, A. S. C.; Yu, W. Y., *Org. Lett.* **2010**, *12* (3), 604-607.

[79] Lo, V. K. Y.; Guo, Z.; Choi, M. K. W.; Yu, W. Y.; Huang, J. S.; Che, C. M., *J. Am. Chem. Soc.* **2012**, *134* (18), 7588-7591.

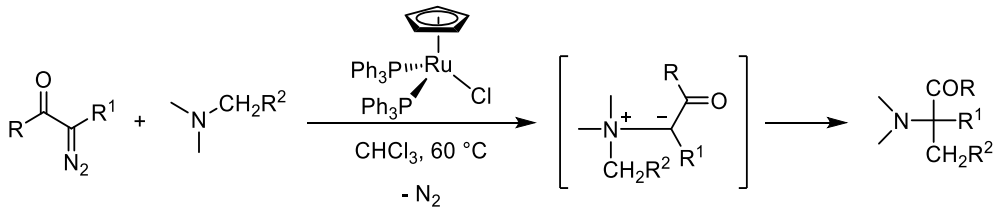
[80] Baratta, W.; Del Zotto, A.; Rigo, P., *Chem. Commun.* **1997**, (22), 2163-2164.

selectively decompose α-diazo carbonyl compounds which, under the reaction conditions, leads to a dimerization of the metal carbene; the olefins were obtained as *cis* isomers exclusively (**Scheme 1.20**).



Scheme 1.20 First CpRu catalyzed decomposition of diazo compounds.

Since then, this catalyst precursor has been used to extend the carbene-carbene coupling reaction scope for the synthesis of functionalized *cis*-alkenes[81] and for highly selective N-H and S-H insertion reactions.[82] Furthermore, the commercially available [$CpRuCl(PPh_3)_2$] complex has shown a very high activity in ammonium ylides generation by reaction between tertiary amines and α-diazo ketones. Successive rearrangement with migration of the less substituted group gives α-amino ketones (**Scheme 1.21**).[83]



Scheme 1.21 CpRu catalyzed generation and rearrangement of ylides.

More recently Basato reported that [CpRu(COD)Cl] (COD = 1,5-cyclooctadiene) can also be an efficient precursor for diazo decomposition, promoting, in presence of an olefin, metathesis and/or cyclopropanation reactions (**Scheme 1.22**).[84] The different

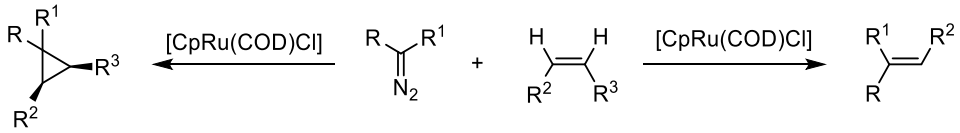
[81] (a) Del Zotto, A.; Baratta, W.; Verardo, G.; Rigo, P., *Eur. J. Org. Chem.* **2000**, (15), 2795-2801; (b) Baratta, W.; Del Zotto, A.; Rigo, P., *Organometallics* **1999**, *18* (24), 5091-5096.

[82] Del Zotto, A.; Baratta, W.; Rigo, P., *J. Chem. Soc., Perkin Trans. 1* **1999**, (21), 3079-3081.

[83] Del Zotto, A.; Baratta, W.; Miani, F.; Verardo, G.; Rigo, P., *Eur. J. Org. Chem.* **2000**, (*22*), 3731-3735.

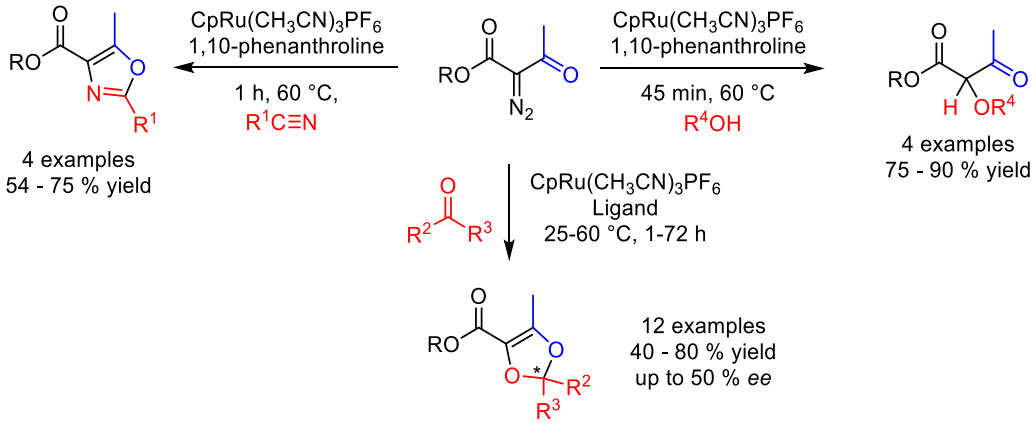
[84] Basato, M.; Tubaro, C.; Biffis, A.; Bonato, M.; Buscemi, G.; Lighezzolo, F.; Lunardi, P.; Vianini, C.; Benetollo, F.; Del Zotto, A., *Chem. Eur. J.* **2009**, *15* (6), 1516-1526.

reactivity can be modulated changing the carbonyl diazo compound or the alkene substituents.



Scheme 1.22 Cyclopropanation *vs* metathesis processes.

Our group recently studied the reactivity of α-diazo-β-ketoesters in presence of $[CpRu(CH_3CN)_3][PF_6]$ complex and diimine ligands, especially 1,10-phenanthroline. In particular, it was shown that this catalytic combination afforded O-H insertion and condensation reactions with Lewis basic moieties such as alcohols, nitriles, aldehydes and ketones (**Scheme 1.23**).[3] Promising enantioselectivities (up to 50 % *ee*) were obtained in the synthesis of dioxole products using the enantioenriched pymox ligand outlined in **Figure 1.12**.



Scheme 1.23 CpRu catalyzed O-H insertion and condensation reactions.

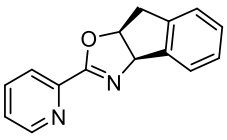


Figure 1.12 Pymox ligand.

The electronic and steric factors that can influence reactivity and selectivity promoted by complexes of ruthenium will be mentioned in the next chapter.

2 CpRu(II) complexes

2.1 Introduction

2.1.1 Preamble

The history of ruthenium actually started in 1804 when the two French chemists Fourcroy and Vauquelin observed the formation of an azure-blue mixture while treating some solutions of known platinum minerals with zinc.[85] The cause of this colour was erroneously ascribed to the presence of iridium. More than twenty years later, the German chemist Gottfried Wilhem Osann published an announcement in the Philosophical magazine:[86] "*I have discovered in the platina of the Uralian mountains three metals, the properties of which are different from those of every other known metal.*" He named them pluranium, polinium and ruthenium. Unfortunately it was not possible for him to isolate them and little time later he was forced to withdraw his statement. Finally, in 1840's the Russian chemist Carl Ernst Claus successfully isolated this unknown metal that he named Ruthenium, like Osann, from the Latin name of Russia (Ruthenia).[87]

2.1.2 Half-sandwich complexes

Ruthenium has the widest scope of oxidation states (from -II in $Ru(CO)_4^{-2}$ to +VIII in RuO_4) of all the elements of the periodic table and different coordination geometries because of its $4d^7 5s^1$ electronic configuration.[88] Such a variety means a great potential for its exploitation as catalyst in organic reactions. However, only in 1980's organic chemists started to prepare and successfully use ruthenium catalysts.[89,90] $RuCl_3 \cdot nH_2O$ is typically

[85] Vauquelin, N. L.; Fourcroy, A.-F., *Ann. Chim*. (Paris) **1804**, *49*, 188 and 219.

[86] Osann, G. W., *Philosophical magazine*, **1827**, *2*, 391.

[87] Claus, C. E., *Philosophical magazine*, **1845**, *27*, 230.

[88] (a) Seddn E. A.; Seddon, K. R., *The chemistry of ruthenium*, Elsevier: Amsterdam, **1984**; (b) Cotton, F. A.; Wilkinson, G., *Adv. Inorg. Chem.*, 4th ed. Wiley **1980**.

[89] (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B., *Chem. Rev*. **2001**, *101* (7), 2067-2096; (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H., *Chem. Rev.* **2012**, *112* (11), 5879-5918; (c) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T., *Angew. Chem. Int. Ed.* **2005**, *44* (41), 6630-6666.

used as starting material for the preparation of most of these species. Among them, the so-called half-sandwich compounds containing cyclopentadienyl-type ligands have been extensively studied.[91,92] This family of ligands allows a modulation of the properties of the metal centre by functionalization of the Cp moiety that is usually strongly coordinated to the metal, especially in the case of ruthenium. Moreover, half-sandwich ruthenium complexes contain three vacant sites to accommodate ligands that can contribute to control the catalyst properties.[93] In this chapter, the attention will be focused on the synthesis of cationic ruthenium(II) complexes of type $[(C_5R_5)RuL_3]^+[X]^-$, which L is an acetonitrile molecule in particular. These complexes have a piano-stool tetrahedral geometry, the organization of the four ligands being controlled by steric factors. Ruthenium has a formal oxidation state of +II. The cyclopentadienyl ligand is formally anionic and it is bond in a η^5-fashion, filling three coordination sites around ruthenium. Three other coordination sites are filled by three formal η^1-two-electron donors neutral ligands, for example three molecules of acetonitrile. The resulting cationic complexes possess eighteen electrons.

2.2 Ligand effect

The lability of acetonitrile ligands in $[(C_5R_5)Ru(CH_3CN)_3]^+[X]^-$ moieties has been extensively studied and exploited for the synthesis of various catalysts containing CpRu and Cp*Ru fragments.[94] Gill and Mann first prepared $[CpRu(CH_3CN)_3]^+[PF_6]^-$ metal salt in 1982. They showed that reactions with an excess of $P(OMe)_3$ gave the possibility to

[90] Murahashi, S.-I., *Ruthenium in organic synthesis*, Wiley-VCH, **2004**.

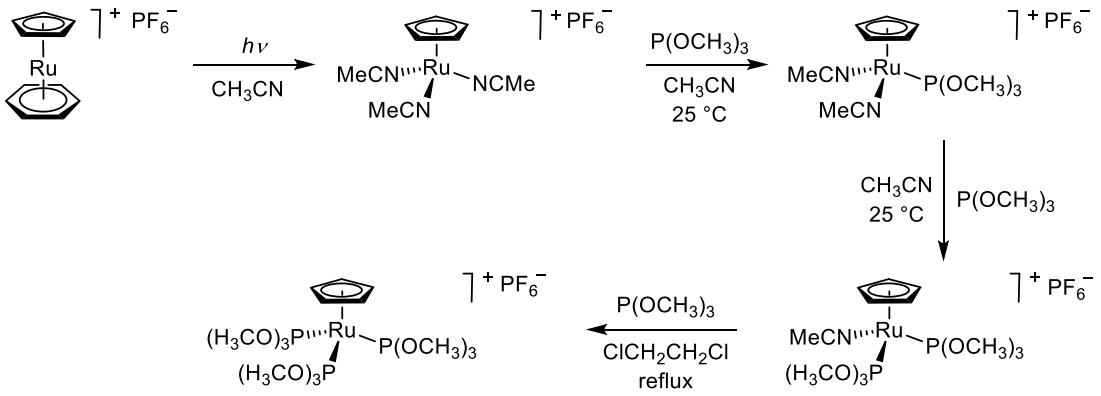
[91] (a) Hartwig J.F. *Organotransition metal chemistry*. (b) Albers, M. O.; Robinson, D. J.; Singleton, E. *Coord. Chem. Rev*. **1987**, *79*, 1-96.

[92] Perekalin, D. S.; Karslyan, E. E.; Trifonova, E. A.; Konovalov, A. I.; Loskutova, N. L.; Nelyubina, Y. V.; Kudinov, A. R., *Eur. J. Inorg. Chem.* **2013**, (4), 481-493.

[93] Kumar, P.; Gupta, R. K.; Pandey, D. S., *Chem. Soc. Rev.* **2014**, *43* (2), 707-733.

[94] (a) Slugovc, C.; Ruba, E.; Schmid, R.; Kirchner, K.; Mereiter, K., *Monatsh Chem* **2000**, *131* (12), 1241-1251; (b) Perekalin, D. S.; Trifonova, E. A.; Nelyubina, Y. V.; Kudinov, A. R., *J. Organomet. Chem.* **2014**, *754* (0), 1-4; (c) Trifonova, E. A.; Loskutova, N. L.; Perekalin, D. S.; Nelyubina, Y. V.; Kudinov, A. R., *Mendeleev Commun.* **2013**, *23* (3), 133-134.

isolate the complexes with one, two or the three acetonitrile ligands replaced by phosphites (**Scheme 2.1**).[95]



Scheme 2.1 First synthesis of $[CpRu(CH_3CN)_3]^+[PF_6]^-$ and consecutive ligand substitution.

This strategy has been applied with other monodentated ligands such as phosphines PR_3[96] and with bidentate ligands like diamines,[94a] bipyridines,[97] aminopyridines[98] and diimines[99] (**Figure 2.1**).

[95] Gill, T. P.; Mann, K. R., *Organometallics* **1982**, *1* (3), 485-488.

[96] (a) Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A., *J. Am. Chem. Soc.* **2007**, *129* (31), 9592-9593; (b) Grotjahn, D. B.; Lo, H. C., *Organometallics* **1996**, *15* (13), 2860-2862; (c) Kumagai, N.; Matsunaga, S.; Shibasaki, M., *Tetrahedron* **2007**, *63* (35), 8598-8608; (d) Kumagai, N.; Matsunaga, S.; Shibasaki, M., *Chem. Commun.* **2005**, (28), 3600-3602; (e) Kumagai, N.; Matsunaga, S.; Shibasaki, M., *J. Am. Chem. Soc.* **2004**, *126* (42), 13632-13633; (f) Ruba, E.; Simanko, W.; Mauthner, K.; Soldouzi, K. M.; Slugovc, C.; Mereiter, K.; Schmid, R.; Kirchner, K., *Organometallics* **1999**, *18* (19), 3843-3850; (g) Standfest-Hauser, C. M.; Mereiter, K.; Schmid, R.; Kirchner, K., *Eur. J. Inorg. Chem.* **2003**, (10), 1883-1892; (h) Standfest-Hauser, C. M.; Mereiter, K.; Schmid, R.; Kirchner, K., *Organometallics* **2002**, *21* (23), 4891-4893; (i) Chevallier, F.; Breit, B., *Angew. Chem. Int. Ed.* **2006**, *45* (10), 1599-1602.

[97] Mbaye, M. D.; Demerseman, B.; Renaud, J. L.; Toupet, L.; Bruneau, C., *Angew. Chem. Int. Ed.* **2003**, *42* (41), 5066-5068.

[98] Gomez, J.; Garcia-Herbosa, G.; Cuevas, J. V.; Arnaiz, A.; Carbayo, A.; Munoz, A.; Falvello, L.; Fanwick, P. E., *Inorg Chem* **2006**, *45* (6), 2483-2493.

[99] (a) Renaud, J. L.; Bruneau, C.; Demerseman, B., *Synlett* **2003**, (3), 408-410; (b) Mbaye, M. D.; Demerseman, B.; Renaud, J. L.; Bruneau, C., *J. Organomet. Chem.* **2005**, *690* (8), 2149-2158.

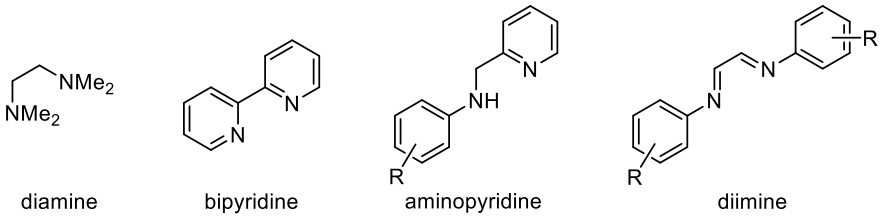


Figure 2.1 Examples of bidentate ligands.

Very recently, Schlaf and co-workers have reported an example on how strong is the influence of the ligand on the reactivity. In this study, the introduction of two noncoordinating amine substituents in the two *orto* position of a bipyridine ligand in the [CpRu(2,2'-bipyridine)(CH_3CN)][OTf] (**Figure 2.2**, (a)) to give the [CpRu(6,6'-diamino-2,2'-bipyridine)(CH_3CN)][OTf] complex (**Figure 2.2**, (b)) results in an increase of its catalytic activity in the hydrogenation of cyclohexanone.[100]

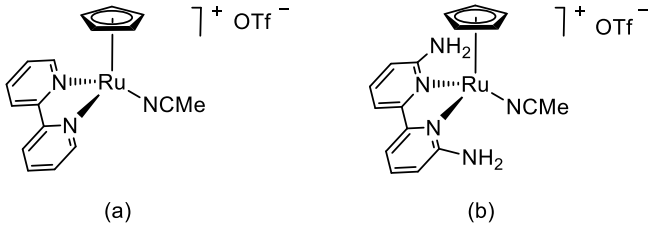


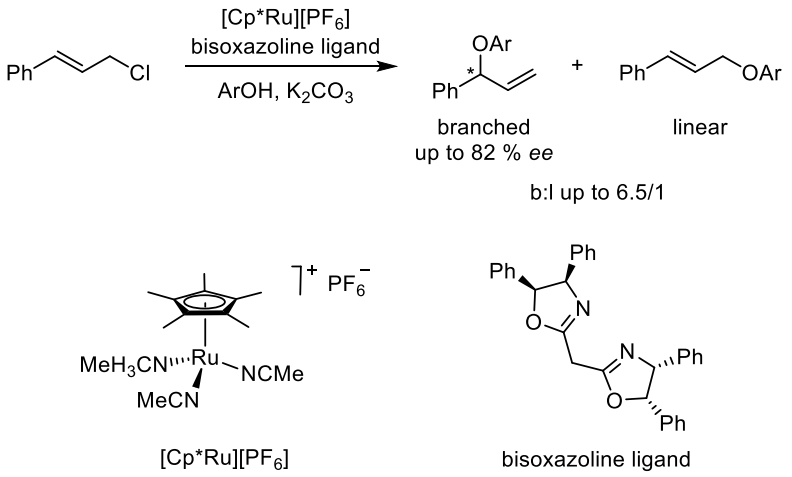
Figure 2.2 [CpRu(2,2'-bipyridine)(CH_3CN)][OTf] (a) and [CpRu(6,6'-diamino-2,2'-bipyridine)(CH_3CN)][OTf] (b) complexes.

In our group and as already mentioned, a combination of $[CpRu(CH_3CN)_3]^+[PF_6]^-$ and 1,10-phenanthroline has been used in the O-H insertion and condensation reactions with alcohols, nitriles, ketones and aldehydes of diazo compounds (**Scheme 1.23**, Paragraph 1.5.3).[3] While chiral bisoxazoline ligands were used with success to achieve enantioselectivity in asymmetric allylic etherification reactions (**Scheme 2.2**),[101] in our group, iminopyridine ligands were preferred in a ruthenium catalyzed Carroll rearrangement.[102] Pyridine-oxazoline (Pymox) ligands[103] (**Figure 1.12,** Paragraph 1.5.3) were later used in ruthenium catalyzed asymmetric decarboxylic allylic etherification.[104]

[100] DiMondo, D.; Thibault, M. E.; Britten, J.; Schlaf, M., *Organometallics* **2013**, *32* (21), 6541-6554.

[101] Mbaye, M. D.; Renaud, J. L.; Demerseman, B.; Bruneau, C., *Chem. Commun.* **2004**, (16), 1870-1871.

[102] Constant, S.; Tortoioli, S.; Muller, J.; Lacour, J., *Angew. Chem. Int. Ed.* **2007**, *46* (12), 2082-2085.



Scheme 2.2 Enantioselective allylic etherification catalyzed by Cp*Ru bisoxazoline complexes.

The cyclopentadienyl moiety can be modified also and a modulation of the characteristics of the complex is achieved. The most popular $[CpRu(CH_3CN)_3]^+[X]^-$ analogue is probably pentamethylcyclopentadienyl $[Cp^*Ru(CH_3CN)_3]^+[X]^-$ that can be synthesize in two steps form $RuCl_3 \cdot nH_2O$.[105] The resulting complex is more sterically demanding and electron rich and these features influence both reactivity and selectivity.[106]

In a very different field, cyclopentadienyl complexes are also essential. For instance, when four phenyl substituents are present on the cyclopentadiene, dimeric complexes are formed. This is the case of Shvo complex $[Ph_4(\eta^5\text{-}C_4CO)]_2H]\ Ru_2(CO)_4(\mu\text{-}H)$[107] (**Scheme 2.3**) that is commonly used as catalyst in transfer hydrogenation reactions. It has been demonstrated that this complex dissociates in two monomeric forms: the first one, the catalytically active one, in which ruthenium has a zero oxidation state (**Scheme 2.3a**) and

[103] Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T., *Chem. Ber.* **1991**, *124* (5), 1173-1180.

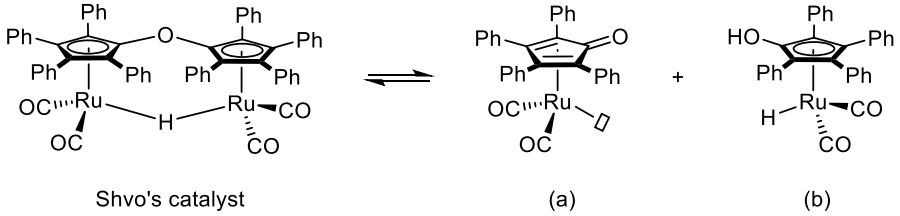
[104] (a) Austeri, M.; Linder, D.; Lacour, J., *Chem. Eur. J.* **2008**, *14* (19), 5737-5741; (b) Austeri, M.; Linder, D.; Lacour, J., *Adv. Synth. Catal.* **2010**, *352* (18), 3339-3347.

[105] (a) Gassman, P. G.; Winter, C. H., *J. Am. Chem. Soc.* **1988**, *110* (18), 6130-6135; (b) Steinmetz, B.; Schenk, W. A., *Organometallics* **1999**, *18* (5), 943-946.

[106] Trost, B. M.; Fraisse, P. L.; Ball, Z. T., *Angew. Chem. Int. Ed.* **2002**, *41* (6), 1059-1061.

[107] Shvo, Y.; Czarkie, D.; Rahamim, Y.; Chodosh, D. F., *J. Am. Chem. Soc.* **1986**, *108* (23), 7400-7402.

the second, in which the ruthenium is formally in the +II oxidation state (**Scheme 2.3b**).[108] Several analogues have been prepared.[109]



Scheme 2.3 Shvo complex and its heterolitic dissociation.

Recently, Trost and co-workers designed an asymmetric variant of $[CpRu(CH_3CN)_3]^+[PF_6]^-$ by introducing a tethered, chiral sulfoxide from the cyclopentadienyl ring (**Scheme 2.4**).[110] Planar-chiral half-sandwich complexes with a three-legged piano stool structure have been obtained by Takahashi and co-workers by substituting the cyclopentadienyl ring (**Scheme 2.4**).[111] These complexes have been successfully applied for the branched-selective asymmetric allylic alkylation and amination reactions.[112]

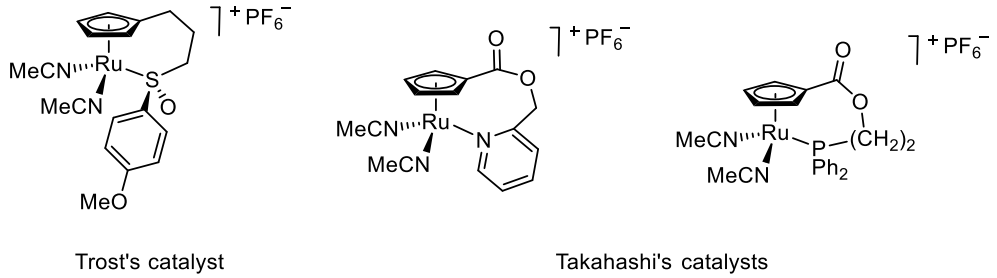
[108] Conley, B. L.; Pennington-Boggio, M. K.; Boz, E.; Williams, T. J., *Chem. Rev.* **2010**, *110* (4), 2294-2312.

[109] (a) Casey, C. P.; Vos, T. E.; Singer, S. W.; Guzei, I. A., *Organometallics* **2002**, *21* (23), 5038-5046; (b) Casey, C. P.; Strotman, N. A.; Beetner, S. E.; Johnson, J. B.; Priebe, D. C.; Vos, T. E.; Khodavandi, B.; Guzei, I. A., *Organometallics* **2006**, *25* (5), 1230-1235; (c) Do, Y.; Ko, S. B.; Hwang, I. C.; Lee, K. E.; Lee, S. W.; Park, J., *Organometallics* **2009**, *28* (15), 4624-4627; (d) Choi, J. H.; Kim, N.; Shin, Y. J.; Park, J. H.; Park, J., *Tetrahedron Lett.* **2004**, *45* (24), 4607-4610.

[110] Trost, B. M.; Rao, M.; Dieskau, A. P., *J. Am. Chem. Soc.* **2013**, *135* (49), 18697-18704.

[111] (a) Dodo, N.; Matsushima, Y.; Uno, M.; Onitsuka, K.; Takahashi, S., *J Chem Soc Dalton* **2000**, (1), 35-41; (b) Matsushima, E.; Komatsuzaki, N.; Ajioka, Y.; Yamamoto, M.; Kikuchi, H.; Takata, Y.; Dodo, N.; Onitsuka, K.; Uno, M.; Takahashi, S., *B Chem. Soc. Jpn.* **2001**, *74* (3), 527-537; (c) Onitsuka, K.; Ajioka, Y.; Matsushima, Y.; Takahashi, S., *Organometallics* **2001**, *20* (15), 3274-3282.

[112] (a) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S., *J. Am. Chem. Soc.* **2001**, *123* (42), 10405-10406; (b) Onitsuka, K.; Okuda, H.; Sasai, H., *Angew. Chem. Int. Ed.* **2008**, *47* (8), 1454-1457; (c) Onitsuka, K.; Kameyama, C.; Sasai, H., *Chem. Lett.* **2009**, *38* (5), 444-445; (d) Kanbayashi, N.; Onitsuka, K., *J. Am. Chem. Soc.* **2010**, *132* (4), 1206-1208; (e) Kanbayashi, N.; Onitsuka, K., *Angew. Chem. Int. Ed.* **2011**, *50* (22), 5197-5199.



Scheme 2.4 Asymmetric CpRu complexes.

2.3 Counterion effect

The nature of the counterion and its interaction with the charged metal complexes have a strong influence on the reactivity of the resulting metal salts. Indeed, anion/cation interactions can dramatically affect the solubility of the metal salt, the reactivity,[113] the reaction rate[114] and the selectivity.[115] Kinetic,[116] theoretical[113b,117] and spectroscopic[114c,118] studies have been performed in order to better understand these phenomena and some aspects have been clarified. For example, it has been demonstrated that the assumption that anions such as BF_4^-, PF_6^- of SbF_6^- are non-coordinating was wrong; on the contrary,

[113] (a) Rifat, A.; Patmore, N. J.; Mahon, M. F.; Weller, A. S., *Organometallics* **2002**, *21* (14), 2856-2865; (b) Macchioni, A.; Zuccaccia, C.; Clot, E.; Gruet, K.; Crabtree, R. H., *Organometallics* **2001**, *20* (11), 2367-2373.

[114] (a) Evans, D. A.; Murry, J. A.; Vonmatt, P.; Norcross, R. D.; Miller, S. J., *Angew Chem Int Edit* **1995**, *34* (7), 798-800; (b) Trost, B. M.; Bunt, R. C., *J. Am. Chem. Soc.* **1998**, *120* (1), 70-79; (c) Kumar, P. G. A.; Pregosin, P. S.; Vallet, M.; Bernardinelli, G.; Jazzar, R. F.; Viton, F.; Kundig, E. P., *Organometallics* **2004**, *23* (23), 5410-5418.

[115] (a) Takenaka, N.; Huang, Y.; Rawal, V. H., *Tetrahedron* **2002**, *58* (41), 8299-8305; (b) Appelhans, L. N.; Zuccaccia, D.; Kovacevic, A.; Chianese, A. R.; Miecznikowski, J. R.; Macchioni, A.; Clot, E.; Eisenstein, O.; Crabtree, R. H., *J. Am. Chem. Soc.* **2005**, *127* (46), 16299-16311; (c) Ludwig, M.; Stromberg, S.; Svensson, M.; Akermark, B., *Organometallics* **1999**, *18* (6), 970-975.

[116] Basallote, M. G.; Besora, M.; Duran, J.; Fernandez-Trujillo, M. J.; Lledos, A.; Manez, M. A.; Maseras, F., *J. Am. Chem. Soc.* **2004**, *126* (8), 2320-2321.

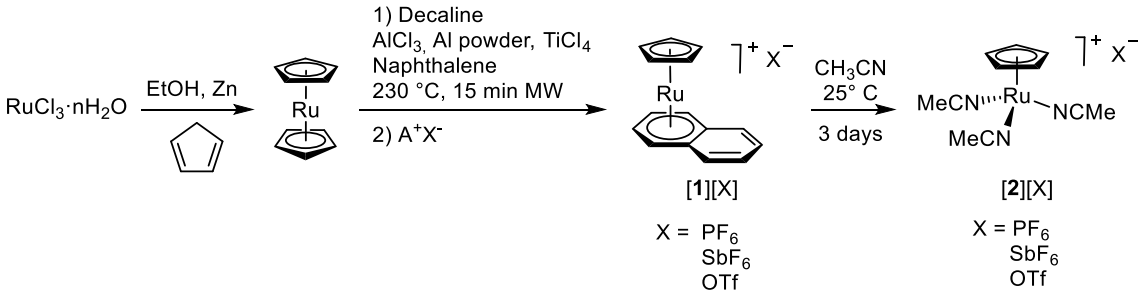
[117] Miecznikowski, J. R.; Grundemann, S.; Albrecht, M.; Megret, C.; Clot, E.; Faller, J. W.; Eisenstein, O.; Crabtree, R. H., *Dalton T* **2003**, (5), 831-838.

[118] (a) Macchioni, A.; Bellachioma, G.; Cardaci, G.; Gramlich, V.; Ruegger, H.; Terenzi, S.; Venanzi, L. M., *Organometallics* **1997**, *16* (10), 2139-2145; (b) Macchioni, A.; Bellachioma, G.; Cardaci, G.; Travaglia, M.; Zuccaccia, C.; Milani, B.; Corso, G.; Zangrando, E.; Mestroni, G.; Carfagna, C.; Formica, M., *Organometallics* **1999**, *18* (16), 3061-3069.

they are able to coordinate to the cation either directly or through hydrogen bonding interactions.[119]

2.4 Synthesis of CpRu(II) complexes

Dr. Thierry Achard, postdoctoral associate in our group, synthesized a series of CpRu complexes that were employed as catalyst precursors in the reactions described in the following chapters. Starting from the common $[CpRu(naphthalene)]^+[X]^-$ or [**1**][X] precursor, a series of $[CpRu(CH_3CN)_3]^+[X]^-$ or [**2**][X] containing different counterions (X = PF_6^-, SbF_6^-, OTf^-) were prepared following the procedure established in Prof. Kundig's group (**Scheme 2.5**).[120]



Scheme 2.5 Synthesis of $[CpRu(CH_3CN)_3]^+[X]^-$ [**2**][X] precatalysts.

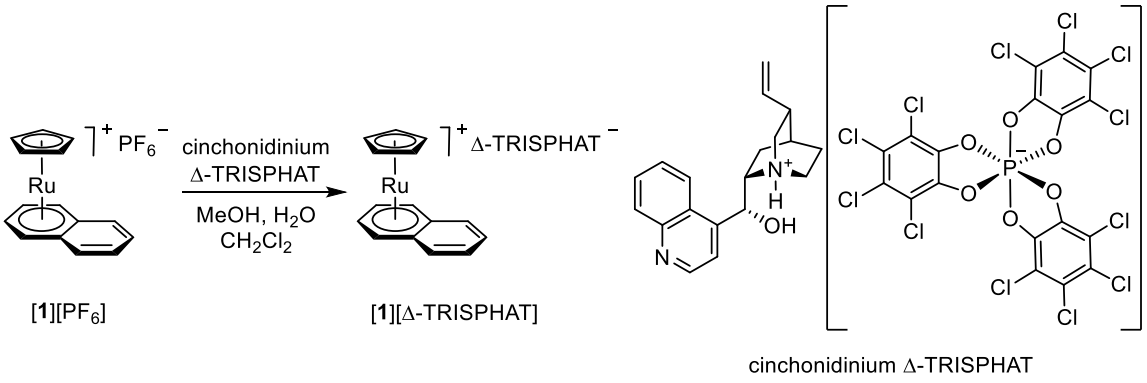
It was possible to introduce a $[\Delta\text{-TRISPHAT}]^-$[121] by anion metathesis with the $[CpRu(Naphthalene)]^+[PF_6]^-$ complex as precursor, in a biphasic system as described by Hintermann (**Scheme 2.6**).[122]

[119] (a) Romeo, R.; Nastasi, N.; Scolaro, L. M.; Plutino, M. R.; Albinati, S.; Macchioni, A., *Inorg. Chem.* **1998**, *37* (21), 5460-5466; (b) Song, J. S.; Szalda, D. J.; Bullock, R. M., *Organometallics* **2001**, *20* (15), 3337-3346.

[120] (a) Mercier, A.; Yeo, W. C.; Chou, J. Y.; Chaudhuri, P. D.; Bernardinelli, G.; Kundig, E. P., *Chem. Commun.* **2009**, (35), 5227-5229; (b) Kundig, E. P.; Monnier, F. R., *Adv. Synth. Catal.* **2004**, *346* (8), 901-904.

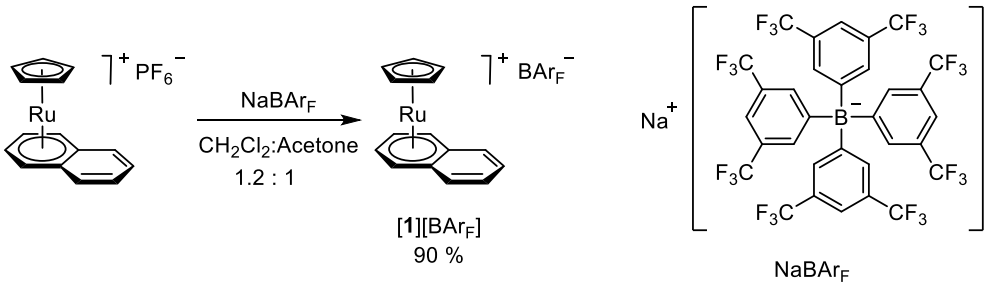
[121] (a) Lacour, J.; Moraleda, D., *Chem. Commun.* **2009**, (46), 7073-7089; (b) Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G., *Angew. Chem. Int. Ed.* **1997**, *36* (6), 608-610.

[122] Hintermann, L.; Xiao, L.; Labonne, A.; Englert, U., *Organometallics* **2009**, *28* (19), 5739-5748.



Scheme 2.6 Counterion exchange with $[\Delta\text{-TRISPHAT}]^-$.

As a direct exchange with $NaBAr_F$ failed using the classic Kundig procedure,[120] the $[BAr_F]^-$ anion similarly also introduced by anion exchange of $[PF_6]^-$ directly on the $[CpRu(Naphthalene)]^+[PF_6]^-$ complex. $NaBAr_F$ salt was added to a 1.2:1 dichloromethane:acetone solution of $[CpRu(Naphthalene)]^+[PF_6]^-$. After 30 min stirring at 25 °C, the formation of a crystalline material was noticed and purification by crystallization from a 3:1 solution of hexanes:CH_2Cl_2 afforded the desired $[CpRu(Naphthalene)]^+[BAr_F]^-$ complex [**1**][Bar_F] in excellent yield (90 %, **Scheme 2.7**).

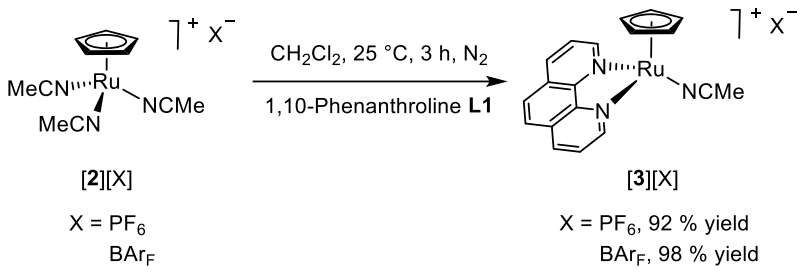


Scheme 2.7 Counterion exchange with $[BAr_F]^-$.

Finally, in both instances, the naphthalene ligand was replaced by three acetonitriles to afford the desired $[CpRu(CH_3CN)_3]^+[X]^-$ complexes [**2**][X] (X = Δ-TRISPHAT, Bar_F). Further ligand exchange reactions of the acetonitriles could then be performed. A series of $[CpRu(1,10\text{-phenanthroline})(CH_3CN)]^+[X]^-$ [**3**][X] complexes have been prepared.[123]

[123] As you will see later in this thesis, 1,10-phenanthroline **L1** has been identified as best ligand for our studies.

This was simply performed by addition of 1.0 equivalent of 1,10-phenanthroline **L1** to a solution of $[CpRu(CH_3CN)_3]^+[X]^-$ complex in dichloromethane (**Scheme 2.8**).



Scheme 2.8 Synthesis of $[CpRu(1,10\text{-phenanthroline})(CH_3CN)]^+[X]^-$ complexes.

In both instances, X-ray quality crystals of $[\mathbf{3}]^+[X]^-$ complexes were obtained and a structural analysis was performed (**Figure 2.3**).

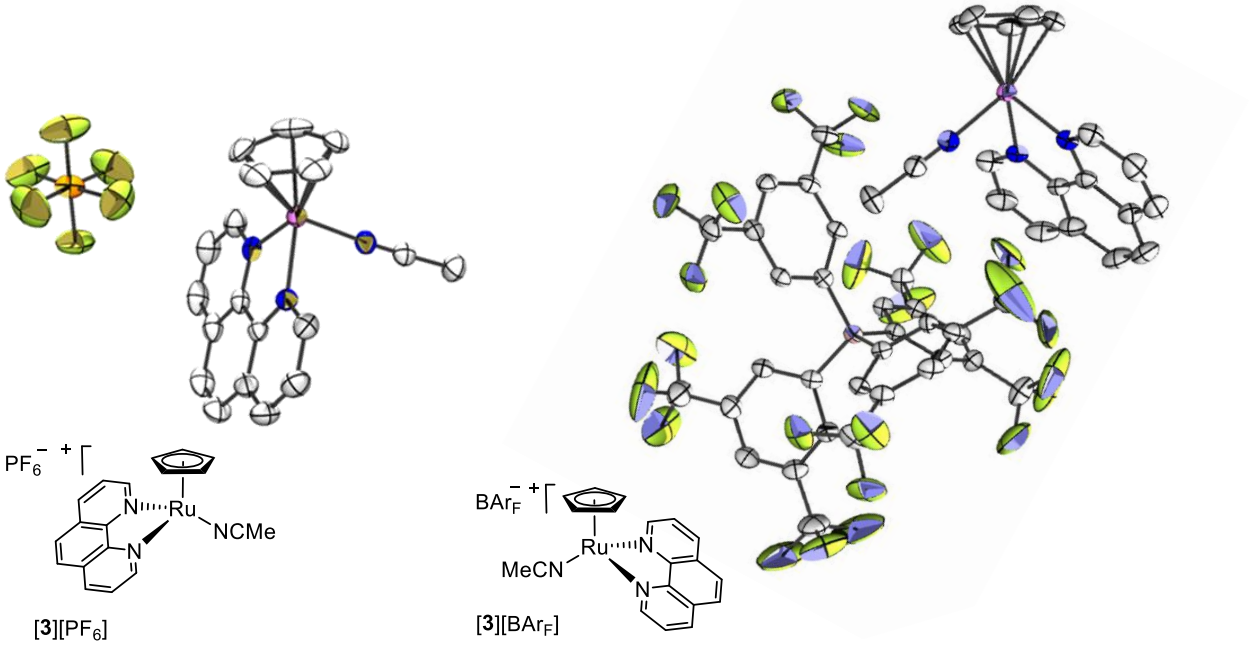


Figure 2.3 ORTEP view of $[\mathbf{3}]^+[PF_6]^-$ and $[\mathbf{3}]^+[BAr_F]^-$ complexes. Thermal ellipsoids are drawn at 50 % probability level. Hydrogen atoms are omitted for clarity.

In 2007, our group reported the synthesis and the resolution of the hexacoordinated phosphate anion TRISPHAT-N (**Figure 2.4**).[124] This anion was shown to be able to coordinate to different metal centers thanks to the presence of a slightly Lewis basic pyridine moiety.[104b,124b]

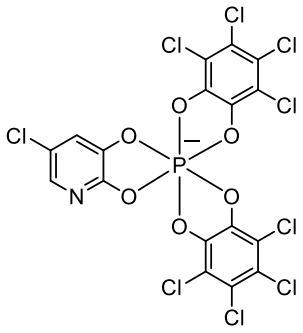


Figure 2.4 *(rac)*-TRISPHAT-N

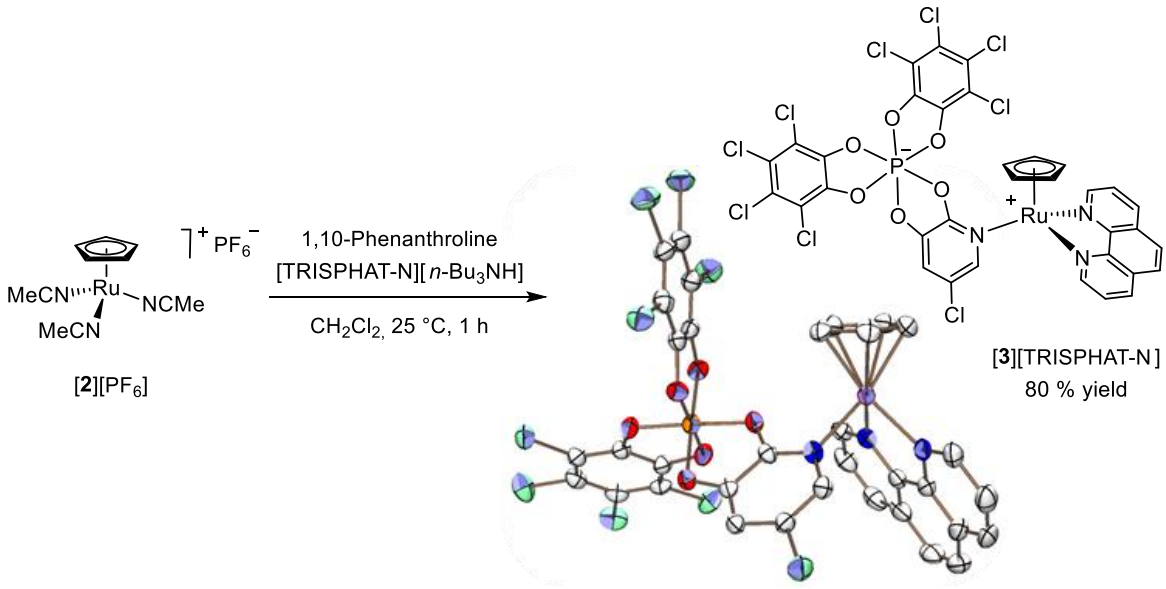
In this case the [CpRu(1,10-phenanthroline)(CH_3CN)]$^+$[(*rac*)-TRISPHAT-N]$^-$ complex was obtained by mixing in dichloromethane equimolar amounts of [CpRu(CH_3CN)$_3$]$^+$[PF_6]$^-$, 1,10-phenanthroline **L1** and [TRISPHAT-N][*n*-Bu_3NH] salt (**Scheme 2.9**). The resulting metal complex was purified by silica gel chromatography thanks to its chemical stability and high eluting ability. The complex [**3**][(*rac*)-TRISPHAT-N] was found to be moderately soluble in a 1:1 mixture of dichloromethane:pentane at -20 °C. X-Ray quality crystals were obtained and a structural analysis was again performed.

2.5 Conclusions

CpRu half-sandwich complexes are interesting organometallic complexes of which characteristics (steric hindrance and electronic properties) are easily modulated by modification the cyclopentadienyl moiety or the other labile ligands. The nature of the counterion may have also an important influence on the properties of the complex.

[124] (a) Constant, S.; Frantz, R.; Muller, J.; Bernardinelli, G.; Lacour, J., *Organometallics* **2007**, *26* (9), 2141-2143; (b) Constant, S.; Tortoioli, S.; Muller, J.; Linder, D.; Buron, F.; Lacour, J., *Angew. Chem. Int. Ed.* **2007**, *46* (47), 8979-8982.

Several novel CpRu complexes were prepared with different large and lipophilic counterions. All these complexes have been exploited as catalyst precursors in this PhD work and the results obtained are detailed in the following chapters.



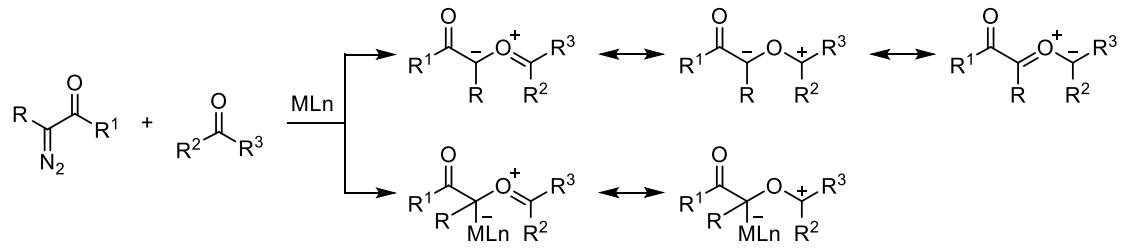
Scheme 2.9 Synthesis and ORTEP view of $[\mathbf{3}]^{+}[(rac)\text{-TRISPHAT-N}]^{-}$ complex. Thermal ellipsoids are drawn at 50 % probability level. Hydrogen atoms are omitted for clarity.

3 Condensation reactions with carbonyl groups

3.1 Introduction

3.1.1 Carbonyl ylides from aldehydes and ketones

Metal carbenes are known to react with aldehydes and ketones.[2] In most cases, the carbonyl group acts as a nucleophile reacting with the electron deficient carbene center to form a metal free carbonyl ylide or metal bonded complexes (**Scheme 3.1**).[125]



Scheme 3.1 Formation of a carbonyl ylide.

In common oxonium ylides the positive charge is mainly localized at the oxygen atom. On the contrary, carbonyl ylides can be described by a different resonance structure in which the positive charge is principally localized at the carbon of the carbonyl. Therefore, these reactive species can also behave as 1,3-dipoles and they can undergo [3+2]-dipolar cycloaddition reactions. Typically, those complexes are used for the synthesis of oxygenated 5-membered heterocycles and natural products.[21c,35,126] In fact, cyclization reactions with dipolarophiles such as double and triple carbon-carbon bonds,[127,128,129] carbonyl groups of aldehydes and ketones,[21c,35,130] imines[131] and nitrile

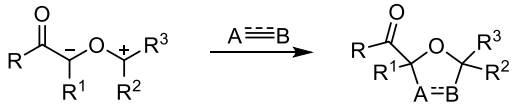
[125] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A., *Chem. Soc. Rev.* **2001**, *30* (1), 50-61.

[126] Padwa, A., *Chem. Soc. Rev.* **2009**, *38* (11), 3072-3081.

[127] Padwa, A.; Pearson, W. H., Synthetic applications of 2,3-dipolar cycloaddition chemistry toward heterocycles and natural products, Wiley, **2003**.

[128] (a) Alt, M.; Maas, G., *Tetrahedron* **1994**, *50* (25), 7435-7444; (b) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S., *Angew. Chem. Int. Ed.* **2006**, *45* (39), 6532-6535; (c) Hodgson, D. M.; Angrish, D., *Adv. Synth. Catal.* **2006**, *348* (16-17), 2509-2514; (d) Hodgson, D. M.; Angrish, D.; Labande, A. H., *Chem. Commun.* **2006**, (6), 627-628; (e) Oguri, H.; Schreiber, S. L., *Org. Lett.* **2005**, *7* (1), 47-50; (f) Muthusamy,

moieties[132] are widely documented in the literature (**Scheme 3.2**) in both intra and intermolecular versions.



Scheme 3.2 [3+2]-dipolar cycloaddition reactions.

The first example of this sort of transformation was reported in 1885 by Büchner and Curtius. Reacting ethyl diazoacetate with benzaldehyde at 160 °C, they obtained product **4** described as depicted in **Figure 3.1**.[133] In a revision of this work 25 years later, Dieckmann recognized the structure of the 1,3-dioxolane product **5**.[134] The mechanism of the reaction was however not clear and the formation of a furodiazole intermediate **6** (**Figure 3.1**) was assumed. In 1982, Huisgen and de March further investigated the process and proposed the carbonyl ylide as intermediate.[129a,135]

S.; Krishnamurthi, J.; Nethaji, M., *Chem. Commun.* **2005**, (*30*), 3862-3864; (g) Anderson, R. J.; Raolji, G. B.; Kanazawa, A.; Greene, A. E., *Org. Lett.* **2005**, *7* (14), 2989-2991; (h) Muthusamy, S.; Gnanaprakasam, B., *Tetrahedron* **2007**, *63* (16), 3355-3362; (i) Molchanov, A. P.; Diev, V. V.; Magull, J.; Vidovic, D.; Kozhushkov, S. I.; de Meijere, A.; Kostikov, R. R., *Eur. J. Org. Chem.* **2005**, (*3*), 593-599.

[129] (a) Huisgen, R.; Demarch, P., *J. Am. Chem. Soc.* **1982**, *104* (18), 4953-4954; (b) Hirata, Y.; Nakamura, S.; Watanabe, N.; Kataoka, O.; Kurosaki, T.; Anada, M.; Kitagaki, S.; Shiro, M.; Hashimoto, S., *Chem. Eur. J.* **2006**, *12* (35), 8898-8925.

[130] (a) Padwa, A., *Helv. Chim. Acta* **2005**, *88* (6), 1357-1374; (b) Padwa, A., *J. Organomet. Chem.* **2005**, *690* (24-25), 5533-5540; (c) Muthusamy, S.; Krishnamurthi, J.; Babu, S. A.; Suresh, E., *J. Org. Chem.* **2007**, *72* (4), 1252-1262.

[131] (a) Torssell, S.; Somfai, P., *Adv. Synth. Catal.* **2006**, *348* (16-17), 2421-2430; (b) Suga, H.; Ebiura, Y.; Fukushima, K.; Kakehi, A.; Baba, T., *J. Org. Chem.* **2005**, *70* (26), 10782-10791.

[132] (a) Ohno, M.; Itoh, M.; Ohashi, T.; Eguchi, S., *Synthesis-Stuttgart* **1993**, (8), 793-796; (b) Wang, Y. L.; Zhu, S. Z., *J Fluorine Chem* **2000**, *103* (2), 139-144; (c) Linder, J.; Moody, C. J., *Chem. Commun.* **2007**, (*15*), 1508-1509; (d) Linder, J.; Blake, A. J.; Moody, C. J., *Org. Biomol. Chem.* **2008**, *6* (21), 3908-3916; (e) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M., *J. Org. Chem.* **1980**, *45* (18), 3657-3664.

[133] Buchner, E.; Curtius, T., *Ber. Dtsch. Chem. Ges.* **1885**, *18* (2), 2371-2377.

[134] Dieckmann, W., *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1024-1031.

[135] Demarch, P.; Huisgen, R., *J. Am. Chem. Soc.* **1982**, *104* (18), 4952-4952.

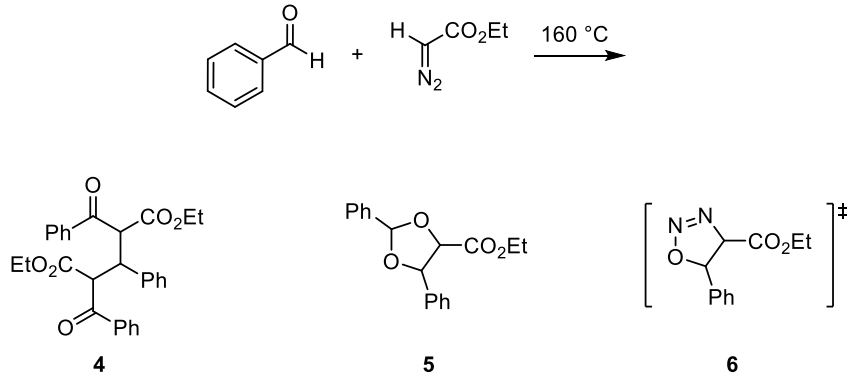
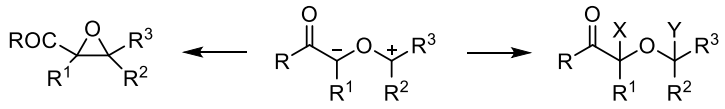


Figure 3.1 Products proposed by Büchner and Curtius (**4)** and Dieckmann (**5**) and furodiazole intermediate **6**.

Along with cycloadditions to double bonds, carbonyl ylides may follow other pathways including rearrangements, ring closure to give epoxides and nucleophilic additions (**Scheme 3.3**).[136]



Scheme 3.3 Reactions of carbonyl ylides.

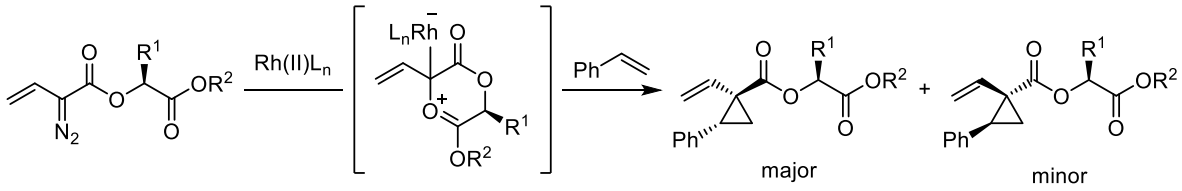
In 1989, studying rearrangement processes, Landgrebe and co-workers observed that the regioselectivity was highly dependent from the metal source.[137] It was thus suggested, for the first time, that a carbonyl ylide transformation could proceed *via* a metal-complexed species: *"it seems inescapable that the catalyst must be present during the [1,4]sigmatropic shift of hydrogen"*.[137] A few years later, Davies and co-workers proposed a metal-complexed carbonyl ylide intermediate to explain the effects of the catalyst structure on the asymmetric cyclopropanation by rhodium(II)-stabilized vinylcarbenes (**Scheme 3.4**).[138] A mechanistic study that provided more direct evidences

[136] Wang, J., *Comprehensive Organometallic chemisty III*; Mingos, D.M.P., Crabtree, R.H. Eds.; *Applications II: Transition metal compounds in organic synthesis 2*; Elsevier: Oxford **2007**; Vol. 11 pp. 151-178.

[137] Lottes, A. C.; Landgrebe, J. A.; Larsen, K., *Tetrahedron Lett.* **1989**, *30* (31), 4093-4096.

[138] Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R.; Olive, J. L., *J. Am. Chem. Soc.* **1993**, *115* (21), 9468-9479.

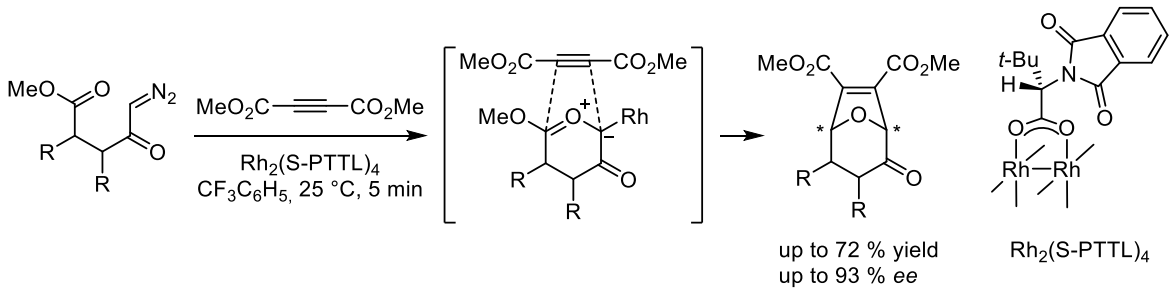
for the involvement of a metal-complexed carbonyl ylide was reported by Padwa and co-workers in 1996.[139]



Scheme 3.4 Metal-complexed carbonyl ylide intermediate in the cyclopropanation reaction.

3.1.2 Carbonyl ylides from esters and amides

The carbonyl group of an ester can undergo the formation of a carbonyl ylide.[2,140] Intramolecular reactions of metal carbenes and esters have been reported by the groups of Padwa,[141] Ibata,[142] Friedrichsen[143] and Hashimoto (**Scheme 3.5**).[144] As shown in these examples, the carbonyl ylides formed can then be trapped in both intra and intermolecular fashion.



Scheme 3.5 Hashimoto's intramolecular carbonyl ylide formation and intermolecular trapping.

[139] Padwa, A.; Austin, D. J.; Hornbuckle, S. F., *J. Org. Chem.* **1996**, *61* (1), 63-72.

[140] Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D., *J. Org. Chem.* **1989**, *54* (4), 817-824.

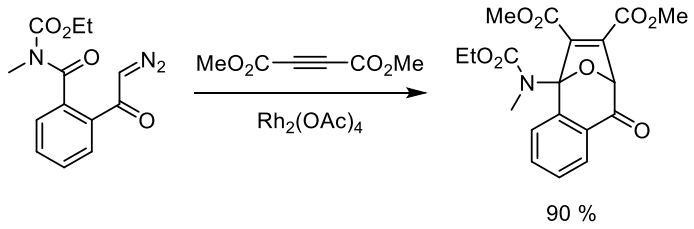
[141] (a) Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D., *J. Am. Chem. Soc.* **1988**, *110* (9), 2894-2900; (b) Padwa, A.; Stull, P. D., *Tetrahedron Lett.* **1987**, *28* (45), 5407-5410.

[142] (a) Ibata, T.; Toyoda, J., *B. Chem. Soc. Jpn.* **1986**, *59* (8), 2489-2493; (b) Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T., *J. Chem. Soc. Chem. Comm.* **1986**, (16), 1266-1267; (c) Ueda, K.; Takebaya.M; Ibata, T., *B. Chem. Soc. Jpn.* **1972**, *45* (9), 2779-2782.

[143] (a) Plug, C.; Friedrichsen, W., *J. Chem. Soc., Perkin Trans. 1* **1996**, (10), 1035-1040; (b) Hildebrandt, K.; Debaerdemaeker, T.; Friedrichsen, W., *Tetrahedron Lett.* **1988**, *29* (17), 2045-2046.

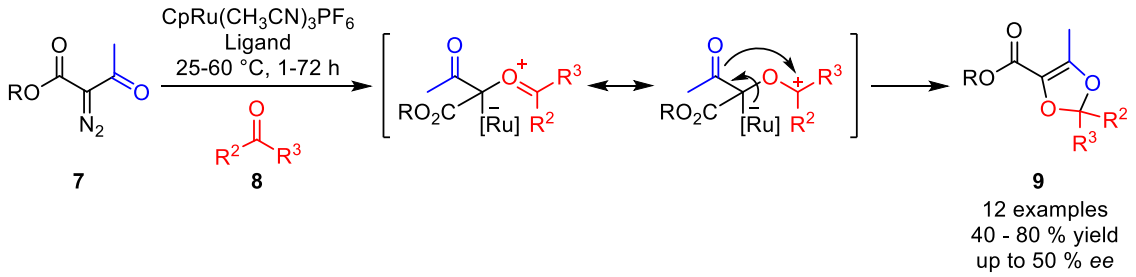
[144] Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S., *Tetrahedron Lett.* **2000**, *41* (31), 5931-5935.

By analogy, addition of a catalytically generated metal carbene to the carbonyl group of an amide is also possible. As happens with esters, also in this case the trapping has only been described in an intramolecular manner.[2] The cyclic carbonyl ylides generated undergo subsequent intra or intermolecular dipolar cycloaddition (**Scheme 3.6**)[145] and intramolecular rearrangement reactions.[146]



Scheme 3.6 Generation of a carbonyl ylide from an amide and subsequent intermolecular cycloaddition.

3.2 Results and discussion



Scheme 3.7 CpRu catalyzed condensation reactions.

As already discussed in the general introduction of this thesis, our group recently reported the CpRu catalyzed reaction between α-diazo-β-ketoesters **7** and aldehydes and ketones **8** (**Scheme 3.7**).[3] In terms of mechanism, the carbonyl group of the aldehyde or

[145] (a) Padwa, A.; Zhi, L., *J. Am. Chem. Soc.* **1990**, *112* (5), 2037-2038; (b) Padwa, A.; Dean, D. C.; Zhi, L., *J. Am. Chem. Soc.* **1989**, *111* (16), 6451-6452; (c) Padwa, A.; Dean, D. C.; Zhi, L., *J. Am. Chem. Soc.* **1992**, *114* (2), 593-601; (d) Padwa, A.; Price, A. T.; Zhi, L., *J. Org. Chem.* **1996**, *61* (7), 2283-2292; (e) Padwa, A.; Hasegawa, T.; Liu, B.; Zhang, Z. J., *J. Org. Chem.* **2000**, *65* (21), 7124-7133; (f) Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheehan, S. M.; Worsencroft, K. J.; Kappe, C. O., *J. Am. Chem. Soc.* **2000**, *122* (34), 8155-8167; (g) Padwa, A.; Boonsombat, J.; Rashatasakhon, P., *Tetrahedron Lett.* **2007**, *48* (34), 5938-5941.

[146] (a) Galt, R. H. B.; Hitchcock, P. B.; McCarthy, S. J.; Young, D. W., *Tetrahedron Lett.* **1996**, *37* (44), 8035-8036; (b) Rodgers, J. D.; Caldwell, G. W.; Gauthier, A. D., *Tetrahedron Lett.* **1992**, *33* (23), 3273-3276.

the ketone is supposed to react with the Ru-metal carbene to form the carbonyl ylide. Subsequent ring closure affords the desired products of type **9**. The scope of such condensation reactions was extended to cyclic carbonyl containing compounds. This strategy would lead to the direct formation of spiro-bicyclic compounds.

3.2.1 Reactivity of cyclic ketones

As benchmark substrates, cyclic ketones **8a-g** were used. Reaction conditions have been slightly modified compared to the procedure developed before:[3] $[CpRu(CH_3CN)_3][BAr_F]$ has been used as precatalyst instead of the PF_6^- salt and ketones have been used in one equivalent only. The results obtained are summarized in **Table 3.1**.

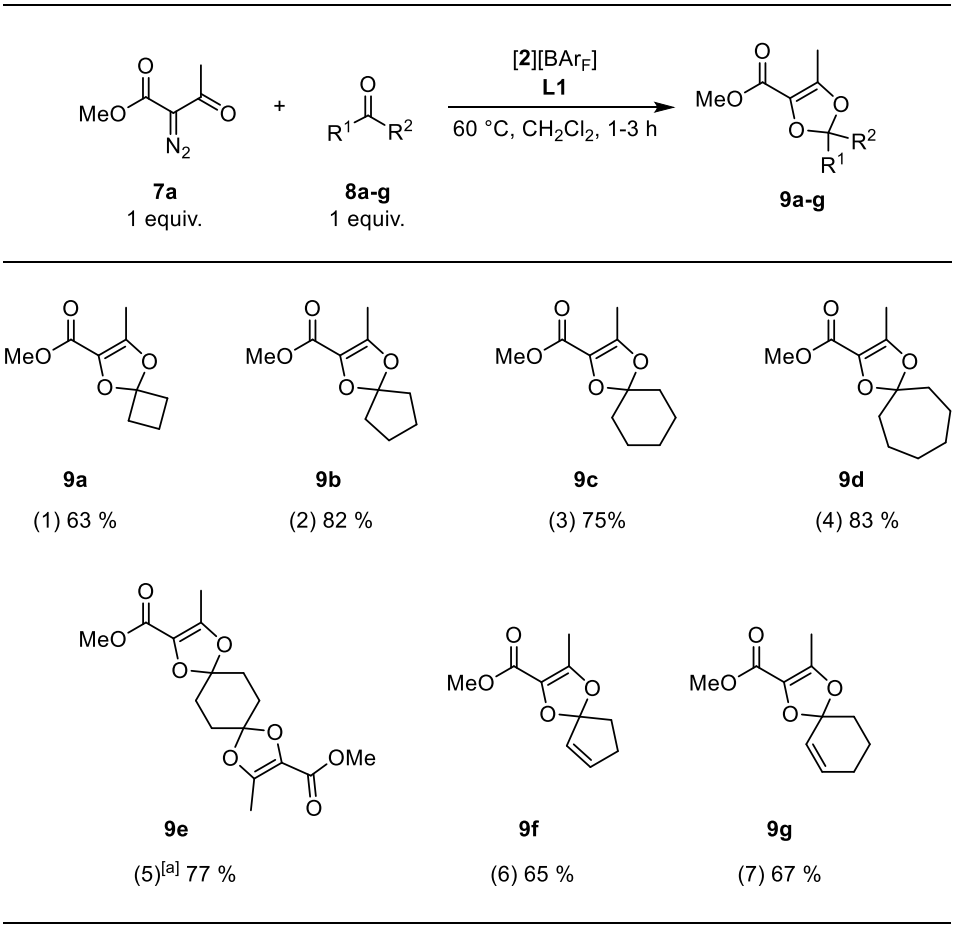


Table 3.1 Reactivity with cyclic ketones **8a-g**. Isolated yields are given as the result of an average of at least two reactions. [a] 2 equivalents of diazo **7a**.

In practice, one equivalent of methyl diazoacetoacetate **7a** was added to a solution of one equivalent of ketone **8a-g** in methylene chloride along with [**2**][BAr_F][147] (2.5 mol %) and **L1** (2.5 mol %). After 1-3 h at 60 °C, full conversion was achieved in all cases, the conversion being determined by ^{1}H NMR (400 MHz) of the clean crude mixture. In all cases, only the corresponding dioxaspiro adducts **9a-g** were isolated in good yields. Increasing the ring size of the cyclic ketone from four to seven membered ring, improved the stability of the corresponding acetals **9** over silica gel, facilitating thus the purification step by chromatography (**Table 3.1**, entries 1-4). Starting from the cyclohexane-1,4-dione **8e**, two equivalents of **7a** were necessary to afford the product of double cycloaddition **9e** which was obtained as single diastereoisomer (**Table 3.1**, entry 5). The diastereoselectivity was established by a detailed NMR analysis and *trans*-configuration was established by X-Ray diffraction studies on X-ray quality crystals (**Figure 3.2**).

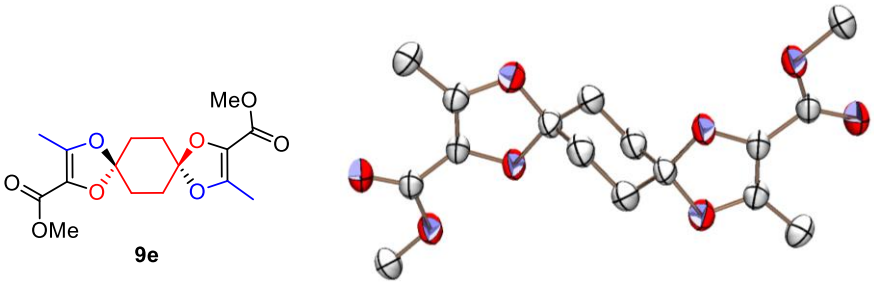


Figure 3.2 ORTEP view of the crystal structure of *trans*-**9e**. Thermal ellipsoids are drawn at 50 % probability.

Using unsaturated substrates **8f** and **8g**, spiro adducts **9f** and **9g** were also obtained as unique products (**Table 3.1**, entries 7 and 8). Products derived from possible cyclopropanations on the electron poor olefin or 1,3-dipolar addition pathways were never observed.[148] However, these adducts were found to be quite more sensitive to acidic conditions, decomposing over SiO_2 during the purification step and in $CDCl_3$ (NMR) after a few hours.

[147] Studies on the counterion effect that are reported in the following chapters have shown that $[CpRu(CH_3CN)_3][BAr_F]$ complex is more efficient than the $[CpRu(CH_3CN)_3][PF_6]$ complex.

[148] Wang, H. B.; Guptill, D. M.; Varela-Alvarez, A.; Musaev, D. G.; Davies, H. M. L., *Chem Sci* **2013**, *4* (7), 2844-2850.

3.2.2 Reactivity of esters and amides

Then esters **10a-f** were tested (**Table 3.2**). Longer reaction time (24 hours) and larger amount of methyl diazoacetoacetate **7a** (3 equivalents) were necessary to obtain the corresponding trioxaspiro adducts **11a-d** in good to excellent yields, demonstrating a "deactivated" nature of such carbonyl group. Again, unsaturated carbonyl groups such as lactones **10b** and **10c** afforded the desired adducts **11b** and **11c** and no evidences of competitive cyclopropanation or epoxide formation could be found (**Table 3.2,** entries 2 and 3). Trioxaspiro adduct **11d**, derived from coumarin **10d**, was found to decompose during chromatography over silica gel or alumina; it was thus recovered in only 64 % yield, despite a complete formation of the desired compound **11d** in the crude (**Table 3.2,** entry 4). Using the 2-bromo-4-methyl-2,5-dihidrofuran **10e** and the 3,4-dibromofuran-2(5H)-one **10f** (**Table 3.2**), no reactivity was however detected, the bromo substituent possibly deactivating further the nucleophilicity of the carbonyl group.

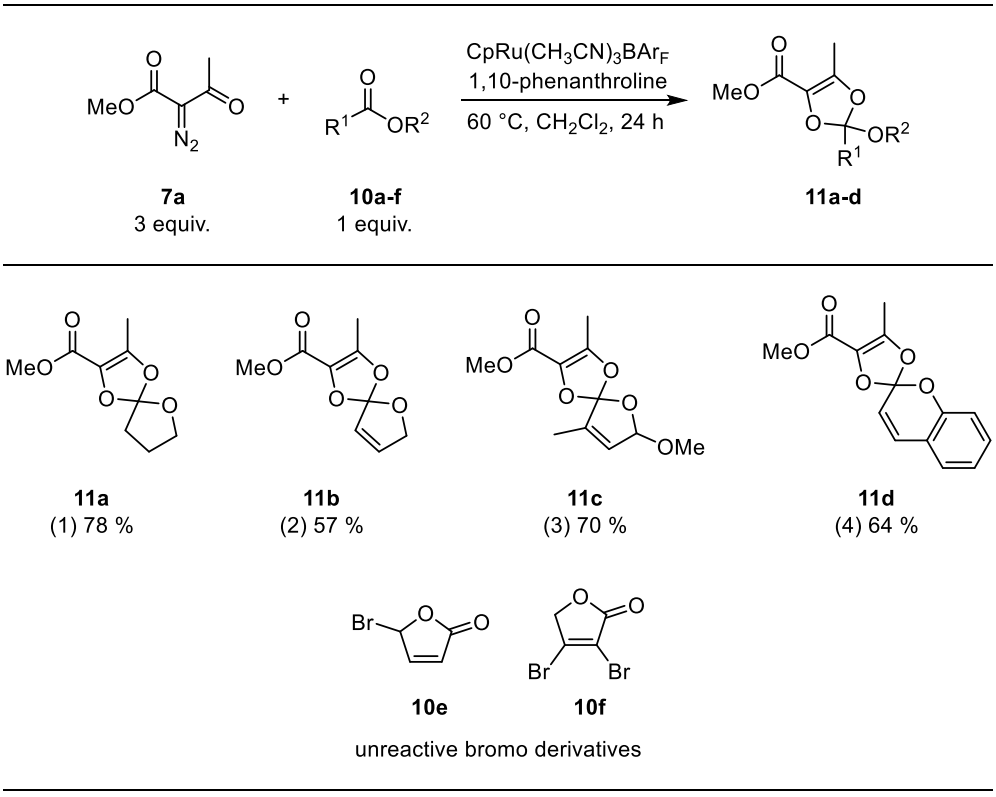


Table 3.2 Reactivity with esters. Isolated yields are given as the result of an average of at least two reactions.

Finally, amide substrates were tested in the form of isatin **12a** and N-methyl isatin **12b** (**Table 3.3**, entries 1 and 2 respectively). In the case of **12a**, both N-H insertion and cycloaddition reactions were observed. Adduct **13a** was recovered as main product but it was isolated in 22 % yield as a 2:1 mixture of isomers (**Table 3.3**, entry 1). This was at first surprisingly as only one compound was expected for this double addition product. Detailed ^{1}H NMR analysis indicated the presence of two signals at 12.85 and 12.81 ppm which suggest a preferred enol form for the β-keto ester chain attached to the nitrogen. The bond distance measured in the X-ray crystal structure (**Figure 3.3**) confirmed this observation. The rotation around the C-N bond is hindered; this bond is thus, an axis of chirality. The presence of two stereogenic elements gives rise to two diastereoisomers.

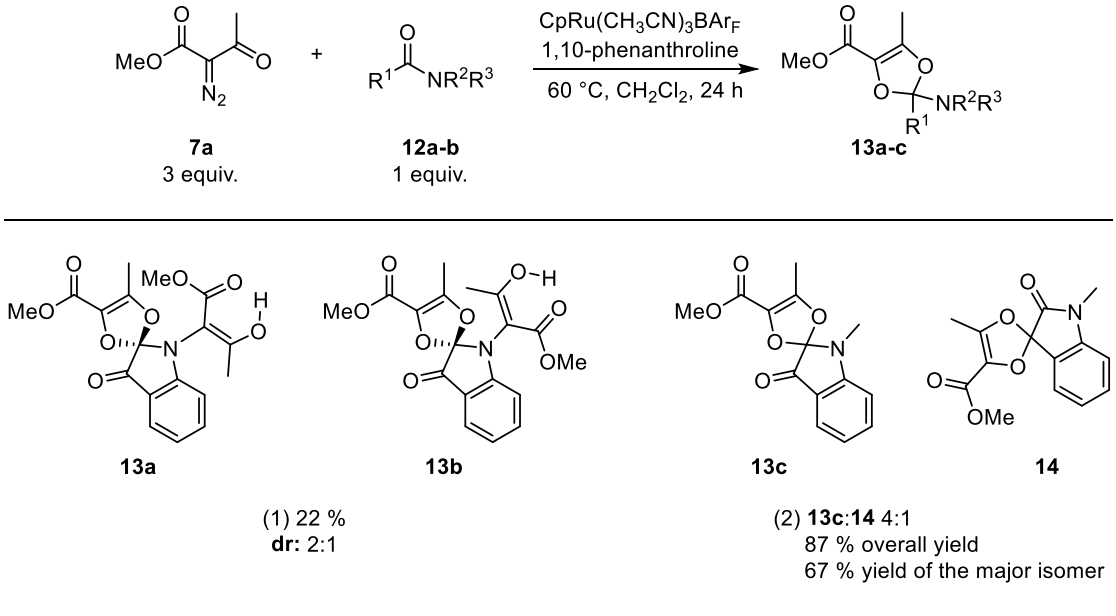


Table 3.3 Reactivity with isatins.

To avoid the N-H insertion, N-methyl isatin **12b** was used. A 4:1 mixture of isomers **13c** and **14** was again obtained corresponding to the formation of the acetal on the "amide" and "keto" groups of **12b** respectively (**Table 3.3**, entry 2). Both IR and NMR spectroscopic analysis showed clearly that the major adduct was the one derived from the attack on the carbonyl group of the amide to give **13c**. This selectivity could be *a priori* rationalized considering a better Lewis basicity of the carbonyl group of an amide compared to that of a ketone. However, this is quite unlikely considering the previous

reactivity of **12b**. The formation of **13c** over **14** being than possibly the result of an alternative intramolecular isomerization process.

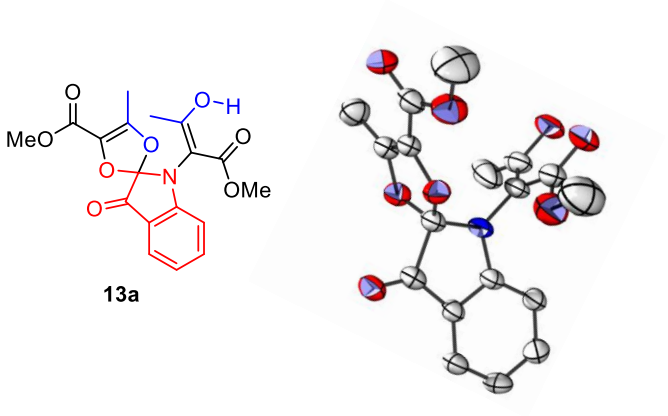
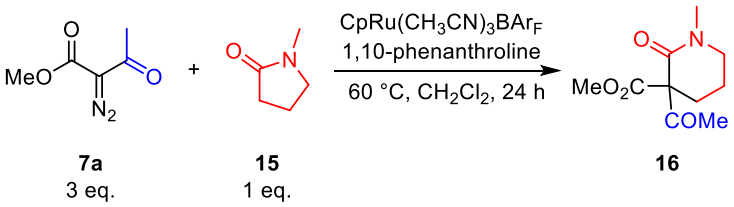


Figure 3.3 ORTEP view of the crystal structure of **13a**. Thermal ellipsoids are drawn at 50 % probability.

A first test with 1-methylpyrrolidin-2-one (NMP) **15** as substrate showed a different and surprising reactivity that has to be confirmed and further investigated.[149] This preliminary result is depicted in **Scheme 3.8**. Using the same catalytic combination, the conversion of **15** in **16** was complete after 1 h. NMR spectroscopic analysis of the reaction mixture indicated the formation of a single product composed of fragments from diazo **7a** and NMP. Based on detailed ^{1}H, ^{13}C and IR analyses, the structure of product **16** was proposed, derived from a C-C insertion next to the carbonyl group.

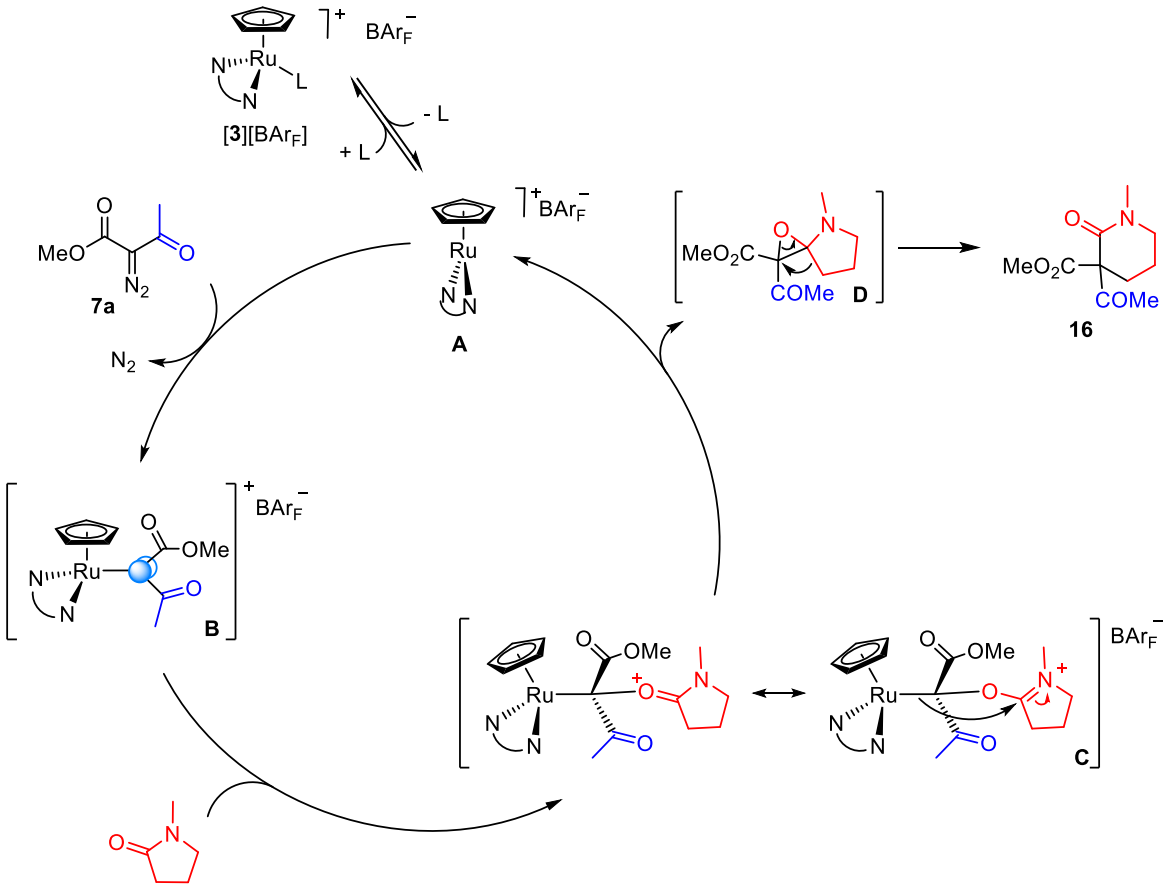


Scheme 3.8 Reactivity with 1-methylpyrrolidin-2-one.

A mechanistic rational is proposed in **Scheme 3.9**. After the *in situ* generation of [**3**][BAr_F], dissociation of the acetonitrile ligand **L** leads to the formation of the catalytically active 16-electrons species **A**. This electron-deficient entity probably promotes the decomposition of diazo reagent **7a** by a classic addition of the "enolate" to

[149] This reactivity has been discovered by Dr. Thierry Achard, postdoctoral associated in our group.

the Lewis acid complex and elimination of molecular nitrogen. It thus affords metal carbene intermediate **B**. At this stage, coordination of the amide generates the carbonyl ylide **C** which can be described by two resonance structures.[150] Cyclization of **C** forms the epoxide intermediate **D**[151] and regenerates the catalyst **A**. Subsequent ring-opening of the epoxide, possibly induced by the lone-pair of the nitrogen atom, and rearrangement would lead to the desired product **16**.



Scheme 3.9 Mechanistic rational.

[150] Kemnitz, C. R.; Loewen, M. J., *J. Am. Chem. Soc.* **2007**, *129* (9), 2521-2528.

[151] (a) Nandra, G. S.; Pang, P. S.; Porter, M. J.; Elliott, J. M., *Org. Lett.* **2005**, *7* (16), 3453-3455; (b) Koduri, N. D.; Scott, H.; Hileman, B.; Cox, J. D.; Coffin, M.; Glicksberg, L.; Hussaini, S. R., *Org. Lett.* **2012**, *14* (2), 440-443; (c) Priebbenow, D. L.; Bolm, C., *Rsc Adv* **2013**, *3* (26), 10318-10322.

3.3 Conclusions

The scope of the reaction of α-diazo-β-ketoesters **7** with ketone moieties catalyzed by CpRu complexes was extended to cyclic ketones **8a-g**. Dioxaspiro compounds **9a-g** were synthesized in a single step and in general good yields. Importantly, in an improvement over the previously reported study,[3] these reactions were performed using a strict stoichiometric amount of ketones only. Clean crude mixtures were obtained as a consequence of highly selective transformations. Moreover, it was shown that the carbonyl group of cyclic esters **10** could be involved in an analogous reactivity. Finally with activated amides **12** as substrates, cyclization on both carbonyl groups was observed while with 1-methypyrrolidin-2-one **15**, an interesting rearrangement occurred. Further investigations are still in progress to better understand this dichotomy.

4 1,3-C-H insertion into THF

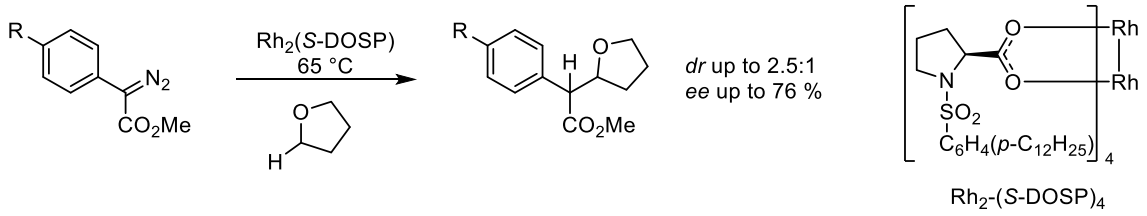
4.1 Introduction

Substituted tetrahydrofurans are ubiquitous motifs in biological and natural product chemistry.[152] The α-functionalization of simple tetrahydrofuran has been achieved through free radical and metal-catalyzed processes.[153] In the field of intermolecular metal carbene C-H insertions,[29] substituted derivatives have been prepared by coupling reactions of diazoacetates or aryldiazoacetates with tetrahydrofuran.[154] For instance, in 1997, Davies and co-workers reported the THF functionalization using rhodium(II) (*S*)-*N*-(*p*-alkylphenyl)sulphonylprolinate (Rh_2(*S*-DOSP)$_4$ complex). Promising regio- and enantioselectivities were obtained (**Scheme 4.1**, *dr* up to 2.5:1 and *ee* up to 76 %).[154a]

[152] (a) Westley, J. W., *Polyether antibiotics : naturally occurring acid ionophores*, (b) M. Dekker, New York, **1982**; Alali, F. Q.; Liu, X. X.; McLaughlin, J. L., *J. Nat. Prod.* **1999**, *62* (3), 504-540; (c) Faul, M. M.; Huff, B. E., *Chem. Rev.* **2000**, *100* (6), 2407-2473; (d) Kang, E. J.; Lee, E., *Chem. Rev.* **2005**, *105* (12), 4348-4378; (e) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S., *Nat. Prod. Rep.* **2005**, *22* (6), 696-716.

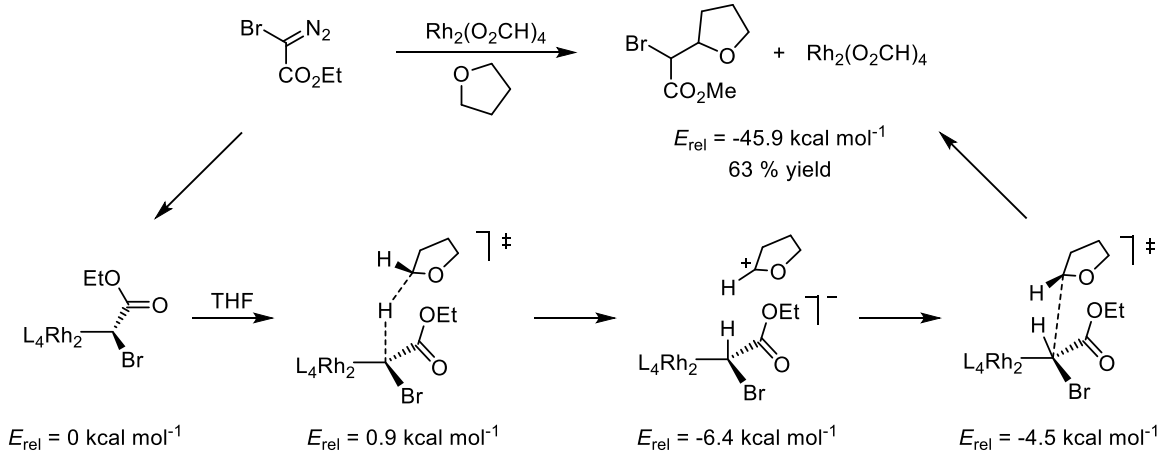
[153] (a) Russell, G. A.; Ngoviwatchai, P., *J. Org. Chem.* **1989**, *54* (8), 1836-1842; (b) Gevorgyan, V.; Priede, E.; Liepins, E.; Gavars, M.; Lukevics, E., *J. Organomet. Chem.* **1990**, *393* (3), 333-338; (c) Matthews, D. P.; Mccarthy, J. R., *J. Org. Chem.* **1990**, *55* (9), 2973-2975; (d) Fontana, F.; Minisci, F.; Yan, Y. M.; Zhao, L. H., *Tetrahedron Lett.* **1993**, *34* (15), 2517-2520; (e) Clark, A. J.; Rooke, S.; Sparey, T. J.; Taylor, P. C., *Tetrahedron Lett.* **1996**, *37* (6), 909-912; (f) Gong, J. C.; Fuchs, P. L., *J. Am. Chem. Soc.* **1996**, *118* (18), 4486-4487; (g) Xiang, J. S.; Mahadevan, A.; Fuchs, P. L., *J. Am. Chem. Soc.* **1996**, *118* (18), 4284-4290; (h) Xiang, J.; Jiang, W. L.; Gong, J. C.; Fuchs, P. L., *J. Am. Chem. Soc.* **1997**, *119* (18), 4123-4129; (i) Inoue, A.; Shinokubo, H.; Oshima, K., *Synlett* **1999**, (*10*), 1582-1584; (j) Kim, S.; Kim, N.; Chung, W. J.; Cho, C. H., *Synlett* **2001**, 937-940; (k) Hirano, K.; Sakaguchi, S.; Ishii, Y., *Tetrahedron Lett.* **2002**, *43* (20), 3617-3620; (l) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K., *Org. Lett.* **2002**, *4* (20), 3509-3511; (m) Yoshimitsu, T.; Arano, Y.; Nagaoka, H., *J. Org. Chem.* **2003**, *68* (2), 625-627; (n) Singh, P. P.; Gudup, S.; Ambala, S.; Singh, U.; Dadhwal, S.; Singh, B.; Sawant, S. D.; Vishwakarma, R. A., *Chem. Commun.* **2011**, *47* (20), 5852-5854; (o) Hao, X.; Liu, C.; Chen, Y.; Zhao, X.; Song, M.; Qian, R.; Guo,H., *Tetrahedron Lett.* **2013**, *54* (50), 6964-6966.

[154] (a) Davies, H. M. L.; Hansen, T., *J. Am. Chem. Soc.* **1997**, *119* (38), 9075-9076; (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R., *J. Am. Chem. Soc.* **2000**, *122* (13), 3063-3070; (c) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J., *J. Am. Chem. Soc.* **2002**, *124* (6), 896-897.



Scheme 4.1 Metal carbene C-H insertion into tetrahydrofuran reported by Davies and co-workers.[154a]

Later, changing the reaction conditions (from 65 to 25 °C) the enantioselectivity of the reaction was improved (up to 97 % *ee*).[154b] In terms of mechanism, a 3-membered transition state was proposed based on several experimental studies.[154b] According to this model, the C-H and C-C bond formations occur in a concerted but non-synchronous way with the build-up of a positive charge at the carbon of the C-H bond α to the oxygen.[2,154b] Recently, for the reaction with ethyl bromodiazoacetate, an alternative mechanism was proposed based on computational studies, which includes two steps with a complete hydride transfer before the formation of the C-C bond (**Scheme 4.2**).[155]



Scheme 4.2 Two steps mechanism proposed by Bonge and Hansen.

Since then, copper,[154c,156] iridium,[157] iron[158] and silver[159] salts or complexes have also been found to efficiently catalyse the insertion of a diazo compound into tetrahydrofurans.

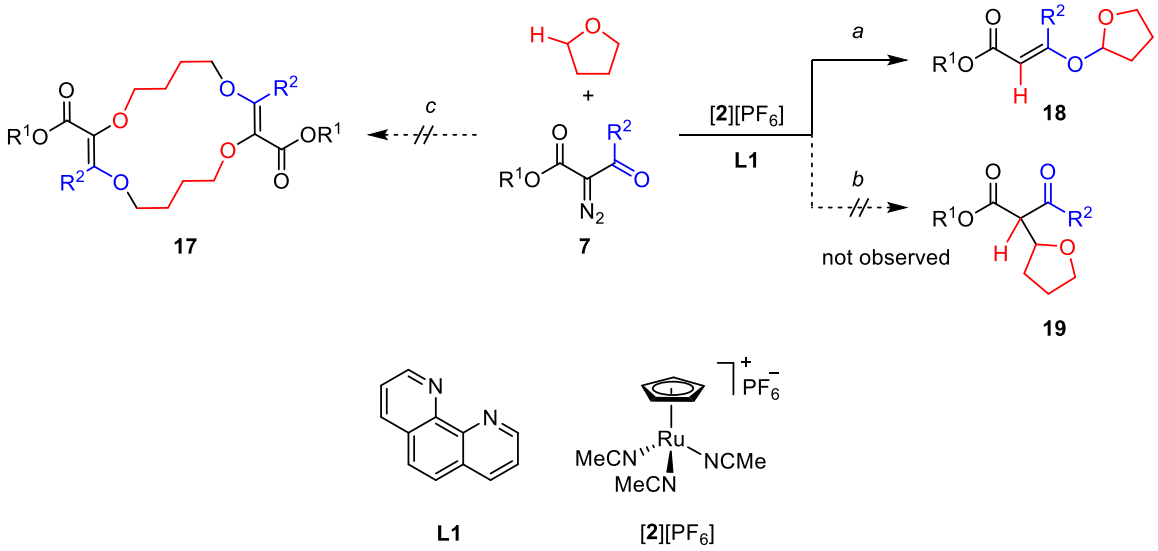
[155] Bonge, H. T.; Hansen, T., *Eur. J. Org. Chem.* **2010**, (23), 4355-4359.

[156] (a) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Roldan, M., *Org. Lett.* **2007**, *9* (4), 731-733; (b) Fraile, J. M.; Mayoral, J. A.; Ravasio, N.; Roldan, M.; Sordelli, L.; Zaccheria, F., *J. Catal.* **2011**, *281* (2), 273-278.

[157] Suematsu, H.; Katsuki, T., *J. Am. Chem. Soc.* **2009**, *131* (40), 14218-14219.

In all these examples, a new C-C bond is formed by insertion of the carbene into a C-H bond α to the oxygen atom of the tetrahydrofuran and 1,1-C-H insertion products were strictly obtained.

4.2 New reactivity with tetrahydrofuran



Scheme 4.3 CpRu catalyzed enol acetate formation via 1,3-C-H insertion reactions of α-diazo-β-ketoesters **7** into THF.

Studying the reactivity of ethyl diazoacetoacetate **7b** in presence of $[CpRu(CH_3CN)_3][PF_6]$ and 1,10-phenanthroline **L1**, Dr. Walid Zeghida (postdoctoral associate in our group) discovered that the acceptor/acceptor carbene reacts with a molecule of tetrahydrofuran by C-H insertion reaction. No evidence for the formation of the macrocyclization adduct of type **17** could be gathered.[64a] NMR spectroscopic analysis of the reaction mixture indicated the formation of a single product composed of fragments of THF and **7b**. However, its structure was not derived from a C-C bond formation between the two fragments and it was different from the already known adduct of type **19**. Based on ^{1}H, ^{13}C NMR and IR spectroscopic analysis, an original enol-acetal product of type **18b** was proposed, obtained through an unprecedented 1,3-C-H insertion reaction

[158] Mbuvi, H. M.; Woo, L. K., *Organometallics* **2008**, *27* (4), 637-645.

[159] Lovely, C. J.; Flores, J. A.; Meng, X. F.; Dias, H. V. R., *Synlett* **2009**, (1), 129-132.

(**Scheme 4.3**). In contrast with what has been observed with donor/acceptor carbenes,[154b] the kinetically favoured formation of C-O instead of C-C bond adducts was attained. In fact, the adduct **18b** was characterized by ^{1}H NMR signals at 5.66 (d, J = 4 Hz, O-CH-O) and 5.32 (s, C=CH) ppm that were at higher frequency that the most deshielded proton of adduct of type **19** (4.43 ppm, m). The *E* configuration of the double bond was determined by NOESY experiment and later confirmed by X-ray diffraction studies, as it will be displayed in Paragraph 4.4.[160] After this initial observation, the purpose of this thesis was to study this original reactivity and extend possibly its scope. Preliminary experiments were carried out using conditions similar to those developed for the cycloaddition and O-H insertion reactions.[3] Methyl diazoacetoacetate **7a** was added to a THF solution of $[CpRu(CH_3CN)_3][PF_6]$ and 1,10-phenanthroline (2.5 mol % each). A moderate heating to 60 °C was necessary to induce gas evolution. At this temperature and under a relatively high concentration (0.5 M in **7a**), the conversion was complete after 3 hours.

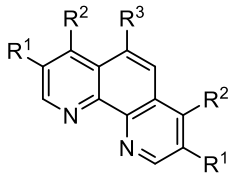
4.3 Optimization of reaction conditions

4.3.1 Ligand screening

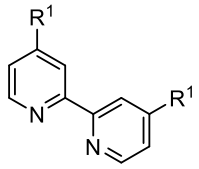
First, trying to improve on the rate of the reaction, a screening study was performed with monodentate and bidentate ligands (**Figure 4.1**) using the following conditions: 60 °C, **7a** 0.5 M in THF, 1:1 ratio of $[CpRu(CH_3CN)_3][PF_6]$ and ligands **L** (2.5 mol % and 5 mol % for bidentate and monodentate ligands respectively). The reaction time was voluntarily set to 2 hours (**L1**: 95 % conv.) and conversions were calculated by ^{1}H NMR, adding 1,3,5-trimethoxybenzene as reference.[161] The results are summarized in **Figure 4.1**. In all the cases in which the reaction was proceeding effectively, **18a** was obtained as the single product. However, conversions of **7a** were lower than with **L1** in all instances. In absence of a ligand, 12 % conversion was observed and a polymerization of THF occurred. No enantioselectivity was observed with enantiopure ligands. Therefore, 1,10-phenanthroline **L1** was selected for further studies.

[160] Tortoreto, C.; Achard, T.; Zeghida, W.; Austeri, M.; Guénée, L.; Lacour, J., *Angew. Chem. Int. Ed.* **2012**, *51* (24), 5847-5851.

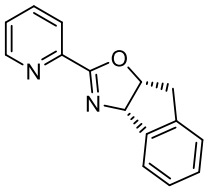
[161] The reference was added at the end of the reaction to avoid interactions with the metal complex.



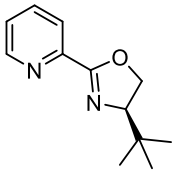
L1: R^1 = H; R^2 = H; R^3 = H; **Conv:** 95 %
L2: R^1 = H; R^2 = Me; R^3 = H; **Conv**: 70 %
L3: R^1 = H; R^2 = OMe; R^3 = H; **Conv**: 48 %
L4: R^1 = H; R^2 = H; R^3 = NO_2; **Conv**: 57 %
L5: R^1 = Me; R^2 = Me; R^3 = H; **Conv**: 50 %
L6: R^1 = H; R^2 = Ph; R^3 = H; **Conv**: 66 %



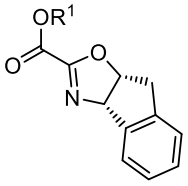
L7: R^1 = H; **Conv**: 27 %
L8: R^1 = OMe; **Conv**: 9 %



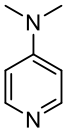
L9; **Conv**: 75 %



L10; **Conv**: 22 %

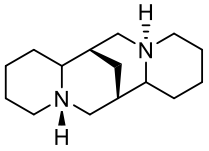


L11; R^1 = Et; **Conv**: 30 %
L12; R^1 = Cs; **Conv**: 0 %

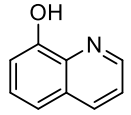


L13; **Conv**: 0 %

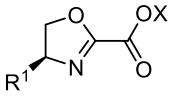
L14; **Conv**: 0 %



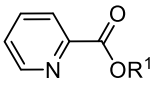
L15; **Conv**: 0 %



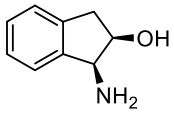
L16; **Conv**: 0 %



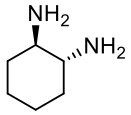
L17: R^1 = *t*-Bu; X = Cs; **Conv:** 0 %
L18: R^1 = *i*-Pr; X = Na; **Conv**: 0 %
L19: R^1 = *i*-Pr; X = Cs; **Conv**: 0 %



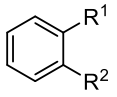
L20: R^1 = H; **Conv:** 7 %
L21: R^1 = Et; **Conv**: 18 %



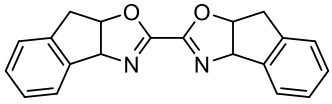
L22; **Conv**: 22 %



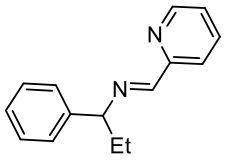
L23; **Conv**: 0 %



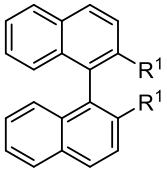
L24: R^1 = R^2 = OH; **Conv**: 30 %
L25: R^1 = R^2 = NH_2; **Conv**: 24 %
L26: R^1 = OH; R^2 = NH_2; **Conv**: 15 %



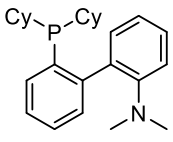
L27; **Conv**: 0 %



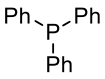
L28; **Conv**: 0 %



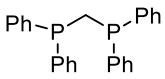
L29: R^1 = R^2 = OH; **Conv**: 15 %
L30: R^1 = R^2 = NH_2; **Conv**: 22 %



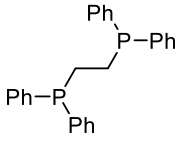
L31; **Conv**: 0 %



L32; **Conv**: 0 %



L33; **Conv**: 0 %



L34; **Conv**: 0 %

Figure 4.1 Ligands **L1-L34**. Conversion of **7a** after 2 h of reaction at 60 °C with 2.5 mol % of $[CpRu(CH_3CN)_3][PF_6]$ and 2.5 and 5 mol % of bidentate and monodentate ligands respectively.

4.3.2 Metal complex selection

Other metal sources were then tested. Copper salts did not induce the formation of the product **18a**. $Rh_2(OAc)_4$ led to the macrocyclization reaction[64a] in favour of **17** (43 % yield) with **18a** observed as side product (10 % yield). Other cyclopentadienyl ruthenium(II) salts were also studied and the results are reported in **Table 4.1**.

Entry	$[Ru]^+$	$Anion^-$	Conv [a]
1	$CpRu(CH_3CN)_3$	PF_6	95
2	$CpRu(CH_3CN)_3$	SbF_6	95
3	$CpRu(CH_3CN)_3$	TRISPHAT[b]	80
4	$CpRu(CH_3CN)_3$	TRISPHAT-N[b]	43
5	$CpRu(CH_3CN)_3$	OTf	30
6	$Cp^*Ru(CH_3CN)_3$	PF_6	90

Reaction conditions: diazo **7a** (0.32 mmol), [**Ru**] and **L1** (2.5 mol %), THF (0.6 mL), 2 h, 60 °C. [a] Conversions of **7a** (^{1}H NMR, 1,3,5-trimethoxybenzene as internal reference). [b] Used in racemic form.

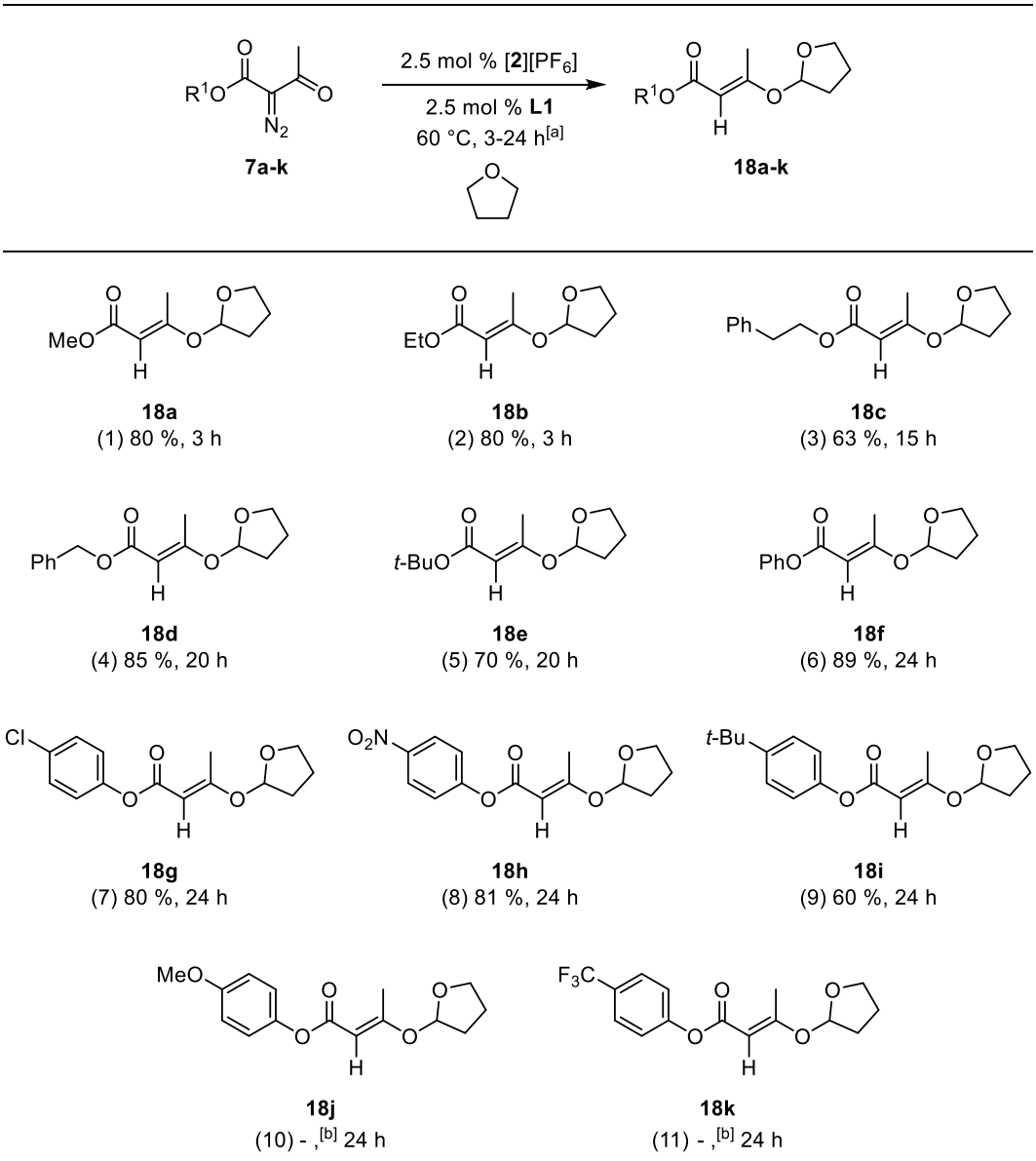
Table 4.1 CpRu complex selection.

Complexes with large lipophilic counterions such as SbF_6 or TRISPHAT had a similar reactivity to that of $[CpRu][PF_6]$ (**Table 4.1**, entries 2 and 3). Lower conversions were observed with anions able to coordinate the metal centre like OTf and TRISPHAT-N (**Table 4.1**, entries 4 and 5). A good conversion was obtained using the $[Cp^*Ru(CH_3CN)_3][PF_6]$ complex but the reaction was accompanied by polymerization of THF. For that reason, the original $[CpRu(CH_3CN)_3][PF_6]$ complex was utilized in all further experiments.

4.4 Scope of the reaction

Variations on the diazo compound were then considered to investigate the scope of the reaction (**Table4.2**). First, substrates with different ester groups were tested (allyl, alkyl, aryl). Reactions were allowed to run until full conversion. With bulkier alkyl esters prolonged reaction times were necessary to afford the corresponding products **18** in

moderate to good yields (**Table4.2**, entries 2-5; up to 20 h, 63-85 %). Moderate yields were often obtained due to the volatility of the products, compounds of type **18** being the only adducts observed in the ^{1}H NMR spectra of the very clean crude mixtures.



Reaction conditions: diazo **7** (0.32 mmol), [**2**][PF_6] and **L1** (2.5 mol %), THF (0.6 mL), 60 °C. Isolated yield are given as the result of an average of at least two reactions. [a] Reaction time at 100 % conversion. [b] Decomposition of the product upon chromatography.

Table 4.2 Substrate scope.

With such mild conditions it was even possible to use aryl esters **7g-k** as reagents leading in all cases to the desired enol acetal motif (**Table4.2**, entries 6-11). In basically

all cases 1,3-C-H insertion products of type **18** were obtained in good yields (60-89 %). After 24 h, complete conversions were achieved with aryl esters bearing reagents possessing either electron-withdrawing and electron-donating substituents in *para* position, this indicating a global lack of electronic effect. Compounds **18j** and **18k** (**Table4.2**, entries 10 and 11) although predominant in the crude mixtures, decomposed however upon chromatography purification over SiO_2 or AlO_3. Product **18g** was found to be moderately soluble in a 4:1 mixture of hexanes and diethyl ether. X-ray quality crystals were afforded and a structural analysis was performed (**Figure 4.2**).

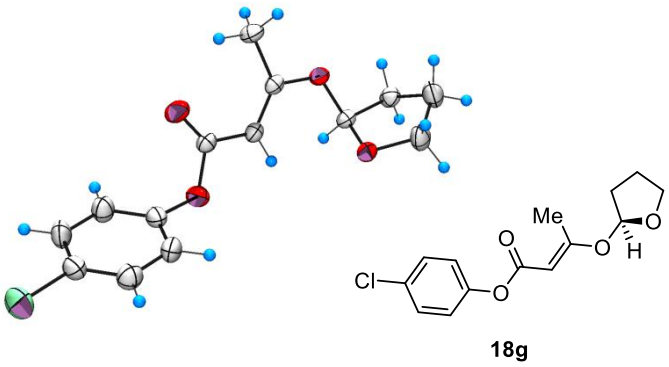
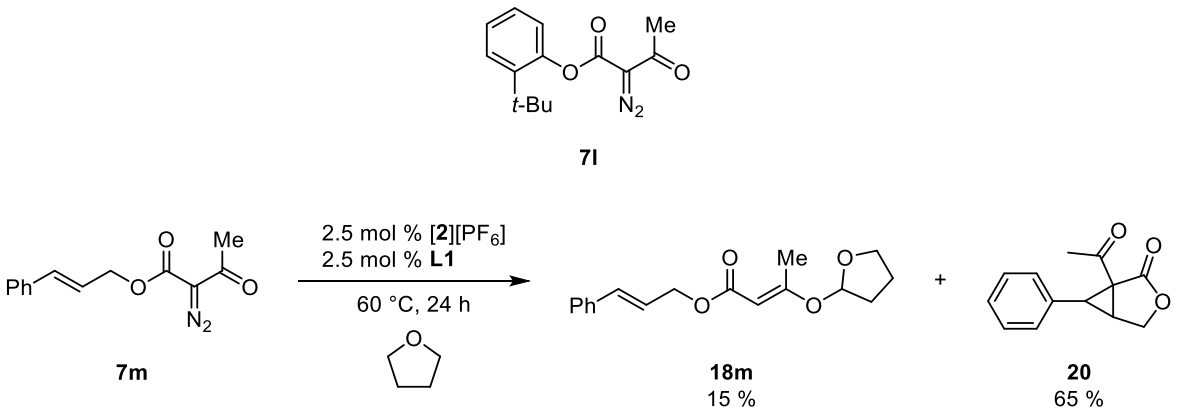


Figure 4.2 ORTEP view of the crystal structure of **18g**. Thermal ellipsoids are drawn at 50 % probability.

Only the highly hindered *ortho-t-Bu*-phenyl reagent **7l** did not lead to any insertion reaction. In this case after 48 h only 25 % conversion of **7l** was observed in favour of a product of dimerization of the diazo reagent (**Scheme 4.4**). Cinnamyl-derived **7m** was also tested (**Scheme 4.4**). In this case, the product of intramolecular cyclopropanation **20** predominated (65 % overall yield, mixture of diastereoisomers) and the corresponding enol acetal **18m** was isolated in 15 % yield only (**Scheme 4.4**).[162]

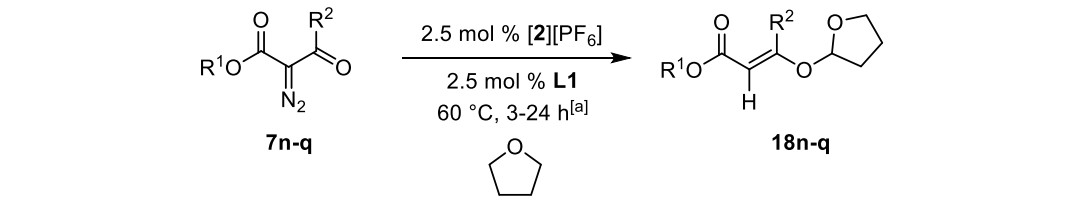
[162] Lin, W.; Charette, A. B., *Adv. Synth. Catal.* **2005**, *347* (11-13), 1547-1552.

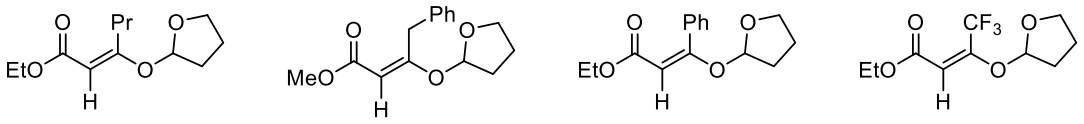


Scheme 4.4 Limitations of the scope.

Then the ketone substituent was modified (**Table 4.3**). With a propyl chain instead of methyl, a similar reactivity was observed and, after 3 h of reaction, the product **18n** was isolated in 65 % yield (**Table 4.3**, entry 1). With benzyl and phenyl residues, reactions were slower and yields lower, indicating a negative contribution of the aromatic moieties (**Table 4.3**, entries 2 and 3). Lower yields were in fact obtained with substrates containing aryl substituents which could be explained by a trapping of the CpRu fragment by the aromatic rings.[163] In the case of **7q** (**Table 4.3**, entry 4) the reaction was fast but the corresponding product **18q** decomposed upon chromatography. This can be due to the fact that the presence of the electron-withdrawing CF_3 group can increase the leaving group ability of the enol fragment, leading to a rapid hydrolysis of the C-O bond during purification.

[163] Hermatschweiler, R.; Fernández, I.; Pregosin, P. S.; Breher, F., *Organometallics* **2006**, *25* (6), 1440-1447.





18n
(1) 65 %, 3 h

18o
(2) 44 %, 24 h

18p
(3)[b] 27 %, 24 h

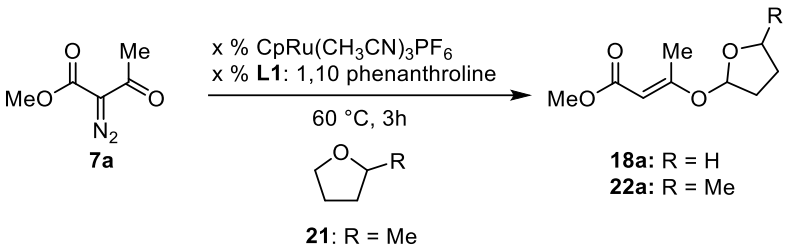
18q
(4) - ,[c] 3 h

Reaction conditions: diazo **7** (0.32 mmol), [**2**][PF_6] and **L1** (2.5 mol %), THF (0.6 mL), 60 °C. Isolated yield are given as the result of an average of at least two reactions. [a] Reaction time at 100 % conversion. [b] Incomplete reaction. Conversion not measurable by ^{1}H NMR. [c] Decomposition of the product upon chromatography.

Table 4.3 Modification of the ketone substituent.

4.5 Regioselectivity

Looking forward to replacing regular THF by more elaborated (less available) ether substrates, the reaction was performed in dichloromethane as solvent, varying the number of equivalents of tetrahydrofuran and 2-methyl-tetrahydrofuran **21**. The results are summarized in **Table 4.4**. The reaction proceeded well even with a 1:1 stoichiometry between **7a** and THF or **21** (**Table 4.4**, entries 2 and 6). A longer reaction time was necessary (24 h instead of 3 h) to achieve complete conversion. However, isolation of **22a** resulted to be much easier using this procedure.



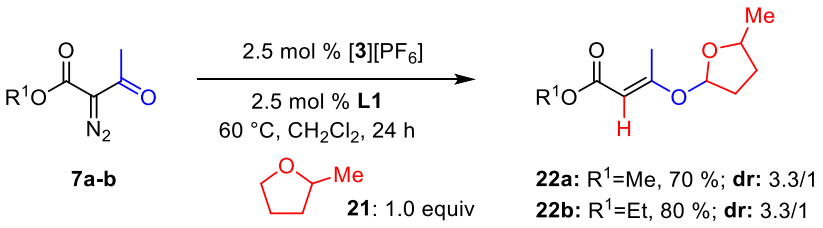
Entry	R	Ether	[**2**][PF_6] (mol %)	Product	Conv (%)
1	H	Solvent	2.5	**18a**	100
2	H	1 equiv	2.5	**18a**	35[a]
3	H	1 equiv	3.5	**18a**	70
4	H	5 equiv	2.5	**18a**	100
5	Me	Solvent	2.5	**22a**	100
6	Me	1 equiv	2.5	**22a**	12[a]
7	Me	1 equiv	3.5	**22a**	95
8	Me	5 equiv	2.5	**22a**	95
9	Me	10 equiv	2.5	**22a**	95

Reaction conditions: diazo (0.32 mmol), [$CpRu(CH_3CN)_3$][PF_6] (2.5 mol %), **L1** (2.5 mol %), THF (0.6 ml) or THF (n equivalents) and CH_2Cl_2 (0.6 ml), 60 °C, 3h. [a] Complete conversion after 24 h.

Table 4.4 Optimization of reaction conditions.

With these conditions in hand, products **22a** and **22b** were obtained, in good yields (70 % and 80 % respectively, **Scheme 4.5**). The C-O bond formation occurred exclusively on the secondary CH_2 carbon. As discussed earlier, a preferential C-H insertion on the tertiary carbon could have been expected based on electronic factors.[164] However, in the present case and in line with previous studies, the regioselectivity is best rationalized on steric ground.[29b,154b,164] Finally, compounds **22a** and **22b** were obtained as 3.3:1 mixtures of diastereoisomers due to a lack of discrimination.

[164] Taber, D. F.; Ruckle, R. E., *J. Am. Chem. Soc.* **1986**, *108* (24), 7686-7693.

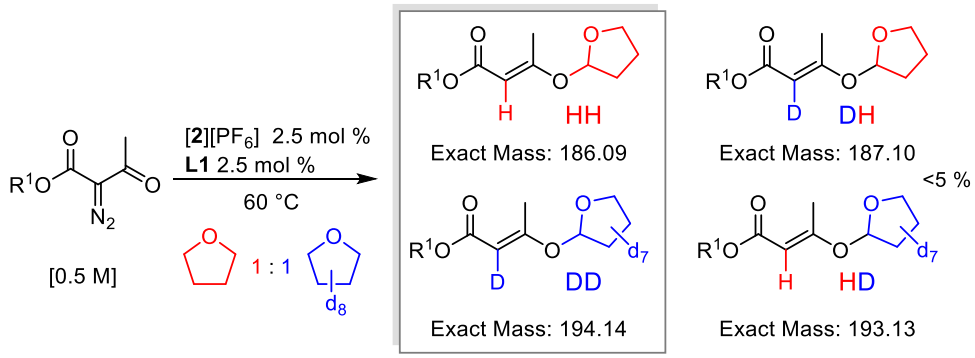


Scheme 4.5 C-H insertion with 2-methyl-tetrahydrofuran **21**.

4.6 Mechanistic studies

4.6.1 Cross over experiments

In order to gain some mechanistic insight on the transformation, series of experiments were performed using diazo **7a**, **7f** and **7h** in 1:1 mixtures of THF and THF-d_8 (**Table 4.5**).



Entry	R^1	Product	Ratio HH / DD[a]
1	Me	**18a**	3.0 / 1.0
2	Ph	**18f**	3.3 / 1.0
3	4-$NO_2C_6H_4$	**18h**	3.4 / 1.0

Reaction conditions: diazo (0.32 mmol), [**2**][PF_6] and **L1** (2.5 mol %), THF (0.6 mL), 60 °C. [a] Measured by ^{1}H NMR and confirmed by ESI-MS.

Table 4.5 Homocoupling and kinetic isotope effect.

Electrospray mass spectra (**Figure 4.3**) were obtained and the analysis indicated the predominant formation of the homocoupling products **HH** and **DD** (more than 95 %) over cross over products **HD** and **DH** (less than 5 %), the small amount of products **DH** and **HD** with (M+1)+1 and (M+1)+7 mass being possibly the result of a cross over after a dissociation and recombination (vide infra).

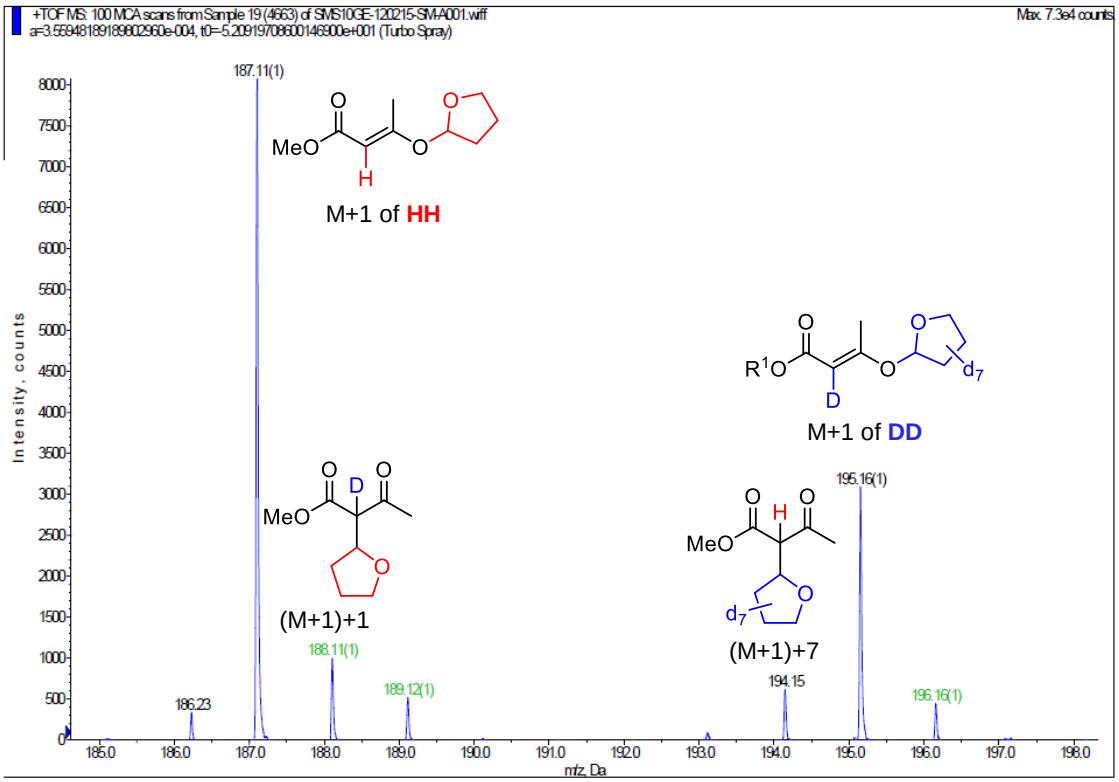


Figure 4.3 HRMS-ESI spectrum of the crude mixture of substrate **14a** (all masses plus 1).

These MS results suggest a concerted hydrogen transfer mechanism. A larger portion of **HH** over **DD** was also denoted (**Table 4.5**). The ratio among the isotopomers was determined by ^{1}H NMR spectroscopic analysis (**Figure 4.4**). The measured k_H/k_D values, in the range of 3.0-3.4, indicates the occurrence of a primary kinetic isotope effect.[165] Those values are in accordance with previously reported results for C-C bond forming reactions.[154b]

[165] Gomez-Gallego, M.; Sierra, M. A., *Chem. Rev.* **2011**, *111* (8), 4857-4963.

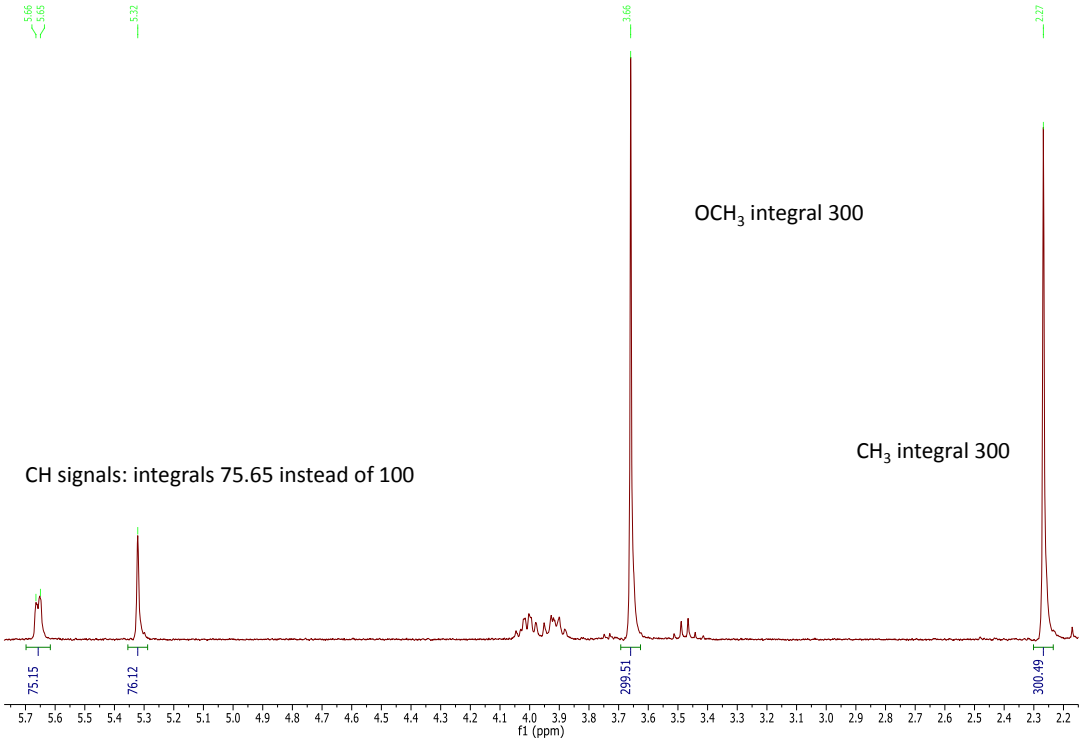


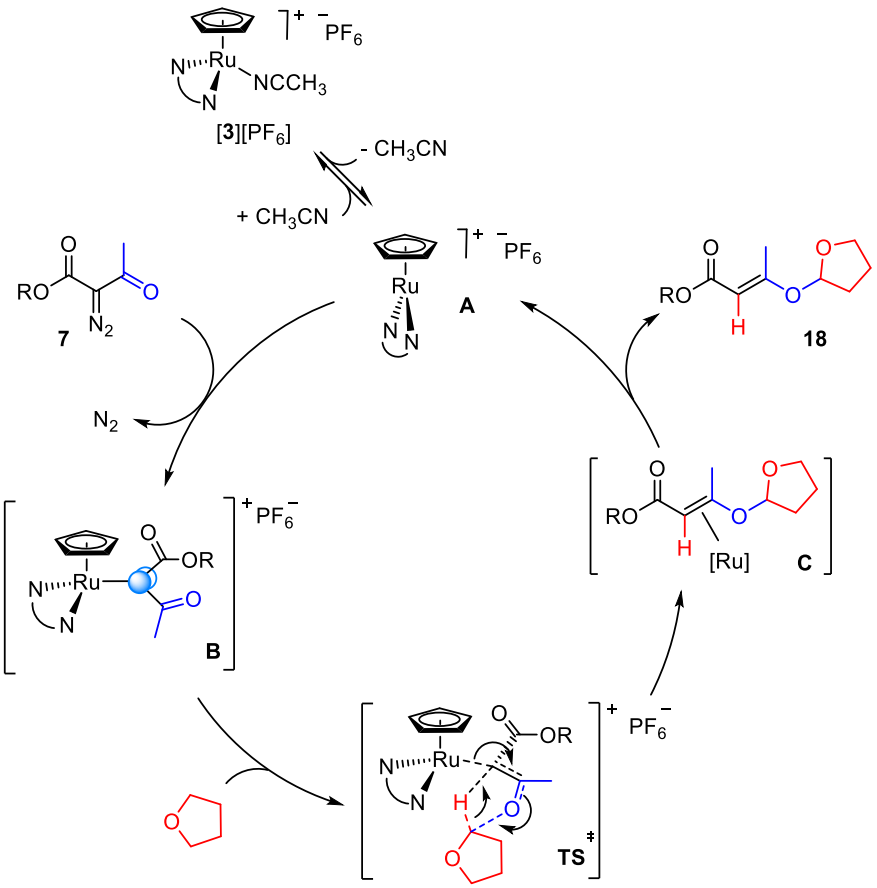
Figure 4.4 ^{1}H NMR spectrum (400 MHz, $CHCl_3$) for compound **18a**. Detailed view.

4.6.2 Mechanistic rationale

As just detailed, the absence of cross-over products suggests a concerted hydrogen transfer. A mechanistic rationale coherent with the gathered information is proposed in **Scheme 4.6**. After the *in situ* generation of [**3**][PF_6] complex, dissociation of the acetonitrile ligand led to the formation of a catalytically active 16-electron species **A**. This electron-deficient entity probably promotes the decomposition of diazo reagents **7** by a classic addition of the "enolate" to the Lewis acidic complex and elimination of molecular nitrogen. It affords the metal carbenes intermediates of type **B**. At this stage, unlike the classical C-H insertions proceeding *via* the 3-membered transition state discussed in the Paragraph 1.4.2, that would lead to compound of type **19** (**Scheme 4.3**),[2] a concerted reaction can occur that involves the keto group of the carbene and the less hindered C_α-H bond of the ether moiety.[166] The concomitant formation of the new C-O and C-H bonds takes place in a 5-membered transition state. This step is

[166] Ozen, C.; Tuzun, N. S., *Organometallics* **2008**, *27* (18), 4600-4610.

stereodetermining as the *s-cis* conformation of the carbonyl group – metal center bond in intermediate **B** is conserved to form the (*E*)-configurated enol **18**. Finally the product is released and the catalyst regenerated.



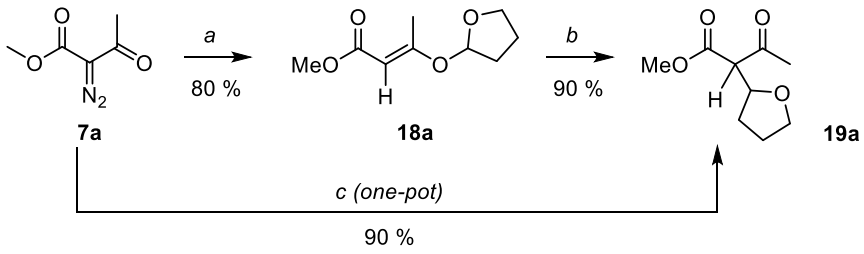
Scheme 4.6 Mechanistic rationale.

4.7 Rearrangement reactions

Last, compounds **18** were treated in the presence of Lewis acids to promote a rearrangement and obtain the "classical" products of C-C bond formation. In fact, under such conditions, the enol fragment behaved as a leaving group.[167] Induced dissociation led to two reactive enolate and oxycarbenium intermediates that recombine to form

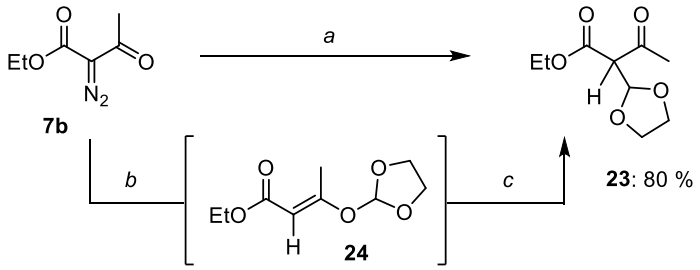
[167] (a) Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W., *J. Chem. Soc., Perkin Trans. 1* **2000**, (12), 1815-1827; (b) Dixon, D. J.; Ley, S. V.; Tate, E. W., *J. Chem. Soc., Perkin Trans. 1* **2000**, (15), 2385-2394; (c) Dixon, D. J.; Ley, S. V.; Tate, E. W., *J. Chem. Soc., Perkin Trans. 1* **1999**, (19), 2665-2667.

adducts of type **19**. This reaction of **18a** giving **19a** can be promoted with a catalytic amount of $Cu(OTf)_2$ or TMSOTf (5 mol %, **Scheme 4.7**). It was also possible to combine the C-H insertion and the rearrangement steps in a one pot sequential process using one equivalent of THF only. **19a** was thus obtained in a higher yield (90 %) than for the two steps procedure (72 % combined).



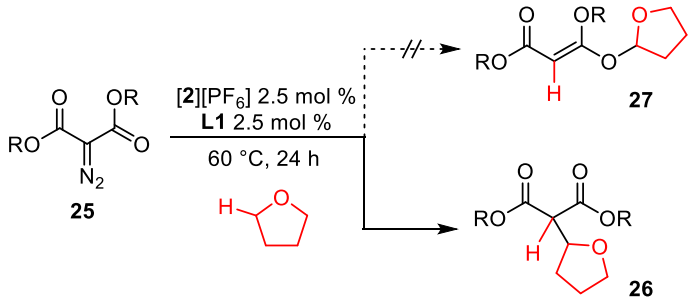
Scheme 4.7 a) [**2**][PF_6] (2.5 mol %), **L1** (2.5 mol %), THF, 60 °C, 3 h; b) TMSOTf or $Cu(OTf)_2$ (5 mol %), CH_2Cl_2, 0 → 25 °C, 1 h; c) **1.**[**2**][PF_6] (2.5 mol %), **L1** (2.5 mol %), THF (1 equiv), CH_2Cl_2, 60 °C, 24 h. **2.** TMSOTf or $Cu(OTf)_2$ (5 mol %), CH_2Cl_2, 0 → 25 °C, 1 h**.**

Noteworthy, using 1,3-dioxolane instead of THF as reactive ether, the insertion proceeded well and, in this case, the rearrangement occurred spontaneously under thermal conditions, without the need for an added Lewis acid (**Scheme 4.8**). In fact, at 60 °C, decomposition of **7b** in presence of 1,3-dioxolane led to the formation of **23** as a single product in 80 % yield after 3 hours. The product of 1,3-insertion **24** was however observed in the crude after 1 hour of reaction at 25 °C. Two hours at 60 °C were then sufficient to induce the rearrangement into **23**. This result indicates again that the 1,3-insertion forming process is kinetically preferred over the classical 1,1-insertion using this catalytic combination.



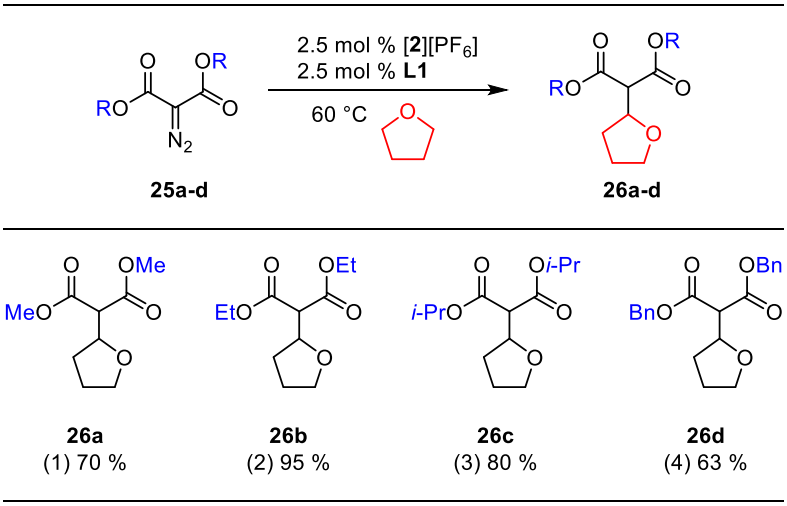
Scheme 4.8 [**2**][PF_6] (2.5 mol %), **L1** (2.5 mol %), 1,3-dioxolane (solvent): a) 60 °C, 3 h; b) 25 °C, 1 h; c) 60 °C, 2 h.

4.8 Reactivity of diazomalonates with THF



Scheme 4.9 Favored C-H insertion reaction of diester diazo compounds with THF.

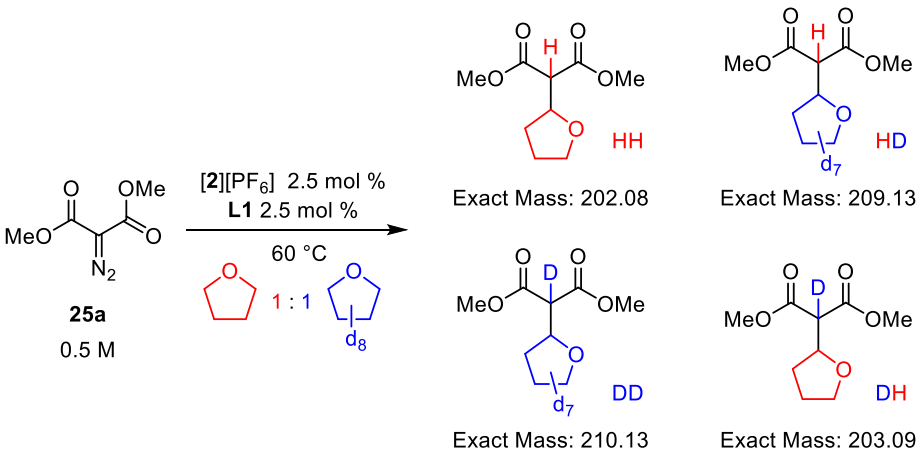
We next turned our attention on the reactivity of diazomalonates. Using diesters **25** instead of β-ketoester diazo compounds, the standard reaction conditions provided the formation of the 1,1-C-H insertion adducts **26** only (**Scheme 4.9**).Several reagents were used (R = Me, Et, *i*Pr, Bn) and compounds of type **22** were obtained in good yields (**Table 4.6**).



Reaction conditions: **21** (0.32 mmol), [**2**][PF_6] and **L1** (2.5 mol %), THF (0.6 mL), 60 °C. Isolated yield are given as the result of an average of at least two reactions.

Table 4.6 Substrate scope.

To gain some mechanistic insights on the reactive dichotomy between diesters **25** and β-ketoester **7** diazo compounds, a first experiment was performed using diazo malonate **25a** in a 1:1 mixture of THF and THF-d_8 (**Figure 4.5**).



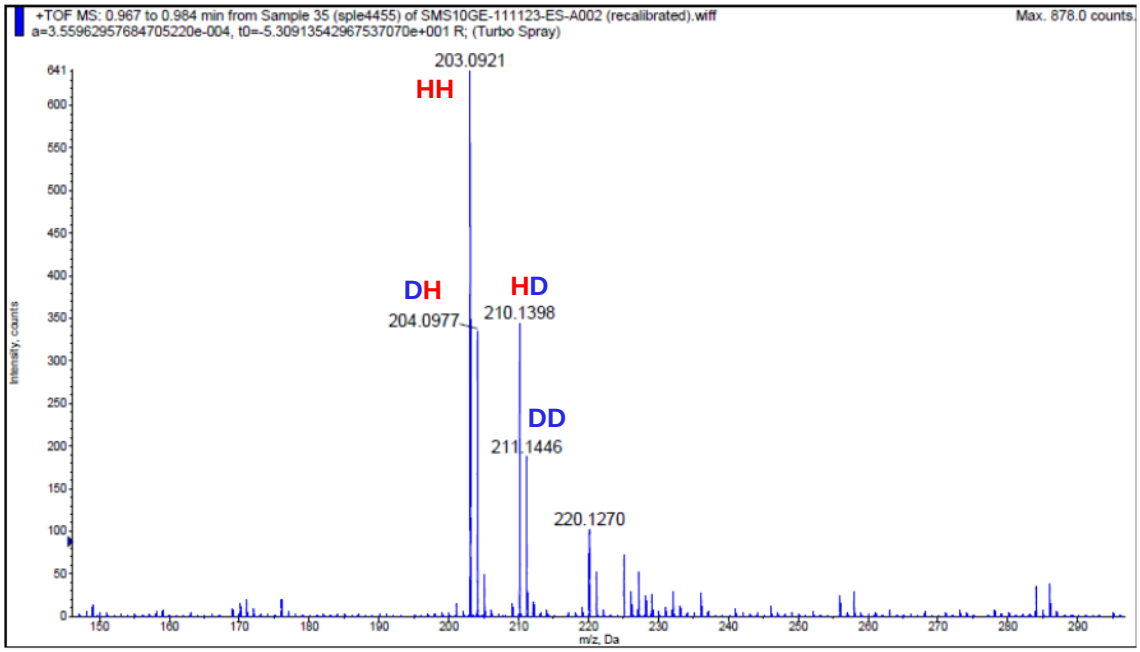
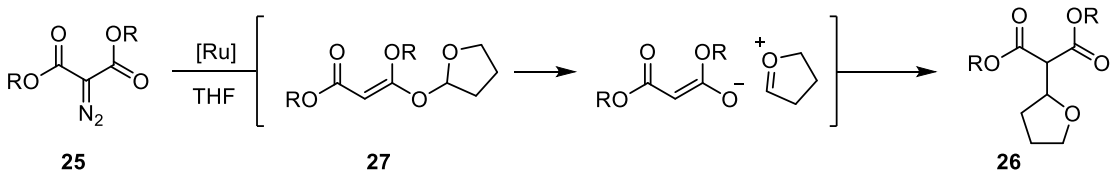


Figure 4.5 HRMS-ESI spectrum of the crude mixture of substrate **22a** (all masses plus 1).

In clear contrast with the previous situation, MS spectrum measurement indicated the formation of both homocoupling products (**HH** and **DD**) and cross over products (**HD** and **DH**), the statistical distribution being however perturbed by the presence of an isotope effect. This result suggests a 1,3-C-H insertion followed by a dissociation/reassociation process in contrast with the commonly-invoked three membered transition state mechanism for the C-H insertion reactions.[2, 154b] Knowing that the enol fragment of products **18** behaves already as a leaving group[167] (Paragraph **4.7**),[160] it was logical to conceive the acrylate fragment act as a leaving group as well. The reaction thus proceeds

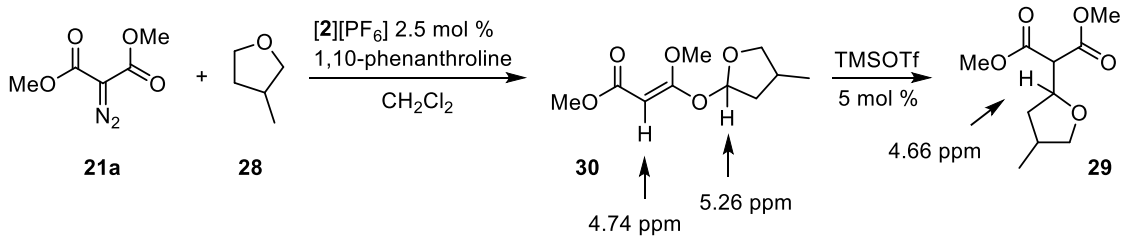
through the formation of an instable intermediate of type **27** that, after a spontaneous or CpRu-promoted dissociation/rearrangement pathway, it provides products of type **26** (**Scheme 4.10**). Trying to validate this hypothesis, an experiment was performed using an *in situ* IR monitoring. Unfortunately, it was not possible to observe the appearance of signals that could correspond to the desired intermediate.



Scheme 4.10 Hypothesis on a possible dissociation/rearrangement pathway.

Using 1 equivalent of 3-methyltetrahydrofuran **28** instead of regular THF as reactive ether and performing the reaction in dichloromethane, it was possible to observe in the ^{1}H NMR of the crude mixture two set of signals at 5.26 (d, J = 5 Hz) and 4.74 (s) ppm that are at quite higher frequency than the most deshielded proton of the product **29** (m, 4.66 ppm). This set of signals looks actually very similar to that one generated from enol acetal adducts of type **18** and thus advocates the possible formation of the intermediate **30** derived from the 1,3-C-H insertion reaction (**Scheme 4.11**).

Compound **30** could be identified as a mixture of diatereoisomers after flash chromatography. Treatment of **30** with TMSOTf (5 mol%) led to the rearrangement to the 1,1-C-H insertion adducts **29**.



Scheme 4.11 Reactivity with 3-methyltetrahydrofuran. Products **29** and **30** were obtained as mixture of isomers but only one is depicted for clarity reasons.

Adduct **31** was synthesized, derived from the reaction between α-diazo-β-ketoester **7a** and 3-methyl THF **28**. A comparison between the ^{1}H NMR spectra of (a) methyl (*E*)-3-((4-methyltetrahydrofuran-2-yl)oxy)but-2-enoate **31**, (b) **30** (crude mixture), (c) **30** after

flash chromatography and (d) **29** after addition of TMSOTf (crude mixture) is reported in **Figure 4.6** (all the products were obtained as mixture of isomers but only one isomer has been drown for clarity reasons).

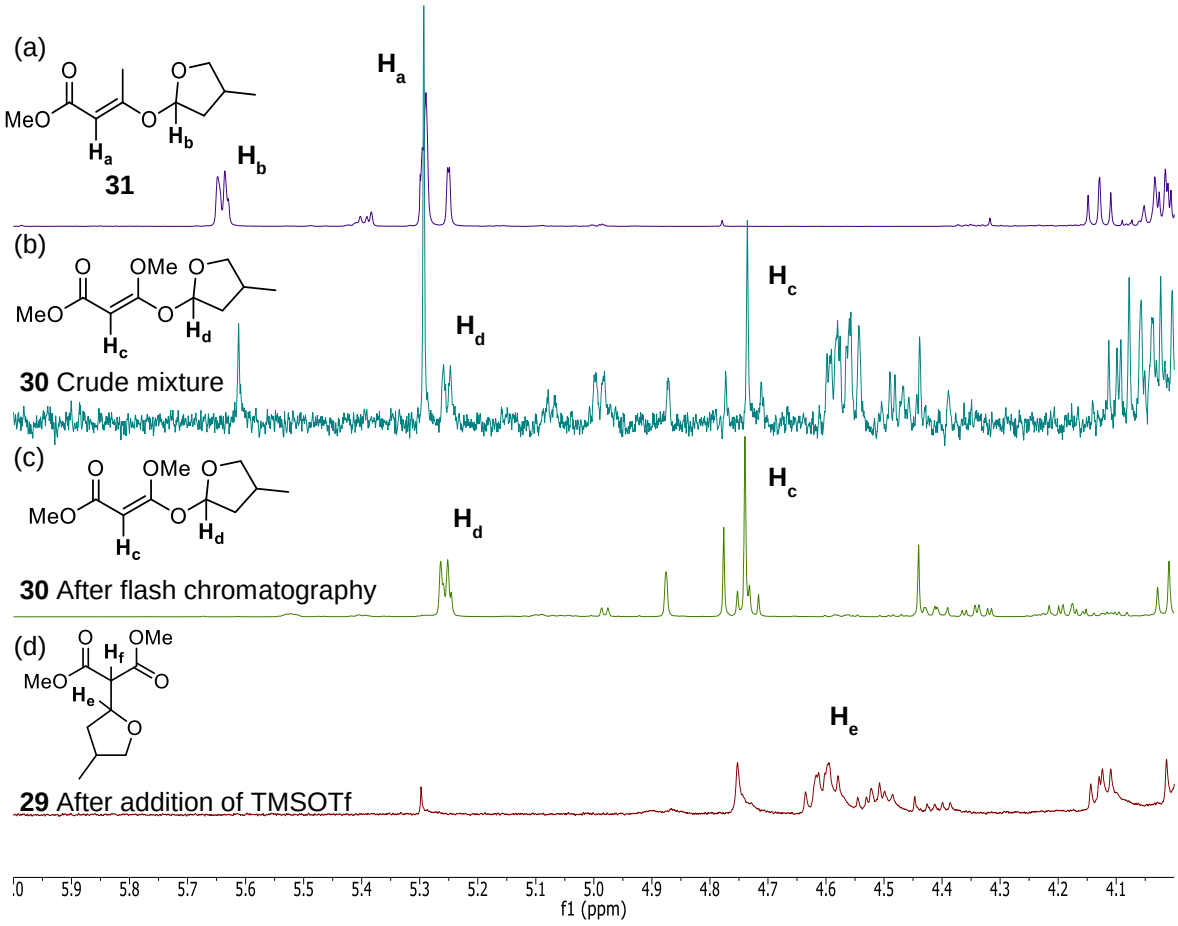


Figure 4.6 ^{1}H NMR of (a) methyl (E)-3-((4-methyltetrahydrofuran-2-yl)oxy)but-2-enoate **31**; (b) methyl (E)-3-methoxy-3-((4-methyltetrahydrofuran-2-yl)oxy)acrylate **30** (crude mixture); (c) methyl (E)-3-methoxy-3-((4-methyltetrahydrofuran-2-yl)oxy)acrylate **30** after flash chromatography; (d) **29**, after addition of TMSOTf (crude mixture). All the products were obtained as mixture of isomers but just one isomer has been drawn to simplify the figure.

4.9 Conclusions

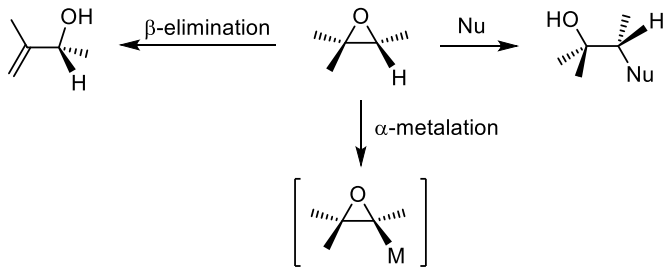
A new reactivity in CpRu-catalyzed decomposition of diazo compounds has been described and, as a consequence, a novel functionalization mode of tetrahydrofurans. To our knowledge, it is the first one-step synthesis of enol acetal moieties by direct C-H activation. It is proposed that this process occurs through a concerted pathway for the hydrogen transfer. A 5-membered transition state has been proposed, in which the

concomitant formation of the new C-H and C-O bonds occurs. The reaction was found to be regio- and stereoselective. The rearrangement of the enol acetal adducts to the classical insertion products was further evidenced in presence of Lewis acids. A different reactivity was observed with diester diazo compounds. With these reagents the rearrangement seems to occur spontaneously under the reaction conditions.

5 Epoxides reactivity

5.1 Introduction

Epoxides or oxiranes are ubiquitous motifs in biological and natural product chemistry.[168] Moreover, they are among the more versatile functional groups in organic synthesis. In fact, the epoxide motif is extensively active, due to the high ring strain energy ($\Delta H_{f\ gas}^{0}$ = -27.5 kcal/mol)[169,170] derived in part from the angles bond within the three membered ring which have to be formally around 60° instead of the ideal tetrahedral angle of 109.5°. This, together with their ready availability rendered them extensively used in a wide range of transformations.[168] Doubtless, the most typical transformations are nucleophilic additions leading to the epoxide ring-opening (**Scheme 5.1**). Also, they react with strong bases to give β-elimination reactions. By abstraction of an α-proton, α-metalated epoxides can be obtained which are useful intermediates in several processes.



Scheme 5.1 Reactivity of epoxides.

In general, many different nucleophiles can react such as nitrogen, sulfur, oxygen, carbon, halide and hydride nucleophiles.[168] For example, amines cleanly open epoxides to

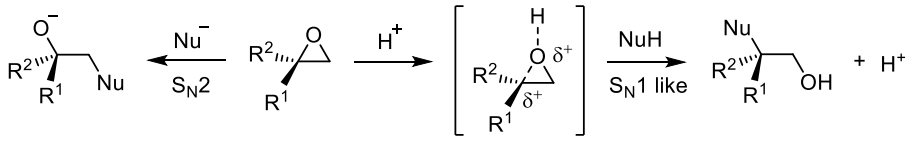
[168] Yudin, A.I., *Aziridines and epoxides in organic synthesis*, Wiley, **2006**.

[169] Morgan, K. M.; Ellis, J. A.; Lee, J.; Fulton, A.; Wilson, S. L.; Dupart, P. S.; Dastoori, R., *J. Org. Chem.* **2013**, *78* (9), 4303-4311.

[170] Cox, J.D.; Pilcher, G. *thermochemistry of organic and organometallic compounds*; academic press: new York **1970** Pedley, J.B. *thermochemical data and structures of organic compounds, thermodynamics research center*: college station TX **1994** vol1 Afeefy H.Y. Liebman, J. F., stein, S. E. In NIST chemistry webbook NIST standard reference database number 69 linstrom P.J., Mallard, W.G. Eds. ; national institute of standards and technology: Gaithersburg, MD.

give amino-alcohols. Hydrolysis in acidic conditions generates glycols. The main advantage of these ring-opening reactions is that the competing elimination processes are disfavoured and the expected compounds can be easily isolated in good yield.

The mechanism of the nucleophilic attack and, consequently, the regioselectivity depend, in general, on the reaction conditions.[171] In presence of a strong nucleophile, the transformation follows a S_N2 mechanism (**Scheme 5.2**). Steric hindrance becomes the controlling factor and the attack occurs on the less substituted carbon.



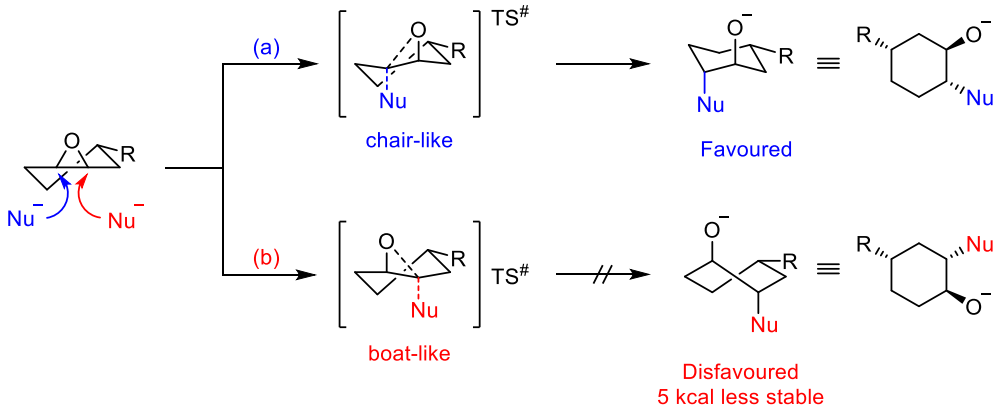
Scheme 5.2 S_N2 *vs* S_N1 like nucleophilic substitution.

In acid-catalysed reactions, a protonation of the substrate takes place first to produce a positively charged intermediate and the reaction assumes than a S_N1-like character. The positive charge is stabilized (delocalized) in the presence of substituents on the carbon of the epoxide; this leads to an elongation of the C-O bond in the direction of the more substituted carbon that accommodates better the developing positive (δ+) charge. The nucleophilic attack than would be favoured on this centre (**Scheme 5.2**). Unfortunately the regioselectivity in this second case is not always high, the substitution at the less hindered carbon remaining often fast for kinetic reasons.

The S_N2 ring opening is stereospecific and it proceeds with inversion of configuration at the carbon that undergoes the nucleophilic attack. In the case of substituted cyclohexene oxides, the nucleophilic attack occurs according to the Fürst-Plattner rule leading to the direct formation of the *trans* diaxial product (**Scheme 5.3**). This stereoselectivity is due to the preferred formation of a chair-like transition state (*vs* a boat-like).[172]

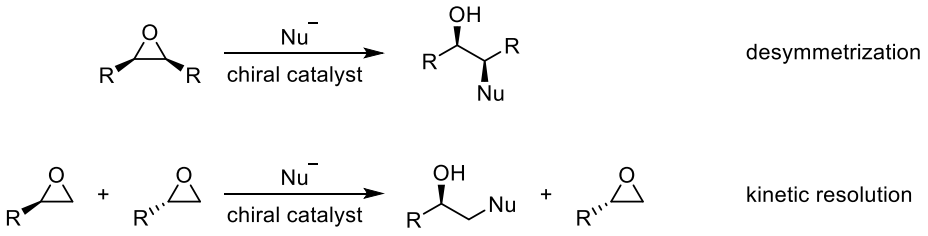
[171] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., *Organic Chemistry*, Oxford University Press, **2001**.

[172] Kirby, A. J., *Stereoelectronic Effects*, New York: Oxford Science Publications, **2002**, p. 54.



Scheme 5.3 Nucleophilic attack on substituted cyclohexene oxides.

Significant efforts have been made also in the development of asymmetric epoxide ring-opening reactions.[168] Selectivity in this case can be obtained through a desymmetrization of *meso*-epoxides or a kinetic resolution of racemic mixture of epoxides (**Scheme 5.4**). It is important to note that the reactivity is highly dependent from the nature (mono, di-, tri-, tetrasubstituted) of the epoxide. [168]



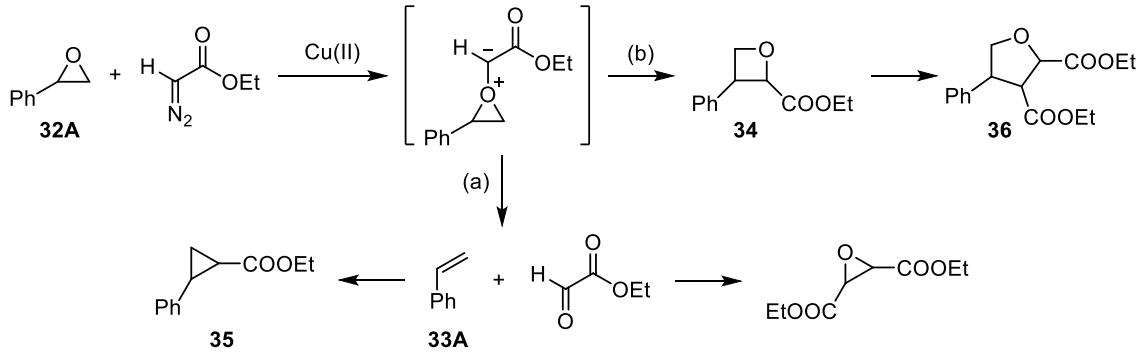
Scheme 5.4 Asymmetric ring-opening reactions.

5.2 Reactivity of epoxides toward metal carbenes

Up to now, only few examples of reactions between metal carbenes and epoxides have been reported.[35] Reactions with metal carbenes are rarely envisaged despite the well-known Wittig-like oxonium ylide chemistry for other cyclic ethers.[2] Noyori and co-workers first described the copper catalyzed decomposition of ethyl diazoacetate in presence of an excess of styrene oxide **32A** leading to a complex mixture of products.[173]

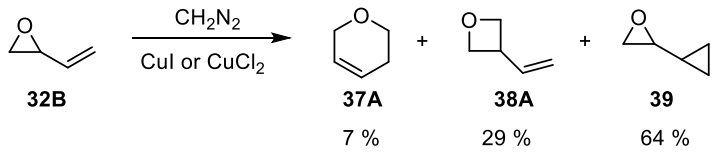
[173] Nozaki, H.; Takaya, H.; Noyori, R., *Tetrahedron* **1966**, *22* (10), 3393-3401.

The formation of a metal free oxygen ylide was hypothesized that could successively lead to the styrene **33A** through a deoxygenation pathway (**Scheme 5.5** (a)) or to the *cis/trans* mixture of oxetanes **34** (**Scheme 5.5** (b)). These products could be attacked a second time to yield respectively a cyclopropane **35** and a substituted tetrahydrofuran **36**, the relative yields depending on reaction conditions (temperature and catalyst).



Scheme 5.5 Noyori's copper catalyzed reaction of ethyl diazoacetate with styrene oxide.

Few years later, Kapps and Kirmse reported the treatment of vinyloxirane **32B** with diazomethane in presence of a catalytic amount of copper(I) or (II) salts that afforded a mixture of 5,6-dihydro-2H-pyran **37A**, 3-vinyloxetane **38A** and cyclopropyloxirane **39** in 7 %, 29 % and 64 % yield respectively (**Scheme 5.6**).[174]

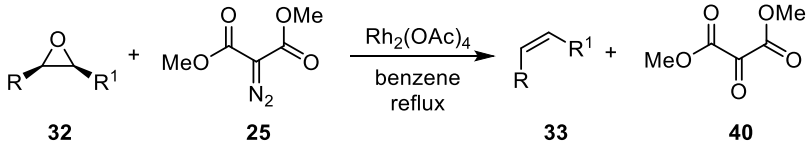


Scheme 5.6 Copper catalyzed reaction of vinyloxirane **32B** with diazomethane.

In 1984, Martin and Ganem described the rhodium(II) catalyzed deoxygenation of epoxides in presence of the acceptor/acceptor dimethyl diazomalonate under mild conditions (**Scheme 5.7**).[175]

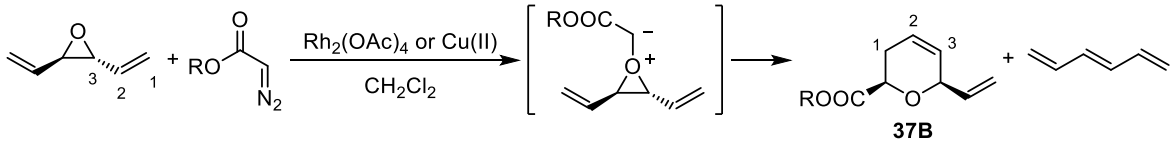
[174] Kapps, M.; Kirmse, W., *Angew. Chem. Int. Ed.* **1969**, *8* (1), 75.

[175] Martin, M. G.; Ganem, B., *Tetrahedron Lett.* **1984**, *25* (3), 251-254.



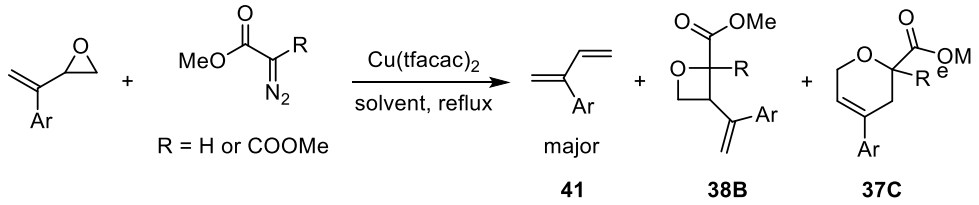
Scheme 5.7 Rhodium catalyzed deoxygenation of epoxides with acceptor/acceptor diester diazo compounds.

More recently, Quinn and co-workers reported the copper(II) or rhodium(II) ring expansion of *trans*-divinyl ethylene oxide by oxonium ylide [2,3]-sigmatropic rearrangement for the synthesis of 2,6-*cis* substituted dihydropirans **37B** (**Scheme 5.8**).[176] The desired products were however obtained in moderate yield and the scope of the reaction was found to be limited by the competitive deoxygenation.



Scheme 5.8 Dihidropyran synthesis by divinyl epoxide ring expansion.

In 2012, Njardarson and co-workers used the same strategy with vinyl oxirane obtaining a mixture of three products, the one derived from a deoxygenation pathway (**41**) being again the predominant. The other two adducts were determined to be the oxetane **38B** derived from a [1,2]-insertion pathway and the dihydropiran **37C** coming from the [2,3]-sigmatropic rearrangement (**Scheme 5.9**).[177]



Scheme 5.9 Ring expansion of vinyl oxirane.

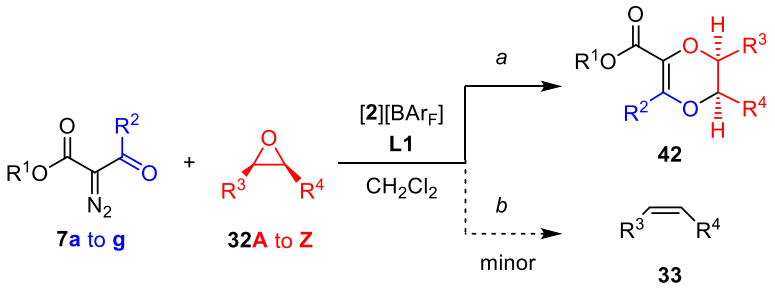
[176] Quinn, K. J.; Biddick, N. A.; DeChristopher, B. A., *Tetrahedron Lett.* **2006**, *47* (41), 7281-7283.

[177] Mack, D. J.; Batory, L. A.; Njardarson, J. T., *Org. Lett.* **2012**, *14* (1), 378-381.

5.3 New reactivity with epoxides

As exemplified in the previous chapter on the THF reactivity, rhodium and ruthenium catalysts can lead to very different products. Since rhodium mainly converts epoxides into alkenes, it seemed interesting to explore the reactivity of this functional group in presence of [CpRu($CH_3CN)_3$][X] complex. Treatment of epoxides of type **32** in presence of classical diazo **7** under the conditions optimized for the reaction of THF, led to an unexpected result, that is the clean formation of dioxene motifs of type **42** through stereoselective ring opening and three atoms insertion reactions (**Scheme 5.10**).[178]

In practice, in the initial experiments, one equivalent of **7a** was added to a methylene chloride solution of styrene oxide **32A** (one equivalent), [**2**][PF_6] complex and **L1** (2.5 mol % each). A moderate heating to 60 °C was necessary to induce a gas evolution. At that temperature and under relatively high concentration (0.5 M in **7a**), the conversion of the diazo reagent was complete after 24 hours. NMR spectroscopic analysis of the reaction mixture indicated the presence of two products in a 4.4:1 ratio; the major product being the heterocycles **42aA** and a minor one (**33A**) the alkene derived from the deoxygenation pathway. Interestingly, the major product **42aA** was present as a single regioisomer.

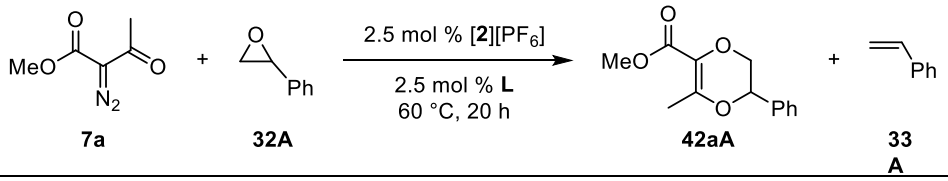


Scheme 5.10 Dioxene formation via three atom insertion reactions of diazocarbonyles **7a** to **g** into epoxides **32A** to **Z**. In product **42xY**, the first and second letters (**x** and **Y**) relate to the reactive diazo **7x** and epoxide **32Y** respectively.

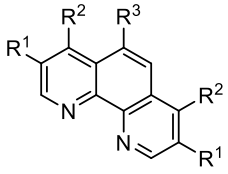
[178] Achard, T.; Tortoreto, C.; Poblador-Bahamonde, A. I.; Guénée, L.; Bürgi, T.; Lacour, J., *Angew. Chem. Int. Ed.* **2014**, *53*, 6140-6144.

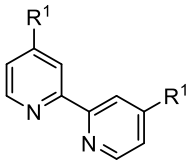
5.4 Optimization of reaction conditions

5.4.1 Ligand screening



7a **32A** **42aA** **33 A**





L1: R^1 = H; R^2 = H; R^3 = H; **Conv:** 60 %; **42aA/33A**: 4.5/1

L2: R^1 = H; R^2 = Me; R^3 = H; **Conv**: 27 %; **42aA/33A**: 1/2.3

L3: R^1 = H; R^2 = OMe; R^3 = H; **Conv**: 33 %; **42aA/33A**: 1/1.7

L4: R^1 = H; R^2 = H; R^3 = NO_2; **Conv**: 32 %; **42aA/33A**: 1/2

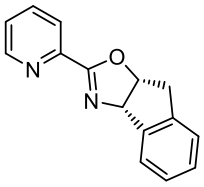
L5: R^1 = Me; R^2 = Me; R^3 = H; **Conv**: 20 %; **42aA/33A**: 1/1

L6: R^1 = H; R^2 = Ph; R^3 = H; **Conv**: 5 %

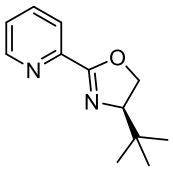
L7: R^1 = H; **Conv**: 0 %

L8: R^1 = OMe; **Conv**: 0 %

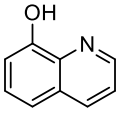
L35: R^1 = Br; **Conv**: 57 %; **42aA/33A**: 1/1.3



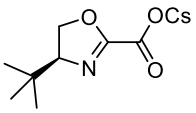
L9; **Conv**: 0 %



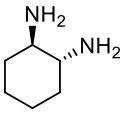
L10; **Conv**: 0 %



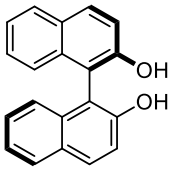
L16; **Conv**: 45 %; **42aA/33A**: 0/1



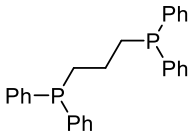
L17; **Conv:** 0 %



L23; **Conv**: 0 %



L29: R^1 = R^2 = OH; **Conv**: 50 %; **42aA/33A**: 1/1; 0 % *ee*



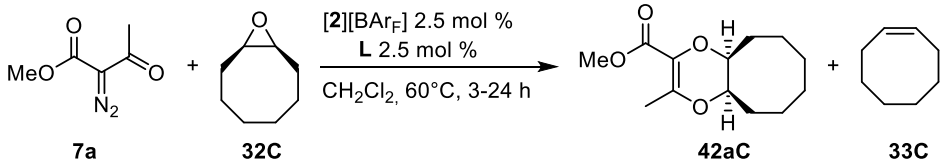
L34; **Conv**: 0 %

Table 5.1 Ligand screening.

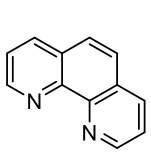
In collaboration with Dr. Thierry Achard, this reactivity was further studied. First, trying to improve on the rate of the reaction, a screening study was performed with bidentate ligands, using the following reaction conditions: 60 °C, **7a** in 0.5 M in methylene chloride, 1:1 ratio of $[CpRu(CH_3CN)_3][PF_6]$ complex and **L** (2.5 mol %) and one equivalent of styrene oxide **32A**. Conversions of the epoxide were calculated by ^1H NMR after addition of 1,3,5-trimethoxybenzene as reference at the end of the reaction.

The reaction time was set to 20 h. The results are summarized in **Table 5.1**. As in the previous study, 1,10-phenanthroline **L1** was found to be the best ligand inducing both high reactivity and selectivity. The reaction proceeded also without any ligand but a higher amount of olefin was then obtained.

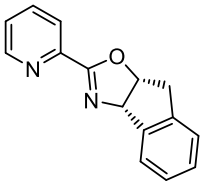
It is well known that reactivity can dramatically change between monosubstituted and disubstituted epoxides.[179] The better ligands were then tested as well in the reaction with cyclooctene oxide **32C**. The results are reported in **Table 5.2**.



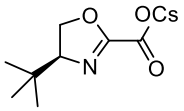
7a **32C** **42aC** **33C**



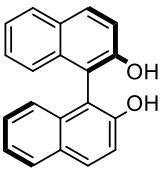
L1; **Conv:** 100 %; **42aC/33C**: 4.4/1



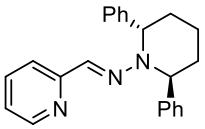
L9; **Conv**: 71 %; **42aC/33C**: 4/1
0 % *ee*



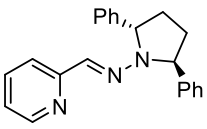
L17; **Conv:** 25 %; **42aC/33C**: 5/1
0 % *ee*



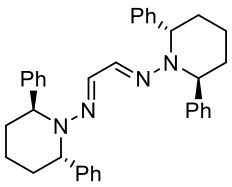
L29: **Conv**: 100 %; **42aC/33C**: 4/1
0 % *ee*



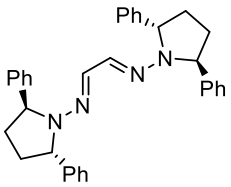
L36; **Conv:** 36 %; **42aC/33C**: 3/1
0 % *ee*



L37; **Conv:** 37 %; **42aC/33C**: 3/1
0 % *ee*



L38; **Conv:** 76 %; **42aC/33C**: 2/1
0 % *ee*



L39; **Conv:** 100 %; **42aC/33C**: 2/1
0 % *ee*

Table 5.2 Ligand screening.

Once again 1,10-phenanthroline **L1** was found to be the best ligand and it was selected for the following studies. No enantioselectivity was observed when enantiopure ligands were used. In collaboration with Prof. Lassaletta (University of Sevilla, Spain)

[179] (a) Parker, R. E.; Isaacs, N. S., *Chem. Rev.* **1959**, *59* (4), 737-799; (b) Muzart, J., *Eur. J. Org. Chem.* **2011**, (25), 4717-4741.

four extra enantiopure ligands were tested without any evidence for enantioselective reaction (**Table 5.2**, entries 5-8).

Noteworthy, ^{1}H NMR spectroscopic analysis indicated the occurrence of a *cis*-junction between the two cycles (^{3}J = 10 Hz). Product **42aC** was found to be moderately soluble in a 3:1 mixture of hexanes and methylene chloride. X-Ray quality crystals were afforded and a structural analysis was performed (**Figure 5.1**) that confirmed this somewhat unexpected *cis*-configuration.

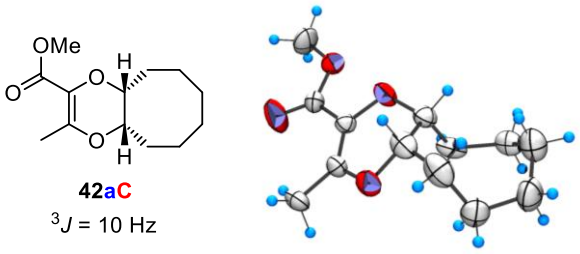


Figure 5.1 ^{1}H NMR and x-ray evidences for the *cis*- configuration of **42aC**. ORTEP view of the crystal structure of **42aC**. Thermal ellipsoid are drawn at 50 % probability.

Interestingly, in sharp contrast with other epoxide openings,[180] the reaction of cyclooctene oxide **32C** was faster and cleaner than the reaction with styrene oxide **32A** and it was therefore used as benchmark substrate for the rest of this study. In all the cases in which the epoxide was not completely consumed, there was no diazo reagent in solution. Diazane adduct **43** depicted in **Figure 5.2** was often obtained as side product, the structure being confirmed by x-ray diffraction studies. For these reasons, we decided to use an excess of diazo reagent (two equivalents instead of one) in the following reactions.

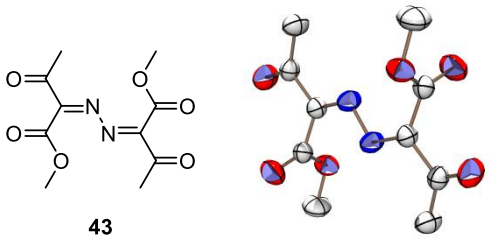


Figure 5.2 ORTEP view of the crystal structure of **43**. Thermal ellipsoids are drawn at 50 % probability.

[180] Denmark, S. E.; Barsanti, P. A.; Wong, K. T.; Stavenger, R. A., *J. Org. Chem.* **1998**, *63* (8), 2428-2429.

5.4.2 Metal complex selection

Other metal sources were also investigated as catalysts in the reaction between methyl diazoacetoacetate **7a** and cyclooctene oxide **32C**. Whereas copper salts did not induce the formation of the product **42aC**, $Rh_2(OAc)_4$ leaded to the formation of the olefin **33C** as main product and **42aC** was obtained in only a small amount (20 %). Other CpRu(II) complexes were tested and the results are reported in **Table 5.3**.

Entry	[Ru]	Anion	Conv [a]	Ratio **42aC**/**33C**
1	CpRuNaphthalene [b]	PF_6	69	2.5/1
2	$CpRu(CH_3CN)_3$	PF_6	85	4.4/1
3	$CpRu(CH_3CN)_3$	SbF_6	94	4.4/1
4	$CpRu(CH_3CN)_3$	BAr_F	100	4.5/1
5	$CpRu(CH_3CN)_3$	TRISPHAT	95	3.7/1
6	$CpRu(CH_3CN)_3$	TRISPHAT-N	45	2.0/1
7	$Cp^*Ru(CH_3CN)_3$	PF_6	63	2.0/1
8	$Cp^*Ru(CH_3CN)_3$	SbF_6	42	2.4/1
9	$(C_{10}H_{12}F_3)Ru(CH_3CN)_3$	PF_6	44	2.4/1

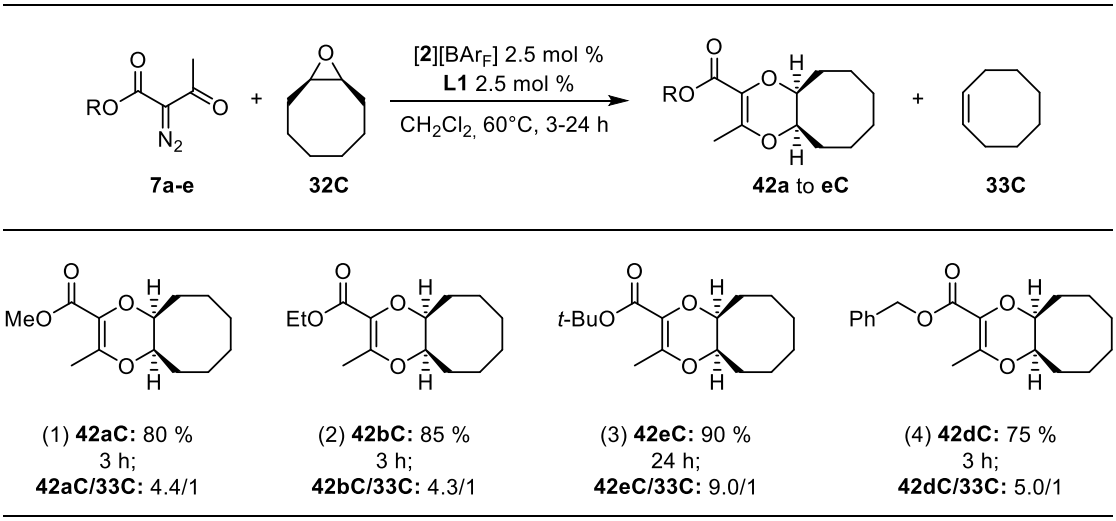
Reaction conditions: diazo **7a** (2 eq., 0.64 mmol), cyclooctene oxide **32C** (1 eq., 0.32 mmol), [**2**][BAr_F] and **L1** (2.5 mol %), CH_2Cl_2 (0.6 mL), 2 h, 60 °C. [a] Conversions of **32C** (^{1}H NMR, 1,3,5-trimethoxybenzene as internal reference). [b] Without ligand.

Table 5.3 CpRu complex selection.

The [CpRuNaphthalene][PF_6] complex induced the diazo decomposition but the reaction was slower and less selective (**Table 5.3**, entry 1). Complexes with large lipophilic counterions such as SbF_6 and TRISPHAT were more reactive but less selective than that one with PF_6 (**Table 5.3**, entries 3 and 5). [$CpRu(CH_3CN)_3$][BAr_F] complex had a better reactivity and a similar selectivity than [PF_6] complex (**Table 5.3**, entry 4). Lower conversion and selectivity were observed with the coordinating TRISPHAT-N (**Table 5.3**, entry 6) and with the more sterically hindered Cp*Ru complexes (**Table 5.3**, entries 7 and 8). [$CpRu(CH_3CN)_3$][BAr_F] complex was thus selected and used in all further experiments.

5.5 Scope of the reaction

Then, the scope of the reaction was investigated. Diazo compounds with different alkyl ester groups were tested and reactions were allowed to run until full conversion (**Table 5.4**). In essentially all the cases, the corresponding products of type **42** were obtained in good to excellent yields (**Table 5.4**, entries 1-4). With the bulkier *t*-Bu ester (**7e**) a prolonged reaction time was necessary to afford product **42eC** in 90 % yield (**Table 5.4**, entry 3). The steric hindrance of the ester substituent seems to be responsible of the better selectivity as the formation of the product **42** is clearly favoured against the deoxygenation pathway.

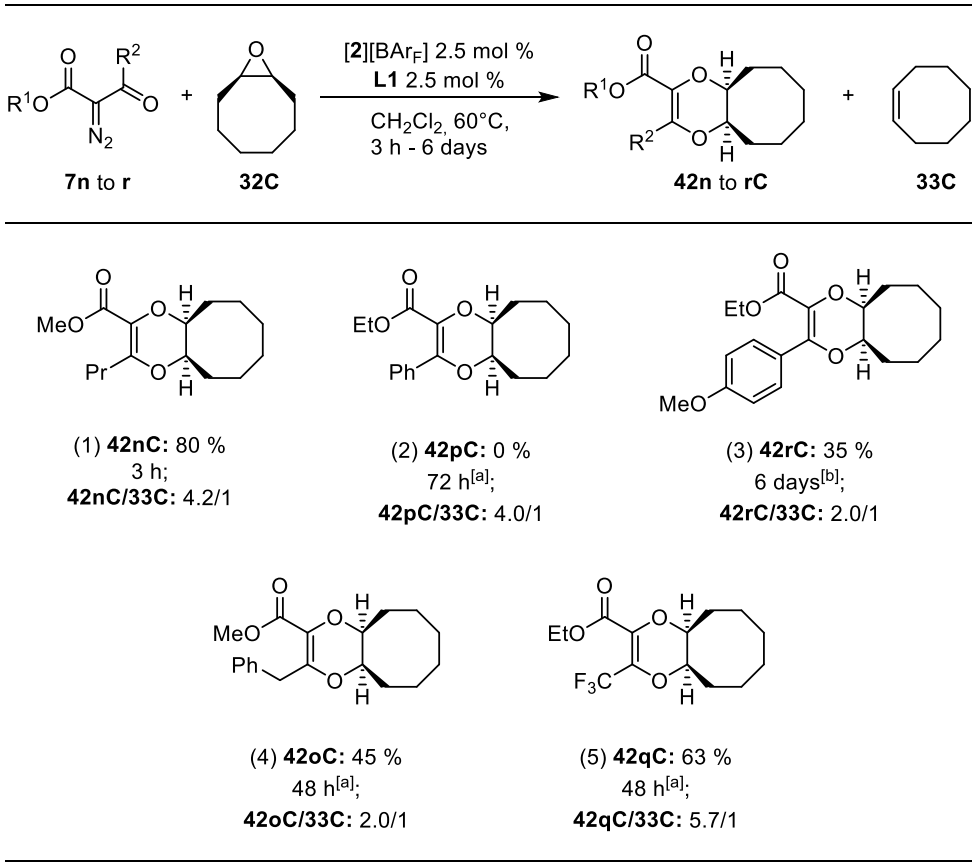


Reaction conditions: diazo **7** (2 eq., 0.64 mmol), cyclooctene oxide **32C** (1 eq., 0.32 mmol), [**2**][BAr_F] and **L1** (2.5 mol %), CH_2Cl_2 (0.6 mL), 60 °C. Isolated yields are given as the result of an average of at least two reactions.

Table 5.4 Substrate scope.

The nature of the ketone substituent was also varied. With a propyl chain a similar reactivity was observed (**42nC**, 80 % yield, 3 h, **Table 5.5**, entry 1). As in the case of THF, aromatic substituents were found to have a negative impact on reactivity (**Table 5.5**, entries 2-4). With the electron withdrawing CF_3 group a longer reaction time was necessary as well to obtain the product with a quite better selectivity (**42qC**, 80 % conversion after 48 h, **Table 5.5**, entry 5). This result is interesting considering that the corresponding trifluoromethylated dihydro-1,4-dioxene adduct has a biological activity as

agrochemicals and fungicide and up to know it was synthesized in at list 6 steps with an overall yield of 25 %.[181]



Reaction conditions: diazo **7** (2 eq., 0.64 mmol), cyclooctene oxide **32C** (1 eq., 0.32 mmol), [**2**][BAr_F] and **L1** (2.5 mol %), CH_2Cl_2 (0.6 mL), 60 °C. Isolated yields are given as the result of an average of at least two reactions. [a] Conv. = 80 %. [b] Conv. = 81 %.

Table 5.5 Substrate scope.

When diketo-, diester- or arylesterdiazo reagents were used, the formation of corresponding dioxene adducts was not observed and the starting oxirane was recovered.

Cyclooctene oxide **32C** was also replaced by other commercially available or readily prepared cyclic symmetrical epoxides **32D** to **K**. The results obtained are reported in **Table 5.6**. In all instances, the corresponding product **42** was obtained in good yields after 3 hours. Selectivity in favour of the ring opening product was observed to increase

[181] (a) Hahn, H. G.; Chang, K. H.; Nam, K. D., *B Kor Chem Soc* **2001**, *22* (2), 149-153; (b) Hahn, H. G.; Chang, K. H.; Dal Nam, K.; Bae, S. Y.; Mah, H., *J Heterocyclic Chem.* **2000**, *37* (4), 1003-1008.

with the size of the ring. Compounds **42aD** and **42aE** were obtained in lower yield due to a partial decomposition upon chromatography over silica gel (**Table 5.6**, entries 1 and 2). Product **42aG** was obtained as a single diastereoisomer. The configuration was confirmed by x-ray structural analysis.

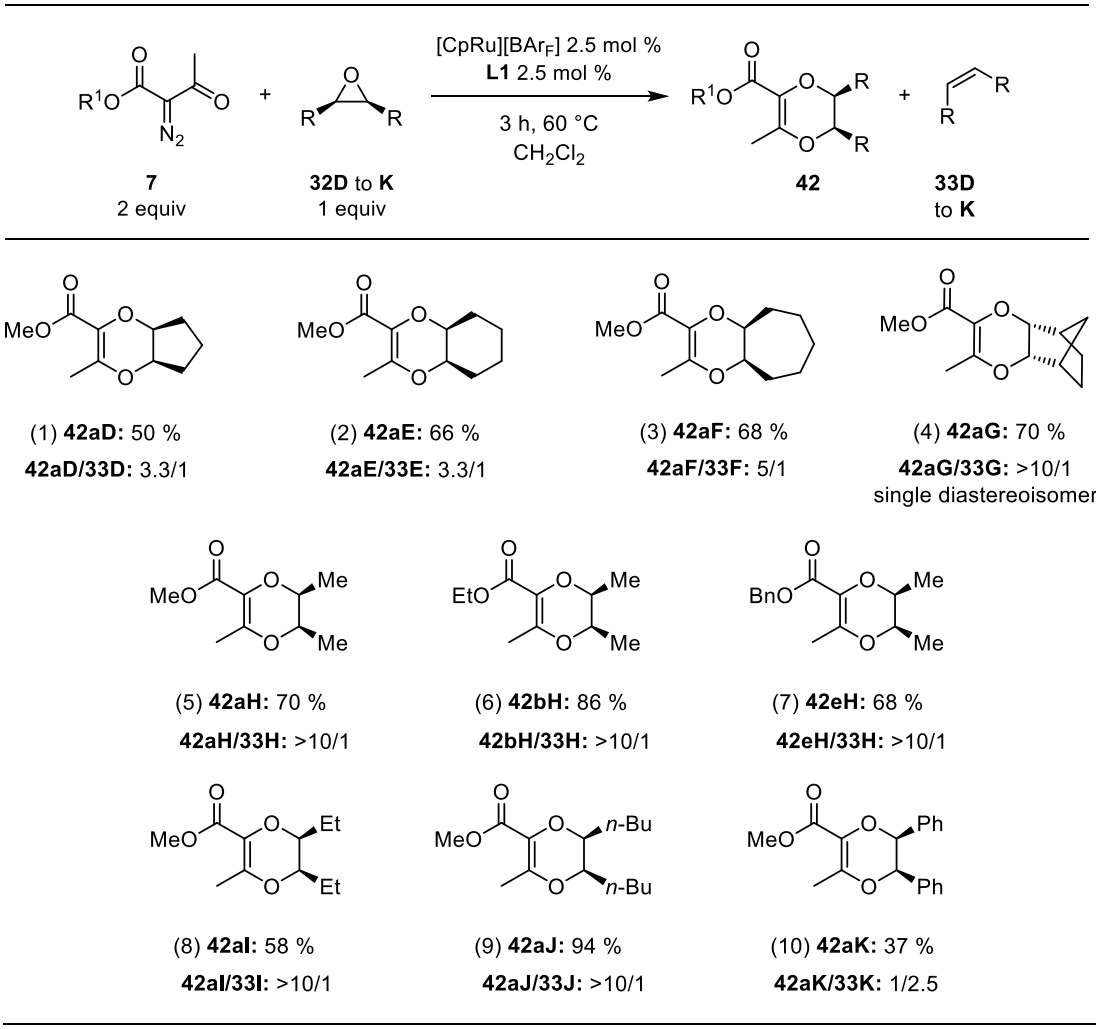


Table 5.6 Dioxene products obtained from cyclic symmetrical epoxides. Isolated yields are the result of an average of at least two reactions.

The procedure was extended to acyclic *cis*-oxiranes **32H** to **K** (**Table 5.6** entries 5-10). Using the same standard conditions, the corresponding products were obtained in 3 hours in good to excellent yields. In the case of 2,3-diphenyl oxirane, a rather large amount of olefin **33K** was consistently recovered and **42aK** was obtained in moderate yield (**Table 5.6**, entry 10). Products **42eH** and **42aK** were found to be moderately soluble in a 3:1 mixture of hexane and methylene chloride. X-Ray quality crystals were

obtained and a structural analysis was performed (**Figure 5.3**) that confirmed the *cis*-stereoselectivity for acyclic compounds this time.

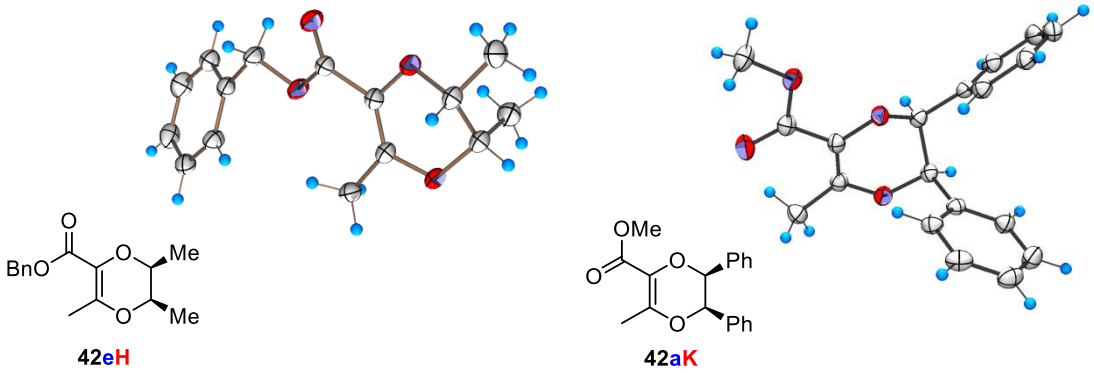
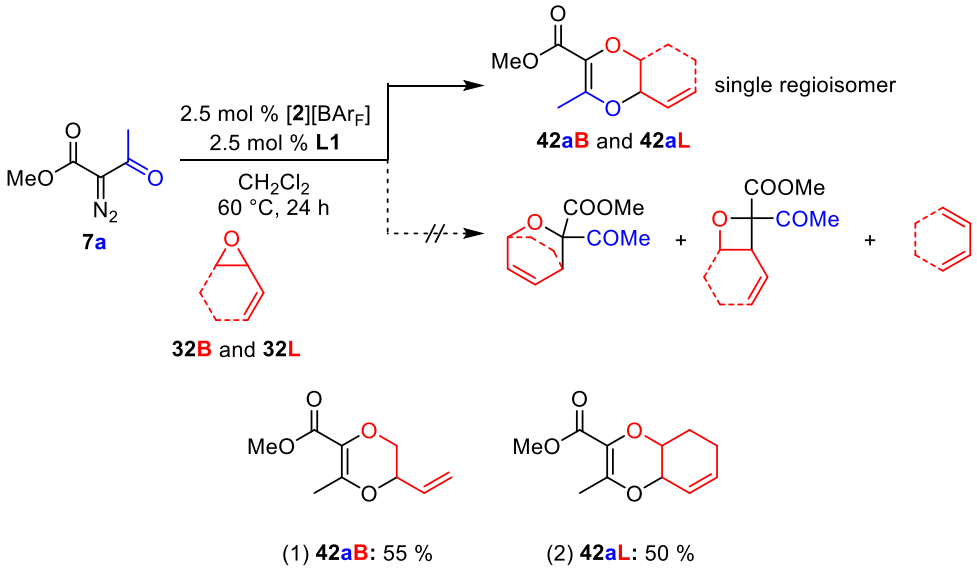


Figure 5.3 ORTEP view of the crystal structure of **42eH** and **42aK**. Thermal ellipsoids are drawn at 50 % probability.

Finally, vinyl epoxides **32B** and **32L** were tested. In spite of precedent literature,[174,176-177] products derived from [1,2]-insertion or [2,3]-sigmatropic rearrangement were not observed in the ^{1}H NMR spectra of the crude mixtures and the dioxene derivatives of type **42** were once again obtained as major adducts and single regioisomers (**Scheme 5.11**).

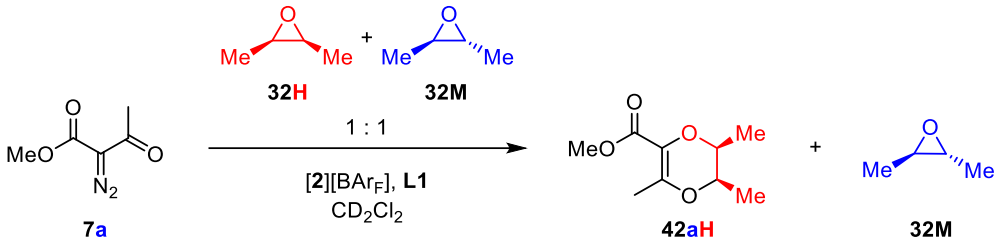


Scheme 5.11 Reactions with vinyl epoxides **32B** and **32L**. Isolated yields are the result of an average of at least two reactions.

5.6 Selectivity

5.6.1 Preferred reactivity of *cis vs trans* epoxides

As detailed above, *cis* epoxides react readily to give exclusively the *cis* products. However, when *trans*-2,3-epoxybutane was tested, it was found to be unreactive. This specificity toward *cis*-epoxides was further investigated by performing a competition experiment with a 1:1 mixture of *cis* and *trans*-2,3-epoxybutane (**Scheme 5.12**).



Scheme 5.12 Competition experiment.

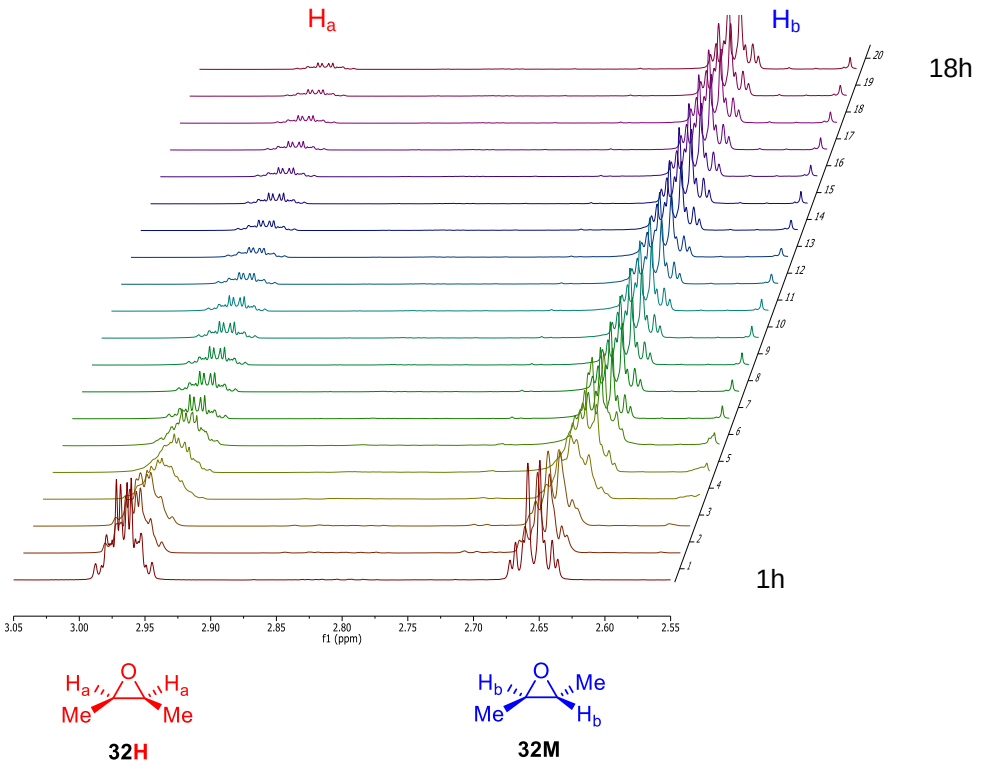
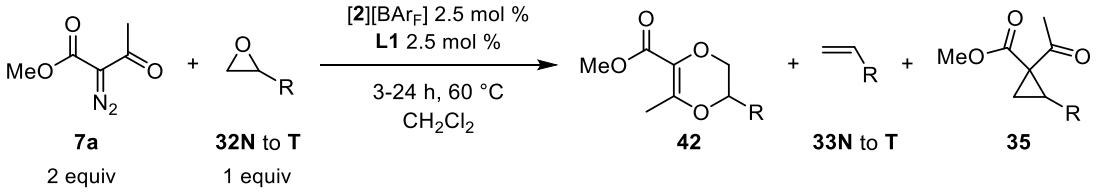


Figure 5.4 Detailed view of the ^{1}H NMR of the competition experiment.

Using a ^{1}H NMR monitoring, it was shown that signal at 2.65 ppm corresponding to the H_b protons of the *trans* epoxide **32M** remained essentially unchanged (a broading is observed but the integration remains the same) while those at 2.97 ppm corresponding to the H_a protons of the *cis* epoxide **32H** decreased continuously over time (**Figure 5.4**).

5.6.2 Regioselectivity

Monosubstituted epoxides **32N** to **T** were then tested (**Table 5.7**). The desired dioxene products **42** were always obtained as a single regioisomer, the opening of the epoxide occurring always at the more substituted carbon. 2-Methyloxirane **32N** provided the corresponding adduct **42aN** in good yield and excellent selectivity (**Table 5.7**, entry 1). However, increasing the size of the alkyl chain led to the formation of the undesired alkene (**Table 5.7**, entry 2).



Entry	R	Product	Ratio **42/33/35**	Yield [a]	Time [b]
1	Me	**42aN**	1/0/0	65	3 h
2	*n*-Bu	**42aO**	1.5/1/0	55	3 h
3	Ph	**42aA**	4/1/1	40	24 h
4	4-OMeC$_6$H$_4$-	**42aP**	1.6/1/1.2	41	1 h
5	4-MeC$_6$H$_4$-	**42aQ**	1/0/1.5	20	24 h
6	4-ClC$_6$H$_4$-	**42aR**	3.5/2/1	38	24 h
7	4-FC$_6$H$_4$-	**42aS**	5.7/1.4/1	38	24 h
8[a]	4-CF$_3$C$_6$H$_4$-	**42aT**	1/1/0	37	24 h

Table 5.7 Reactions whit monosubstituted epoxides. [a] [**2**][PF$_6$] used as metal complex. Isolated yields, values obtained as an average of at least two reactions.

With aryl substituents a larger amount of olefin **33** was observed in all cases in the crude mixture. In these cases, the *in situ* generated electron-rich olefin **33** further reacted

with the carbene complex to yield the product of cyclopropanation **35** (**Table 5.7**, entries 3-8).[2] The presence of an electron-donating *p*-methoxy group accelerated the reaction as only 1 hour was necessary to completely consume the starting epoxide **32P** (**Table 5.7**, entry 4). On the contrary, the reaction was slowed down by electron withdrawing substituents, indicative of a strong electronic effect (**Table 5.7**, entries 6 and 7). These reactions provided mixtures of dioxene **42**, alkene **33** and cyclopropane **35** products. Prolonged reaction times allowed full conversion of alkenes into cyclopropane adducts of type **35**. As expected, with electron poor olefins, the cyclopropanation reaction was diminished. The stronger electron withdrawing CF_3 substituent completely inhibited this last pathway (**Table 5.7**, entry 8).

In order to compare the substrate affinity of the epoxides and olefins for the metal centre, a mixture of styrene oxide **32A** (1 equivalent) and styrene **33A** (1 equivalent) was stirred, under standard reaction conditions, in presence of diazo **7a** (1 equivalent). The cyclopropane adduct **33aA** was exclusively obtained, along with the unreacted styrene oxide, showing that styrene reacts faster than the epoxide whit the ruthenium-metal carbene.

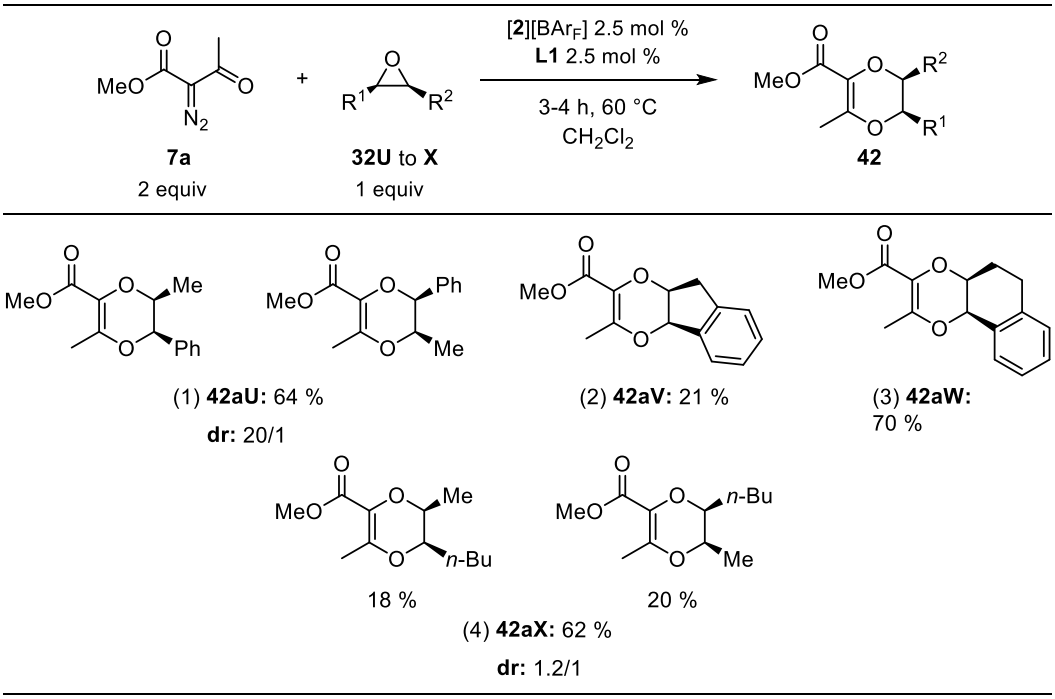


Table 5.8 Reactions with non-symmetrical disubstituted epoxides **32U** to **X**. Isolated yields are given as the result of an average of at least two reactions.

Regioselectivity in the case of asymmetrical disubstituted epoxides was also investigated. Once again *cis*-epoxides gave *cis*-dioxenes. Significantly, a perfect regioselectivity was observed using 2-methy-3-phenyl oxirane **32U** (**Table 5.8**, entry 1). The same trend was observed with two more epoxides containing an alkyl and an aryl substituent (**32V** and **32W**). The ring opening of the epoxide always occurred on the carbon carrying the aryl group (**Table 5.8**, entries 2 and 3). This regioselectivity can be rationalized on electronic grounds and it suggests the presence of an intermediate with a carbenium character, the positive charge being better stabilized at a benzilic position. This is in line with what observed for styrene oxide. Regioselectivity was confirmed by structural analysis performed on x-ray quality crystals obtained of adducts **42aA** and **42aW** (**Figure 5.5**).

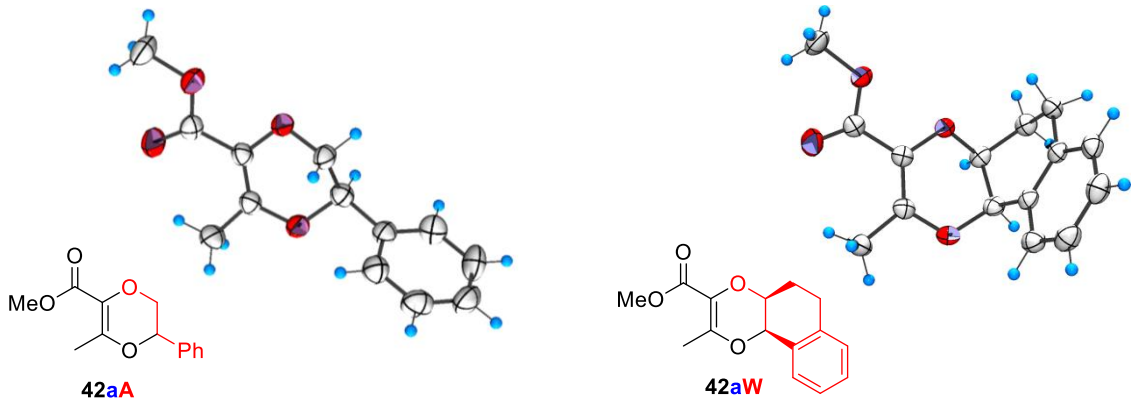


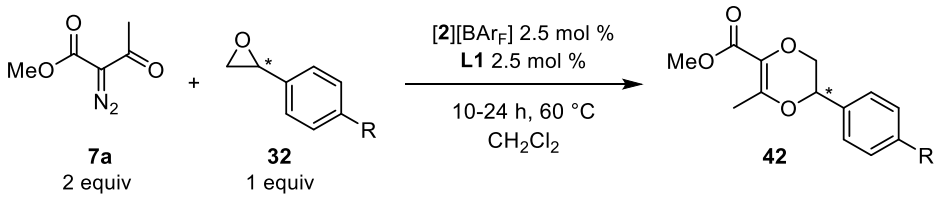
Figure 5.5 ORTEP view of the crystal structure of **42aA** and **42aW**. Thermal ellipsoid are drawn at 50 % probability.

Finally, using **32X** as substrate possessing two substituents with a similar electronic character, a lack of discrimination was observed; a 1:1.2 mixture of the two possible products was obtained (**Table 5.8**, entry 4).

5.6.3 Chirality transfer (enantiospecificity)

As shown previously, with monosubstituted epoxides, the ring opening occurs by the breakage of the C-O bond at the stereogenic center. It was immediately recognized that a use of a enantiopure substrates would shed much light on the stereochemical nature of the process (retention, inversion or racemization), affording direct mechanistic informations.

Therefore, several reactions were performed with enantioenriched styrene oxides. The results are summarized in **Table 5.9**.

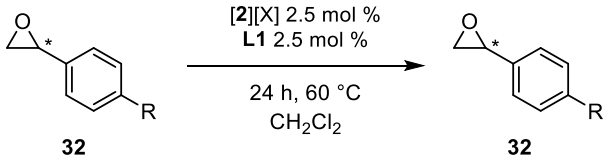


Entry	R	Product	*ee* % epoxide	[**2**][BAr_F] *ee* % product, 10 h	[**2**][PF_6] *ee* % product, 24 h
1	H	**42aA**	99 (−)-(*S*)	94 (+)	94 (+)
2	H	**42aA**	99 (+)-(*R*)	94 (−)	93 (−)
3	F	**42aS**	97 (+)-(*R*)	88 (−)	88 (−)
4	OMe	**42aP**	99 (+)-(*R*)	54 (−)	52 (−)

Table 5.9 Reactions with enantioenriched epoxides.

Importantly, using both [**2**][BAr_F] and [**2**][PF_6] salts as catalyst, products **42aA** were obtained in similar yields than in the racemic series and with excellent enantiomeric excess (94 % *ee*, **Table 5.9**, entries 1 and 2). Introduction of electron-withdrawing substituent led to a small reduction of *ee* values (88 % *ee*, **Table 5.9**, entry 3). With electron-donor methoxy substituent, strong decrease in the enantiospecificity of the reaction was noticed (54 % *ee*, Table 5.9, entry 5), the origin of this variation being discussed in the mechanism section.

In a control experiment, the enantioenriched oxiranes **32** were subjected to the reaction conditions in absence of the diazo compound. A slow racemization process was observed with both [**2**][BAr_F] and [**2**][PF_6] complexes (**Table 5.10**). This racemization can explain the loss of the enantiomeric excess in the reactions performed with epoxide **32F**, the reaction being quite slower when the electron withdrawing substituent is introduced.



32 32

Entry	R	*ee* % epoxide	*ee* % ([**2**][BAr_F])	*ee* % ([**2**][PF_6])
1	H	99 (−)-(*R*)	72 (−)-(*R*)	70 (−)-(*R*)
2	F	97 (+)-(*R*)	-	71 (−)
3	OMe	99 (+)-(*R*)	-	57 (−)

Table 5.10 Control experiment for the racemization process of the epoxides.

Finally, solutions of (*S*)-styrene oxide **32A** were prepared with different enantiomeric purity (0 %, 25 %, 43%, 50% and 75%) and tested in the catalytic process. The *ee* % of the dioxene adduct **42aA** was plotted *vs* the *ee* % of **32A** and a linear relationship was found (**Figure 5.6**). Such a correlation rules out possible non-linear effects.

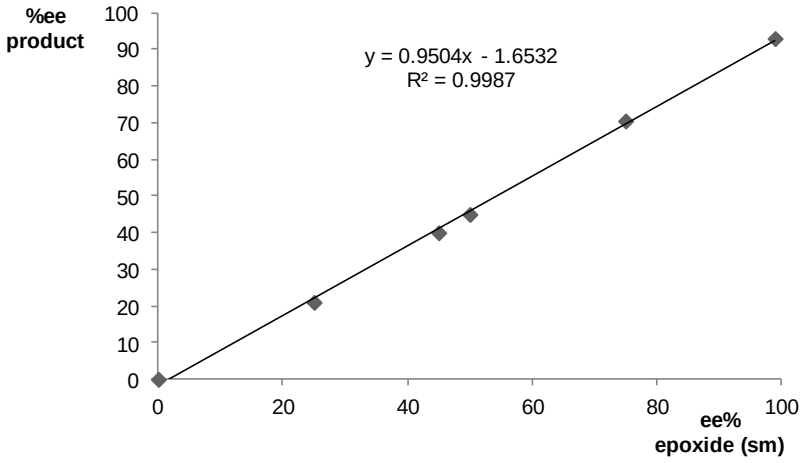


Figure 5.6 Linear correlation between the *ee* % of the starting **32A** and of the final adducts **42aA**.

5.6.4 Assignation of absolute configuration

However, even more important than a high conservation of the *ee* values was the determination of the absolute configuration of products to determine the exact (*syn* or *anti*) allure of the reactions. For this, circular dichroism spectroscopy, which measures the differences in absorptions that chiral molecules have under left and right circularly polarized light, was used. The VCD (Vibrational Circular Dichroism)[182] is the extension of this kind of spectroscopy into infrared and near infrared regions of the spectrum, where vibrational transitions occur in the ground electronic state of the molecule. This spectroscopic technique is sensitive to the orientation of the groups of the molecule; therefore it provides information on its three-dimensional structure. Efficient instrumentation for the measurement of VCD spectra and software for their calculation have been developed. VCD is nowadays a very efficient technique for the unequivocal determination of the absolute configuration of molecules of a moderate complexity and with a quite rigid structure.[183]

Clearly, the conservation of the enantiomeric purity in the reactions described above (**Table 5.9**) can result either from an inversion or a retention of the configuration of the reacting stereocenter of the starting epoxide. Assigning the absolute configuration of the final product was thus crucial to determine the exact mechanism of the ring opening. In view of the relative rigidity (simple conformation analysis) of adducts of type **42**, VCD techniques were chosen to determine the absolute configuration of the products **42aA**. In collaboration with Prof. Bürgi (University of Geneva), infrared absorption and VCD spectra of the adduct **42aA** derived from both the (*S*)- and the (*R*)-styrene oxide were recorded and compared to the weighted average spectrum calculated for the possible conformations of the product. A stereochemical analysis showed four possible conformations, the most stable having a geometry similar to that determined by X-ray crystallographic analysis (vide infra). The geometry optimization, vibrational frequencies, IR absorption and VCD intensities were calculated with Density Functional Theory (DFT) using (b3lyp) functionals combined with 6-311++G(d,p) basis set. Overall, a good

[182] Nafie, L. A.; Keiderling, T. A.; Stephens, P. J., *J. Am. Chem. Soc.* **1976**, *98* (10), 2715-2723.

[183] (a) Freedman, T. B.; Cao, X. L.; Dukor, R. K.; Nafie, L. A., *Chirality* **2003**, *15* (9), 743-758; (b) Stephens, P. J.; Devlin, F. J.; Pan, J. J., *Chirality* **2008**, *20* (5), 643-663.

agreement between the experimental and the calculated spectra was observed, thus allowing the assignment of the (*S*)-configuration to the stereogenic centre of the (+)-adduct derived from the (*S*)-styrene oxide (**Figure 5.7**). The reaction occurs thus with retention of configuration at the stereogenic center through a *syn* ring opening mechanism.

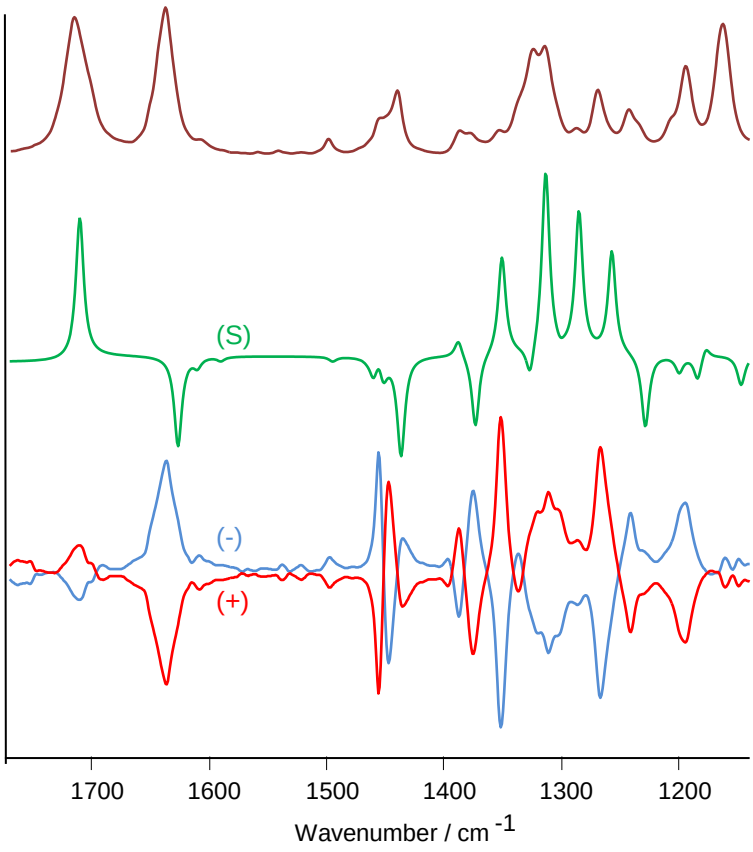


Figure 5.7 Experimental IR absorption (top, brown) and VCD (bottom) spectra (CD_2Cl_2, 298 K) of (+)-**42aA** (red) and (−)-**42aA** (blue). Calculated spectrum of (*S*)-**42aA** (green).

This result was confirmed by X-ray analysis carried out on a crystal obtained from the dextrorotatory product (99 % ee, purified by preparative chiral HPLC and obtained starting from the (S)-styrene oxide). Determination of the flack parameter (0.0(2)) indicated also an (*S*)-configuration for the stereocenter. Due to the absence of heavy atoms, a rather large margin of error which, in this case, can be considered with ease in view of the previous VCD result.

5.7 Mechanistic rationale

The different experiments detailed previously indicates a perfect *syn* stereoselectivity for the reactions as *cis* epoxides afford exclusively *cis* adducts and styrene oxides react with pure retention of configuration. Moreover and at first hand in conflict with the above information, the regioselectivity suggest that the reaction proceeded with a S_N1-like mechanism, the products being formed through intermediates with strong carbenium character (tertiary or benzylic). In fact, for such a mechanism, a racemization rather than a retention of configuration would be expected. Further insights were thus looked for.

5.7.1 S_N1 *vs* S_N2 mechanism

As discussed in the introduction of this chapter, S_N2 ring openings of cyclic epoxides are usually stereoselective in favour of *anti* (*trans* diaxial) mechanism due to the referred chair-like conformation of the transition state. As such, using a compound like the 4-methyl-1,2-cyclohexene oxide **32Y**, one regio- and diastereoisomer is strongly favoured (see **Scheme 5.3**). At the present case, as the reaction mechanism seems to be quite different from a S_N2, such substrate should react differently and thus would establish the occurrence of a different pathway. In fact, experiments performed using a mixture of *cis* and *trans*-4-methyl-1,2-cyclohexene oxides **32Y** led to four products **42aY** and with a modest regioselectivity only (calculated in the ^{1}H NMR of the crude mixture). These products are detailed in **Figure 5.8**.

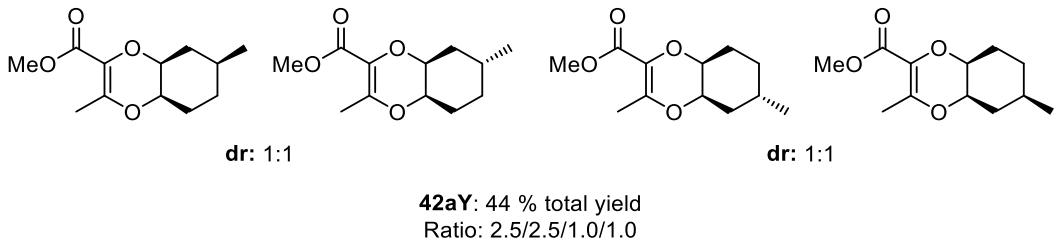


Figure 5.8 Selectivity obtained with *cis* and *trans*-4-methyl-1,2-cyclohexene oxide **32Y** as substrates.

Similar results were observed starting from the mixture of *cis* and *trans*-3-methyl-1,2-cyclohexene oxide **32Z**, the four products **42aZ** being observed in a 3.9/3.9/1/1 ratio (calculated in the ^{1}H NMR of the crude mixture, **Figure 5.9**). In both cases, a modest

selectivity was thus observed in favour of one of the two couples of diastereoisomers. The structure of one of the diastereoisomers of compound **42aZ** was confirmed by x-ray diffraction studies.

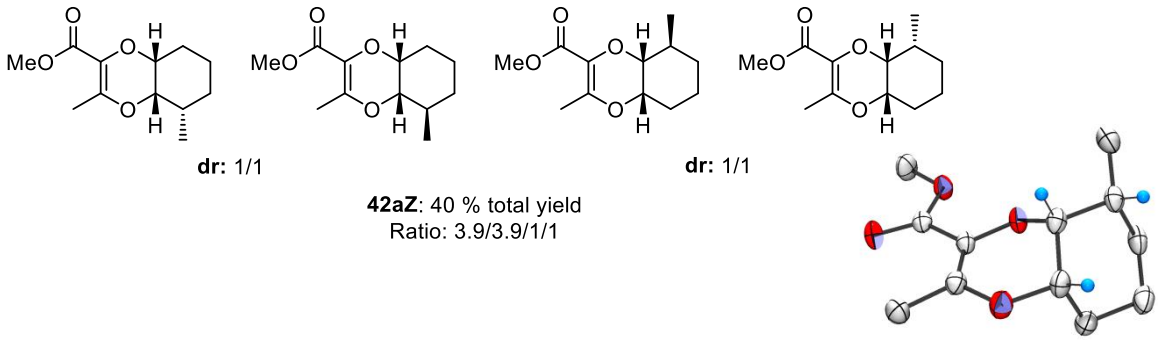
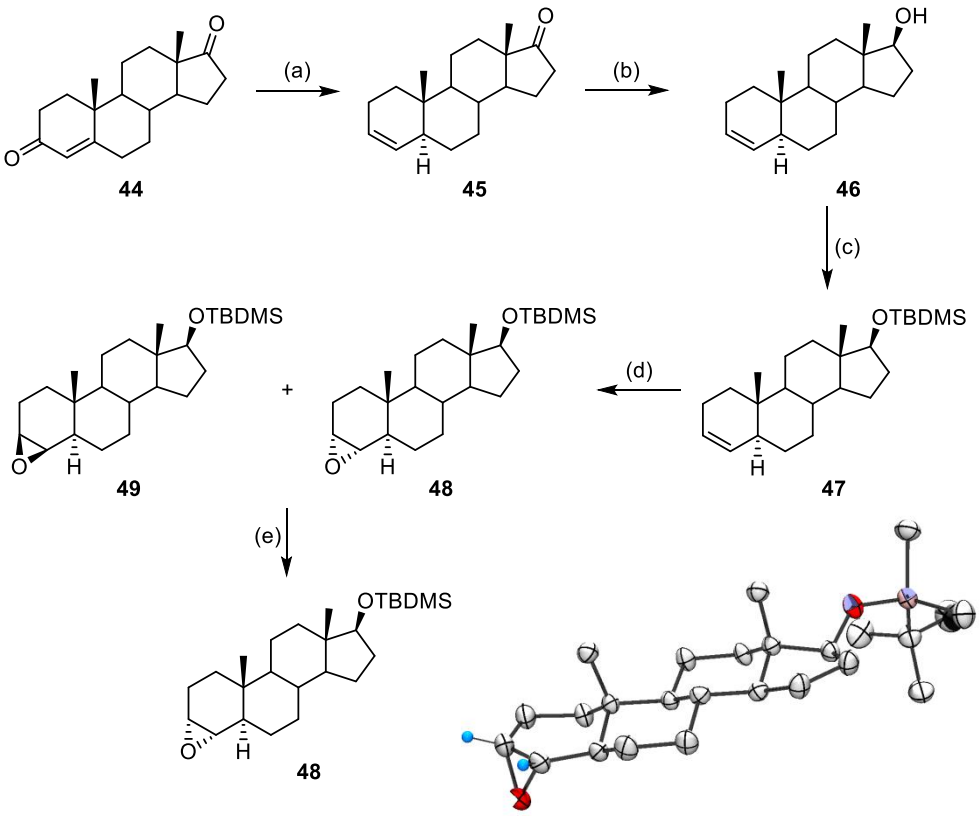


Figure 5.9 Selectivity obtained with *cis* and *trans*-3-methyl-1,2-cyclohexene oxide as substrates. ORTEP view of the crystal structure of a diastereoisomer of compounds **42aZ**. Thermal ellipsoids are drawn at 50 % probability.

Even if those two previous experiments were already indicating that the classical Fürst-Plattner rule was not in application for the reaction, it was realized that the large number of similar product was hampering the analysis. Care was thus taken to minimize the number of possible products. It was decided to study the ring opening with a diastereomerically pure substrate. Rigid steroid **48** was selected. It was synthesized started from androsterone **44** and isolated according to the procedure described in **Scheme 5.13**.[184] Reduction of the carbonyl group was necessary to avoid later competition to the metal carbene.[185] Two diastereomeric epoxides resulted from the synthesis and the α-epoxy steroid **48** was isolated easily by a selective crystallization in hexane. X-Ray quality crystals were obtained and structural analysis was performed that confirmed the stereochemistry.

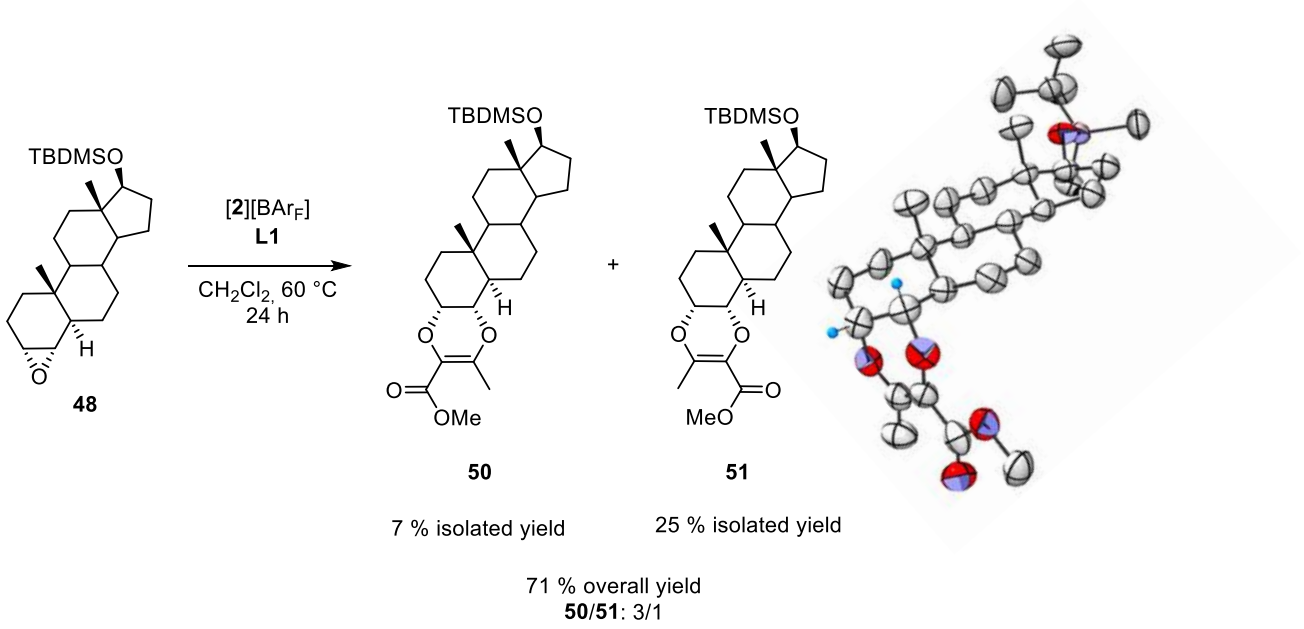
[184] (a) Cepa, M. M. D. S.; da Silva, E. J. T.; Correia-da-Silva, G.; Roleira, F. M. F.; Teixeira, N. A. A., *Steroids* **2008**, *73* (14), 1409-1415; (b) Cepa, M. M. D. S.; da Silva, E. J. T.; Correia-Da-Silva, G.; Roleira, F. M. F.; Teixeira, N. A. A., *J. Med. Chem.* **2005**, *48* (20), 6379-6385; (c) da Silva, E. J. T.; Roleira, F. M. F.; Melo, M. L. S. E.; Neves, A. S. C.; Paixao, J. A.; de Almeida, M. J.; Silva, M. R.; Andrade, L. C. R., *Steroids* **2002**, *67* (3-4), 311-319.

[185] Hosoda, H.; Yamashita, K.; Ikegawa, S.; Nambara, T., *Chem Pharm Bull* **1977**, *25* (10), 2545-2553.



Scheme 5.13 Synthesis of the 3α,4α-epoxy-5α-androstan-17β-ol tert-buthyldimethylsilyl ether **48**. (a) Zn dust, CH_3CO_2H, 15 min, reflux; (b) $NaBH_4$ (3.5 equiv.), MeOH, 1 h, 20 °C; (c) TBDMSCl (5 equiv.), imidazole (10 equiv.), DMF, 2 h, 20 °C; (d) Formic acid (1.8 equiv.), H_2O_2 (4.8 equiv.), CH_2Cl_2, 6 h, 20 °C. (e) Isolation by crystallization in hexane. ORTEP view of the crystal structure of the isomer **48**. Thermal ellipsoids are drawn at 50 % probability.

With substrate **48** in hands, Ru-catalyzed C-O-insertion reaction was tested (**Scheme 5.14**). The two regioisomers **50** and **51** were obtained in a 3/1 ratio with an overall yield of 71 % and as a single diastereoisomer each which could be isolated in 7 % and 25 % yield respectively. 22 % of product derived from a deoxygenation pathway was observed in the ^{1}H NMR of the crude mixture. The minor isomer **51** was found to be partially soluble in diethyl ether. X-Ray quality crystals were afforded and a structural analysis was performed that confirmed the structure of the adduct (**Scheme 5.14**). In our view, the modest regioselectivity observed in this set of experiments confirms the absence of an S_N2-like mechanism.



Scheme 5.14 Reactivity of the 3α,4α-epoxy-5α-androstan-17β-ol *tert*-buthyldimethylsilyl ether **48**. ORTEP view of the crystal structure of the minor isomer obtained **51**. Thermal ellipsoids are drawn at 50 % probability.

5.7.2 *In situ* IR-monitoring

Trying to observe the formation of a possible intermediate, a reaction was performed using an *in situ* IR-monitoring. Due to the sensitivity of the technique and for practical reasons, the reaction temperature was decreased to 25 °C and IR spectra were recorded every two minutes. The results are reported in **Figure 5.10**. It was possible to observe the signal relative to diazo reagent **7a** at 2139 cm^{-1} decreasing over time (1st order behaviour) and, at the same time, the signals growing of the carbonyl groups of the ester (1712 cm^{-1}) and of the ketone (1635 cm^{-1}) of the product **42aC**. However, in contrast with reactions in our group involving oxonium ylide intermediates and Rh(II) catalyst, it was not possible to observe signals that would indicate the occurrence of an intermediate sufficiently stable to be accumulated in detectable quantity.

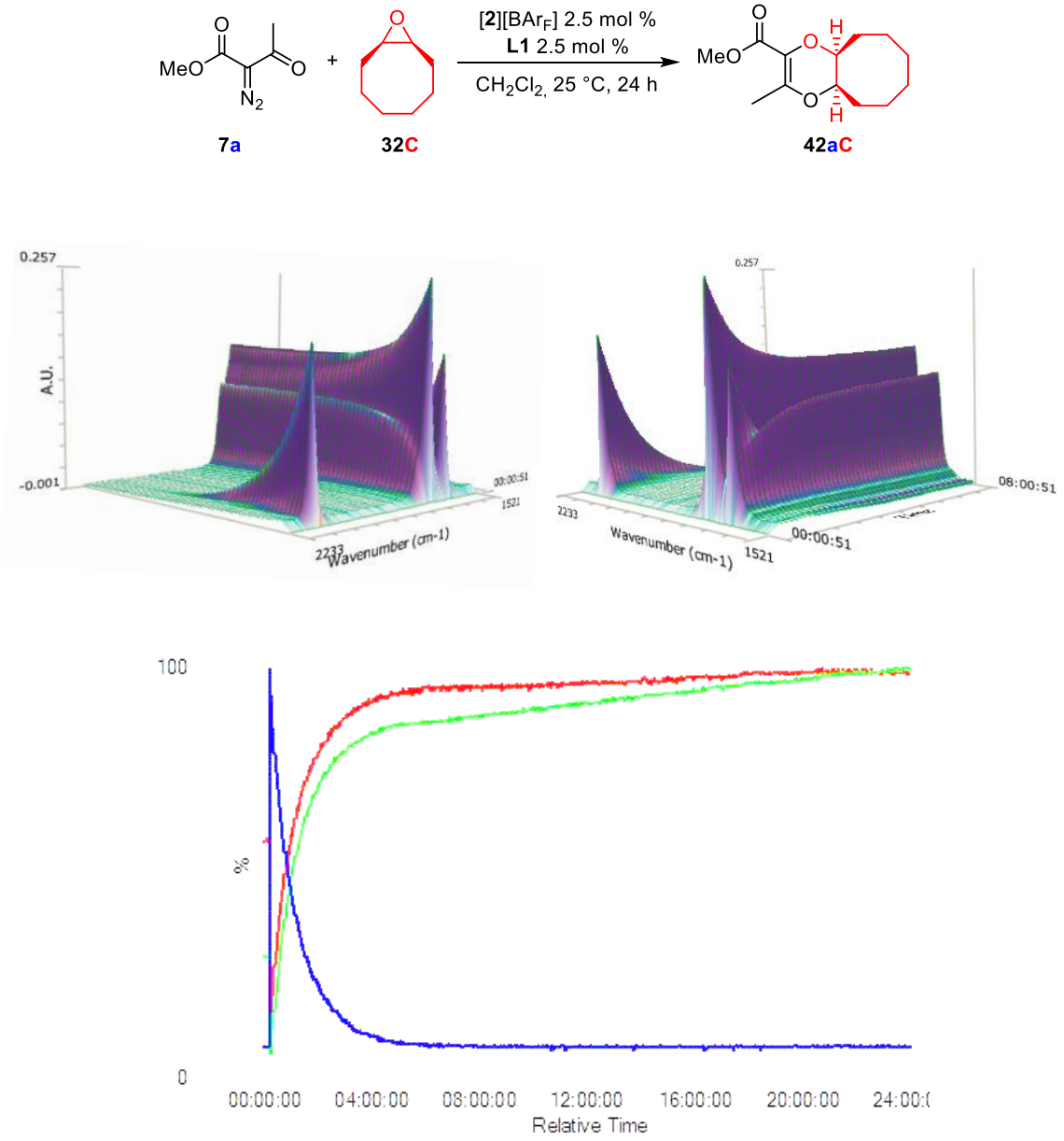
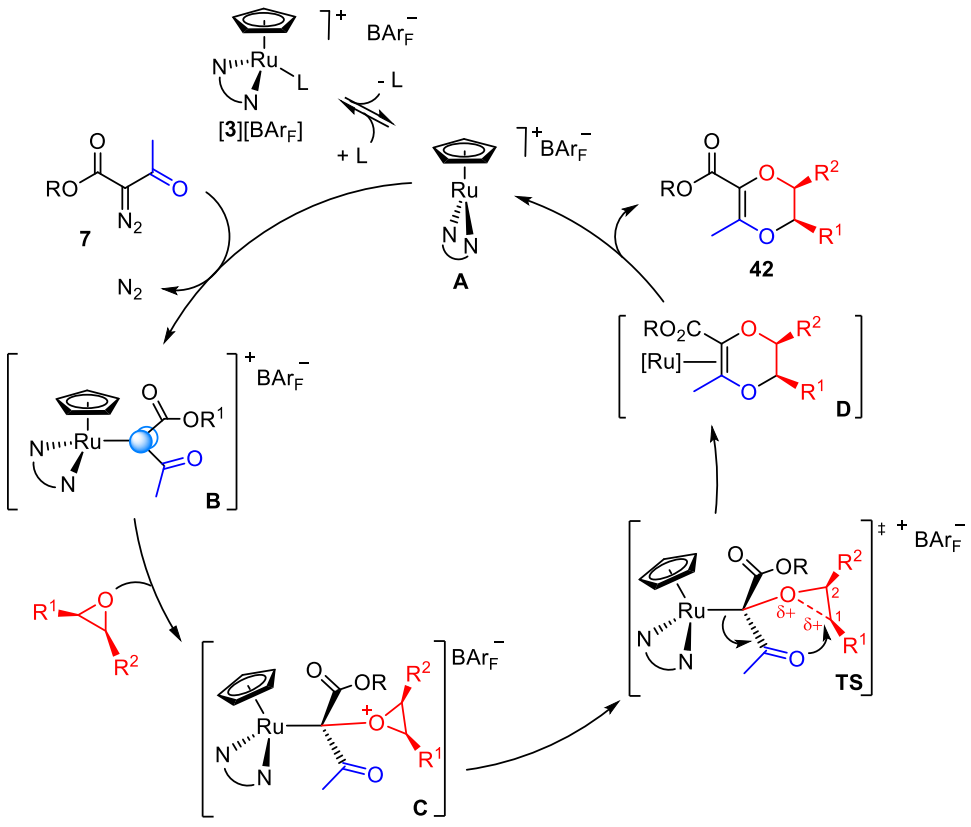


Figure 5.10 IR monitored reaction. (**7a** (2139 cm^{-1}); **42aC** OC=O (ester 1712 cm^{-1}); **42aC** C=C-O (enol-ether 1635 cm^{-1}).

5.7.3 Mechanistic rationale

A mechanistic rationale coherent with all the experimental information collected is proposed in **Scheme 5.15**. After the *in situ* generation of [**3**][BAr_F] complex, dissociation of the acetonitrile ligand led to the formation of the catalytically active, Lewis acidic, 16-electrons species **A**. It is proposed that this electron deficient species reacts with the diazo reagents **7** to afford the metal carbene intermediate **B**. At this stage, a nucleophilic attack

of the epoxide occurs and a metal oxonium ylide intermediate **C** is formed. Possibly promoted by strain, the new C-O bond formation takes place through a transition state **TS** with a high carbenium character (S_N1 like pathway). The nucleophilic attack occurs at the carbon that is better able to stabilize the developing positive charge, explaining the observed regioselectivity. The cyclization step must be fast to avoid an epimerization (racemization) at the electrophile site that would come from the formation of a more carbocationic center and a rotation by total elongation around the C_1-C_2 bond. It is fortunately happening only with substrate **32P** for which intermediate with a carbenium character is strongly stabilized by the para-methoxy group. The "sp^2" hybridization of the reactive electrophilic carbon renders his reaction a six-*endo*-*trig*-like cyclization which is favored according to the Baldwin's rules. After this step, the product **42** is released and the catalyst regenerated.



Scheme 5.15 Mechanistic rationale. $\overset{\frown}{\text{N N}}$ represents ligand **L1**. R^1>R^2 donor character.

5.7.4 Computational studies

To ascertain this mechanistic proposal, computational studies were performed by Dr. Amalia Isabel Poblador-Bahamonde (University of Geneva). All calculations were accomplished with the Gaussian '09[186] software package, using the B3PW91 functional.[187] For the optimization of geometry, the ruthenium atom was described with the Stuttgard/Dresden (SDD) pseudo potential and the associated basis sets,[188] augmented by a *f* polarization function.[189] The remaining atoms (C, N, O, H) were represented by a 6-31G**(*d,p*) basis set.

First, the structure and the conformations of the metal carbene were calculated. Starting from the x-ray structures of [**3**][X] complexes obtained as described in chapter 2 (**Figure 2.3**), the molecule of acetonitrile was substituted with the reactive carbene. The results of the conformational optimization are reported in **Figure 5.11**. Rotation around the C-Ru bond was analysed. The most stable conformations are those in which the methyl or the methoxy group of the carbene is eclipsed with the cyclopentadienyl ligand. The difference in energy between these conformers and the staggered conformers is of around 6-8 kcal / mol. Coordination of the epoxide on all these three conformers has been studied and no significant differences have been founded. Therefore, only one of them will be reported in the following discussion.

[186] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[187] (a) Perdew, J. P.; Wang, Y., *Phys Rev B* **1992**, *45* (23), 13244-13249; (b) Becke, A. D., *J Chem Phys* **1993**, *98* (7), 5648-5652.

[188] Peterson, K. A.; Figgen, D.; Dolg, M.; Stoll, H., *J Chem Phys* **2007**, *126*, 124101-124112.

[189] Ehlers, A. W.; Bohme, M.; Dapprich, S.; Gobbi, A.; Hollwarth, A.; Jonas, V.; Kohler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G., *Chem Phys Lett* **1993**, *208* (1-2), 111-114.

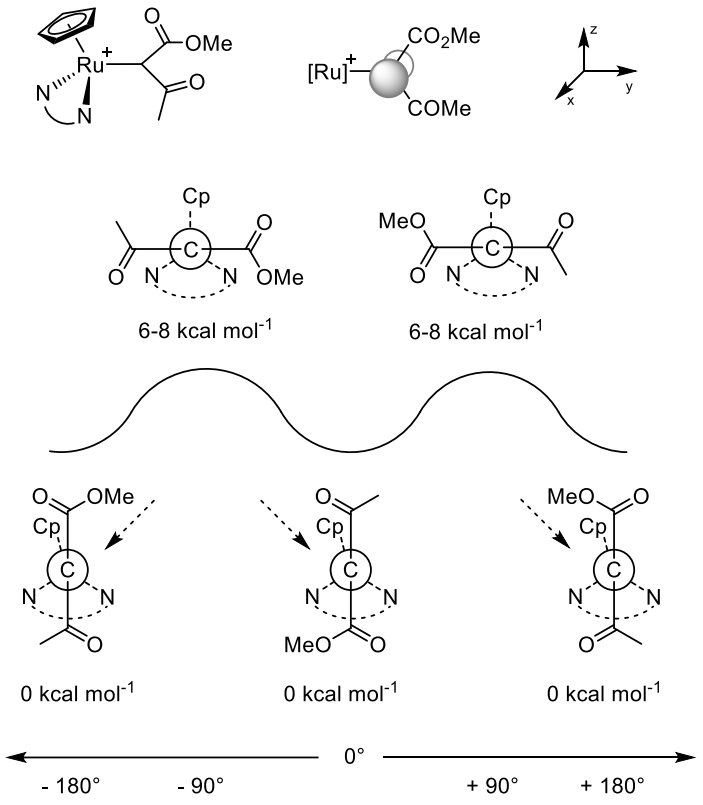


Figure 5.11 Conformational analysis of the metal carbene.

Figure 5.12 shows the computed reaction profiles for C-O insertion of the carbene into the (*R*)-styrene oxide leading to the observed regioisomer. Coordination of epoxide is predicted to occur with a 9.8 kcal / mol energy barrier. The complex obtained has to overcame a barrier of 1.7 kcal / mol only to form the carbocation intermediate **Int II**. Ring closure is essentially instantaneous and provides the desired regioisomer of the product through an in fact S_N1-like pathway with retention of configuration. A similar reaction profile has been calculated for the (*S*)-styrene oxide.

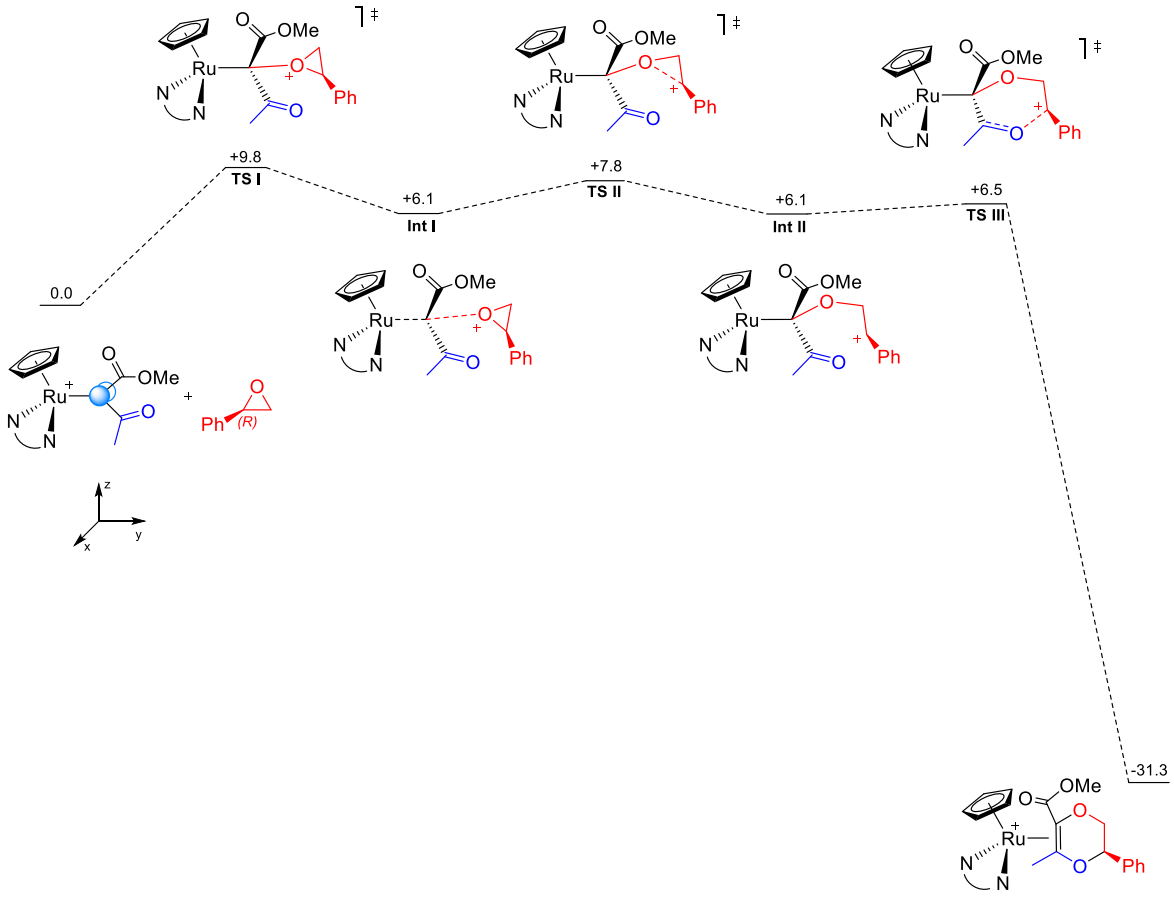


Figure 5.12 Computed reaction profiles (kcal / mol).

5.8 Conclusions

CpRu catalyzed decomposition of α-diazo-β-ketoesters leads, in presence of epoxides, to an original reactivity. Unique dioxene species have been obtained in one step synthesis. These substituted 1,4-dioxenes are known to be useful substrates in a wide range of organic reactions[190] and to have important biological activity for agrochemicals as fungicide.[180a,191] Since now, their synthesis has been achieved by functionalization of unsubstituted 1,4-dioxene[180a, 190-192] or by O-H insertion of α-diazo-β-ketoesters with a

[190] (a) Hanna, I.; Michaut, V., *Org. Lett.* **2000**, *2* (8), 1141-1143; (b) Hanna, I., *Tetrahedron Lett.* **1995**, *36* (6), 889-892; (c) Baylon, C.; Hanna, I., *Tetrahedron Lett.* **1995**, *36* (36), 6475-6478.

[191] (a) Hassall K.A., in *The biochemistry and uses of pesticides*, 2nd edition; VCH: Weinheim, **1990**; pp 327-331. (b) Dekeyser, M. A.; Davis, R. A., *J Agr Food Chem* **1998**, *46* (7), 2827-2829.

[192] Moss, R. D.; Paige, J., *J Chem Eng Data* **1967**, *12* (3), 452-454.

diol.[193] In all these instances, a consistent number of steps were required and the products were obtained in rather low yields.[180a] Mechanistic studies have been performed in order to gain some insight on the nature of the transformation. The experiments detailed indicate a perfect *syn* stereoselectivity for the reactions as *cis* epoxides afford exclusively *cis* adducts and styrene oxides react with pure retention of configuration. Moreover, a perfect regioselectivity was observed, in favour of the products formed through intermediates with strong carbenium character (tertiary or benzylic). Based on both experimental results and computational studies, a transition-metal induced and controlled S_N1-like pathway with full retention of configuration is proposed.

[193] Hilgenkamp, R.; Brogan, J. B.; Zercher, C. K., *Heterocycles* **1999**, *51* (5), 1073-1078.

6 Conclusions and perspectives

6.1 Conclusions

During this PhD, the field of $[CpRu(CH_3CN)_3][X]$ catalyzed decomposition of α-diazo-β-ketoesters was studied. The aim of this PhD work was indeed the study of ruthenium promoted decomposition of α-diazo-β-ketoesters and the subsequent reactivity of the acceptor/acceptor metal carbene formed with oxygen containing Lewis basic moieties.

The scope of the cyclization reaction of metal carbenes with a carbonyl group has been extended to cyclic ketones to afford dioxaspiro compounds. The reactivity was then extended for the first time to deactivated esters, leading to the formation of orthoester-spiro adducts. The reaction was further applied to isatin moieties to afford nitrogen-containing spiro compounds.

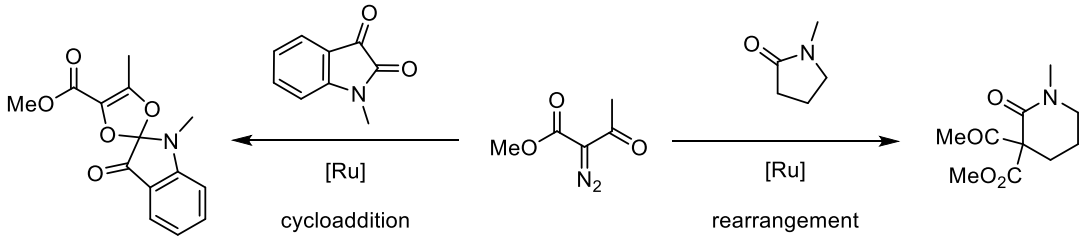
The reactivity of the metal carbene complexes with THF as Lewis base was investigated. Unprecedented 1,3-C-H insertion reactions led to the first one-step synthesis of enol acetal moieties. The reaction was found to be completely regio- and stereoselective. Some mechanistic aspects were studied and a concerted pathway for the hydrogen transfer was proposed. The rearrangement of those adducts into the classical insertion product was also demonstrated. A different reactivity was observed when α-diazo-β-ketoesters were replaced with diester diazo compounds.

An original reactivity was observed using epoxides as reactive partners. Dioxene species were obtained as major products. The reaction was completely regioselective. Stereoselectivity has been strongly investigated. Conservation of the chiral information was observed and this through a retention of configuration at the reactive stereocenter. Efforts were done to gain some mechanistic insights on the nature of the transformation. Both experimental and computational experiments have been performed and a S_N1 like pathway with retention of configuration was finally proposed.

6.2 Perspectives

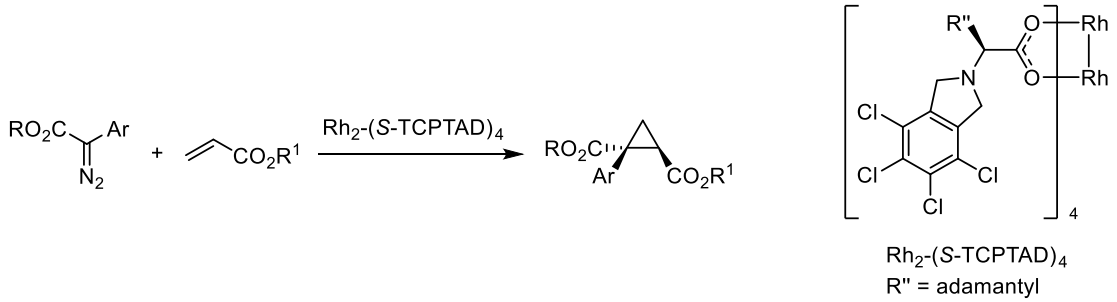
The results obtained during this PhD work are a good incentive to further explore the field of CpRu catalyzed decomposition of diazo compounds.

Preliminary results on cyclization reactions on the carbonyl group of amides are reported in this thesis and many further studies can be pursued. Many efforts should probably concentrate on further investigate the dichotomy observed when isatin and NMP are used as substrates (**Scheme 6.1**).



Scheme 6.1 Different reactivity between isatin and NMP substrates.

Recently, Davies and co-workers reported the rhodium-catalyzed enantioselective cyclopropanation of electron-deficient alkenes with aryldiazoacetates (**Scheme 6.2**).[148] Electron-deficient alkenes could be tested in presence of CpRu and α-diazo-β-ketoesters. The cyclopropanation pathway could in this case become disfavoured compared to the formation of the carbonyl ylide and the subsequent cyclization reaction.



Scheme 6.2 Cyclopropanation of electron-deficient alkenes.

In the contest of the C-H insertion into THF, the fundamental role of the ketone moiety of the diazo compound is evident in this reaction. It has been also confirmed by an

experiment carried on using the methyl 2-diazo-3-[(1,1-dimethylethyl)dimethylsiloxy]-3-butenoate (**Figure 6.1**).[194] No conversion of the diazo was obtained in this case, the carbonyl group being protected.

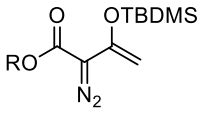


Figure 6.1 Methyl 2-diazo-3-[(1,1-dimethylethyl)dimethylsiloxy]-3-butenoate.

In order to examine if the role played by the ester part is as crucial as the ketone, the scope of the diazo substrate could be extended to the reagents reported in **Figure 6.2**. The synthesis of these compounds has been published by Taber[195] and Padwa.[196]

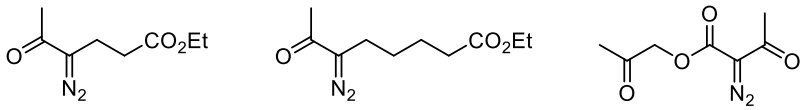


Figure 6.2 Different diazo compounds to test.

An intramolecular version of the C-H insertion reaction into tetrahydrofuran moieties could be also investigated, to possibly form bridged bicyclic compounds. Substrates[197] illustrated in **Figure 6.3** could be tested to challenge the chemistry.

[194] Davies, H. M. L.; Ahmed, G.; Churchill, M. R., *J. Am. Chem. Soc.* **1996**, *118* (44), 10774-10782.

[195] (a) Taber, D. F.; Teng, D. W., *J. Org. Chem.* **2002**, *67* (5), 1607-1612; (b) Taber, D. F.; Kanai, K., *J. Org. Chem.* **1999**, *64* (21), 7983-7987.

[196] Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L., *J. Org. Chem.* **1993**, *58* (17), 4646-4655.

[197] (a) Villalobos, M. N.; Wood, J. L., *Tetrahedron Lett.* **2009**, *50* (47), 6450-6453; (b) Bulbule, V. J.; Borate, H. B.; Munot, Y. S.; Deshpande, V. H.; Sawargave, S. P.; Gaikwad, A. G., *J Mol Catal. Chem.* **2007**, *276* (1-2), 158-161; (c) Yang, J. H.; Ji, C. B.; Zhao, Y. M.; Li, Y. F.; Jiang, S. Z.; Zhang, Z. W.; Ji, Y. Q.; Liu, W. Y., *Synthetic Communications* **2010**, *40* (7), 957-963; (d) Liu, B.; Liu, G.; Xin, Z. L.; Serby, M. D.; Zhao, H. Y.; Schaefer, V. G.; Falls, H. D.; Kaszubska, W.; Collins, C. A.; Sham, H. L., *Bioorg. Med. Chem. Lett.* **2004**, *14* (20), 5223-5226; (e) Oku, A.; Sawada, Y.; Schroeder, M.; Higashikubo, I.; Yoshida, T.; Ohki, S., *J. Org. Chem.* **2004**, *69* (4), 1331-1336.

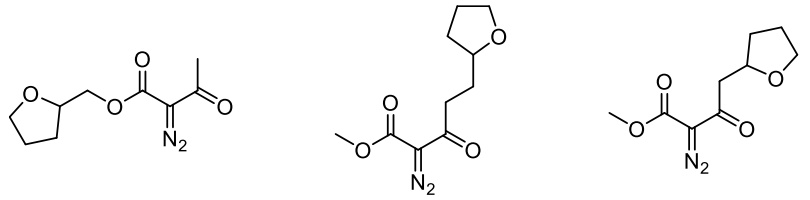
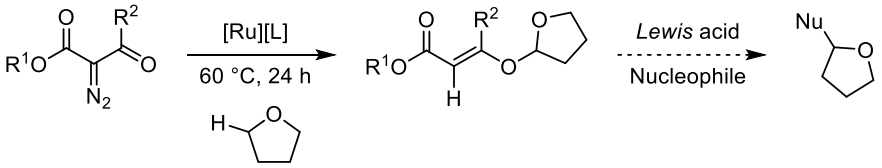


Figure 6.3 Substrates for an intramolecular version of the 1,3-C-H insertion reaction.

Few more applications of this reactivity could be developed. The possibility to rearrange, in presence of a Lewis acid, the enol-acetal product obtained proves the good ability of this moiety to act as a leaving group. This capacity could be exploited to further functionalize substituted tetrahydrofuran rings. After the insertion step, the addition in the reaction mixture of a better nucleophile than the *in situ* generated enol ether would provide a variety of new synthetic adducts (**Scheme 6.3**).



Scheme 6.3 Possible nucleophilic attack on the THF moiety.

Only few unsuccessful attempts have been done, at the beginning of this PhD work, using indole as nucleophile and diethylaluminium chloride as Lewis acid. An intensive screening of nucleophiles and Lewis acids would be advisable.

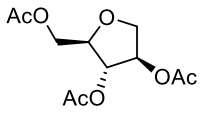


Figure 6.4 2,3,5-tri-O-acetyl-1,4-anhydro-D-arabinitol.

Of particular interest would be to apply this strategy to the direct synthesis of nucleoside-analogues. Initially a reaction was tried on the ribose derivative[198] depicted in

[198] Monrad, R. N.; Madsen, R., *J. Org. Chem.* **2007**, *72* (25), 9782-9785.

Figure 6.4. Due to the presence of carbonyl group in the acetate protecting moiety, a complex mixture of products was obtained. It would be interesting to choose different protecting groups for the hydroxyls in order to avoid the competitive reactions. Computational studies could be performed to possibly confirm the 5-membered transition state proposed in the mechanistic rational proposed in **Scheme 4.6**.

Other Lewis basic substrates could be tested in the reaction with acceptor/acceptor α-diazo-β-ketoesters and oxetanes in particular. Oxetanes have basicity higher than that one of THF and oxiranes.[199] It is possible to imagine that they can react with this catalytic combination to give a C-H or a C-O insertion reaction similar to those described in this work. As in the case of THF, it is expected not to observe the macrocyclization obtained with rhodium catalyst.[64c] Pyrrolidine and aziridine moieties could be tried as well. C-H insertion or rearrangement reactions would lead to the formation of interesting N-containing heterocyclic compounds.

Despite few attempts to perform the reactions in presence of enantiopure ligands, no enantioselectivity has been achieved in the three atoms insertion reactions with both THF and epoxides. A larger ligand screening could be performed; in particular the bidentate ligands synthesized by Kitamura and co-workers[200] depicted in **Figure 6.5** could be tested.

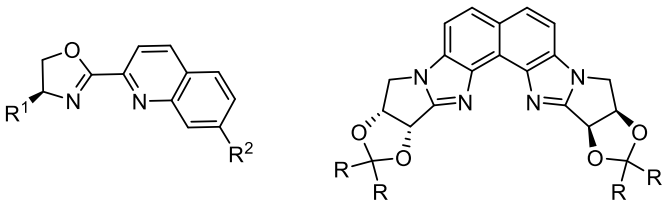


Figure 6.5 Kitamura's ligands.

[199] (a) Darensbourg, D. J.; Chung, W. C., *Polyhedron* **2013**, *58*, 139-143; (b) Searles, S.; Tamres, M., *J. Am. Chem. Soc.* **1951**, *73* (8), 3704-3706; (c) Berthelot, M.; Besseau, F.; Laurence, C., *Eur. J. Org. Chem.* **1998**, (5), 925-931.

[200] (a) Miyata, K.; Kutsuna, H.; Kawakami, S.; Kitamura, M., *Angew. Chem. Int. Ed.* **2011**, *50* (20), 4649-4653; (b) Miyata, K.; Kitamura, M., *Synthesis-Stuttgart* **2012**, *44* (14), 2138-2146.

Recently, Ye and Cramer described a class of chiral cyclopentadienyl analogues that desymmetrize a half-sandwich rhodium(III)-catalyzed C-H bond functionalization.[201] Their strategy is based on the selective ligand association on the chiral-at-metal complexes, the selectivity being imposed by the enantiopure Cp ligand. This approach could be applied to ruthenium complexes that could be used as catalyst precursors in the reactions described in this PhD work.

Charette and co-workers recently showed how the nature of the substituents on the diazo moiety could influence the stereoselectivity of the rhodium catalyzed cyclopropanation reaction.[51,202] To do that, diazo with different electron-withdrawing substituents, have been prepared (**Figure 6.6**). These compounds could be tested in the CpRu catalyzed reactions with the different Lewis base moieties.

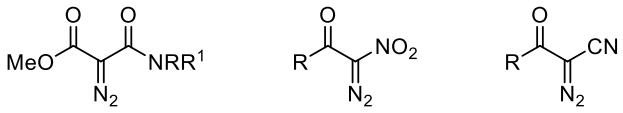


Figure 6.6 Acceptor/acceptor diazo compounds.

Other carbene precursors, such as iodine compounds and triazoles, could be tested as well in order to verify if CpRu complexes are able to generate carbenes from them.

Looking for new types of reactivity, other transition metal sources could be considered. Recently, cobalt(II) complexes of porphyrins have been described as a new class of catalysts for diazo decomposition.[203] Zhang and co-workers reported that this new catalytic combination leads to unique reactivities and exceptional selectivities such as in the cyclopropanation of olefins.[204] For example, compared to dirhodium catalysts, that were shown to promote additions to simple and conjugated olefins, cobalt(II) appeared to be active even with unsaturated ester and nitriles. This original reactivity suggested a very

[201] Ye, B. H.; Cramer, N., *Science* **2012**, *338* (6106), 504-506.

[202] Lindsay, V. N. G.; Nicolas, C.; Charette, A. B., *J. Am. Chem. Soc.* **2011**, *133* (23), 8972-8981.

[203] Doyle, M. P., *Angew. Chem. Int. Ed.* **2009**, *48* (5), 850-852.

[204] (a) Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B., *J. Am. Chem. Soc.* **2010**, *132* (31), 10891-10902; (b) Cui, X.; Xu, X.; Lu, H. J.; Zhu, S. F.; Wojtas, L.; Zhang, X. P., *J. Am. Chem. Soc.* **2011**, *133* (10), 3304-3307; (c) Xu, X.; Lu, H. J.; Ruppel, J. V.; Cui, X.; de Mesa, S. L.; Wojtas, L.; Zhang, X. P., *J. Am. Chem. Soc.* **2011**, *133* (39), 15292-15295; (d) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P., *J. Am. Chem. Soc.* **2012**, *134* (49), 19981-19984.

different character of the carbene intermediate compared to the generic transition metal electrophilic carbene intermediates. In fact, after combined experimental and computational studies on cyclopropanation reactions, an unusual radical-type mechanism was proposed via diradical intermediates.[203a]

In the last decade, Zhang and co-workers also showed that commercially available Iron (III) porphyrin complexes efficiently catalyzed the decomposition of ethyl diazoacetate to give selective olefination of a variety of aldehydes and ketones.[205] Thanks to the stability of this complex, the reactions were carried out under standard laboratory conditions.

Gold has been studied only relatively recently compared to all the other transition metals. In 2005, Pérez and co-workers reported the first example of gold-catalyzed decomposition of ethyl diazoacetate and subsequent carbene transfer.[206] Since then, reports of that kind of transformation have been limited to the use of achiral gold complexes, with ethyl diazoacetate as main carbene source.[207] Recently Davies and co-workers reported the first gold(I)-catalyzed asymmetric cyclopropenation of internal alkynes.[208] This study showed that chiral Au(I) complexes containing various BINAP-type ligands, developed by Toste,[209] could decompose donor/acceptor diazo compounds to promote cyclopropenation with high asymmetric induction. Furthermore, it appeared that the gold carbene was more electrophilic and less sterically demanding compared to

[205] (a) Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P., *J. Org. Chem.* **2003**, *68* (9), 3714-3717; (b) Chen, Y.; Huang, L. Y.; Zhang, X. P., *J. Org. Chem.* **2003**, *68* (15), 5925-5929; (c) Chen, Y.; Huang, L. Y.; Zhang, X. P., *Org. Lett.* **2003**, *5* (14), 2493-2496.

[206] Fructos, M. R.; Belderrain, T. R.; de Fremont, P.; Scott, N. M.; Nolan, S. P.; Diaz-Requejo, M. M.; Perez, P. J., *Angew. Chem. Int. Ed.* **2005**, *44* (33), 5284-5288.

[207] (a) Prieto, A.; Fructos, M. R.; Diaz-Requejo, M. M.; Perez, P. J.; Perez-Galan, P.; Delpont, N.; Echavarren, A. M., *Tetrahedron* **2009**, *65* (9), 1790-1793; (b) Corma, A.; Dominguez, I.; Rodenas, T.; Sabater, M. J., *J. Catal.* **2008**, *259* (1), 26-35; (c) Flores, J. A.; Dias, H. V. R., *Inorg Chem* **2008**, *47* (11), 4448-4450; (d) Fructos, M. R.; de Fremont, P.; Nolan, S. P.; Diaz-Requejo, M. M.; Perez, P. J., *Organometallics* **2006**, *25* (9), 2237-2241; (e) Corma, A.; Iglesias, M.; Xamena, F. X. L. I.; Sanchez, F., *Chemistry-a European Journal* **2010**, *16* (32), 9789-9795.

[208] Briones, J. F.; Davies, H. M. L., *J. Am. Chem. Soc.* **2012**, *134* (29), 11916-11919.

[209] (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D., *J. Am. Chem. Soc.* **2004**, *126* (14), 4526-4527; (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D., *Angew. Chem. Int. Ed.* **2004**, *43* (40), 5350-5352; (c) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D., *J. Am. Chem. Soc.* **2007**, *129* (9), 2452-2453; (d) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D., *J. Am. Chem. Soc.* **2005**, *127* (51), 18002-18003; (e) Watson, I. D. G.; Ritter, S.; Toste, F. D., *J. Am. Chem. Soc.* **2009**, *131* (6), 2056-2057; (f) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D., *Science* **2007**, *317* (5837), 496-499.

the corresponding dirhodium catalysts. Reactivity and, eventually, selectivity of cobalt, iron and gold complexed acceptor/acceptor carbenes could be tested in presence of cyclic ethers.

7 Experimental Part

7.1 Generalities

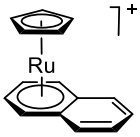
All reactions were carried out under dry N_2 by means of an inert gas/vacuum double manifold line and standard Schlenk techniques with magnetic stirring, unless otherwise stated. Dry toluene, dichloromethane, hexane diethylether and tetrahydrofuran were obtained by filtration through appropriate activated-alumina drying columns. Analytical thin-layer chromatography (TLC) was performed with Merck SIL G/UV_{254} plates. Unless otherwise stated, column chromatography (Fluka silicagel 60, 40 µm or Fluka basic alumina type 5016A) was performed in air. NMR spectra were recorded on Bruker ARX-300 or AMX-400 or ARX-500 at room temperature unless otherwise stated. ^{1}H NMR: chemical shifts are given in ppm relative to Me_4Si with solvent resonances used as internal standards (7.26 ppm for $CDCl_3$ and 5.32 ppm for CD_2Cl_2). Data were reported as follows: chemical shift (δ) in ppm on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, and m = multiplet), coupling constant (Hz) and integration. ^{13}C NMR: chemicals shifts were given in ppm relative to Me_4Si with solvent resonances used as internal standards (77.16 ppm for $CDCl_3$ and 54.00 ppm for CD_2Cl_2). ^{31}P NMR: chemical shifts are reported in ppm relative to H_3PO_4. Assignments may have been achieved using DEPT, COSY, HSQC, HMBC and/or NOESY experiments. IR spectra were recorded with a Perkin-Elmer S100 spectrometer using a universal ATR sampling. Melting points (Mp) were measured in open capillary tubes on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. React-IR™ 45m instrument was used for *in-situ* measurement in a special Schlenk tube fitted with an immersible in-situ FT-IR DiComp probe. High resolution electrospray mass spectra (ESI-HR-MS) were obtained on a Finnigan SSQ 7000 spectrometer by the Department of Mass Spectroscopy of the University of Geneva. HPLC analyses were performed on an Agilent 1100 apparatus (binary pump, auto-sampler, column thermostat and diode array detector). Unless otherwise stated, all chemicals were obtained from Fluka, Aldrich, Pressure Chemicals or Acros and used as received or purified according to standard literature procedures.

7.2 Experimental part of Chapter 2

7.2.1 Procedures for the synthesis and analysis data of CpRu complexes

[CpRuNaphthalene][BAr_F] ([1][BAr_F])

[CpRuNaphthalene][PF_6] was prepared according to the literature procedure.[120b] A shlenk tube was charged with $NaBAr_F$ (1.01 eq, 0.75 mmol, 0.660 g) and [CpRuNaphthalene][PF_6] (1 eq, 0.74 mmol, 0.576 g). Dry and degassed acetone (35 ml) and methylene chloride (19 ml) were added and the yellow solution was stirred for 30 min. The solution was transferred in a separatory funnel containing water (60 ml). After shaking, the mixture obtained was filtered on cotton. The organic phase was separated and the aqueous phase was back extracted with CH_2Cl_2. The combined organic phase was filtered over a column of neutral Al_2O_3 (10 x 2 cm), eluting with CH_2Cl_2. The yellow filtrate was evaporated to dryness and the crude obtained was crystallised by slow diffusion of hexane in a solution of [**1**][BAr_F] in CH_2Cl_2 at 4 °C for 4 days. The desired compound was obtained as yellow crystals in 90 % yield.

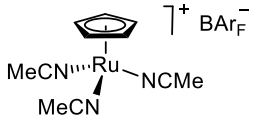


Complex obtained as a yellow solid (0.66 mmol, 90% yield); **Mp:** > 250 °C (decomp.); **^{1}H NMR (500 MHz, CD_2Cl_2):** δ 7.74 - 7.71 (m, 8H), 7.64 (s, 4H) 7.56 (s, 4H), 6.82 (dd, *J* = 4 and 2 Hz, 2H), 6.12 (dd, *J* = 5 and 2 Hz, 2H) and 4.89 (s, 5H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2):** δ 162.3 (q, *J* = 50 Hz, 4 x $C_{ipso}BAr_F$), 135.4 (8 x $C_{ortho}BAr_F$), 133.0 (2 x CH), 129.4 (qq, *J* = 32 and 3 Hz, 8 x $\underline{C}CF_3$), 129.3 (2 x CH, overlapped signal), 125.2 (4, *J* = 272 Hz, 8 x CF_3), 118.1 (p, *J* = 4 Hz, 4 x $C_{para}BAr_F$), 97.8 (2 x C), 85.9 (2 x CH), 84.0 (2 x CH) and 80.2 (5 x CH_{Cp}) ppm; **IR (neat):** 1354, 1273 and 1113 cm^{-1}; **Elemental analysis** found: C, 48.72; H, 2.25; N, 0.00; calculated for $C_{47}H_{25}BF_{24}Ru$: C, 48.77; H, 2.18; N, 0.00.

[$CpRu(CH_3CN)_3$][BAr_F] ([2][BAr_F])

The naphthalene complex [**1**][BAr_F] (0.66 mmol) was placed in a shlenk tube. Dry (on molecular sieves for 15 hours) and degassed acetonitrile (0.5 ml) was added and the orange solution was stirred at 25 °C for 24 h. The naphthalene was extracted with hexane

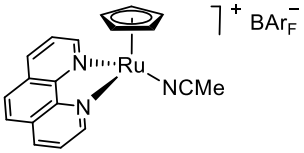
(3 x 1 ml). The extraction was repeated after 24 h. After a total of 3 days stirring, the extraction was repeated and the solution was dried in a vacuum pump. The solid obtained was washed with hexane (3 x 1 ml) to give the product as a yellow powder in a quantitative yield.



Complex obtained as a yellow solid (0.66 mmol, quantitative yield); **Mp:** > 250 °C (decomp.); **IR (neat):** 1355, 1274 and 1117 cm^{-1}.

[CpRu(1,10-Phenanthroline)(CH_3CN)][BAr_F] ([3][BAr_F])

To a solution of [**2**][BAr_F] complex (0.66 mmol) in dry and degassed methylene chloride (2 ml), 1,10-phenanthroline (1eq., 0.66 mmol) was added and the resulting deep red solution was stirred at 25 °C for 4 h. The solvent was removed under vacuum. The crude obtained was crystallised by slow diffusion of hexane in a solution of [**2**][BAr_F] in CH_2Cl_2 at 0 °C for 2 days. The desired compound was obtained as dark red crystals in 98 % yield.

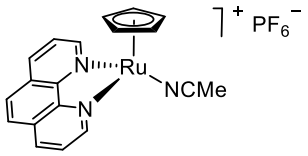


Complex obtained as a dark red solid (0.65 mmol, 98% yield); **Mp:** > 250 °C (decomp.); **^{1}H NMR (500 MHz, CD_2Cl_2):** δ 9.66 (dd, *J* = 5 and 1 Hz, 2H), 8.41 (dd, *J* = 8 and 1 Hz, 2H), 7.96 (s, 2H), 7.77 (dd, *J* = 8 and 5 Hz, 2H), 7.72 (dt, *J* = 5 and 2 Hz, 8H), 7.54 (s, 4H), 4.46 (s, 5H) and 1.92 (s, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2):** δ 162.3 (dd, *J* = 100 and 50 Hz, 4 x $C_{ipso}BAr_F$), 155.8 (2 x CH), 148.3(2 x C), 136.3(2 x CH), 135.4 (8 x $C_{ortho}BAr_F$), 130.9 (2 x C), 129.5 (qdd, *J* = 31, 6 and 3 Hz, qq, 8 x $\underline{C}CF_3$), 127.8 (2 x CH), 125.5 (2 x CH), 125.1 (q, *J* = 272 Hz, 8 x CF_3), 124.2 ($CH_3\underline{C}N$), 118.1 (p, *J* = 4 Hz, 4 x $C_{para}BAr_F$), 71.5 (5 x CH_{Cp}) and 4.2 ($\underline{C}H_3CN$) ppm; **IR (neat):** 1355, 1275 and 1117 cm^{-1}; **Elemental analysis** found: C, 48.87; H, 2.29; N, 3.30; calculated for $C_{51}H_{28}BF_{24}N_3Ru$: C, 48.98; H, 2.26; N, 3.36.

[CpRu(1,10-Phenanthroline)(CH_3CN)][PF_6] ([3][PF_6])

To a solution of [**2**][PF_6] complex (0.66 mmol) in dry and degassed methylene chloride (2 ml), 1,10-phenanthroline (1eq., 0.66 mmol) was added and the resulting deep red solution

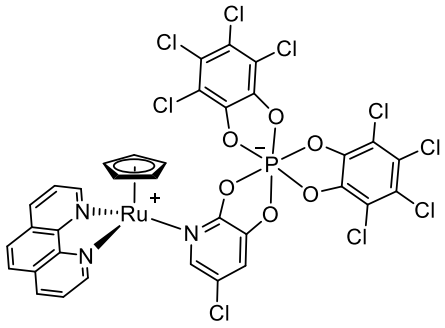
was stirred at 25 °C for 2 h. The solvent was removed under vacuum. The crude obtained was crystallized by slow diffusion of hexanes in a solution of [**2**][PF_6] in THF at 0 °C for 2 days. The desired compound was obtained as dark red crystals in 92 % yield.



Complex obtained as a dark red solid (0.61 mmol, 92% yield); **Mp:** > 250 °C (decomp.); **^{1}H NMR (500 MHz, CD_2Cl_2):** δ 9.71 (dd, *J* = 5 and 1 Hz, 2H), 8.49 (dd, *J* = 8 and 1 Hz, 2H), 8.03 (s, 2H), 7.84 (dd, *J* = 8 and 5 Hz, 2H), 4.48 (s, 5H) and 1.98 (s, 3H) ppm; **IR (neat):** 1429, 835 and 505 cm^{-1}.

[CpRu(1,10-phenanthroline)][TRISPHAT-N] ([3][TRISPHAT-N])

To a solution of [**2**][PF_6] complex (0.25 mmol) in dry and degassed methylene chloride (2 ml), 1,10-phenanthroline (1eq., 0.25 mmol) and [TRISPHAT-N][*n*-Bu_3NH] (1 eq., 0.25 mmol) was added and the resulting deeply red solution was stirred at 25 °C for 20 min. The solvent was removed under vacuum. The crude obtained was purified by column chromatography on silica gel eluting with dry methylene chloride. The desired compound was obtained as dark red solid in 80 % yield. X-Ray quality crystals were obtained by slow diffusion of pentane in a solution of [**3**][TRISPHAT-N] in CH_2Cl_2 at - 20 °C for 4 weeks.



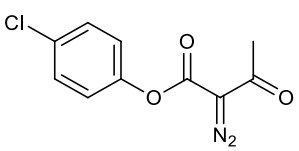
Complex obtained as a dark red solid (0.20 mmol, 80% yield); **Mp:** > 250 °C (decomp.); Rf: 0.98 (SiO_2, CH_2Cl_2); **^{1}H NMR (500 MHz, CD_2Cl_2):** δ 10.01 (dd, *J* = 5 and 1 Hz, 1H), 9.66 (dd, *J* = 5 and 1 Hz, 1H), 8.39 (dd, *J* = 8 and 1 Hz, 1H), 8.29 (dd, *J* = 8 and 1 Hz, 1H), 7.95 (dd, *J* = 5 and 3 Hz, 1H), 7.92 (d, *J* = 12 Hz, 2H), 7.42 (dd, *J* = 8 and 5 Hz, 1H), 7.03 (dd, *J* = 2 and 1 Hz, 1H), 6.76 (dd, *J* = 2 and 1 Hz, 1H) and 4.22 (s, 5H); **^{13}C NMR (126 MHz, CD_2Cl_2):** δ 158.3 (d, J_{C-P} = 14 Hz, C), 157.3 (CH), 155.4 (CH), 148.5 (C), 148.2 (C), 142.4 (d, J_{C-P} = 6 Hz, C), 142.2 (d, J_{C-P} = 6 Hz, C), 142.0 (d, J_{C-P} = 7 Hz, C), 141.9 (d, J_{C-P} = 7 Hz, C), 140.3 (C), 136.5 (CH), 135.6 (CH), 135.4 (CH),130.6 (2 x C), 127.8 (CH), 127.4 (CH), 125.8 (CH), 125.0 (CH), 124.1 (C), 123.6 (C), 123.4 (C), 117.3 (d, J_{C-P} = 18

Hz, CH), 114.7 (d, J_{C-P} = 20 Hz, C), 114.5 (d, J_{C-P} = 20 Hz, C), 114.3 (d, J_{C-P} = 20 Hz, C) and 71.1 (5 x C) ppm; **^{31}P NMR (162 MHz, CD_2Cl_2):** δ - 85.03 ppm; **IR (neat):** 2914, 1452 and 825 cm^{-1}.

7.3 Generic procedure for the synthesis and analysis data of diazo compounds

Diazo of type **7** and **25** were readily prepared by using diazo-transfer reagents, such as p-acetamidobenzenesulfonyl azide (p-ABSA). A-diazo-β-ketoesters **7a**,[210] **7b**,[211] **7c**,[33] **7d**,[212] **7e**,[213] **7f**,[214] **7m**,[60] **7n**,[215] **7o**[164] and **7p**[216] were synthesized as described and all data corresponded to previously reported material. The aryl α-diazo-β-ketoesters **7f** to **7l** were prepared according to the procedure reported in literature.[211] Diazomalonates **25** were synthesized as reported in the literature and had spectroscopic characteristics identical to those already described.

4-chlorophenyl 2-diazo-3-oxobutanoate (7g).



Diazo obtained as a white solid (132 mg, 80% yield); **Mp:** 38.5 °C; **Rf** = 0.27 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 (d, *J* = 9 Hz, 2H), 7.10 (d, *J* = 9 Hz, 2H) and 2.52 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 189.8 (C), 160.0 (C), 148.3 (C), 132.1 (C), 129.9 (2 x CH), 123.2 (2 x CH) and 28.6 (CH_3) ppm ($C=N_2$ signal not detected); **IR (neat):** 2137, 1728 and 1648 cm^{-1}.

[210] Brehm, W. J.; Levenson, T., *J. Am. Chem. Soc.* **1954**, *76* (21), 5389-5391.

[211] Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D., *Synthetic Communications* **1987**, *17* (14), 1709-1716.

[212] Meyer, M. E.; Ferreira, E. M.; Stoltz, B. M., *Chem. Commun.* **2006**, (*12*), 1316-1318.

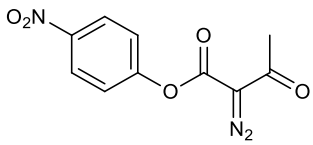
[213] Harned, A. M.; Sherrill, W. M.; Flynn, D. L.; Hanson, P. R., *Tetrahedron* **2005**, *61* (51), 12093-12099.

[214] Hrytsak, M.; Durst, T., *J Chem Soc Chem Comm* **1987**, (15), 1150-1151.

[215] Chiara, J. L.; Suarez, J. R., *Adv. Synth. Catal.* **2011**, *353* (4), 575-579.

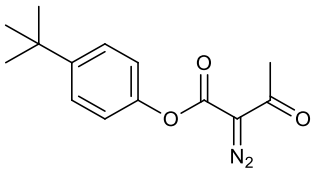
[216] Davies, J. R.; Kane, P. D.; Moody, C. J., *Tetrahedron* **2004**, *60* (18), 3967-3977.

4-nitrophenyl 2-diazo-3-oxobutanoate (7h).



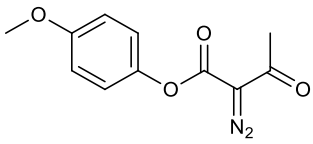
Diazo obtained as a light yellowish solid (120 mg, 75% yield); **Mp:** 84.5 °C; **Rf** = 0.36 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.32 (d, *J* = 9 Hz, 2H), 7.37 (d, *J* = 9 Hz, 2H) and 2.54 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$) :** δ 189.4 (C), 159.1 (C), 154.4 (C), 145.9 (C), 125.6 (2 x CH), 122.7 (2 x CH) and 28.6 (CH_3) ppm (C=N_2 signal not detected); **IR (neat):** 2952, 2146, 1720 and 1654 cm^{-1}.

4-chlorophenyl 2-diazo-3-oxobutanoate (7i).



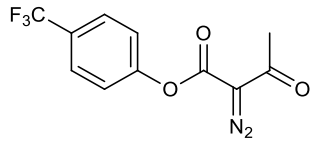
Diazo obtained as a white solid (127 mg, 75% yield); **Mp:** 69.0 °C; **Rf** = 0.44 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 (d, *J* = 9 Hz, 2H), 7.07 (d, *J* = 9 Hz, 2H), 2.53 (s, 3H) and 1.33 (s, 9H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.2 (C), 160.5 (C), 149.6 (C), 147.5 (C), 126.7 (2 x CH), 121.1 (2 x CH) 34.8 (C), 31.6 (3 x CH_3) and 28.6 (CH_3) ppm (C=N_2 signal not detected); **IR (neat):** 2152, 1720 and 1649 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{14}H_{16}O_3N_2$ 261.1233 observed 261.1231.

4-chlorophenyl 2-diazo-3-oxobutanoate (7j).



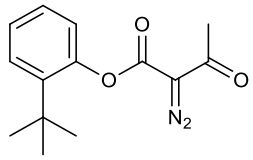
Diazo obtained as a yellowish oil (136 mg, 90% yield); **Rf** = 0.33 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):**δ 7.06 (d, *J* = 9 Hz, 2H), 6.92 (d, *J* = 9 Hz, 2H), 3.81 (s, 3H) and 2.52 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.1 (C), 160.7 (C), 157.9 (C), 143.3 (C), 122.6 (2 x CH), 114.8 (2 x CH), 55.9 (CH_3) and 28.6 (CH_3) ppm (C=N_2 signal not detected); **IR (neat):** 2142, 1727, 1652 and 1509 cm^{-1}.

4-chlorophenyl 2-diazo-3-oxobutanoate (7k).



Diazo obtained as white solid (111 mg, 63% yield); **Mp:** 46.6 °C; **Rf** = 0.42 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.70 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H) and 2.53 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 189.6 (C), 159.6 (C), 152.3 (C), 127.24 (C), 127.20 (2 x CH), 127.16 (C), 122.3 (2 x CH) and 28.6 (CH_3) ppm (C=N_2 signal not detected); **^{19}F NMR (282 MHz, $CDCl_3$):** δ -45.63 ppm; **IR (neat):** 2151, 1721 and 1657 cm^{-1}.

4-chlorophenyl 2-diazo-3-oxobutanoate (7l).



Diazo obtained as a yellowish oil (84 mg, 50% yield); **Rf** = 0.17 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43 (dd, *J* = 8 and 2 Hz, 1H), 7.29-7.19 (m, 2H), 7.05 (dd, *J* = 8 and 2 Hz, 1H), 2.55 (s, 3H) and 1.35 (s, 9H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.2 (C), 160.4 (C), 148.3 (C), 141.5 (C), 127.7 (CH), 127.3 (CH), 126.6 (CH), 124.2 (CH), 34.7 (C), 30.6 (CH_3) and 28.59 (CH_3) ppm (C=N_2 signal not detected); **IR (neat):** 2137, 1731 and 1662 cm^{-1}.

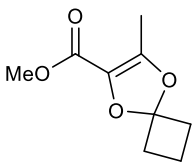
7.4 Experimental part of chapter 3

7.4.1 Generic procedure for the synthesis of compounds 9

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (1.5 mg, 8 μmol, 2.5 mol %) and [CpRu(CH_3CN)$_3$][BAr_F] (9 mg, 8 μmol, 2.5 mol %) were dissolved in 0.60 mL of dry CH_2Cl_2. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 minutes at 25 °C before the addition of desired cyclic ketone **8** (1 eq., 0.32 mmol) and diazo **7a** (1 eq., 0.32 mmol). The solution was stirred at 60 °C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Pentane/Et_2O, SiO_2) to afford insertion products of type **9**.

7.4.2 Analysis data of compounds **9**

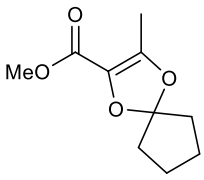
Methyl 7-methyl-5,8-dioxaspiro[3.4]oct-6-ene-6-carboxylate (9a).



Starting from the corresponding α-diazo-β-ketoester **7a** (46 µl, 0.32 mmol) and cyclobutanone (24 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (37 mg, 63 % yield).

Rf = 0.54 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.81 (s, 3H), 2.65-2.42 (m, 4H), 2.19 (s, 3H) and 1.84-1.69 (m, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.3 (C), 148.2 (C), 126.3 (C), 115.2 (C), 51.7 (CH_3), 37.2 (2 x CH_2), 11.6 (CH_2) and 10.8 (CH_3) ppm; **IR (neat):** 1712, 1677, 1350, 1290, 1125, 908 and 731 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_9H_{13}O_4^+$ 185.0808 observed 185.0809.

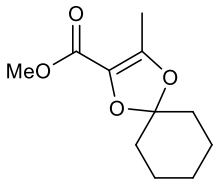
Methyl 3-methyl-1,4-dioxaspiro[4.4]non-2-ene-2-carboxylate (9b).



Starting from the corresponding α-diazo-β-ketoester **7a** (46 µl, 0.38 mmol) and cyclopentanone (28 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (52 mg, 82 % yield).

Rf = 0.54 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.80 (s, 3H), 2.18 (s, 3H), 2.12-1.88 (m, 4H) and 1.86-1.66 (m, 4H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.6 (C), 148.5 (C), 126.5 (C), 124.8(C), 51.7 (CH_3), 37.2 (2 x CH_2), 23.4 (2 x CH_2) and 11.7 (CH_3) ppm; **IR (neat):** 1711, 1674, 1345, 1193, 1134 and 1095 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{10}H_{15}O_4^+$ 199.0965 observed 199.0965.

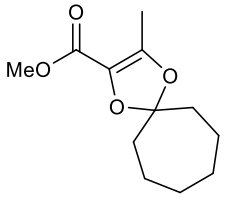
methyl 3-methyl-1,4-dioxaspiro[4.5]dec-2-ene-2-carboxylate (9c).



Starting from the corresponding α-diazo-β-ketoester **7a** (46 µl, 0.32 mmol) and cyclohexanone (33 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (68 mg, 75 % yield).

Rf = 0.55 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, Acetone-*d*$_6$):** δ 3.71 (s, 3H), 2.14 (s, 3H), 1.78 (t, *J* = 6 Hz, 4H), 1.63 (m, 4H) and 1.46 (q, *J* = 6 Hz, 2H) ppm; **^{13}C NMR (100 MHz, Acetone-*d*$_6$):** δ 161.8 (C), 148.3 (C), 127.0 (C), 115.9 (C), 51.3 (CH_3), 35.3 (2 x CH_2), 25.1 (CH_2), 23.7 (2 x CH_2) and 11.6 (CH_3) ppm; **IR (neat):** 1712, 1670, 1346, 1139 and 1107 cm^{-1}.

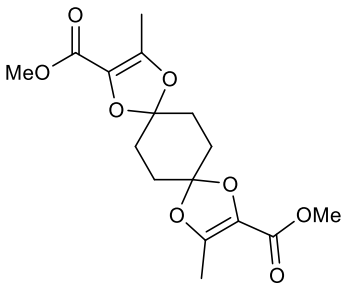
Methyl 3-methyl-1,4-dioxaspiro[4.6]undec-2-ene-2-carboxylate (9d).



Starting from the corresponding α-diazo-β-ketoester **7a** (46 µl, 0.32 mmol) and cycloheptanone (38 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (60 mg, 83 % yield).

Rf = 0.71 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.79 (s, 3H), 2.17 (s, 3H), 2.06-2.02 (m, 4H) and 1.68-1.57 (m, 8H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.9 (C), 148.2 (C), 126.0 (C), 119.8 (C), 51.6 (CH_3), 38.5 (2 x CH_2), 29.3 (2 x CH_2), 21.6 (2 x CH_2) and 11.8 (CH_3) ppm; **IR (neat):** 1711, 1672, 1345, 1137 and 1100 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{12}H_{19}O_4^+$ 227.1278 observed 227.1279.

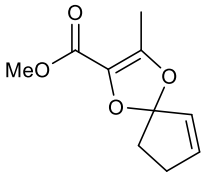
Dimethyl 3,11-dimethyl-1,4,9,12-tetraoxadispiro[4.2.4^{8}.2^{5}]tetradeca-2,10-diene-2,10-dicarboxylate (9e).



Starting from the corresponding α-diazo-β-ketoester **7a** (2 eq., 92 µl, 0.64 mmol) and furan-2(5H)one γ-crotonolactone (72 mg, 0.64 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a white solid (115 mg, 53 % yield).

Mp: 181.0 °C; **Rf** = 0.42 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.80 (s, 6H), 2.18 (s, 6H) and 2.15-2.02 (m, 8H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.6 (2 x C), 148.3 (2 x C), 126.5 (2 x C), 113.9 (2 x C), 51.7 (2 x CH_3), 31.0 (4 x CH_2) and 11.7 (2 x CH_3) ppm; **LR-MS (EI)** m/z observed 341.4; **IR (neat):** 1711, 1678, 1344, 1118 and 1078 cm^{-1}.

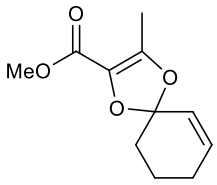
Methyl 3-methyl-1,4-dioxaspiro[4.4]nona-2,6-diene-2-carboxylate (9f).



Starting from the corresponding α-diazo-β-ketoester **7a** (46 µl, 0.32 mmol) and cyclopent-2-en-1-one (27 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 9:1) as a colourless oil (40 mg, 65 % yield).

Rf = 0.40 (SiO_2, pentane:Et_2O, 9:1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.21 (dt, *J* = 6 and 2 Hz, 1H), 5.85 (dt, *J* = 6 and 2 Hz, 1H), 3.80 (s, 3H), 2.52-2.43 (m, 2H), 2.43-2.22 (m, 2H) and 2.20 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.4 (C), 148.4 (C), 140.1 (CH), 134.8 (C), 128.2 (CH), 126.5 (C), 51.7 (CH_3), 35.2 (CH_2), 29.8 (CH_2) and 11.6 (CH_3) ppm; **IR (neat):** 1718, 1674, 1352, 1138 and 1107 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{10}H_{13}O_4^{+}$ 197.0808 observed 197.0809.

Methyl 3-methyl-1,4-dioxaspiro[4.5]deca-2,6-diene-2-carboxylate (9g).



Starting from the corresponding α-diazo-β-ketoester **7a** (46 µl, 0.32 mmol) and cyclohex-2-en-1-one (31 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 9:1) as a colourless oil (45 mg, 67 % yield).

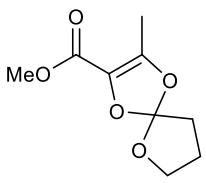
Rf = 0.39 (SiO_2, pentane:Et_2O, 9:1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.09 (dt, *J* = 10 and 4 Hz, 1H), 5.85-5.76 (m, 1H), 3.79 (s, 3H), 2.19 (s, 3H), 2.12-2.00 (m, 4H) and 1.92-1.73 (m, 2H) ppm; **^{13}C NMR (100 MHz, Acetone):** δ 161.6 (C), 148.4 (C), 136.0 (CH), 126.8 (C), 125.7 (CH), 112.2 (C), 51.3 (CH_3), 33.8 (CH_2), 25.1 (CH_2), 20.4 (CH_2) and 11.4 (CH_3) ppm; **IR (neat):** 1714, 1674, 1350, 1148 and 1107 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{11}H_{15}O_4^+$ 211.0965 observed 211.0963.

7.4.3 Generic procedure for the synthesis of compounds **11** and **13**

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (1.5 mg, 8 µmol, 2.5 mol %) and [$CpRu(CH_3CN)_3$][Bar_F] (9 mg, 8 µmol, 2.5 mol %) were dissolved in 0.60 mL of dry CH_2Cl_2. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 minutes at 25 °C before the addition of desired cyclic ester **10** or amide **12** (1 eq., 0.32 mmol) and diazo **7a** (3 eq., 0.96 mmol). The solution was stirred at 60 °C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Pentane/Et_2O, SiO_2) to afford insertion products of type **11** and **13**.

7.4.4 Analysis data of compounds **11** and **13**

Methyl 3-methyl-1,4,6-trioxaspiro[4.4]non-2-ene-2-carboxylate (11a).

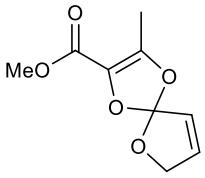


Starting from the corresponding α-diazo-β-ketoester **7a** (165 µl, 0.96 mmol) and γ-butyrolactone (26 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification

by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (14 mg, 22 % yield).

Rf = 0.26 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.10 (td, *J* = 7 and 3 Hz, 2H), 3.81 (s, 3H), 2.43-2.29 (m, 2H), 2.24 (s, 3H) and 2.18-2.09 (m, 2H) ppm; **^{13}C NMR (100 MHz, Acetone):** δ 160.9 (C), 147.0 (C), 132.7 (C), 126.6 (C), 69.3 (CH_2), 51.5 (CH_3), 34.9 (CH_2), 24.8 (CH_2) and 11.2 (CH_3) ppm; **IR (neat):** 1720, 1681, 1353, 1126 and 10662 cm^{-1}.

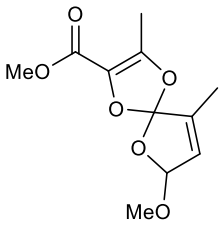
Methyl 3-methyl-1,4,6-trioxaspiro[4.4]nona-2,8-diene-2-carboxylate (11b).



Starting from the corresponding α-diazo-β-ketoester **7a** (138 µl, 0.96 mmol) and furan-2(5H)one γ-crotonolactone (27 µl, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 6:4) as a colourless oil (36 mg, 57 % yield).

Rf = 0.40 (SiO_2, pentane:Et_2O, 6:4); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.53 (dt, *J* = 6 and 2 Hz, 1H), 5.81 (dt, *J* = 6 and 2 Hz, 1H), 4.75-4.72 (m, 2H), 3.82 (s, 3H) and 2.27 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 160.7 (C), 146.9 (C), 136.1 (CH), 133.8 (C), 126.2 (C), 122.2 (CH), 73.9 (CH_2), 51.8 (CH_3) and 11.3 (CH_3) ppm.

Methyl 3-methyl-1,4,6-trioxaspiro[4.4]nona-2,8-diene-2-carboxylate (11c).

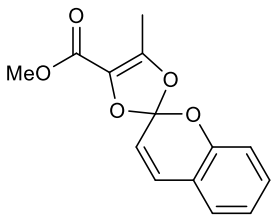


Starting from the corresponding α-diazo-β-ketoester **7a** (138 µl, 0.96 mmol) and 5-methoxifuran-2(5H)-one (37 mg, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (54 mg, 70 % yield). The product is obtained as a 1:1 mixture of two diastereisomers.

Rf = 0.19 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.88 (dt, *J* = 3 and 2 Hz, 2H), 5.70 (t, *J* = 1 Hz, 1H), 5.66 (t, *J* = 1 Hz, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.43 (s, 3H), 3.39 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H) and 1.81 (s, 6H) ppm; **^{13}C NMR (100 MHz,**

$CDCl_3$): δ 160.6 (C), 160.5 (C), 147.7 (C), 147.1 (C), 142.8 (C), 137.4 (C), 137.3 (C), 130.6 (C), 128.5 (2 x CH), 127.1 (C), 126.6 (C), 105.7 (CH), 105.3 (CH), 55.3 (CH_3), 54.4 (CH_3), 51.9 (CH_3), 51.8 (CH_3), 11.4 (CH_3), 11.3 (CH_3), 10.54 (CH_3) and 10.53 (CH_3) ppm; **IR (neat):** 1716, 1208, 1094 and 1009 cm^{-1}.

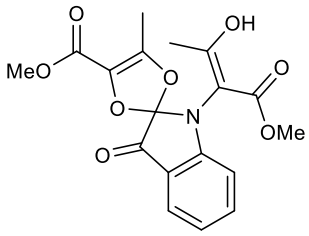
Methyl 5'-methylspiro[chromene-2,2'-[1,3]dioxole]-4'-carboxylate (11d).



Starting from the corresponding α-diazo-β-ketoester **7a** (138 µl, 0.96 mmol) and coumarin (47 mg, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (53 mg, 64 % yield).

Rf = 0.56 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, Acetone):** δ 7.44-7.32 (m, 2H), 7.17 (dd, *J* = 10 and 1 Hz, 1H), 7.10 (td, *J* = 8 and 1 Hz, 1H), 7.01 (ddt, *J* = 8, 1 and 0.5 Hz, 1H), 5.95 (d, *J* = 10 Hz, 1H), 3.78 (s, 3H) and 2.27 (s, 3H) ppm; **^{13}C NMR (100 MHz, Acetone):** δ 160.7 (C), 151.0 (C), 146.6 (C), 131.5 (CH), 131.4 (CH), 128.4 (CH), 126.5 (C), 123.4 (CH), 121.2 (C), 119.1 (C), 116.7 (2 x CH), 51.8 (CH_3) and 11.1 (CH_3) ppm; **IR (neat):** 1721, 1684, 1350, 1257, 1156, 1113 and 1039 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{14}H_{13}O_5^+$ 261.0758 observed 261.0757.

Methyl (E)-1-(3-hydroxy-1-methoxy-1-oxobut-2-en-2-yl)-5'-methyl-3-oxospiro[indoline-2,2'-[1,3]dioxole]-4'-carboxylate (13a).

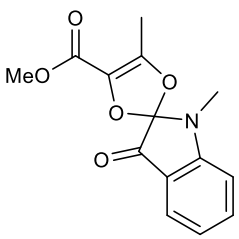


Starting from the corresponding α-diazo-β-ketoester **7a** (138 µl, 0.96 mmol) and 1 isatin (47 mg, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 1:1 with 1 % of triethylamine) as a colourless oil (26 mg, 22 % yield).The product was obtained as a mixture of diatereoisomers in a 1:2 ratio.

Rf = 0.44 (SiO_2, pentane:Et_2O, 1:1); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 12.85 (s, $1H^{maj}$), 12.81 (s, $1H^{min}$), 7.62 (ddd, *J* = 8, 1.4 and 0.8 Hz, 1H), 7.50 (ddd, *J* = 8, 7 and 1 Hz, 1H),

6.91 (td, *J* = 8 and 1 Hz, 1H), 6.53 (dt, *J* = 8 and 1 Hz, $1H^{maj}$), 6.52 (dt, *J* = 8 and 1 Hz, $1H^{min}$), 3.80 (s, $3H^{min}$), 3.78 (s, $3H^{maj}$), 3.70 (s, $3H^{maj}$), 3.69 (s, $3H^{min}$), 2.24 (s, 3H) and 2.09 (d, *J* = 1 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 190.69 (C^{maj}), 190.66 (C^{min}), 181.0 (C^{min}), 179.9 (C^{maj}), 171.94 (C^{maj}), 171.92 (C^{min}), 160.0 (C^{min}), 159.8 (C^{maj}), 158.33 (C^{maj}), 158.27 (C^{min}), 148.4 (C^{min}), 148.2 (C^{maj}), 139.2 (CH), 127.70 (C^{maj}), 127.65 (C^{mim}), 125.8 (CH^{maj}), 125.7 (CH^{min}), 121.0 (CH^{maj}), 120.9 (CH^{min}), 116.7 (C^{maj}), 116.6 (C^{min}), 111.01 (C^{maj}), 110.96 (C^{min}), 109.24 (C^{maj}), 109.21 (C^{min}), 98.1 (C^{maj}), 97.8 (C^{min}), 52.2 (CH_3^{maj}), 52.1 (CH_3^{min}), 51.90 (CH_3^{min}), 51.83 (CH_3^{maj}), 18.7 (CH_3^{min}), 18.5 (CH_3^{maj}), 11.2 (CH_3^{maj}) and 11.1 (CH_3^{min}) ppm; **IR (neat):** 2957, 1740, 1613, 1350, 1263 and 1226 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{18}H_{18}NO_8^+$ 376.1027 observed 376.1027.

Methyl 1,5'-dimethyl-3-oxospiro[indoline-2,2'-[1,3]dioxole]-4'-carboxylate (13b).



Starting from the corresponding α-diazo-β-ketoester **7a** (138 µl, 0.96 mmol) and 1-methyl isatin (51 mg, 0.32 mmol) and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 1:1 with 1 % of triethylamine) as a colourless oil (59 mg, 67 % yield).

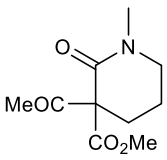
Rf = 0.22 (SiO_2, pentane:Et_2O, 1:1); **^{1}H NMR (400 MHz, Acetone):** δ 7.69-7.61 (m, 1H), 7.57-7.51 (m, 1H), 6.93 (d, *J* = 8 Hz, 2H), 3.78 (s, 3H), 2.96 (s, 3H) and 2.30 (s, 3H) ppm; **^{13}C NMR (100 MHz, Acetone):** δ 191.3 (C), 160.3 (C), 159.8 (C), 149.3 (C), 140.3 (CH), 128.7 (C), 125.9 (CH), 120.9 (CH), 117.1 (C), 112.2 (C), 109.6 (CH), 51.8 (CH_3), 26.5 (CH_3) and 11.1 (CH_3) ppm; **IR (neat):** 1736, 1617, 1351, 1155 and 1114 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{14}H_{14}NO_5^+$ 276.0867 observed 276.0867.

7.4.5 Generic procedure for the synthesis and analysis data of compound **16**

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (1.5 mg, 8 µmol, 2.5 mol %) and [$CpRu(CH_3CN)_3$][Bar_F] (9 mg, 8 µmol, 2.5 mol %) were dissolved in 0.60 mL of dry CH_2Cl_2. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 minutes at 25 °C before the addition of N-

methyl-2-pyrrolidone (1 eq., 0.32 mmol) and diazo **7a** (3 eq., 0.96 mmol). The solution was stirred at 60 °C for 24 h. The crude mixture was purified by column chromatography (Pentane/Et_2O, SiO_2) to afford insertion products of type **16**.

Methyl 3-acetyl-1-methyl-2-oxopiperidine-3-carboxylate (16).



Rf = 0.18 (SiO_2, pentane:Et_2O, 6:4); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.65 (s, 3H), 3.35 (t, *J* = 7 Hz, 2H), 3.15 (t, *J* = 8 Hz, 2H), 3.03 (s, 3H) and 2.19 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.1 (C), 165.1 (C), 153.3 (C), 109.7 (C), 57.36 (CH_3), 51.0 (CH_2), 35.8 (CH_2), 33.6 (CH_3), 21.5 (CH_3) and 20.9 (CH_2) ppm; **IR (neat):** 1752, 1688, 1599, 1280 and 1222 cm^{-1}.

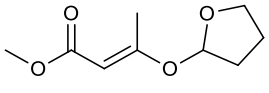
7.5 Experimental part for chapter 4

7.5.1 Generic procedure for the C-H activation of THF

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (1.5 mg, 8 μmol, 2.5 mol %) and [CpRu(CH_3CN)$_3$][PF_6] (3.5 mg, 8 μmol, 2.5 mol %) were dissolved in 0.60 mL of dry THF. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 minutes at 25 °C before the addition of desired diazo keto-ester **7** (0.32 mmol). The solution was stirred at 60 °C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Hexane/Et_2O, SiO_2) to afford insertion products of type **18**.

7.5.2 Analysis data of compounds of type **18**

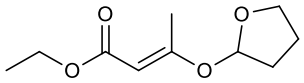
(*E*)-methyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18a).



Starting from the corresponding α-diazo-β-ketoester **7a** (50 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (48 mg, 80% yield).

Rf = 0.31 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.66 (d, *J* = 4 Hz, 1H), 5.32 (s, 1H), 4.05-3.98 (m, 1H), 3.95-3.88 (m, 1H), 3.66 (s, 3H), 2.27 (s, 3H), 2.11-2.01 (m, 3H) and 1.93-1.85 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.5 (C), 168.6 (C), 101.6 (CH), 93.9 (CH), 68.9 (CH_2), 51.0 (CH_3), 32.6 (CH_2), 23.4 (CH_2) and 19.1 (CH_3) ppm; **IR (neat):** 1712, 1622 and 1139 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_9H_{14}O_4Na$ 209.0784 observed 209.0783.

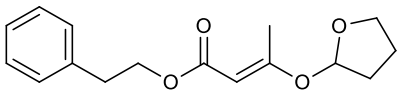
(*E*)-ethyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18b).



Starting from the corresponding α-diazo-β-ketoester **7b** (50 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (51 mg, 80 % yield).

Rf = 0.37 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.66 (d, *J* = 4, 1H), 5.31 (s, 1H), 4.12 (q, *J* = 7 Hz, 2H), 4.04-3.99 (m, 1H), 3.94-3.89 (m, 1H), 2.26 (s, 3H), 2.10-2.02 (m, 2H), 1.93-1.87 (m, 1H) and 1.25 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.3 (C), 168.2 (C), 101.6 (CH), 94.3 (CH), 68.9 (CH_2), 59.5 (CH_2), 32.6 (CH_2), 23.4 (CH_2), 19.1 (CH_3) and 14.6 (CH_3) ppm; **IR (neat):** 1708, 1622 and 1137 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{10}H_{16}O_4$ 200.1049 obtained 200.1050.

(*E*)-phenethyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18c).

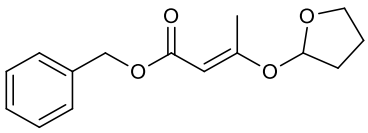


Starting from the corresponding α-diazo-β-ketoester **7c** (74 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (56 mg, 63 % yield).

Rf = 0.34 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.28 (m, 2H), 7.24-7.20 (m, 3H), 5.66 (d, *J* = 4 Hz, 1H), 5.31 (s, 1H), 4.28 (t, *J* = 7 Hz, 2H), 4.02 (dd, *J* = 13 and 7 Hz, 1H), 3.93 (dd, *J* = 9 and 7 Hz, 1H), 2.95 (t, *J* = 7 Hz, 2H), 2.25 (s, 3H), 2.12-2.02 (m, 3H) and 1.95-1.88 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.6 (C), 168.1 (C), 138.4 (C), 129.1 (2 x CH), 128.7 (2 x CH), 126.6 (CH), 101.6 (CH), 94.1

(CH), 68.9 (CH_2), 64.3 (CH_2), 35.5 (CH_2), 32.6 (CH_2), 23.4 (CH_2) and 19.1 (CH_3) ppm; **IR (neat):** 1710, 1623 and 1140 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{16}H_{20}O_4Na$ 299.1253 obtained 299.1242.

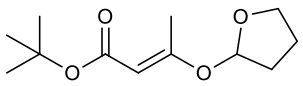
(*E*)-benzyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18d).



Starting from the corresponding α-diazo-β-ketoester **7d** (70 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (71 mg, 85 % yield).

Rf = 0.20 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.39-7.27 (m, 5H), 5.66 (d, *J* = 4 Hz, 1H), 5.38 (s, 1H), 5.12 (s, 2H), 4.05-3.97 (m, 1H), 3.94-3.87 (m, 1H), 2.29 (s, 3H), 2.13-2.01 (m, 3H) and 1.96-1.87 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.9 (C), 167.9 (C), 136.9 (C), 128.7 (2 x CH), 128.4 (2 x CH), 128.1 (CH), 101.7 (CH), 94.0 (CH), 68.9 (CH_2), 65.5 (CH_2), 32.6 (CH_2), 23.3 (CH_2) and 19.2 (CH_3) ppm; **IR (neat):** 1710, 1621 and 1136 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{15}H_{18}O_4Na$ 285.1097 obtained 285.1090.

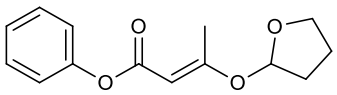
(*E*)-tert-butyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18e).



Starting from the corresponding α-diazo-β-ketoester **7e** (118 mg, 0.64 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (102 mg, 70 % yield).

Rf = 0.51 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.65 (d, *J* = 4 Hz, 1H), 5.24 (s, 1H), 4.05-3.99 (m, 1H), 3.94-3.89 (m, 1H), 2.23 (s, 3H), 2.10-1.99 (m, 3H), 1.96-1.88 (m, 1H) and 1.46 (s, 9H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.2 (C), 167.7 (C), 101.4 (CH), 96.0 (CH), 79.3 (C), 68.8 (CH_2), 32.6 (CH_2), 28.6 (3 x CH_3), 23.4 (CH_2) and 18.9 (CH_3) ppm; **IR (neat):** 1703, 1622 and 1129 cm^{-1}; **HR-MS (EI):** *m/z* calculated for $C_{12}H_{20}O_4Na$ 251.1254 obtained 251.1253.

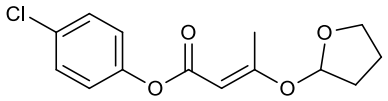
(*E*)-phenyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18f).



Starting from the corresponding α-diazo-β-ketoester **7f** (65 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (48 mg, 60 % yield).

Rf = 0.20 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.33 (m, 2H), 7.22-7.17 (m, 1H), 7.12-7.07 (m, 2H), 5.76 (d, *J* = 3 Hz, 1H), 5.56 (s, 1H), 4.10-4.03 (m, 1H), 4.00-3.93 (m, 1H), 2.31 (s, 3H), 2.18-2.05 (m, 3H) and 1.97-1.94 (m, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.7 (C), 166.7 (C), 151.2 (C), 129.5 (2 x CH), 125.5 (CH), 122.2 (2 x CH), 101.9 (CH), 93.3 (CH), 69.1 (CH_2), 32.7 (CH_2), 23.7 (CH_2) and 19.4 (CH_3) ppm; **IR (neat):** 1720, 1126 and 986 cm^{-1};

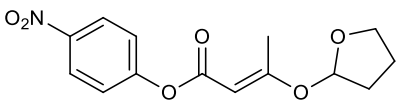
(*E*)-4-chlorophenyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18g).



Starting from the corresponding α-diazo-β-ketoester **7g** (76 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a white solid (72 mg, 80 % yield).

Mp: 81.6 °C; **Rf** = 0.42 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 (d, *J* = 9 Hz, 2H), 7.04 (d, *J* = 9 Hz, 2H), 5.76 (d, *J* = 3 Hz, 1H), 5.54 (s, 1H), 4.11-4.01 (m, 1H), 4.01-3.91 (m, 1H), 2.31 (s, 3H), 2.20-2.02 (m, 3H) and 2.00-1.92 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.2 (C), 166.4 (C), 149.7 (C), 130.8 (C), 129.5 (2 x CH), 123.6 (2 x CH), 102.0 (CH), 92.9 (CH), 69.1 (CH_2), 32.7 (CH_2), 23.3 (CH_2) and 19.5 (CH_3) ppm; **IR (neat):** 1730, 1619, 1485, 1122 and 1079 cm^{-1}; **HR-MS (ESI):** calculated for $C_{14}H_{15}ClO_4$: 283.0731 obtained 283.0727.

(*E*)-4-nitrophenyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18h).

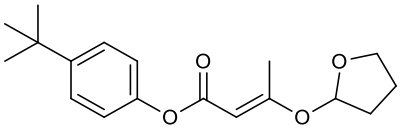


Starting from the corresponding α-diazo-β-ketoester **7h** (89 mg, 0.32 mmol) and 0.6 mL of THF and following

the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a soft white solid (75 mg, 80 % yield).

Rf: 0.24 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.25 (d, *J* = 9 Hz, 2H), 7.28 (d, *J* = 9 Hz, 2H), 5.76 (d, *J* = 4 Hz, 1H), 5.56 (s, 1H), 4.11-4.03 (m, 1H), 4.02-3.93 (m, 1H), 2.32 (s, 3H), 2.21-2.03 (m, 3H) and 2.03-1.90 (m, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.4 (C), 165.5 (C), 156.3 (C), 145.0 (C), 125.3 (2 x CH), 122.9 (2 x CH), 102.2 (CH), 92.5 (CH), 69.2 (CH_2), 32.7 (CH_2), 23.3 (CH_2) and 19.7 (CH_3) ppm; **IR (neat)**: ν_{max} = 2921, 2850, 1730, 1572, 1515 and 1338 cm^{-1}; **HR-MS (ESI):** calculated for $C_{14}H_{15}NO_6$: 294.0972 obtained 294.0964.

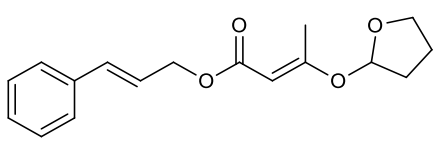
(*E*)-4-(tert-butyl)phenyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18i).



Starting from the corresponding α-diazo-β-ketoester **7i** (83 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a white solid (59 mg, 60 % yield).

Mp: 93.3 °C; **Rf:** 0.40 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 (d, *J* = 9 Hz, 2H), 7.01 (d, *J* = 9 Hz, 2H), 5.76 (d, *J* = 3 Hz, 1H), 5.55 (s, 1H), 4.09-4.04 (m, 1H), 4.00-3.92 (m, 1H), 2.31 (s, 3H), 2.17-2.07 (m, 3H), 2.00-1.91 (m, 1H) and 1.31 (s, 9H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.5 (C), 166.9 (C), 148.8 (C), 148.3 (C), 126.4 (2 x CH), 121.5 (2 x CH), 101.9 (CH), 93.4 (CH), 69.1 (CH_2), 34.6 (C), 32.7 (CH_2), 31.7 (3 x CH_3), 23.4 (CH_2) and 19.4 (CH_3) ppm; **IR (neat):** 1729, 1620, 1125 and 987 cm^{-1}; **HR-MS (ESI):** calculated for $C_{18}H_{24}O_4$: 305.1747 obtained 305.1746.

(*E*)-cinnamyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (18m)

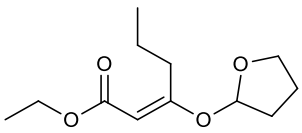


Starting from the corresponding α-diazo-β-ketoester **7m** (156 mg, 0.64 mmol) and 1.2 mL of THF and following the general procedure, the desired

compound was obtained after purification by column of silica gel (Hexanes:Et_2O, 8:2) as a colorless oil (28 mg, 15 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7 Hz , 2H), 7.31 (t, *J* = 7 Hz, 3H), 6.65 (d, *J* = 16 Hz, 1H), 6.31 (dt, *J* = 16 and 6 Hz, 1H), 5.68 (d, *J* = 4 Hz, 1H), 5.37 (s, 1H), 4.74 (d, *J* = 6 Hz, 2H), 4.06-3.98 (m, 1H), 3.96-3.87 (m, 1H), 2.29 (s, 3H), 2.13-2.02 (m, 3H) and 1.97-1.88 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.9 (C), 167. 9 (C), 136.7 (C), 133.7 (CH), 128.8 (2 x CH), 128.1 (C), 126.8 (2 x CH), 124.3 (CH), 101.7 (CH), 93.9 (CH), 68.9 (CH_2), 64.3 (CH_2), 32.6 (CH_2), 23.4 (CH_2) and 19.2 (CH_3) ppm; **IR (neat):** ν_{max} = 1708, 1621, 1139, 906 and 726 cm^{-}1; **HR-MS (ESI):** *m/z* calculated for $C_{17}H_{20}O_4Na^+$ 311.1254 obtained 311.1256.

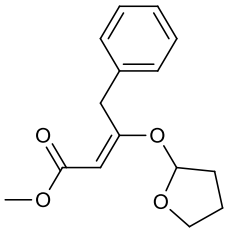
(E)-ethyl 3-((tetrahydrofuran-2-yl)oxy)hex-2-enoate (18n).



Starting from the corresponding α-diazo-β-ketoester **7n** (59 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (Hexanes:Et_2O, 8:2) as a colorless oil (47 mg, 64 % yield).

Rf: 0.30 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.65 (d, *J* = 4 Hz, 1H), 5.28 (s, 1H), 4.11 (q, *J* = 7 Hz, 2H), 4.03-3.97 (m, 1H), 3.95-3.88 (m, 1H), 2.69 (td, *J* = 7 and 2 Hz, 2H), 2.13-2.00 (m, 3H), 1.96-1.87 (m, 1H), 1.58-1.53 (sex, *J* = 7 Hz, 2H), 1.27-1.24 (t, *J* = 7 Hz, 3H) and 0.93 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.8 (C), 167.9 (C), 101.4 (CH), 93.8 (CH), 68. 8 (CH_2), 59.5 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 23.3 (CH_2), 21.1 (CH_2), 14.6 (CH_3) and 14.0 (CH_3) ppm; **IR (neat):** ν_{max} = 1711, 1621, 1143 and 1050 cm^{-}1; **HR-MS (ESI):** *m/z* calculated for $C_{12}H_{20}O_4Na$ 251.1254 obtained 251.1253.

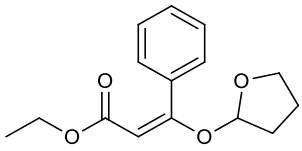
(*E*)-ethyl 3-phenyl-3-((tetrahydrofuran-2-yl)oxy)acrylate (18o).



Starting from the corresponding α-diazo-β-ketoester **7o** (70 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colorless oil (39 mg, 44 % yield).

Rf: 0.42 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.26 (m, 3H), 7.25-7.13 (m, 2H), 5.63 (d, *J* = 3, 1H), 5.39 (s, 1H), 4.16 (d, *J* = 14 Hz, 1H), 4.00 (d, *J* = 14 Hz, 1H), 3.85 (t, *J* = 7 Hz, 2H), 3.78-3.71 (m, 1H), 3.69 (s, 3H) and 2.07-1.79 (m, 4H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.2 (C), 168.3 (C), 138.2 (C), 129.2 (CH), 128.4 (CH), 126.5 (CH), 101.6 (CH), 94.3 (CH), 68.8 (CH_2), 51.1 (CH_3), 37.5 (CH_2), 32.5 (CH_2) and 23.1 (CH_2) ppm; **IR (neat):** ν_{max} = 1711, 1621, 1135 and 1044 cm^{-}1; **HR-MS (ESI):** *m/z* calculated for $C_{15}H_{18}O_4Na$ 285.1097 obtained 285.1095.

(*E*)-ethyl 3-phenyl-3-((tetrahydrofuran-2-yl)oxy)acrylate (18p).



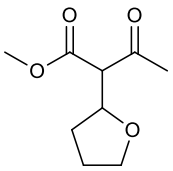
Starting from the corresponding α-diazo-β-ketoester **7p** (70 mg, 0.32 mmol) and 0.6 mL of THF and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colorless oil (23 mg, 27 % yield).

Rf: 0.35 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44-7.33 (m, 5H), 5.80 (d, *J* = 5 Hz, 1H), 5.62 (s, 1H), 4.10-3.93 (m, 4H), 2.19-2.04 (m, 3H), 1.97-1.89 (m, 1H) and 1.13 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.7 (C), 167.1 (C), 135.3 (C), 129.8 (CH), 129.2 (2 x CH), 127.9 (2 x CH), 102.7 (CH), 96.1 (CH), 68.9 (CH_2), 59.8 (CH_2), 32.8 (CH_2), 23.4 (CH_2) and 14.4 (CH_3) ppm; **IR (neat):** ν_{max} = 1718, 1621, 1114 and 1064 cm^{-}1; **HR-MS (ESI):** *m/z* calculated for $C_{15}H_{18}O_4Na$ 285.1100 obtained 285.1100.

7.5.3 Procedure for the synthesis of compound **19** and analysis data

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, (*E*)-methyl 3-((tetrahydrofuran-2-yl)oxy)but-2-enoate (**18a**) (59.6 mg, 0.32 mmol) was dissolved in 1 mL dry CH_2Cl_2. The vial was flushed with argon and capped. The resulting solution was cooled down to 0 °C before the addition of trimethylsilyl trifluoromethanesulfonate (7.1 mg, 5.7 µl, 0.032 mmol). The resulting mixture was stirred at 0 °C for 1 h and then quenched by the addition of a phosphate buffer. The phases were separated and the aqueous layer was back extracted by diethyl ether. The combined organic layer was dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude obtained was purified by column chromatography (Hexane/Et_2O, SiO_2) to afford the desired insertion product **19** in a 1:1 mixture of diastereoisomers as a colorless oil (54 mg, 90 % yield). The data correspond to previously reported material.[217]

Methyl 2-(tetrahydrofuran-2-yl)-3-oxobutanoate) (19)



Rf: 0.42 and 0.32 (SiO_2, Hexanes:EtOAc, 1:1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.45-4.41 (m, 1H), 3.84 (m, 2H), 3.77 (s, 1.5H), 3.73 (s, 1.5H), 3.57 (d, *J* = 8.5 Hz, 0.5H), 3.50 (t, *J* = 10 Hz, 0.5H), 2.31 (s, 1.5H), 2.25 (s, 1.5H), 2.16 (m, 1H), 1.90 (m, 2H) and 1.60 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.8 (C), 201.2 (C), 168.3 (C), 167.9 (C), 77.1 (CH), 76.8 (CH), 67.9 (CH_2), 67.8 (CH_2), 64.9 (CH), 64.5 (CH), 52.3 (CH_3), 52.1 (CH_3), 30.2 (CH_2), 29.6 (CH_3), 29.59 (CH_3), 25.3 (CH_2) and 25.0 (CH_2) ppm.

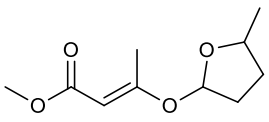
7.5.4 Generic procedure for the synthesis of compounds **22** and analysis data

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (1.5 mg, 8 µmol, 2.5 mol %) and $[CpRu(CH_3CN)_3][PF_6]$ (3.5 mg, 8 µmol, 2.5 mol %) were dissolved in 0.60 mL of dry CH_2Cl_2. The vial was flushed with argon and capped.

[217] (a) Bihovsky, R.; Kumar, M. U.; Ding, S.; Goyal, A., *J. Org. Chem.* **1989**, *54* (18), 4291-4293; (b) Moriya, O.; Urata, Y.; Ikeda, Y.; Ueno, Y.; Endo, T., *J. Org. Chem.* **1986**, *51* (24), 4708-4709.

The resulting deep red solution was stirred for 20 minutes at 25 °C before the addition of 2-methyl tetrahydrofuran (32 μl, 0.32 mmol) and methyl diazoacetoacetate **7a** (0.50 mg, 0.32 mmol). The solution was stirred at 60 °C and followed by ^{1}H-NMR until full conversion. The crude mixture was purified by column chromatography (Hex/Et_2O, SiO_2) to afford the insertion product of type **22**.

(*E*)-methyl 3-((5-methyltetrahydrofuran-2-yl)oxy)but-2-enoate (22a)



Starting from the corresponding THF derivative (84 mg, 0.96 mmol) and following the general procedure, **22a** was obtained after purification by column of silicagel (hexane:diethyl ether 8:2) as a colourless oil (67 mg, 70 % yield). For identification purpose, the two diastereomers can be separated by preparative TLC (hexane:diethyl ether 9:1).

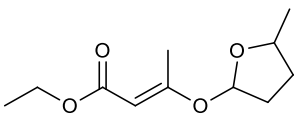
Diastereomer 1 obtained as a colorless oil.

Rf: 0.39 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$): δ** 5.66 (d, *J* = 4 Hz, 1H), 5.32 (s, 1H), 4.30 (q, *J* = 6 Hz, 1H), 3.66 (s, 3H), 2.27 (s, 3H), 2.22-1.96 (m, 3H), 1.52-1.42 (m, 1H) and 1.24 (d, *J* = 6 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$): δ** 170.4 (C), 168.4 (C), 101.7 (CH), 93.7 (CH), 76.0 (CH), 50.7 (CH_3), 32.3 (CH_2), 30.7 (CH_2), 20.8 (CH_3) and 18.9 (CH_3) ppm; **IR** (neat): 1713, 1623 and 1143 cm^{-1}.

Diastereomer 2 obtained as a colorless oil.

Rf: 0.40 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.58 (d, *J* = 4 Hz, 1H), 5.29 (s, 1H), 4.26-4.21 (m, 1H), 3.66 (s, 3H), 2.27 (s, 3H), 2.19-1.96 (m, 3H), 1.10-1.67 (m, 1H) and 1.29 (d, *J* = 6.2 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 170.3 (C), 168.5 (C), 101.5 (CH), 93.5 (CH), 78.1 (CH), 50.7 (CH_3), 33.5 (CH_2), 30.6 (CH_2), 22.6 (CH_3) and 18.9 (CH_3) ppm; **IR** (neat): 1713, 1622 and 1144 cm^{-1}.

(*E*)-ethyl 3-((5-methyltetrahydrofuran-2-yl)oxy)but-2-enoate (22b)



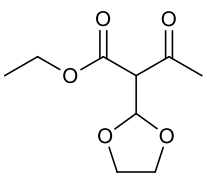
Starting from the corresponding THF derivative (28 mg, 0.32 mmol) and following the general procedure, **22b** was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (55 mg, 80 % yield).

Rf: 0.35 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.67 (d, *J* = 2 Hz, 1H), 5.66 (d, *J* = 2 Hz, 1H), 5.30 (s, 2H), 4.30 (sex, *J* = 6 Hz, 2H), 4.12 (q, *J* = 7 Hz, 4H), 2.27 (s, 6H), 2.25-2.20 (m, 6H), 1.55-1.45 (m, 2H), 1.26 (t, *J* = 7 Hz, 6H) and 1.26 (d, *J* = 6 Hz, 6H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.4 (C), 168.3 (C), 101.9 (CH), 94.2 (CH), 76.2 (CH), 59.5 (CH_2), 32.6 (CH_2), 30.9 (CH_2), 21.1 (CH_3), 19.1 (CH_3) and 14.6 (CH_3) ppm; **IR** (neat): 1708, 1620 and 1138 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{11}H_{18}O_4$ 214.1205 observed 214.1203.

7.5.5 Procedure for the synthesis and analysis data of compound **23**

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-Phenanthroline (1.5 mg, 8 μmol, 2.5 mol%) and [CpRu($CH_3CN)_3$][PF_6] (3.5 mg, 8 μmol, 2.5 mol %) were dissolved in 0.6 mL dry 1,3-dioxolane. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 minutes at room temperature before the addition of ethoxy methyldiazoacetoacetate **7b** (50 mg, 0.32 mmol). The solution was stirred at 60 °C for 3 h. The crude mixture was purified by column chromatography (Hex/Et_2O, SiO_2) to afford product **23** as colourless oil (20 mg, 78 % yield).

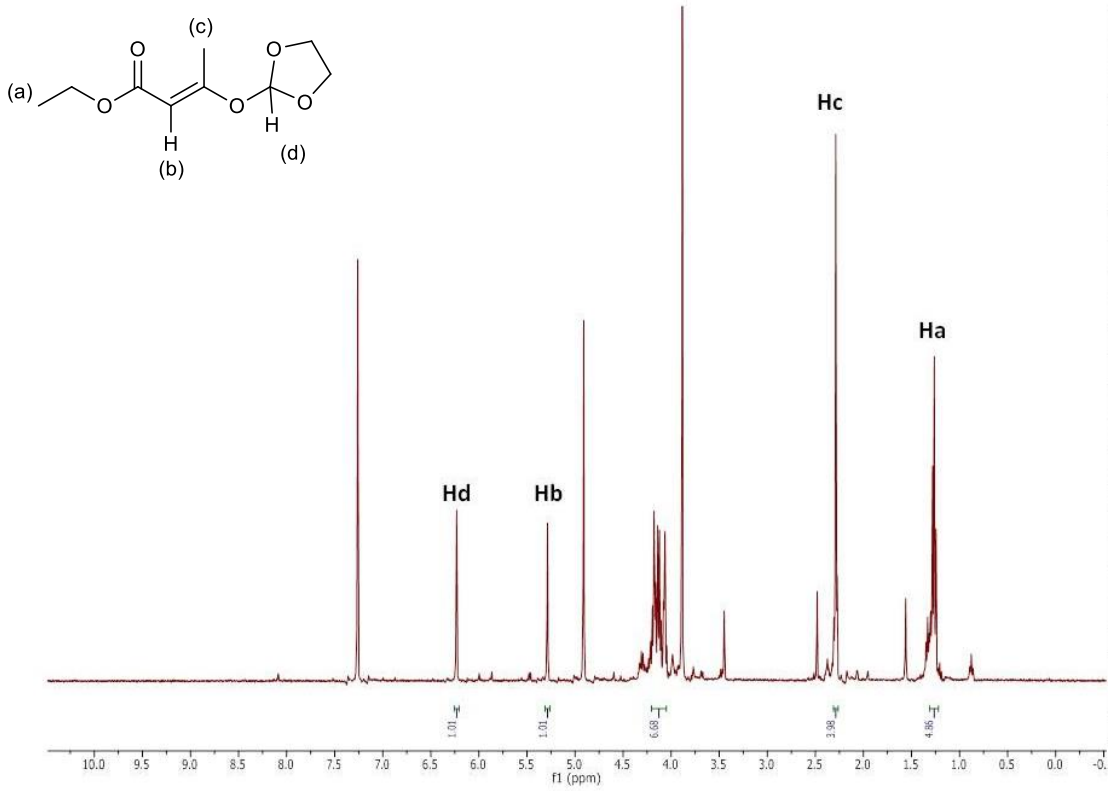
Ethyl 2-(1,3-dioxolan-2-yl)-3-oxobutanoate (23)



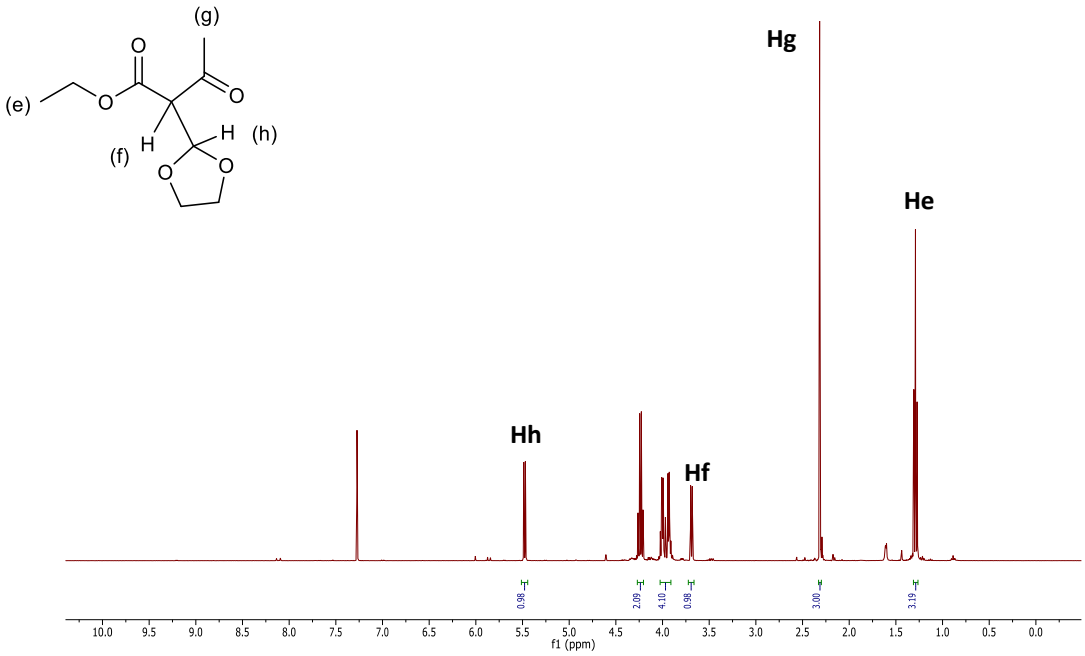
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (d, *J* = 7 Hz, 1H), 4.22 (q, *J* = 7 Hz, 2H), 4.05-3.85 (m, 4H), 3.68 (d, *J* = 7 Hz, 1H), 2.30 (s, 3H) and 1.28 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.0 (C), 166.4 (C), 102.2 (CH), 65.5 (CH_2), 65.3 (CH_2), 64.4 (CH), 61.9 (CH_2), 30.6 (CH_3) and 14.6(CH_3) ppm; **IR (neat):** 2971, 1740, 1716 and 1365 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_9H_{14}NO_5$ 220.1179 observed 220.1186.

NMR observation of intermediate 24 (crude mixture, 1 hour of reaction at 25 °C) & comparison with final product 23:

^{1}H NMR (400 MHz) $CDCl_3$: Intermediate **24** (crude NMR)



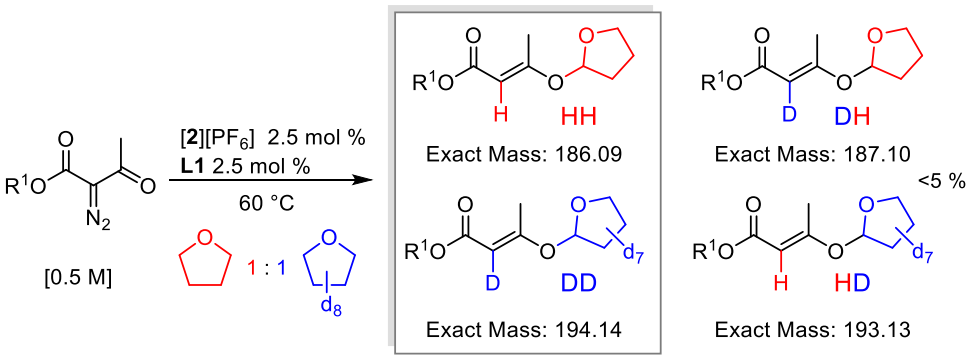
^{1}H NMR (400 MHz) $CDCl_3$: Final product **23**



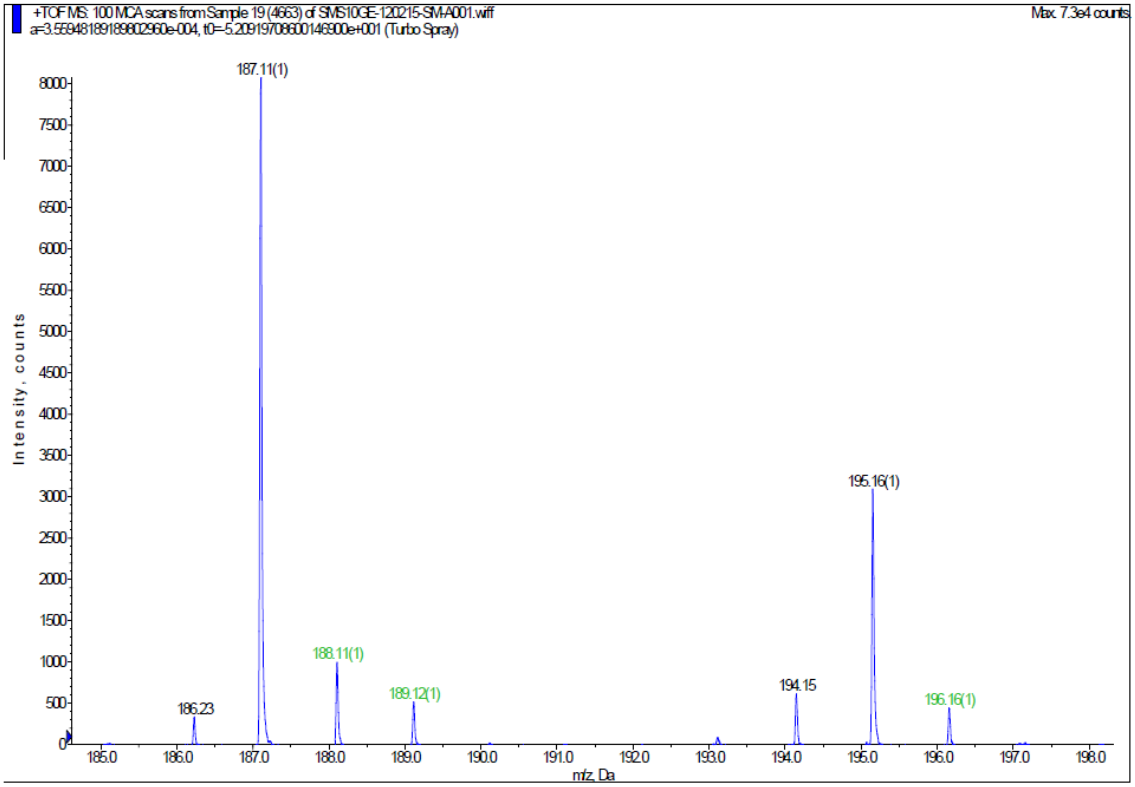
7.5.6 Generic procedure for isotope effect study

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (1.5 mg, 8 μmol, 2.5 mol %) and [$CpRu(CH_3CN)_3$][PF_6] (3.5 mg, 8 μmol, 2.5 mol %) were dissolved in 0.30 mL of dry THF and 0.30 mL of dry THF-d_8. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 minutes at 25 °C before the addition of desired diazo keto-ester **7** (0.32 mmol). The solution was stirred at 60 °C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Hexane/Et_2O, SiO_2) to afford insertion products of type **18**. k_H/k_D were determined by ^{1}H NMR and confirmed by ESI-MS.

HRMS-ESI and ^{1}H NMR spectrum of substrate 18a shown as example:

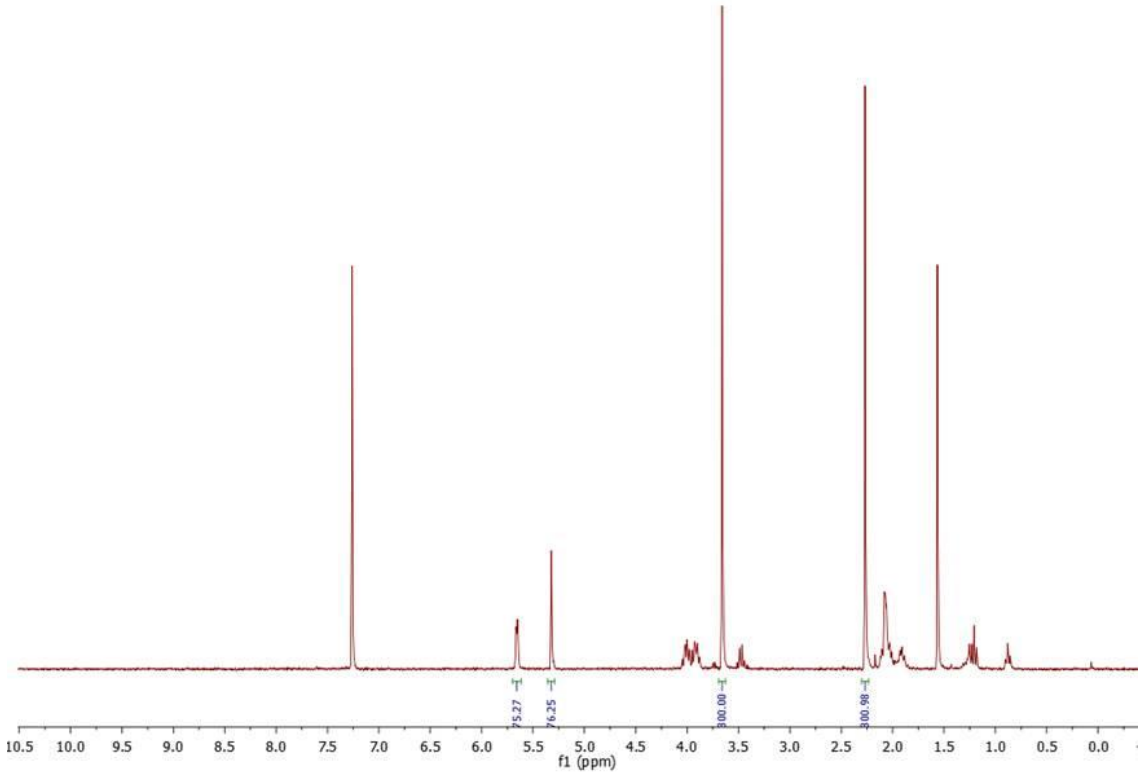


High Resolution Mass Spectroscopic analysis of the crude mixture (all masses plus 1)

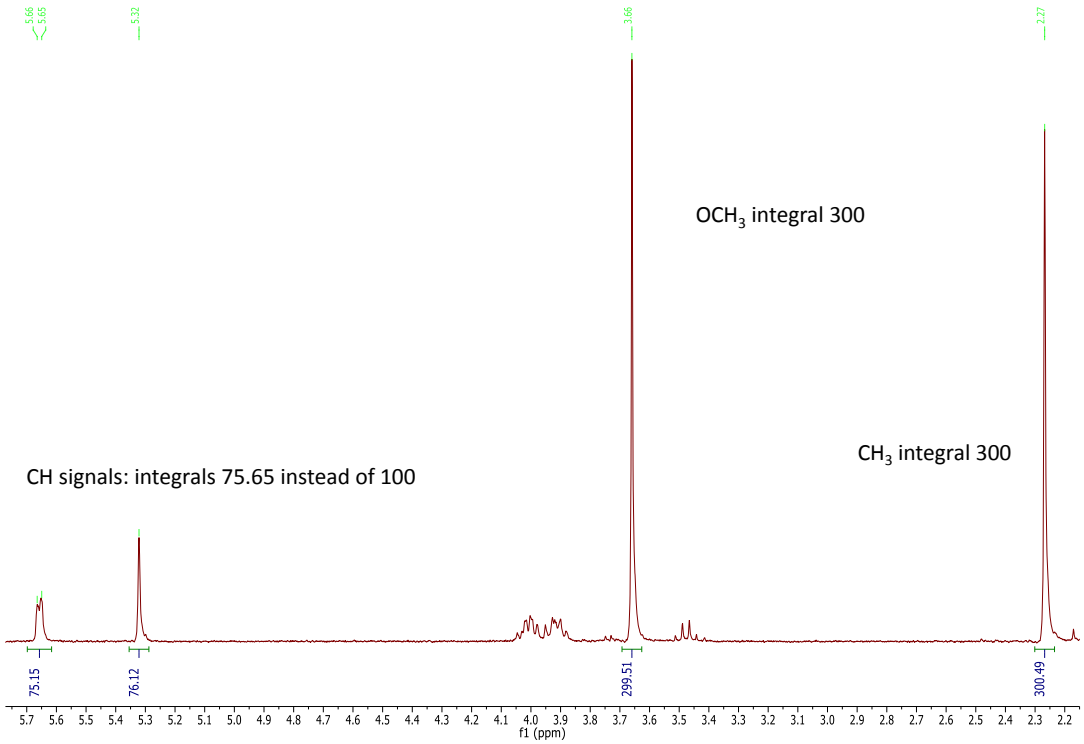


^{1}H NMR spectra (400 MHz, $CDCl_3$)

General view



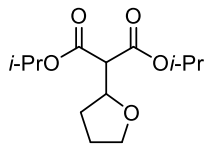
Detailed view



7.5.7 Generic procedure for the synthesis and analysis data of compounds **26**

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (1.5 mg, 8 μmol, 2.5 mol %) and [CpRu($CH_3CN)_3$][PF_6] (3.5 mg, 8 μmol, 2.5 mol %) were dissolved in 0.60 mL of dry THF. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 10 minutes at 25 °C before the addition of desired diazomalonate **25** (0.32 mmol). The solution was stirred at 60 °C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Pentane/Et_2O, SiO_2) to afford insertion products of type 2**6**. Adducts **26a**[218] and **26b**[216b] have spectroscopic characteristics identical to those already described.

diisopropyl 2-(tetrahydrofuran-2-yl)malonate (26c)

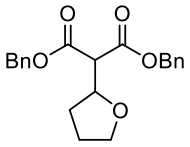


Starting from the corresponding diazomalonate **25c** (69 mg, 0.32 mmol) and following the general procedure, **26c** was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (66 mg, 80 % yield).

Rf: 0.25 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.07 (ddq, *J* = 22, 13 and 6 Hz, 2H), 4.42 (dt, *J* = 9 and 7 Hz, 1H), 3.89-3.72 (m, 2H), 3.36 (d, *J* = 9 Hz, 1H), 2.14 (dddd, *J* = 12, 8, 7 and 6 Hz, 1H), 1.97-1.84 (m, 2H), 1.73 (ddt, *J* = 12, 9 and 7 Hz, 1H) and 1.28-1.22 (m, 12H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 167.1 (C), 166.8 (C), 76.9 (CH, signal overlapped with solvent), 68.92 (CH), 68.88 (CH), 68.2 (CH_2), 57.9 (CH), 29.9 (CH_2), 25.5 (CH_2), 21.59 (2 x CH_3) and 21.55 (2 x CH_3) ppm; **IR (neat):** 1728, 1100 and 1068 cm^{-1}.

[218] Katritzky, A. R.; Abdel-Fattah, A. A. A.; Idzik, K. R.; El-Gendy, B. E.-D. M.; Soloducho, J., *Tetrahedron* **2007**, *63* (28), 6477-6484.

dibenzyl 2-(tetrahydrofuran-2-yl)malonate (26d)



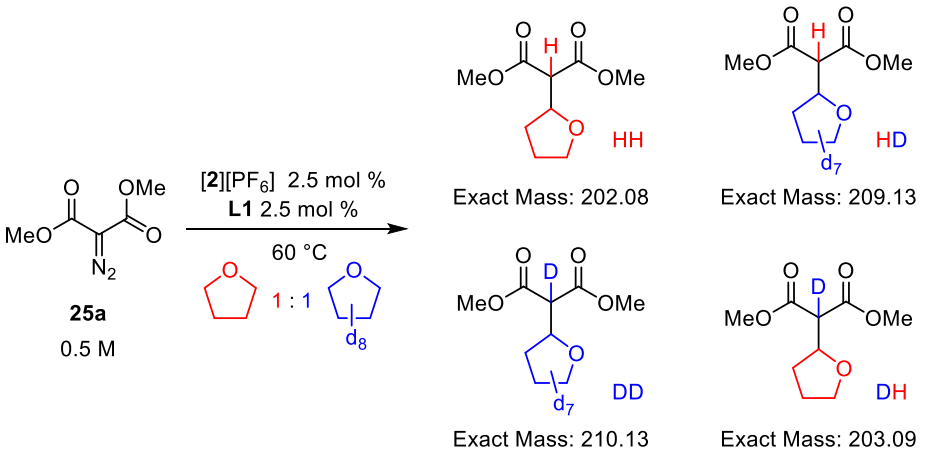
Starting from the corresponding diazomalonate **25d** (99 mg, 0.32 mmol) and following the general procedure, **26d** was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (71 mg, 63 % yield).

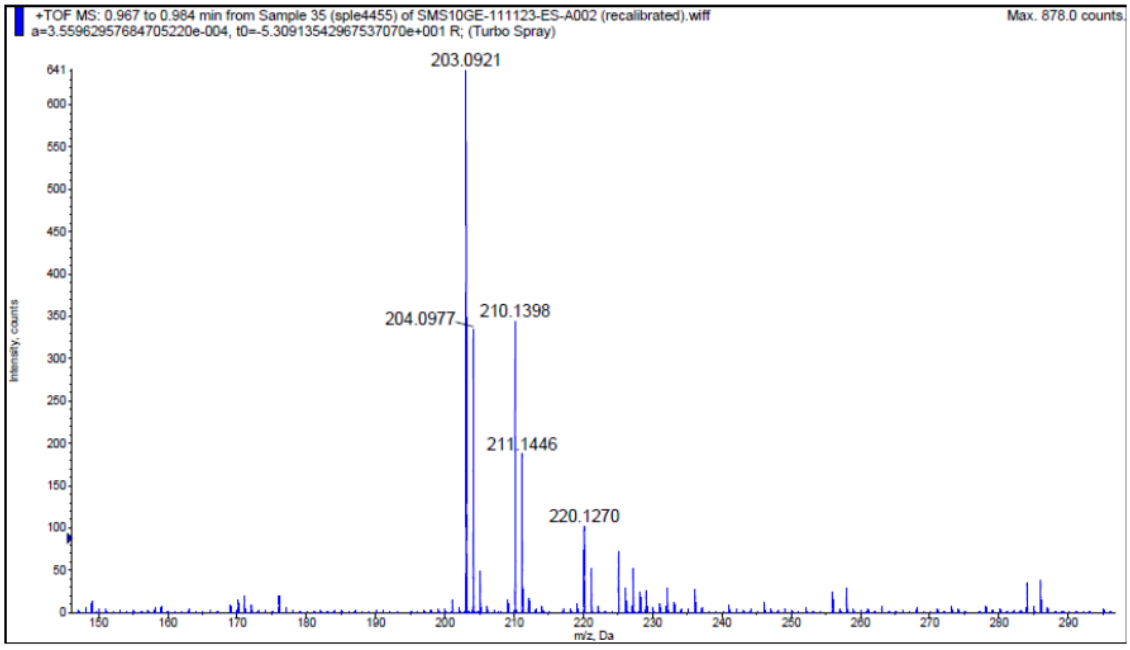
Rf: 0.29 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35-7.27 (m, 10H), 5.16 (dd, *J* = 20 and 1 Hz, 4H), 4.50 (dt, *J* = 9 and 7 Hz, 1H), 3.80 (ddt, *J* = 27, 8 and 7 Hz, 2H), 3.58 (d, *J* = 9 Hz, 1H), 2.12 (dt, *J* = 13 and 7 Hz, 1H), 1.89 (dq, *J* = 9 and 7 Hz, 2H) and 1.77-1.67 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.4 (C), 167.0 (C), 135.5 (C), 135.3 (C), 128.69 (2 x CH), 128.62 (2 x CH), 128.51 (CH), 128.35 (CH), 128.29 (2 x CH), 128.21 (2 x CH), 77.1 (CH, signal overlapped with solvent), 68.4 (CH_2), 67.3 (2 x CH_2), 57.5 (CH), 30.0 (CH_2) and 25.6 (CH_2) ppm; **IR** (neat): 1731, 1148, 1066 and 696 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{21}H_{23}O_5$ 355.154 observed 355.1543.

7.5.8 Procedure for the cross over experiment

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, $[CpRu(CH_3CN)_3][PF_6]$ (3.5 mg, 8 μmol, 2.5 mol%) and 1,10-phenanthroline monohydrate (1.5 mg, 8 μmol, 2.5 mol%) were dissolved in 0.30 mL of dry THF and 0.30 mL of dry THF-d_8. The vial is flushed with argon and capped. The resulting deep red solution was stirred for 20 minutes at 25 °C before the addition of desired diazo malonate **25** (0.32 mmol). The solution was stirred at 60 °C until full conversion (^{1}H NMR monitoring). The crude obtained was purified by column chromatography on silica gel (Pentane:Diethyl ether 8:2, Rf = 0.38) to afford the desired products **26**. HRMS experiment showed the presence of the four possible products of cross-over.

High Resolution Mass Spectroscopic analysis of the crude mixture (all masses plus 1)



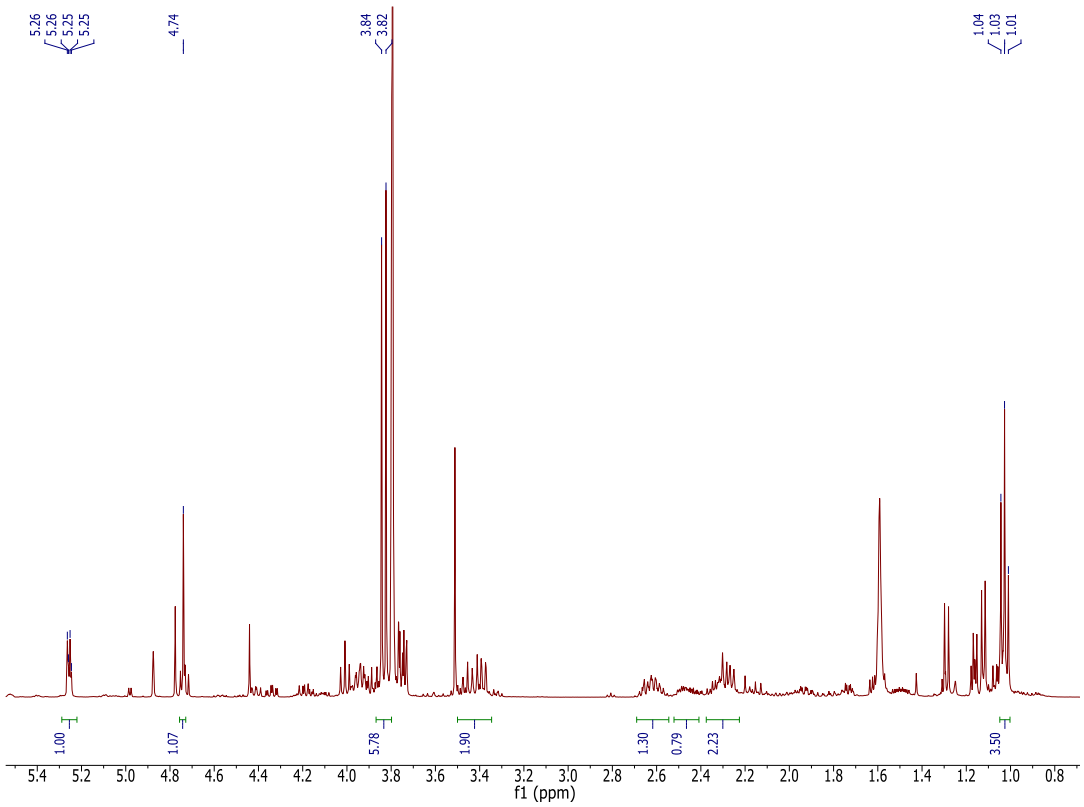


7.5.9 Generic procedure for the synthesis of compounds of type **30**

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline monohydrate (1.5 mg, 8 µmol, 2.5 mol %) and $[CpRu(CH_3CN)_3][PF_6]$ (3.5 mg, 8 µmol, 2.5 mol %) were dissolved in 0.60 mL of dry 3-methyl tetrahydrofuran. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 10 minutes at 25 °C before the addition of desired diazomalonate **25a** (0.32 mmol). The solution was stirred at 60 °C until full conversion (^{1}H NMR monitoring, 24 h). The crude mixture was

purified by column chromatography (Penatne/Et_2O, SiO_2) to afford insertion products of type 30 as a mixture of regio- and diatereoisomers.

^1H NMR spectra (400 MHz, $CDCl_3$) of the mixture of regio- and siastereoisomers.

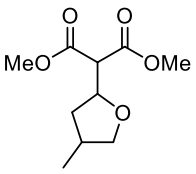


7.5.10 Generic procedure for the synthesis of compounds of type **29**

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, the mixture of isomers **30** (0.32 mmol) was dissolved in 1 mL of dry CH_2Cl_2. The vial was flushed with argon and capped. The resulting solution was cooled down to 0 °C before the addition of trimethylsilyl trifluoromethanesulfonate (7.1 mg, 5.7 µl, 0.032 mmol). The resulting mixture was stirred at 0 °C for 1 h and then quenched by the addition of a phosphate buffer. The phases were separated and the aqueous layer was back extracted by diethyl ether. The combined organic layer was dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude obtained was purified by column chromatography (Pentane/Et_2O, SiO_2) to afford product **29** in a 1:1 mixture of diastereoisomers as a colorless oil (90 % yield).

Dimethyl 2-(4-methyltetrahydrofuran-2-yl)malonate (29)

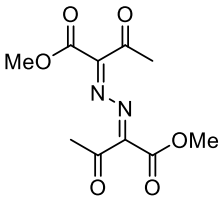
First eluted diastereoisomer



Rf: 0.25 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.58 (q, *J* = 7 Hz, 1H), 3.98 (t, *J* = 8 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 4H), 3.48 (d, *J* = 9 Hz, 1H), 3.32 (t, *J* = 8 Hz, 1H), 2.34 (h, *J* = 7 Hz, 1H), 1.98-1.86 (m, 1H), 1.82-1.75 (m, 1H) and 1.04 (d, *J* = 7 Hz, 3H) ppm.

7.6 Experimental part of chapter 5

Dimethyl 2,2'-(hydrazine-1,2-diylidene)(2E,2'E)-bis(3-oxobutanoate) 43.

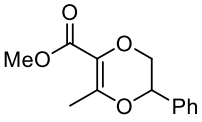


Yellow solid; **Rf** = 0.13 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.87 (s, 6H) and 2.48 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 193.6 (2 x C), 160.6 (2 x C), 53.2 (2 x OCH_3) and 25.7 (2 x CH_3) ppm; **IR (neat):** 1734, 1692, 1223 and 1059 cm^{-1}.

7.6.1 Generic procedure and analysis data for the synthesis of compounds **42**

In a 2 mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline monohydrate (1.5 mg, 8 µmol, 2.5 mol %) and [$CpRu(CH_3CN)_3$][BAr_F] (9 mg, 8 µmol, 2.5 mol %) were dissolved in 0.60 mL of dry CH_2Cl_2. The vial is flushed with argon and capped. The resulting orange solution was stirred for 10 minutes at 25 °C before the addition of first the desired epoxide **32** (0.32 mmol) followed by desired diazo keto-ester **7** (0.64 mmol). The solution is stirred at 60 °C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Pentane/Et_2O, SiO_2) to afford dioxene products of type **42**.

***Rac*-Methyl 3-methyl-5-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aA)**



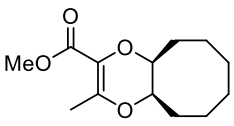
Starting from the epoxide **32A** (36 µL, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil at 25 °C and soft white solid at 0 °C (30 mg, 40% yield).

Rf = 0.24 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.43 (m, 5H); 5.01 (dd, *J* = 8 and 3 Hz, 1H), 4.31 (dd, *J* = 11 and 3 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 11 and 8 Hz, 1H) and 2.35 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.3 (C) 148.2 (C), 135.9 (C), 129.0 (CH), 128.9 (2 x CH), 126.5 (2 x CH), 124.9 (C), 76.2 (CH), 68.6 (CH_2), 51.9 (OCH_3) and 17.9 (CH_3) ppm; **IR (neat):** 1715, 1636, 1161 and 1105 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{13}H_{15}O_4$ 235.0964 observed 235.0970.

(*S*)-Methyl 3-methyl-5-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aA). Compound prepared following the general method and purified to a 99 % *ee* by semi-preparative CSP-HPLC (IB; Hexane/i-Pr 95/5; 2 ml/min; 23 °C). For this sample, the optical rotation was measured. $[\alpha]_D$ = + 36.5 (CH_2Cl_2, 0.1)

(*R*)-Methyl 3-methyl-5-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aA). Compound prepared following the general method and obtained with a 94 % *ee*. For this sample, the optical rotation was measured. $[\alpha]_D$ = −28.5 (CH_2Cl_2, 0.1).

***Rac-cis-M*ethyl 3-methyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42aC).**

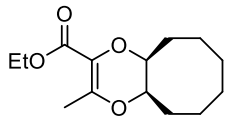


Starting from the epoxide **32C** (81 mg, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a white solid (123 mg, 80 % yield).

Mp: 44.8 °C; **Rf** = 0.35 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.24 (dt, *J* = 9 and 3 Hz, 1H), 4.12 (dt, *J* = 10 and 3 Hz, 1H), 3.77 (s, 3H), 2.21 (s, 3H), 2.03-

1.98 (m, 2H),1.85-1.75 (m, 2H) and 1.63-1.57 (m, 8H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.8 (C), 147.0 (C), 123.3 (C), 76.0 (CH), 73.7 (CH), 51.7 (OCH_3), 28.0 (CH_2), 27.7 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 23.8 (CH_2), 22.9 (CH_2) and 17.8 (CH_3) ppm; **IR (neat):** 1712, 1635, 1309, 1147 and 1085 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{13}H_{21}O_4$ 241.1434observed 241.1438.

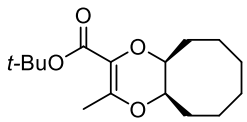
***Rac-cis*-Ethyl 3-methyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42bC).**



Starting from the epoxide **32C** (40 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7b** (100 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil (69 mg, 85 % yield).

Rf = 0.35 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.30-4.18 (m, 3H), 4.13 (dd, *J* = 9 and 3 Hz, 1H), 2.20 (s, 3H), 1.99-1.86 (m, 2H), 1.78-1.68 (m, 4H), 1.62-1.52 (m, 6H) and 1.31 (t, *J* = 7Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.5 (C), 146.7 (C), 123.4 (C), 75.9 (CH), 73.6 (CH), 60.5 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 25.9 (CH_2), 25.3 (CH_2), 24.0 (CH_2), 22.7 (CH_2), 17.9 (CH_3) and 14.6 (CH_3) ppm; **IR (neat):** 2925, 1710, 1638, 1303 and 1088 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{14}H_{23}O_4$ 255.1590 observed 255.1588.

***Rac-cis-tert*-Butyl 3-methyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42eC).**

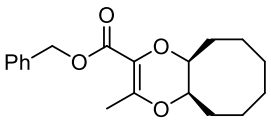


Starting from the epoxide **32C** (40 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7e** (118 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 9:1) as a colourless oil (81 mg, 90 % yield).

Rf = 0.42 (SiO_2, pentane:Et_2O, 9:1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.20 (d, *J* = 9 Hz, 1H), 4.10-4.02 (m, 1H), 2.15 (s, 3H), 1.92 (ddd, *J* = 19, 12 and 9 Hz, 2H), 1.83-1.65 (m,

5H), 1.56-1.53 (m, 5H) and 1.51 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 163.9 (C), 145.2 (C), 124.5 (C), 81.0 (C), 75.8 (CH), 73.5 (CH), 28.5 (CH_3), 28.1 (CH_2), 27.7 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 23.6 (CH_2), 23.2 (CH_2) and 18.3 (3 x CH_3) ppm; **IR (neat):** 1705, 1639, 1146 and 1089 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{16}H_{27}O_4$ 283.1904 observed 283.1896.

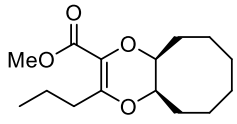
***Rac-cis*-Benzyl 3-methyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42dC).**



Starting from the epoxide **32C** (28 µL, 0.32 mmol) and corresponding α-diazo-β-ketoester **7d** (70 mg, 0.32 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (65 mg, 65 % yield).

Rf = 0.44 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42-7.27 (m, 5H), 5.28-5.18 (m, 2H), 4.22 (dt, *J* = 9.3 and 2.7 Hz, 1H), 4.12 (dt, *J* = 9.5 and 2.7 Hz, 1H), 2.19 (s, 3H), 2.02-1.84 (m, 2H), 1.83-1.67 (m, 4H) and 1.63-1.45 (m, 6H).ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.26 (C), 147.11 (C), 136.49 (C), 128.57 (2 x CH), 128.24 (2 x CH), 128.09 (CH), 123.29 (C), 75.95 (CH), 73.47 (CH), 66.06 (CH_2), 27.90 (CH_2), 27.63 (CH_2), 25.81 (CH_2), 25.28 (CH_2), 23.89 (CH_2), 22.75 (CH_2) and 18.01 (CH_3) ppm; **IR (neat):** 1709, 1634, 1296, 1147 and 1072 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{19}H_{25}O_4$ 317.1747 observed 317.1744.

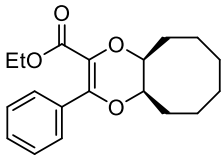
***Rac-cis*-Methyl 3-propyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42nC).**



Starting from the epoxide **32C** (40 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7n** (107 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil (71 mg, 80 % yield).

Rf = 0.24 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, CD_2Cl_2):** δ 4.24 (dt, *J* = 9 and 3 Hz, 1H), 4.06 - 3.98 (m, 1H), 3.70 (s, 3H), 2.66 (ddd, *J* = 14, 8 and 7 Hz, 1H), 2.47 (ddd, *J* = 14, 8 and 7 Hz, 1H), 2.01-1.83 (m, 2H), 1.81-1.46 (m, 12H), 0.92 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (100 MHz, CD_2Cl_2):** δ 164.8 (C), 150.5 (C), 124.0 (C), 76.2 (CH), 73.9 (CH), 51.7 (OCH_3), 33.1 (CH_2), 28.4 (CH_2), 28.1 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 23.9 (CH_2), 23.5 (CH_2), 21.5 (CH_2) and 14.0 (CH_3) ppm; **IR (neat):** 2929, 1714, 1632, 1302, 1149 and 1102 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{15}H_{25}O_4$ 269.1747 observed 269.1749.

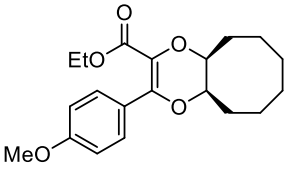
***Rac-cis*-Ethyl 3-phenyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42pC).**



Starting from the epoxide **32C** (40 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7p** (130 mg, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (61 mg, 60 % yield).

Rf = 0.33 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 (s, 5H), 4.39 (dt, *J* = 9 and 3 Hz, 1H), 4.30 (dt, *J* = 9 and 3 Hz, 1H), 4.03 (q, *J* = 7 Hz, 2H), 2.13-1.99 (m, 1H), 1.96-1.71 (m, 4H), 1.70-1.51 (m, 7H) and 0.99 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.0 (C), 146.5 (C), 134.9 (C), 129.3 (2 x CH), 129.0 (CH), 127.8 (2 x CH), 125.0 (C), 76.3 (CH), 74.1 (CH), 60.6 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 23.5 (CH_2), 23.1 (CH_2) and 13.9 (CH_3) ppm; **IR (neat):** 2929, 1713, 1287, 1170 and 1093 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{19}H_{25}O_4$ 317.1747 observed 317.1747.

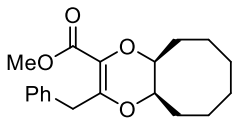
***Rac-cis*-Ethyl 3-(4-methoxyphenyl)-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42rC).**



Starting from the epoxide **32C** (40 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7r** (150 mg, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a coulorless oil (56 mg, 50 % yield).

Rf = 0.33 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.33-7.27 (m, 2H), 6.90-6.84 (m, 2H), 4.37 (dt, *J* = 9 and 3 Hz, 1H), 4.29 (dt, *J* = 9 and 3 Hz, 1H), 4.07 (qd, *J* = 7 and 1 Hz, 2H), 3.82 (s, 3H), 2.08-2.00 (m, 2H), 1.92-1.83 (m, 2H), 1.82-1.70 (m, 2H), 1.70-1.56 (m, 6H) and 1.06 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.1 (C), 160.3 (C), 146.4 (C), 130.7 (2 x CH), 127.2 (C), 124.6 (C), 113.2 (2 x CH), 76.3 (CH), 74.1 (CH), 60.6 (OCH_3), 55.4 (OCH_3), 27.9 (CH_2), 27.7 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 23.6 (CH_2), 23.0 (CH_2) and 14.1 (CH_3) ppm; **IR (neat):** 2933, 1711, 1607, 1294, 1248, 1173 and 1093 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{20}H_{27}O_5$ 347.1853 observed 347.1853.

***Rac-cis*-Methyl 3-benzyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42oC).**

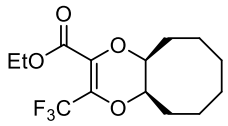


Starting from the epoxide **32C** (40 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7o** (139 μL, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (46 mg, 45 % yield).

Rf = 0.29 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31-7.27 (m, 4H), 7.22-7.18 (m, 1H), 4.24 (dt, *J* = 9 and 3 Hz, 1H), 4.11 (dt, *J* = 9and 3 Hz, 1H), 4.06-3.93 (m, 2H), 3.79 (s, 3H), 1.96-1.74 (m, 3H), 1.74-1.61 (m, 3H) and 1.61-1.52 (m, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.5 (C), 148.4 (C), 138.5 (C), 128.8 (2 x CH), 128.4 (2 x CH), 126.4 (CH), 124.1 (C), 76.0 (CH), 73.9 (CH), 51.9 (CH_3), 36.7 (CH_2), 27.8

(CH_2), 27.8 (CH_2), 25.6 (CH_2), 25.6 (CH_2), 23.5 (CH_2) and 23.2 (CH_2).ppm; **IR (neat):** 2925, 2137, 1714, 1635, 1300, 1191 and 1079 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{19}H_{25}O_4$ 317.1747 observed 317.1749.

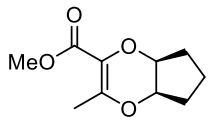
***Rac-cis*-Ethyl 3-(trifluoromethyl)-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b][1,4]dioxine-2-carboxylate (42qC).**



Starting from the epoxide **32C** (80 mg, 0.64 mmol) and corresponding α-diazo-β-ketoester **7q** (243 mg, 1.28 mmol) in 1.2 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 95:5) as a colourless oil (124 mg, 63 % yield).

Rf = 0.24 (SiO_2, pentane:Et_2O, 95:5); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.33-4.22 (m, 4H), 2.06-1.92 (m, 2H), 1.80 (m, 4H), 1.67-1.48 (m, 6H) and 1.32 (t, *J* = 7 Hz, 3H). ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 161.8 (C), 132.0 (q, J_{C-F} = 38 Hz, C), 130.6 (q, J_{C-F} = 3 Hz, C), 120.58 (q, J_{C-F} = 272 Hz, C), 75.8 (CH), 75.0 (CH), 62.1 (CH_2), 27.43 (CH_2), 27.37 (CH_2), 25.4 (2 x CH_2), 23.09 (CH_2), 23.05 (CH_2) and 14.0 (CH_3) ppm; **^{19}F NMR (282 MHz, CD_2Cl_2):** δ -64.06 ppm; **IR (neat):** 2931, 1735, 1124 and 1010 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{14}H_{19}F_3O_4$ 309.1308 observed 309.1306.

***Rac-cis*-Methyl 3-methyl-4a,6,7,7a-tetrahydro-5H-cyclopenta[b][1,4]dioxine-2-carboxylate (42aD).**

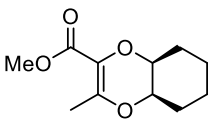


Starting from the epoxide **32D** (55 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil (63 mg, 50 % yield).

Rf = 0.40 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.31 (ddd, *J* = 7, 6 and 3 Hz, 1H), 4.15 (td, *J* = 5 and 3 Hz, 1H), 3.78 (s, 3H), 2.25 (s, 3H), 1.98-1.85 (m, 4H), 1.82-1.72 (m, 1H) and 1.70-1.54 (m, 1H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.8 (C), 146.6 (C), 122.5 (C), 77.1 (CH, signal overlapped with solvent), 74.1 (CH),

51.8 (CH_3), 28.1 (CH_2), 27.5 (CH_2), 19.0 (CH_2), 17.9 (CH_3) ppm; **IR (neat):** 2949, 1715, 1638, 1310, 1160 and 1091 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{10}H_{15}O_4$ 199.0965 observed 199.0969.

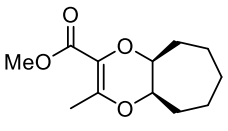
***Rac-cis*-Methyl 3-methyl-4a,5,6,7,8,8a-hexahydrobenzo[b][1,4]dioxine-2-carboxylate (42aE).**



Starting from the epoxide **32E** (31.4 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil (45 mg, 66 % yield).

Rf = 0.41 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.11 (dt, *J* = 8 and 3 Hz, 1H), 4.02 (dq, *J* = 8 and 3 Hz, 1H), 3.78 (s, 3H), 2.23 (s, 3H), 1.89 (qd, *J* = 9 and 6 Hz, 2H), 1.73-1.58 (m, 4H), 1.43-1.32 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.9 (C), 146.1 (C), 122.8 (C), 73.2 (CH), 70.9 (CH), 51.7 (CH_3), 27.9 (CH_2), 27.1 (CH_2), 21.6 (CH_2), 21.5 (CH_2) and 17.9 (CH_3) ppm; **IR (neat):** 2943, 1715, 1635, 1299, 1145 and 1088 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{11}H_{17}O_4$ 213.1121 observed 213.1113.

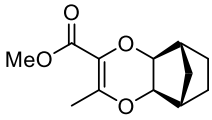
***Rac-cis-M*ethyl 3-methyl-5,6,7,8,9,9a-hexahydro-4aH-cyclohepta[b][1,4]dioxine-2-carboxylate (42aF).**



Starting from the epoxide **32F** (72 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil (99 mg, 68 % yield).

Rf = 0.39 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.22-4.14 (m, 1H), 4.05 (dddd, *J* = 8, 4, 3 and 1 Hz, 1H), 3.77 (s, 3H), 2.22 (s, 3H), 2.00-1.69 (m, 6H) and 1.61-1.33 (m, 4H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.8 (C), 146.8 (C), 123.3 (C), 76.5 (CH), 74.3 (CH), 51.7 (CH_3), 29.4 (CH_2), 28.9 (CH_2), 27.8 (CH_2), 22.04 (CH_2), 21.96 (CH_2) and 17.8 (CH_3) ppm; **IR (neat):** 2932, 1713, 1635, 1304, 1141 and 1088 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{12}H_{19}O_4$ 227.1278 observed 227.1280.

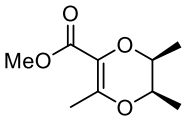
***Rac-cis*-Methyl 3-methyl-4a,5,6,7,8,8a-hexahydro-5,8-methanobenzo[b][1,4]dioxine-2-carboxylate (42aG).**



Starting from the epoxide **32G** (110 mg, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as white solid (74 mg, 52 % yield).

Mp: 70.9 °C; **Rf** = 0.55 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.94 (dt, *J* = 5 and 1 Hz, 1H), 3.87 - 3.82 (m, 1H), 3.78 (s, 3H), 2.54-2.49 (m, 1H), 2.42 (dt, *J* = 3 and 2 Hz, 1H), 2.23 (s, 3H), 1.99 (dt, *J* = 10 and 2 Hz, 1H), 1.56 (ddt, *J* = 8, 3and 1 Hz, 2H), 1.22 (dt, *J* = 11 and 2 Hz, 1H) and 1.14 - 1.07 (m, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.4 (C), 152.9 (C), 127.8 (C), 82.9 (CH), 82.8 (CH), 51.7 (OCH_3), 42.6 (CH), 42.3 (CH), 32.8 (CH_2), 24.7 (CH_2), 24.0 (CH_2) and 17.6 (CH_3) ppm; **IR (neat):** 2959, 1714, 1649, 1309 and 1091 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{12}H_{17}O_4$ 225.1121 observed 225.1121.

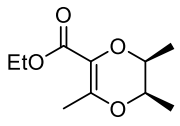
***Rac*-Methyl *cis*-3,5,6-trimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aH).**



Starting from the epoxide **32H** (28 µL, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as colourless oil (51 mg, 85 % yield).

Rf = 0.20 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, CD_2Cl_2):** δ 4.16 (qd, *J* = 7 and 2 Hz, 1H), 3.99 (qd, *J* = 7 and 2 Hz, 1H), 3.71 (s, 3H), 2.18 (s, 3H) and 1.17 (dd, *J* = 7 and 4 Hz, 6H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.7 (C), 146.4 (C), 123.2 (C), 73.2 (CH), 70.7 (CH), 51.8 (OCH_3), 17.8 (CH_3), 14.3 (CH_3) and 14.2 (CH_3) ppm; **IR (neat):** 1715, 1634, 1302, 1120 and 1073 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_9H_{15}O_4$ 187.0964 observed 187.0968.

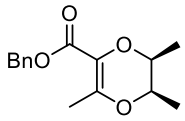
***Rac-cis*-ethyl 3,5,6-trimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42bH).**



Starting from the epoxyde **32H** (28 µL, 0.32 mmol) and corresponding α-diazo-β-ketoester **7b** (92 µL, 0.64 mmol) in 0.6 mL of DCM, the desired compound is obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a soft white solid (55 mg, 92 % yield).

Rf = 0.29 (SiO2, Hexanes:Et2O, 8:2); **^{1}H NMR (400 MHz, CDCl3):** δ 4.25 (p, *J* = 7 Hz, 2H), 4.16 (qd, *J* = 7 and 2 Hz, 1H), 4.06 (qd, *J* = 7 and 2 Hz, 1H), 2.21 (s, 3H), 1.33 (t, *J* = 7 Hz, 3H) and 1.21 (dd, *J* = 7 and 5 Hz, 6H) ppm; **^{13}C NMR (126 MHz, CDCl3):** δ 164.2 (C), 145.8 (C), 72.8 (CH), 70.5(CH), 60.4 (CH2), 17.7 (CH3), 14.3 (CH3), 14.1 (CH3) and 13.8 (CH3) ppm; **IR (neat):** 1711, 1635, 1301, 1121 and 1071 cm^{-1}; **HR-MS (ESI):** m/z calculated for $C_{10}H_{17}O_4$ 201.1121 observed 201.1123.

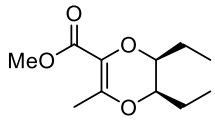
***Rac*-Benzyl *cis*-3,5,6-trimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42dH).**



Starting from the epoxide **32H** (28 µL, 0.32 mmol) and α-diazo-β-ketoester **7d** (150 mg, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (50 mg, 60 % yield).

Rf = 0.35 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.45-7.27 (m, 5H), 5.31-5.19 (m, 2H), 4.18 (qd, *J* = 6.6 and 2.3 Hz, 1H), 4.06 (qd, *J* = 6.5 and 2.3 Hz, 1H), 2.21 (s, 3H) and 1.22 (dd, *J* = 6.6 and 4.0 Hz, 6H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.2 (C), 146.5 (C), 136.5 (C), 128.6 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 123.2 (C), 73.2 (CH), 70.7 (CH), 66.2 (CH_2), 18.1 (CH_3), 14.4 (CH_3) and 14.1 (CH_3) ppm; **IR (neat):** 1710, 1633, 1297, 1159, 1118 and 1065 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{15}H_{18}O_4Na$ 285.1097 obtained 285.1111.

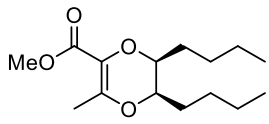
***Rac*-Methyl *cis*-5,6-diethyl-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aI).**



Starting from the epoxide **32I** (65 µL, 0.64 mmol) and the corresponding α-diazo-β-ketoester **7a** (180 µl, 1.28 mmol) in 1.2 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (80 mg, 58 % yield).

Rf = 0.60 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.97 (ddd, *J* = 10, 4 and 2 Hz, 1H), 3.82 (ddd, *J* = 10, 4 and 2 Hz, 1H), 3.78 (s, 3H), 2.23 (s, 3H), 1.69-1.52 (m, 2H), 1.52-1.38 (m, 2H), 1.01 (td, *J* = 8 Hz, 3H) and 1.01 (td, *J* = 8 Hz, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164. 8 (C), 146.7 (C), 123.2 (C), 78.1 (CH), 75.8 (CH), 51.7 (OCH_3), 21.6 (CH_2), 21.1 (CH_2), 17.7 (CH_3), 10.19 (CH_3) and 10.16 (CH_3) ppm; **IR (neat):** 2945, 1717, 1637, 1316 and 1082 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{11}H_{19}O_4$ 215.1278 observed 215.1277.

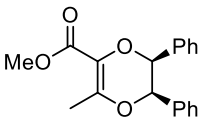
***Rac*-Methyl *cis*-5,6-dibutyl-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aJ).**



Starting from the epoxide **32J** (110 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil (163 mg, 94 % yield).

Rf = 0.69 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.02 (ddd, *J* = 10, 4 and 2 Hz, 1H), 3.87 (ddd, *J* = 10, 4 and 2 Hz, 1H), 3.77 (s, 3H), 2.22 (s, 3H), 1.65-1.26 (m, 12H) and 0.91 (t, *J* = 7 Hz, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.8 (C), 146.7 (C), 123.4 (C), 76.9 (CH), 74.7 (CH), 51.7 (OCH_3), 28.0 (CH_2), 27.91 (CH_2), 27.86 (CH_2), 27.82 (CH_2), 22.74 (CH_2), 22.69 (CH_3), 17.7 (CH_3) and 14.1 (2 x CH_3) ppm; **IR (neat):** 2951, 1717, 1637, 1315 and 1086 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{15}H_{27}O_4$ 271.1904 observed 271.1905.

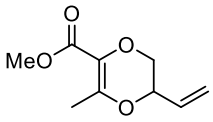
***Rac*-Methyl 3-methyl-*cis*-5,6-diphenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aK).**



Starting from the epoxide **32K** (62.8 mg, 0.32 mmol) and the corresponding α-diazo-β-ketoester **7a** (90 µl, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (hexane:diethyl ether 8:2) as a colourless oil (37 mg, 37 % yield).

Rf = 0.38 (SiO_2, Hexanes:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.18 (td, *J* = 7 and 4 Hz, 5H), 7.04 (s, 1H), 7.01-6.89 (m, 4H), 5.35 (d, *J* = 3 Hz, 1H), 5.22 (d, *J* = 3 Hz, 1H), 3.82 (s, 3H) and 2.43 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.3 (C), 148.2 (C), 135.9 (2 x C), 129.03 (2 x CH), 128.98 (4 x CH), 126.5 (4 x CH), 125.0 (C), 76.2 (CH), 68.6 (CH), 51.9 (CH_3) and 17.9 (CH_3) ppm; **IR (neat):** 1715, 1639, 1299, 1160 and 1092 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{19}H_{19}O_4$ 311.1277 observed 311.1265.

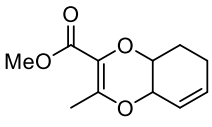
***Rac*-Methyl 3-methyl-5-vinyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aB).**



Starting from the epoxide **32B** (26 µl, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (33 mg, 55 % yield).

Rf = 0.46 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.82 (ddd, *J* = 17, 11 and 6 Hz, 1H), 5.44 (dt, *J* = 17 and 1 Hz, 1H), 5.35 (dt, *J* = 11 and 1 Hz, 1H), 4.53 (dddd, *J* = 7, 6, 3 and 1 Hz, 1H), 4.15 (dd, *J* = 11 and 3 Hz, 1H), 3.80 (s, 3H), 3.76-3.64 (m, 1H) and 2.28 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.3 (C), 147.4 (C), 132.0 (CH), 124.8 (C), 119.3 (CH_2), 74.9 (CH), 66.8 (CH_2), 51.8 (OCH_3) and 17.9 (CH_3) ppm; **IR (neat):** 1716, 1637, 1315 and 1108 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_9H_{13}O_4$ 185.0808 observed 185.0810.

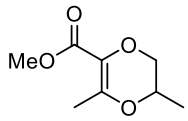
***Rac-cis*-Methyl 3-methyl-4a,7,8,8a-tetrahydrobenzo[b][1,4]dioxine-2-carboxylate (42aL).**



Starting from the epoxide **32L** (29 µl, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (33 mg, 50 % yield).

Rf = 0.39 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.95 (dtd, *J* = 10, 4 and 1 Hz, 1H), 5.70 (dddt, *J* = 10, 4, 3 and 1 Hz, 1H), 4.48 (ddt, *J* = 4, 3 and 1 Hz, 1H), 4.20 (dt, *J* = 9 and 3 Hz, 1H), 3.78 (s, 3H), 2.41-2.29 (m, 1H), 2.23 (s, 3H), 2.19-1.97 (m, 2H) and 1.86-1.74 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.8 (C), 145.3 (C), 133.1 (CH), 124.0 (CH), 123.2 (C), 69.3 (CH), 68.9 (CH), 51.8 (OCH_3), 23.6 (CH_2), 23.2 (CH_2) and 18.0 (CH_3) ppm; **IR (neat):** 1714, 1640 and 1093 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{11}H_{15}O_4$ 211.0964 observed 211.0965.

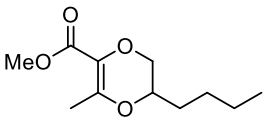
***Rac*-Methyl 3,5-dimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aN).**



Starting from the epoxide **32N** (45 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a coulorless oil (72 mg, 65% yield).

Rf = 0.25 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.17 (ddd, *J* = 7, 6 and 2 Hz, 1H), 4.11 (dd, J = 11 and 2 Hz, 1H), 3.79 (s, 3H), 3.59 (dd, *J* = 11 and 7 Hz, 1H), 2.23 (s, 3H) and 1.29 (d, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.4 (C), 147.6 (C), 124.4 (C), 70.6 (CH), 68.2 (CH_2), 51.8 (OCH_3) 17.9 (CH_3) and 16.5 (CH_3). Ppm; **IR (neat):** 1713, 1630, 1312, 1109 and 1079 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_8H_{13}O_4$ 173.0808 observed 173.0810.

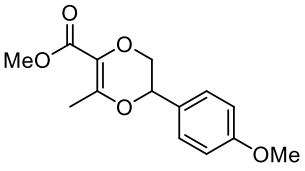
***Rac*-Methyl 3-methyl-5-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aO).**



Starting from the epoxide **32O** (39 µL, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (37 mg, 55% yield).

Rf = 0.31 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.11 (dd, *J* = 11 and 2 Hz, 1H), 4.01 (tdd, *J* = 8, 5 and 2 Hz, 1H), 3.79 (s, 3H), 3.65 (dd, *J* = 11 and 7 Hz, 1H), 2.24 (s, 3H), 1.68-1.28 (m, 6H) and 0.92 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.5 (C), 147.7 (C), 124.5 (C), 74.5 (CH), 67.1 (CH_2), 51.8 (OCH_3), 30.6 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 18.0 (CH_3) and 14.1 (CH_3) ppm. **IR (neat):** 2938, 1717, 1635, 1316 and 1114 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{11}H_{19}O_4$ 215.1277 observed 215.1272.

***Rac*-Methyl 5-(4-methoxyphenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aP)**



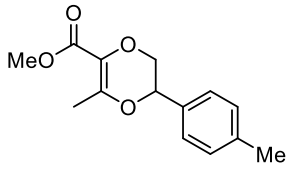
Starting from the epoxide **32P** (80 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a colourless oil (70 mg, 41% yield).

Rf = 0.20 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, CD_2Cl_2):** δ 7.26 (d, *J* = 9 Hz, 2H), 6.95-6.90 (m, 2H), 4.95 (dd, *J* =8 and 3 Hz, 1H), 4.22 (dd, *J* =11 and 3 Hz, 1H), 3.80 (s, 3H), 3.77-3.69 (m, 4H) and 2.29 (s, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2):** δ 164.7 (C), 160.7 (C), 148.2 (C), 128.7 (C), 128.3 (2 x CH), 125.4 (C), 114.6 (2 x CH), 76.3 (CH), 68.8 (CH_2), 55.9 (OCH_3), 51.9 (OCH_3) and 18.1 (CH_3) ppm; **IR (neat):** 1713, 1634, 1248, 1159 and 1099 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{14}H_{17}O_5$ 265.1071 observed 265.1073.

(*R*)-Methyl 5-(4-methoxyphenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aP)

Compound prepared following the general method and obtained with a 54 % *ee*. For this sample, the optical rotation was measured. $[\alpha]_D = -6.0$ (CH_2Cl_2, 0.1).

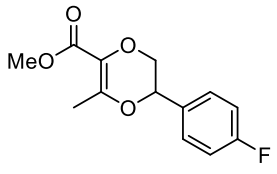
***Rac*-Methyl 3-methyl-5-(*p*-tolyl)-5,6-dihydro-1,4-dioxine-2-carboxylate (42aQ)**



Starting from the epoxide **32Q** (75 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a coulorless oil (60 mg, 40% yield).

Rf = 0.26 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.22 (s, 4H), 4.98 (dd, *J* = 8 and 3 Hz, 1H), 4.28 (dd, *J* = 11 and 3 Hz, 1H), 3.82 (s, 3H), 3.76 (dd, *J* = 11 and 8 Hz, 1H), 2.36 (s, 3H) and 2.34 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.2 (C), 148.1 (C), 138.8 (C), 132.8 (C), 129.5 (2 x CH), 126.3 (2 x CH), 124.7 (C), 76.0 (CH), 68.5 (CH_2), 51.7 (OCH_3), 21.2 (CH_3) and 17.8 (CH_3) ppm; **IR (neat):** 1715, 1635, 1100, 908 and 727 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{14}H_{17}O_4$ 249.1121 observed 249.123.

***Rac*-Methyl 5-(4-fluorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aS)**

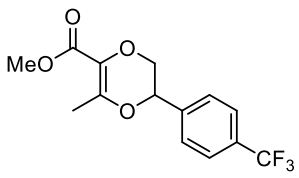


Starting from the epoxide **32S** (146 µL, 1.28 mmol) and corresponding α-diazo-β-ketoester **7a** (368 µL, 2.56 mmol) in 2.4 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a coulorless oil (123 mg, 38% yield).

Rf = 0.31 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.33-7.30 (m, 2H), 7.11-7.08 (m, 2H), 5.00 (dd, *J* = 8 and 3 Hz, 1H), 4.28 (dd, *J* = 11 and 3 Hz, 1H), 3.82 (s, 3H), 3.76-3.71 (m, 1H) and 2.34 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.2

(C), 163.1 (d, J_{C-F} = 248 Hz, C), 148.0 (C), 131.8 (d, J_{C-F} = 3 Hz, C), 128.3 (d, J_{C-F} = 8 Hz, CH), 125.0 (C), 115.9 (d, J_{C-F} = 22 Hz, 2 x CH), 75.5 (2 x CH), 68.5 (CH_2), 51.9 (OCH_3) and 17.9. (CH_3) ppm; **^{19}F NMR (282 MHz, $CDCl_3$):** δ - 112.7 ppm; **IR (neat):** 1747, 1513, 1224, 1160 and 1110 cm^{-1}; **HR-MS (EI)** *m/z* . not stable on HRMS.

Rac-Methyl 3-methyl-5-(4-(trifluoromethyl)phenyl)-5,6-dihydro-1,4-dioxine-2-carboxylate (42aT)



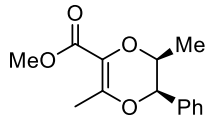
Starting from the epoxide **32T** (120 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2 and following the general procedure, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a coulorless oil (69 mg, 37% yield).

Rf = 0.22 (SiO_2, pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, CD_2Cl_2):** δ 7.71-7.66 (m, 2H), 7.53-7.47 (m, 2H), 5.12 (dd, *J* = 8 and 3 Hz, 1H), 4.29 (dd, *J* = 11 and 3, 1H), 3.77-3.73 (m, 1H), 3.76 (s, 3H) and 2.33 (s, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2):** δ 164.5 (C), 147.7 (C), 140.8 (C), 131.1 (q, J_{C-F} = 32 Hz, C), 127.2 (2 x CH), 126.2 (d, J_{C-F} = 4 Hz, 2 x CH), 125.7 (C), 124.6 (q, J_{C-F} = 272 Hz, C), 75.8 (CH), 68.5 (CH_2), 52.0 (OCH_3) and 17.9 (CH_3) ppm; **^{19}F NMR (282 MHz, CD_2Cl_2):** δ - 62.75 ppm; **IR (neat):** 1716, 1639, 1324, 1162, 1102 and 1066 cm^{-1}; **HR-MS (EI)** *m/z* calculated for $C_{14}H_{14}F_3O_4$ 303.0839 observed 303.0840.

(*R*)-Methyl 5-(4-fluorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aS)

Compound prepared following the general method and obtained with a 88 % *ee*. For this sample, the optical rotation was measured. $[\alpha]_D = -46.0$ (CH_2Cl_2, 0.1).

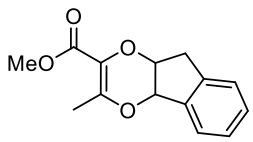
***Rac-cis*-Methyl 3,6-dimethyl-5-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aU).**



Starting from the epoxide **32U** (86 mg, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as colourless oil (96 mg, 60 % yield).

Rf = 0.38 (SiO_2, hexanes:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.41-7.28 (m, 5H), 5.09 (d, *J* = 3 Hz, 1H), 4.41 (qd, *J* = 7 and 3 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 3H) and 1.04 (d, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.7 (C), 147.1(C), 136.5 (C), 128.7 (2 x CH), 128.4 (CH), 126.4 (2 x CH), 123.3 (C), 78.5 (CH), 71.5 (CH), 51.9 (CH_3), 17.7 (CH_3) and 12.8 (CH_3) ppm; **IR (neat):** 1716, 1638, 1306, 1154 and 1085 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{14}H_{17}O_4$ 249.1121 observed 249.1123.

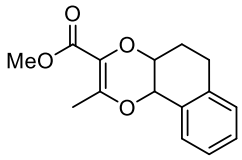
***Rac-cis*-Methyl (4*R*,9*S*) and (4*S*,9*R*) 3-methyl-9,9a-dihydro-4aH-indeno[1,2-b][1,4]dioxine-2-carboxylate (42aV).**



Starting from the epoxide **32V** (42 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a soft white solid (17 mg, 21 % yield).

Mp: 132.5 °C; **Rf** = 0.28 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (400 MHz, CD_2Cl_2):** δ 7.41-7.38 (m, 1H), 7.34-7.22 (m, 3H), 5.42 (dd, *J* = 4 and 1 Hz, 1H), 4.55 (q, *J* = 4 Hz, 1H), 3.68 (s, 3H), 3.13 (d, *J* = 4 Hz, 2H) and 2.27 (s, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.5 (C), 147.9 (C), 139.8 (C), 139.7 (C), 129.5 (CH), 127.4 (CH), 126.0 (CH), 124.7 (CH), 123.4 (C), 78.4 (CH), 73.9 (CH), 51.8 (CH_3), 36.3 (CH_2) and 18.0 (CH_3) ppm; **IR (neat):** 1714, 1639, 1322, 1164 and 1090 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{14}H_{15}O_4$ 247.0964 observed 247.0964.

***Rac*-*cis*-Ethyl 2-methyl-4a,5,6,10b-tetrahydronaphtho[1,2-b][1,4]dioxine-3-carboxylate (42aW).**



Starting from the epoxide **32W** (47 mg, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired compound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a soft white solid (58 mg, 70 % yield). X-Ray quality crystals were obtained by slow diffusion of pentane in a solution of **42aw** in diethyl ether.

Mp: 85.0 °C; **Rf** = 0.41 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.41 (dd, *J* = 7 and 2 Hz, 1H), 7.32-7.20 (m, 2H), 7.18-7.13 (m, 1H), 4.99 (d, *J* = 3 Hz, 1H), 4.43 (dt, *J* = 10 and 3 Hz, 1H), 3.77 (s, 3H), 3.09 (dt, *J* = 17 and 6 Hz, 1H), 2.91-2.81 (m, 1H), 2.30-2.17 (m, 4H) and 2.05-1.95 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.6 (C), 145.6 (C), 136.5 (C), 133.1 (C), 129.6 (CH), 129.0 (CH), 128.9 (CH), 126.6 (CH), 123.4 (C), 72.3 (CH), 69.7 (CH), 51.8 (CH_3), 26.6 (CH_2), 23.7 (CH_2) and 17.9 (CH_3) ppm; **IR (neat):** 1628, 1155 and 1064 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{15}H_{17}O_4$ 261.1121 observed 261.1126.

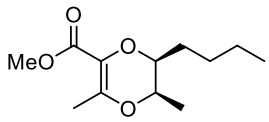
***Rac*-Methyl *cis*-butyl-dimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate (42aX) (mixture of regioisomers).**

Starting from the epoxide **32X** (90 mg, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired coumpound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a mixture of two diastereoisomers as colourless oil (73 mg, 62 % yield).

Pure fraction of each regioisomer have been obtained after semi-preparative TLC pentane:diethyl ether 8:2.

***Rac*-methyl *cis*-6-butyl-3,5-dimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate**

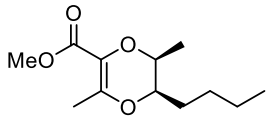
Regioisomer 1: colorless oil (29 mg, 20 % yield).



Rf = 0.40 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.23 (qd, *J* = 7 and 2 Hz, 1H), 3.80 (ddd, *J* = 9, 4 and 2 Hz, 1H), 3.77 (s, 3H), 2.21 (s, 3H), 1.65-1.56 (m, 2H), 1.54-1.28 (m, 4H), 1.19 (d, *J* = 7 Hz, 3H) and 0.91 (t, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.7 (C), 146.6 (C), 123.5 (C), 74.9 (CH), 73.0 (CH), 51.7 (CH_3), 28.7 (CH_2), 27.8 (CH_2), 22.7 (CH_2), 17.8 (CH_3), 14.1 (CH_3) and 13.9 (CH_3) ppm; **IR (neat):** 2952, 1715, 1634, 1312 and 1081 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{12}H_{21}O_4$ 229.1434 observed 229.1433.

***Rac*-methyl *cis*-5-butyl-3,6-dimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate.**

Regioisomer 2: colorless oil (26 mg, 18 % yield).

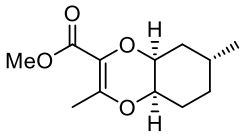


Rf = 0.33 (SiO_2, Pentane:Et_2O, 8:2); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.13 (qd, *J* = 7 and 2 Hz, 1H), 3.97 (ddd, *J* = 9, 4 and 2 Hz, 1H), 3.78 (s, 3H), 2.23 (s, 3H), 1.62-1.29 (m, 6H), 1.21 (d, *J* = 7 Hz, 3H) and 0.92 (t, J = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.7 (C), 146.5 (C), 123.1 (C), 77.0 (CH), 70.5 (CH), 51.7 (CH_3), 28.6 (CH_2), 27.7 (CH_2), 22.7 (CH_2), 17.7 (CH_3), 14.1 (CH_3) and 13.7 (CH_3) ppm; **IR (neat):** 2952, 1715, 1635, 1312 and 1081 cm^{-1}; **HR-MS (ESI)** *m/z* calculated for $C_{12}H_{21}O_4$ 229.1434 observed 229.1433.

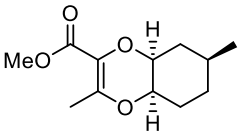
***Rac-cis*-Methyl 3,7-dimethyl-4a,5,6,7,8,8a-hexahydrobenzo[b][1,4]dioxine-2-carboxylate (42aY, mixture of isomers)**

Starting from the epoxide **32Y** (mixture of stereoisomers, 80 µL, 0.64 mmol) and corresponding α-diazo-β-ketoester **7a** (184 µL, 1.28 mmol) in 1.2 mL of CH_2Cl_2, the desired coumpound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a mixture of four regioisomers as colourless oil (64 mg, 44 % yield).

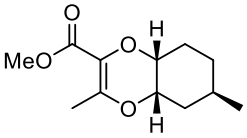
Pure fraction of three regioisomers have been obtained after semi-preparative TLC pentane:diethyl ether 8:2.



Rf = 0.60 (SiO_2, Pentane:Et_2O, 8:2), first eluted;**^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.12-4.03 (m, 1H), 3.94 (q, *J* = 3 Hz, 1H), 3.78 (s, 3H), 2.22 (s, 4H), 1.86 (dtt, *J* = 8, 6 and 3 Hz, 1H), 1.80-1.65 (m, 3H), 1.22 (ddd, *J* = 14, 12 and 3 Hz, 1H), 1.08-0.95 (m, 1H) and 0.89 (d, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** 164.8 (C), 146.0 (C), 123.6 (C), 74.9 (CH), 70.0 (CH), 51.7 (OCH_3), 37.6 (CH_2), 32.1 (CH_2), 25.8 (CH_2), 25.7 (CH), 21.4 (CH_3) and 18.0 (CH_3) ppm, **IR (neat):** 2928, 1715, 1634, 1165 and 1085 cm^{-1}.



Rf = 0.53 (SiO_2, Pentane:Et_2O, 8:2), second eluted;**^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.11 (ddd, *J* = 12, 5 and 3 Hz, 1H), 3.91 (d, *J* = 3 Hz, 1H), 3.78 (s, 3H), 2.24 (ddt, *J* = 7, 5 and 3 Hz, 1H), 2.22 (s, 3H), 1.76-1.66 (m, 1H), 1.53-1.21 (m, 5H) and 0.95 (d, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.8 (C), 145.9 (C), 123.5 (C), 74.9 (CH), 69.1 (CH), 51.7 (OCH_3), 34.4 (CH_2), 30.8 (CH), 29.1 (CH_2), 27.9 (CH_2), 22.0 (CH_3) and 18.0 (CH_3) ppm; **IR (neat):** 2928, 1715, 1634, 1165 and 1085 cm^{-1}.

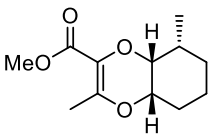


Rf = 0.42 (SiO_2, Pentane:Et_2O, 8:2), third eluted;**^{1}H NMR (500 MHz, CD_2Cl_2):** δ 4.13-4.09 (m, 1H), 4.07-4.02 (m, 1H), 3.71 (s, 3H), 2.18 (s, 3H), 2.05 (dtd, *J* = 14, 4 and 3 Hz, 1H), 1.78-1.69 (m, 2H), 1.69-1.60 (m, 1H), 1.32-1.20 (m, 2H), 1.11-0.99 (m, 1H) and 0.90 (d, *J* = 7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2):** δ 165.2 (C), 146.2 (C), 122.6 (C), 72.2 (CH), 72.1 (CH), 51.8 (OCH_3), 38.0 (CH_2), 32.4 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 21.5(CH_3) and 17.9 (CH_3) ppm; **IR (neat):** 2937, 1714, 1635, 1139 and 1085 cm^{-1}.

***Rac-cis*-Methyl 3,8-dimethyl-4a,5,6,7,8,8a-hexahydrobenzo[b][1,4]dioxine-2-carboxylate (42aZ, mixture of isomers)**

Starting from the epoxide **32Z** (mixture of stereoisomers, 40 µL, 0.32 mmol) and corresponding α-diazo-β-ketoester **7a** (92 µL, 0.64 mmol) in 0.6 mL of CH_2Cl_2, the desired coumpound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a mixture of four regioisomers as colourless oil (29 mg, 40 % yield).

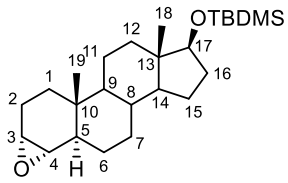
Pure fraction of one regioisomer has been obtained after semi-preparative TLC pentane:diethyl ether 8:2. X-Ray quality crystals were obtained by slow diffusion of pentane in a solution of **42aZ** in CH_2Cl_2 at 0 °C.



Rf = 0.67 (SiO_2, Pentane:Et_2O, 8:2), first eluted; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.09 (ddd, *J* = 12, 5 and 2 Hz, 1H), 3.78 (s, 3H), 3.75-3.68 (m, 1H), 2.24 (s, 3H), 1.83-1.61 (m, 4H), 1.46-1.25 (m, 3H) and 1.16 (d, *J* = 7 Hz, 3H) ppm; **IR (neat):** 2931, 1704, 1629 and 1036 cm^{-1}; **LR-MS (ESI):** *m/z* observed 227.6; **IR (neat):** 2931, 1704, 1630 and 1036 cm^{-1}.

3α,4α-epoxy-5α-androstan-17β-ol tert-butyldimethylsilyl ether 48

Compound **xx** was synthesized as reported in the literature[183b, 184] and had spectroscopic characteristics identical to those already described. X-Ray quality crystals were obtained by slow diffusion of pentane in a solution of **48** in diethyl ether.

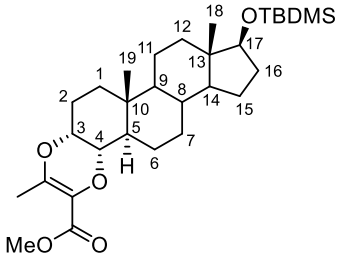


^{1}H NMR (500 MHz, $CDCl_3$): δ 3.53 (dd, *J* = 9 and 8 Hz, $1H^{17}$), 3.15 (t, *J* = 3 Hz, $1H^3$), 2.69 (d, *J* = 4 Hz, $1H^4$), 0.87 (s, 9H), 0.76 (s, $3H^{19}$), 0.68 (s, $3H^{18}$) and - 0.01 (d, *J* = 3 Hz, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 81.9 ($C^{17}H$), 56.1 (C^4H), 53.6 (C^{13}), 53.1 (CH), 52.4 (C^3H), 50.7 (CH), 47.0 (C^5H), 43.5 (C^{10}), 37.3 ($C^{12}H_2$), 35.6 (C^8H), 34.3 (C^{21}), 31.7 (CH_2), 31.1 (CH_2), 30.6 (CH_2), 26.9 (C^6H_2), 26.0 (CH_3), 23.6 ($C^{15}H_2$), 21.5 (C^2H_2), 21.1 ($C^{11}H_2$), 13.7 ($C^{19}H_3$), 11.6 ($C^{18}H_3$), -4.4 (CH_3) and -4.7 (CH_3) ppm.

7.6.2 Generic procedure for the synthesis of compounds **50** and **51**

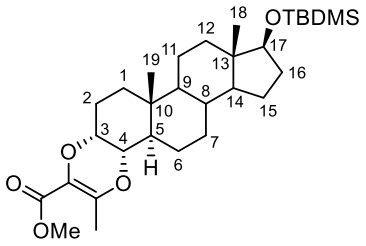
Starting from the epoxide **48** (35 mg, 0.086 mmol) and corresponding α-diazo-β-ketoester **7a** (22 µL, 0.17 mmol) in 0.2 mL of CH_2Cl_2, the desired coumpound was obtained after purification by column of silica gel (pentane:diethyl ether 8:2) as a mixture of two regioisomers as a white solid (31 mg, 71 % yield). Pure fractions of the two regioisomers have been obtained by selective crystallization from diethyl ether. X-Ray quality crystals were obtained for the minor regioisomer.

Methyl 3α,4α-[1,4]dioxine-2-carboxylate 5α-androstan-17β-ol tert-butyldimethylsilyl ether 50



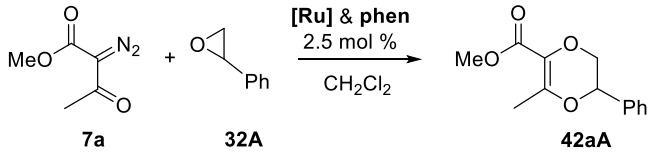
Mp: 124.9 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.15 (q, *J* = 3 Hz, 1H^{4}), 3.98 (dd, *J* = 12 and 3 Hz, 1H^{3}), 3.77 (s, 3H), 3.57-3.46 (t, *J* = 8 Hz, 1H^{17}), 2.23 (s, 3H), 0.87 (s, 9H) and - 0.00 (d, *J* = 2 Hz, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 165.0 (C), 147.0 (C), 121.4 (C), 81.9 (C^{17}H), 72.7 (C^{3}H), 71.5 (C^{4}H), 54.6, 51.7 (CH_3), 50.8, 43.3(C), 42.0, 37.7 (C), 37.2 (CH_2), 35.3, 31.8 (CH_2), 31.14 (CH_2), 31.05 (CH_2), 29.9 (CH_2), 26.0 (3 x CH_3), 25.8 (CH_2), 23.6 (CH_2), 22.4 (CH_2), 20.6 (CH_2), 18.3, 17.8, 12.4, 11.5, - 4.3 (CH_3) and - 4.7 (CH_3) ppm; **IR (neat):** 2938, 1714, 1638 and 1085 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{30}H_{50}O_5Si$ 519.3500 observed 519.3505.

methyl 3α,4α-[1,4]dioxine-2-carboxylate 5α-androstan-17β-ol tert-butyldimethylsilyl ether 51



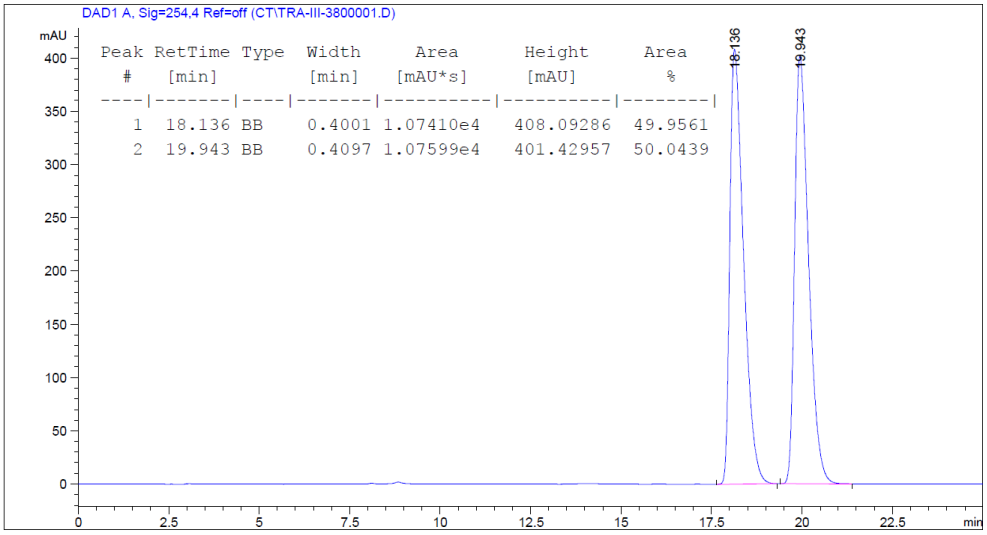
Mp: 123.5 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.98 (dd, *J* = 12 and 3 Hz, 1H^{4}), 3.91 (q, *J* = 3 Hz, 1H^{3}), 3.78 (s, 3H), 3.52 (t, *J* = 8 Hz, 1H^{17}), 2.22 (s, 3H), 2.12 (ddt, *J* = 15, 4 and 3 Hz, 1H^{2}), 1.91-1.82 (m, 1H), 1.80-1.67 (m, 4H), 1.53-1.33 (m, 8H), 1.27-1.18 (m, 4H), 0.98-0.74 (m, 2H, overlapped signal), 0.87 (s, 9H, overlapped signal), 0.84 (s, 3H^{18}, overlapped signal), 0.68 (s, 3H^{19}) and -0.00 (d, *J* = 3 Hz, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 13C NMR (126 MHz, CDCl3) δ 164.8 (C), 145.9 (C), 124.0 (C), 81.9 (C^{17}H), 75.9 (C^{4}H), 69.6 (C^{3}H), 54.3, 51.7 (CH_3), 50.7, 43.4 (C), 43.3, 37.6 (C), 37.2, 35.3, 31.8 (CH_2), 31.0 (CH_2), 26.0 (3 x CH_3), 25.7 (CH_2), 23.6 (CH_2), 22.5 (CH_2), 20.5 (CH_2), 18.3, 17.9, 12.4, 11.5, -4.3 (CH_3) and -4.7 (CH_3) ppm; **IR (neat):** 2938, 1714, 1638 and 1085 cm^{-1}; **HR-MS (ESI):** *m/z* calculated for $C_{30}H_{50}O_5Si$ 519.3500 observed 519.3505.

7.6.3 CSP-HPLC traces for **42aA**, **42aS** and **42aP**



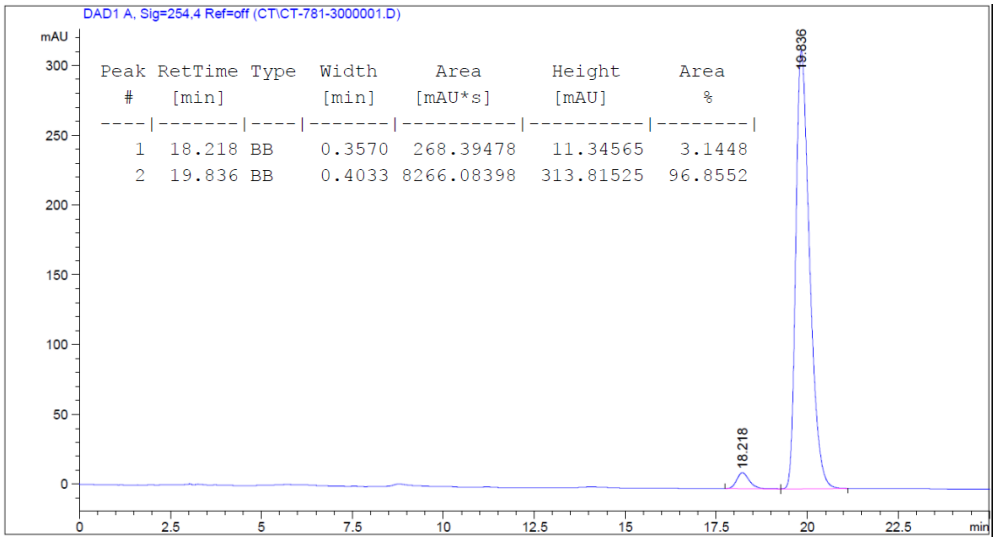
7a **32A** **42aA**

Racemic:



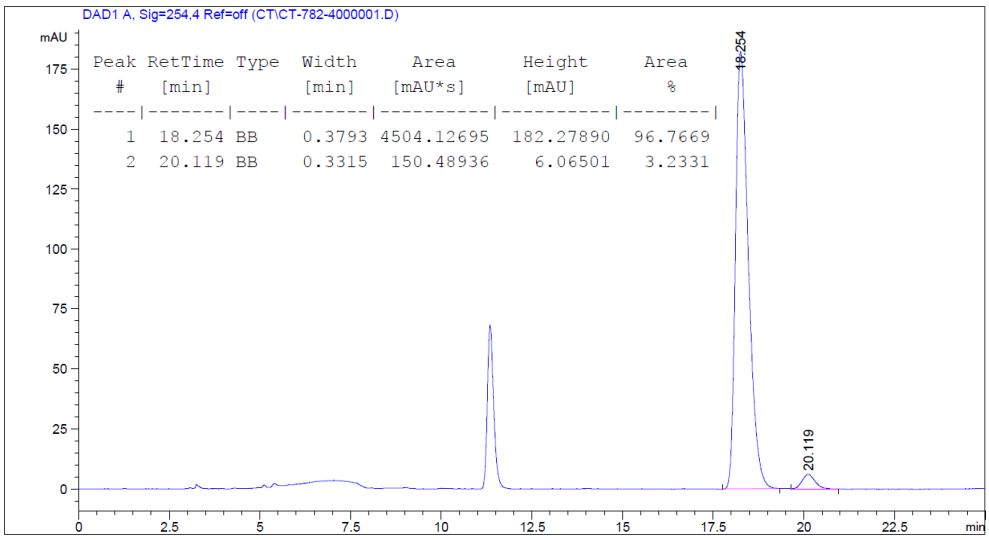
CSP-HPLC (Chiracel OJ-H) Hex/i-Pr 90:10, flow 1 ml/min, 23 °C.

(−)-(*R*)-enantiomer:

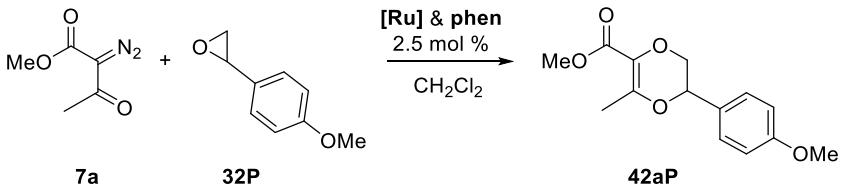


CSP-HPLC (Chiracel OJ-H) Hex/i-Pr 90:10, flow 1 ml/min, 23 °C.

(+)-(*S*)-enantiomer:

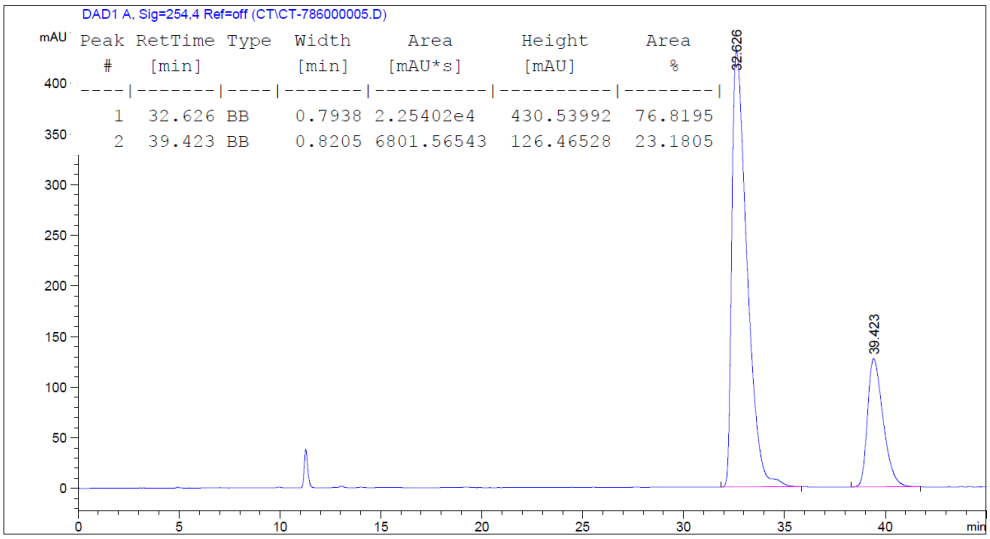


CSP-HPLC (Chiracel OJ-H) Hex/i-Pr 90:10, flow 1 ml/min, 23 °C.

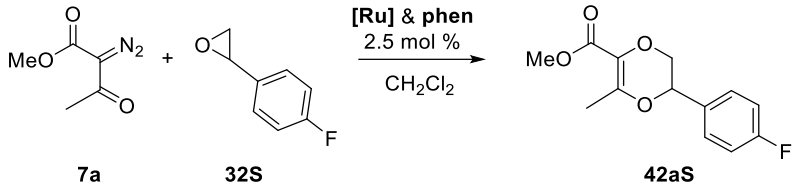


7a **32P** **42aP**

(−)-enantiomer:

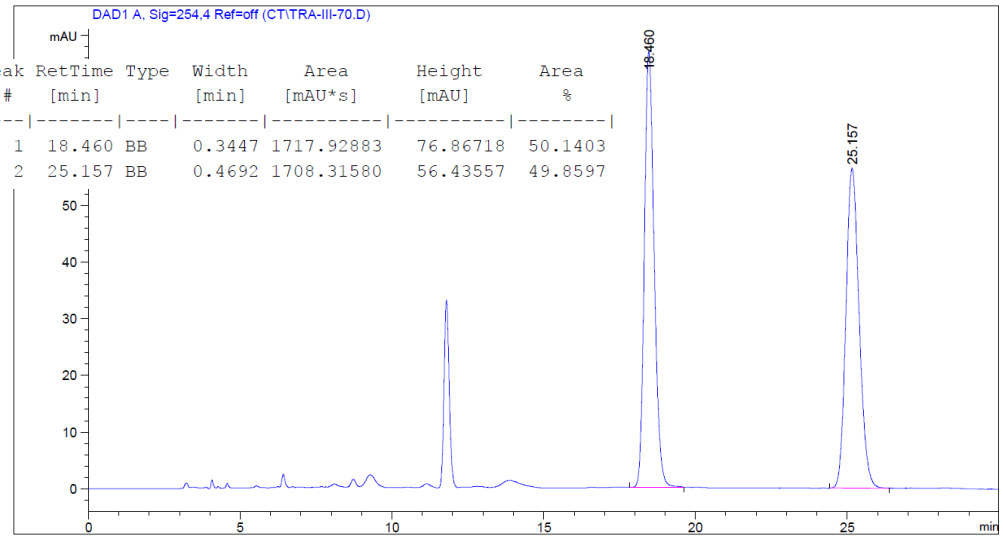


CSP-HPLC (Chiracel OJ-H) Hex/i-Pr 90:10, flow 1 ml/min, 23 °C.



7a **32S** **42aS**

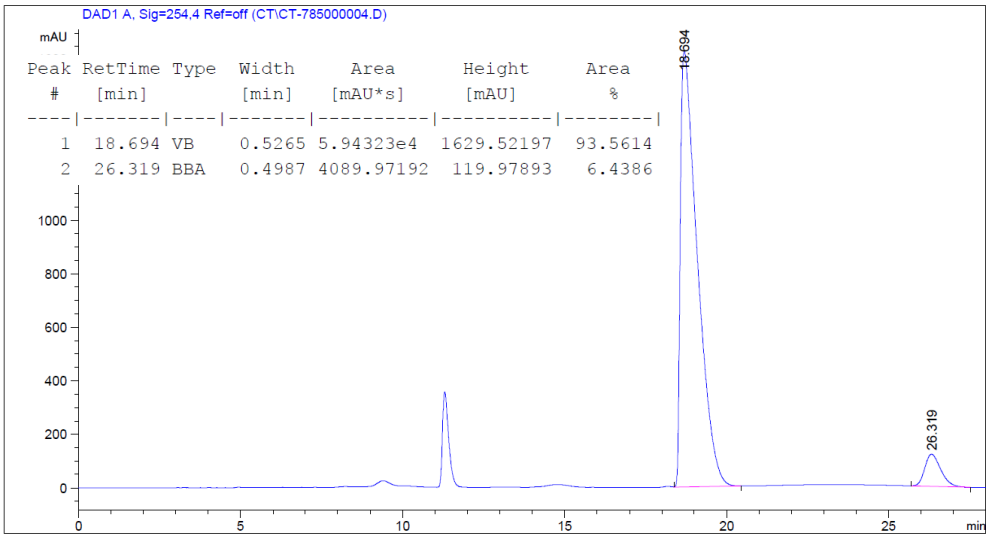
Racemic:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.460	BB	0.3447	1717.92883	76.86718	50.1403
2	25.157	BB	0.4692	1708.31580	56.43557	49.8597

CSP-HPLC (Chiracel OJ-H) Hex/i-Pr 90:10, flow 1 ml/min, 23 °C.

(−)-enantiomer:



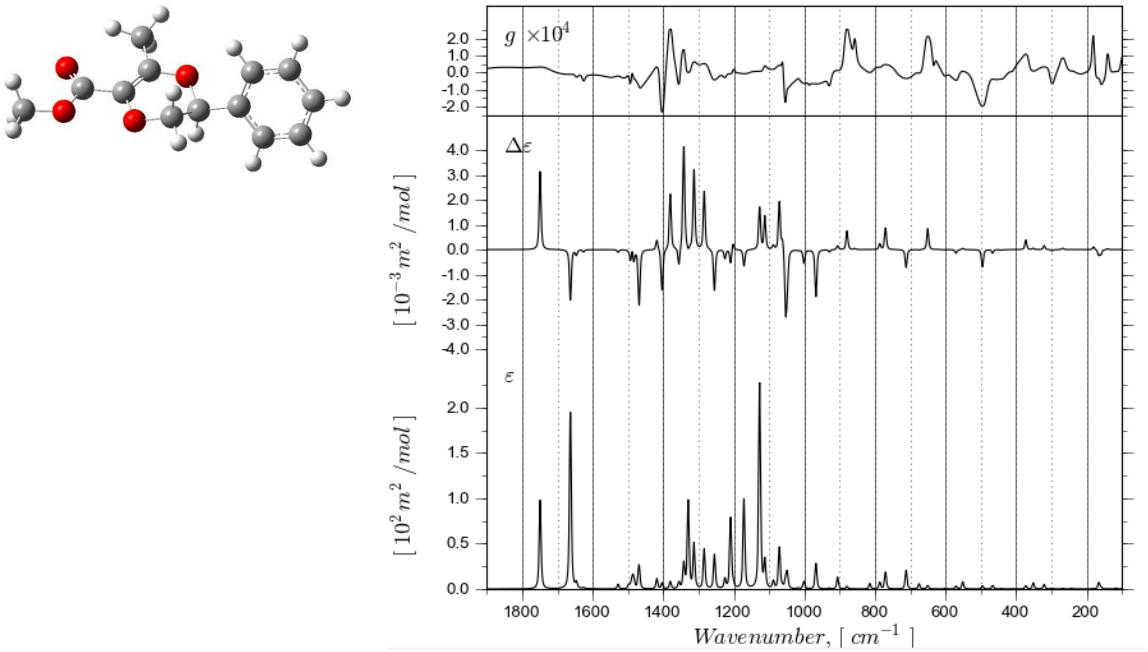
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.694	VB	0.5265	5.94323e4	1629.52197	93.5614
2	26.319	BBA	0.4987	4089.97192	119.97893	6.4386

CSP-HPLC (Chiracel OJ-H) Hex/i-Pr 90:10, flow 1 ml/min, 23 °C.

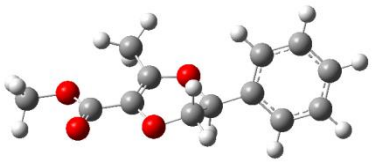
7.6.4 IR and VCD measurement/calculated

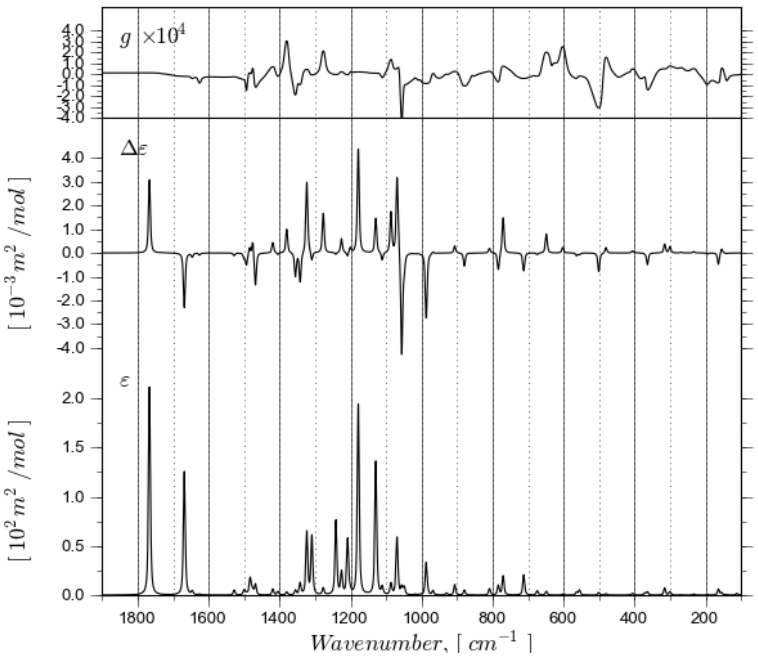
IR and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at l/4 retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter (< 1800 cm-1) in front of the photoelastic modulator was used to enhance the signal/noise ratio. Spectra were recorded with a transmission cell equipped with CaF2 windows and a 0.2 mm Teflon spacer. Solutions of (–)-**3pA** and (+)-**3pA** in CD_2Cl_2 at concentrations of 18 mg in 0.5 CD_2Cl_2 were measured under identical conditions and subtracted to each other in order to eliminate artifacts. Samples were measured at a resolution of 4 cm^{-1} by averaging about 24'000 scans for both enantiomers. Spectra are presented without further data processing.

Calculated spectra (top VCD, bottom IR) for different conformers

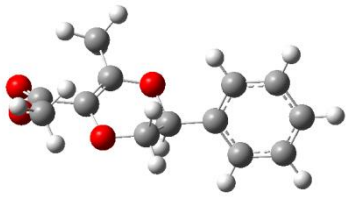


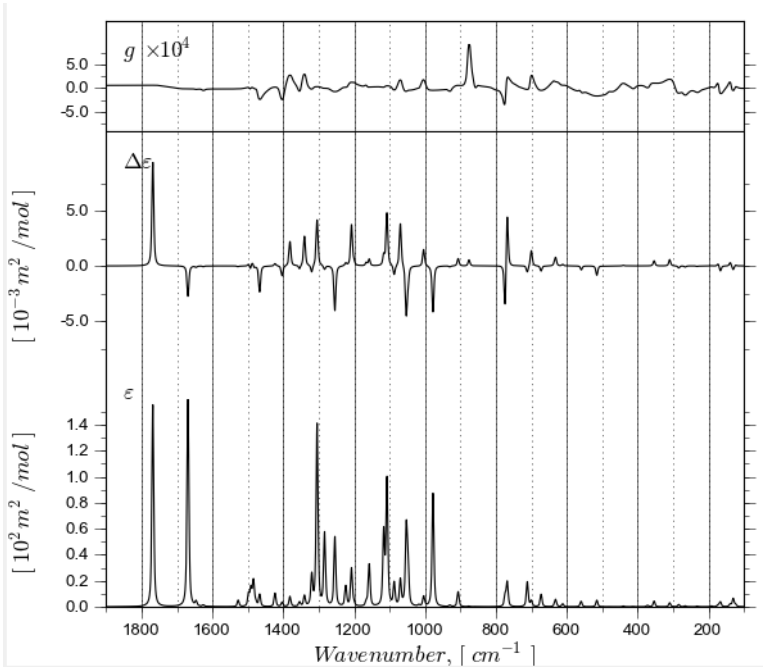
-804.91257708



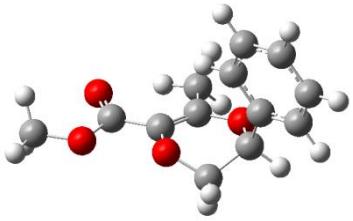


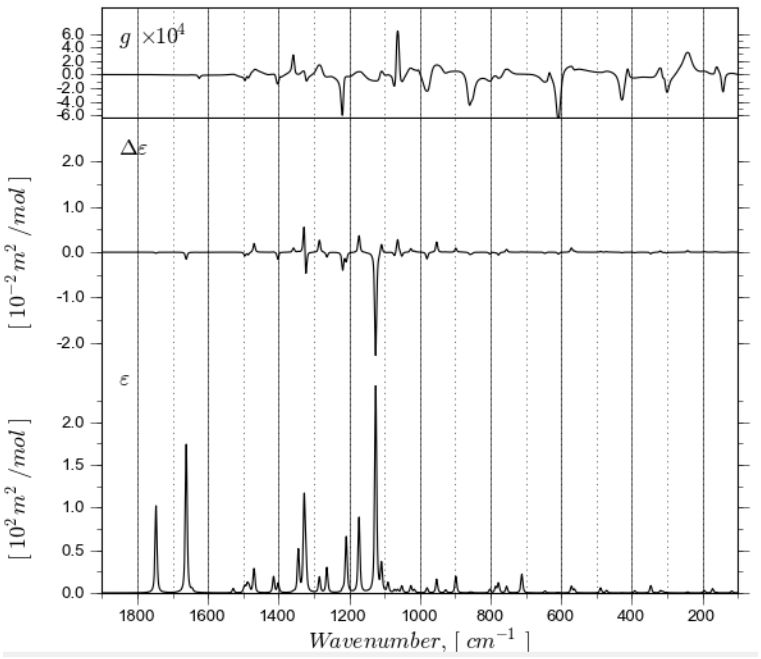
-804.90972465



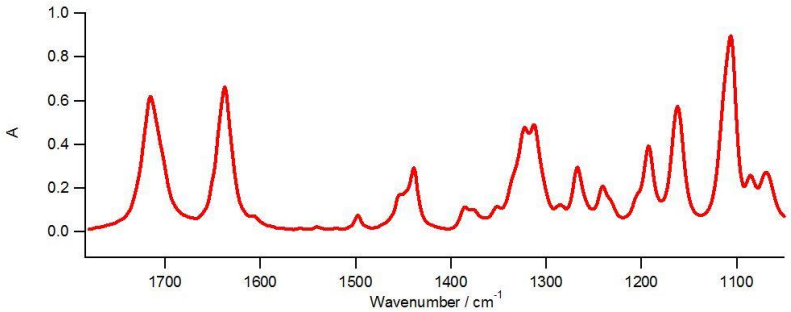


-804.89880503





-804.90893337



7.7 Crystallographic data

The crystals were mounted on kapton loop with protection oil. Cell dimensions and intensities were measured at 180 K on a Agilent Supernova diffractometer with mirror-monochromated Cu[Kα] radiation (λ= 1.54184 Å). Data were corrected for Lorentz and polarization effects and for absorption. The structures were solved by direct methods (SIR97 or ShelXS-97), all other calculation were performed with ShelXl systems and ORTEP3 programs.

7.7.1 Crystallographic data of compound [**3**][PF_6]

Table 7.1 Crystal data and structure refinement for [**3**][PF_6]

Identification code	shelxl	
Empirical formula	$C_{50}\ H_{56}\ F_{12}\ N_6\ O_3\ P_2\ Ru_2$	
Chemical formula moiety	$2(C_{19}\ H_{16}\ N_3\ Ru)$, $3(C_4\ H_8\ O)$, $2(F_6\ P)$	
Formula weight	1281.09	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.9798(4) Å	α= 96.615(3)°.
	b = 12.0916(5) Å	β= 109.000(4)°.
	c = 12.1642(5) Å	γ = 105.987(4)°.
Volume	1299.89(9) $Å^3$	
Z	1	
Density (calculated)	1.637 Mg/m^3	
Absorption coefficient	6.094 mm^{-1}	
F(000)	648	
Crystal size	0.2990 x 0.1859 x 0.0988 mm^3	
Theta range for data collection	3.90 to 73.21°.	
Index ranges	-10<=h<=12, -14<=k<=13, -14<=l<=14	
Reflections collected	8675	
Independent reflections	5074 [R(int) = 0.0215]	
Completeness to theta = 66.97°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.627 and 0.389	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5074 / 13 / 323	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0391, wR2 = 0.1062	
R indices (all data)	R1 = 0.0412, wR2 = 0.1084	
Largest diff. peak and hole	1.294 and -0.641 e.$Å^{-3}$	

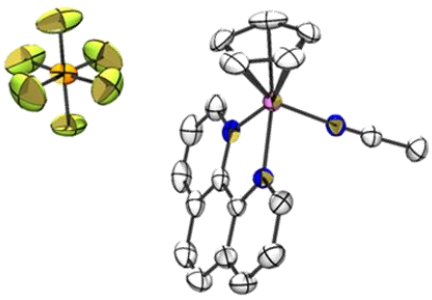


Figure 7.1 ORTEP view of the crystal structure of [**3**][PF_6].
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for [**3**][PF_6]. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ru(1)	3024(1)	1289(1)	4954(1)	30(1)
N(1)	4530(3)	1550(2)	6715(2)	30(1)
N(2)	4805(3)	2804(2)	5126(3)	33(1)
N(3)	2118(3)	2395(2)	5680(3)	34(1)
C(14)	2990(5)	260(4)	3388(4)	64(1)
C(1)	4361(4)	894(3)	7504(3)	38(1)
C(2)	5447(5)	1131(4)	8643(3)	46(1)
C(3)	6754(5)	2081(4)	8997(3)	48(1)
C(4)	6954(4)	2798(3)	8197(3)	41(1)
C(5)	8244(5)	3830(4)	8459(4)	53(1)
C(6)	8365(4)	4486(3)	7656(4)	51(1)
C(7)	7228(4)	4182(3)	6495(4)	42(1)
C(8)	7287(5)	4802(3)	5583(5)	53(1)
C(9)	6154(5)	4410(4)	4505(5)	54(1)
C(10)	4920(5)	3413(4)	4289(4)	45(1)
C(11)	5952(4)	3186(3)	6207(3)	34(1)
C(12)	5809(4)	2499(3)	7068(3)	32(1)
C(13)	2955(5)	-443(4)	4225(4)	56(1)
C(15)	1665(6)	590(4)	3088(4)	63(1)
C(16)	865(4)	67(4)	3764(4)	52(1)
C(17)	1634(5)	-565(3)	4444(4)	52(1)
C(18)	1538(4)	2929(3)	6060(3)	34(1)
C(19)	748(5)	3595(4)	6524(4)	47(1)
P(1)	7912(1)	2546(1)	2678(1)	44(1)
F(1)	8825(5)	1737(4)	3162(4)	110(1)
F(2)	8815(5)	3065(3)	1913(3)	107(2)
F(3)	6881(5)	3325(4)	2243(4)	108(1)
F(4)	6887(4)	2040(3)	3405(3)	86(1)
F(5)	6849(5)	1483(3)	1564(3)	95(1)
F(6)	8944(4)	3624(3)	3781(3)	77(1)
O(1S)	2595(5)	2416(5)	1257(4)	100(1)
C(2SA)	3092(13)	1805(12)	478(9)	82(1)
C(3SA)	2049(13)	1508(12)	-729(10)	82(1)
C(4SA)	833(13)	1959(13)	-695(9)	82(1)
C(5SA)	1052(12)	2280(12)	584(9)	82(1)
C(2SB)	2862(18)	1464(15)	618(13)	82(1)
C(3SB)	1788(17)	1068(16)	-527(14)	82(1)
C(4SB)	557(16)	1505(16)	-489(15)	82(1)
C(5SB)	1259(16)	2570(14)	506(14)	82(1)
O(3)	3523(14)	4360(10)	-1067(11)	115(3)
C(10S)	3680(20)	5050(20)	-38(18)	110(3)
C(11S)	5270(20)	5470(20)	909(17)	110(3)
C(12S)	6030(20)	4800(20)	206(16)	110(3)
C(13S)	5060(20)	4750(20)	-1048(17)	110(3)

Table 7.3 Bond lengths [Å] and angles [°] for [**3**][PF_6].

Ru(1)-N(3)	2.074(3)
Ru(1)-N(1)	2.105(3)
Ru(1)-N(2)	2.106(3)
Ru(1)-C(14)	2.137(4)
Ru(1)-C(15)	2.151(4)
Ru(1)-C(13)	2.152(4)
Ru(1)-C(16)	2.156(4)
Ru(1)-C(17)	2.178(4)
N(1)-C(1)	1.337(4)
N(1)-C(12)	1.361(4)
N(2)-C(10)	1.338(5)
N(2)-C(11)	1.357(5)
N(3)-C(18)	1.129(5)
C(14)-C(13)	1.402(7)
C(14)-C(15)	1.432(8)
C(14)-H(14)	0.9500
C(1)-C(2)	1.392(5)
C(1)-H(1)	0.9500
C(2)-C(3)	1.379(6)
C(2)-H(2)	0.9500
C(3)-C(4)	1.401(6)
C(3)-H(3)	0.9500
C(4)-C(12)	1.400(5)
C(4)-C(5)	1.440(5)
C(5)-C(6)	1.342(7)
C(5)-H(5)	0.9500
C(6)-C(7)	1.423(6)
C(6)-H(6)	0.9500
C(7)-C(11)	1.401(5)
C(7)-C(8)	1.416(6)
C(8)-C(9)	1.349(7)
C(8)-H(8)	0.9500
C(9)-C(10)	1.392(6)
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(11)-C(12)	1.428(5)
C(13)-C(17)	1.400(7)
C(13)-H(13)	0.9500
C(15)-C(16)	1.408(7)
C(15)-H(15)	0.9500
C(16)-C(17)	1.383(7)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(18)-C(19)	1.458(5)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
P(1)-F(1)	1.552(3)
P(1)-F(2)	1.562(3)
P(1)-F(6)	1.587(3)
P(1)-F(3)	1.587(4)
P(1)-F(5)	1.589(3)
P(1)-F(4)	1.604(3)
O(1S)-C(5SB)	1.425(13)
O(1S)-C(2SA)	1.427(10)
O(1S)-C(5SA)	1.441(10)
O(1S)-C(2SB)	1.448(13)
C(2SA)-C(3SA)	1.431(12)
C(2SA)-H(2SA)	0.9900
C(2SA)-H(2SB)	0.9900
C(3SA)-C(4SA)	1.471(12)
C(3SA)-H(3SA)	0.9900
C(3SA)-H(3SB)	0.9900
C(4SA)-C(5SA)	1.488(12)
C(4SA)-H(4SA)	0.9900
C(4SA)-H(4SB)	0.9900
C(5SA)-H(5SA)	0.9900
C(5SA)-H(5SB)	0.9900
C(2SB)-C(3SB)	1.382(15)
C(2SB)-H(2SC)	0.9900
C(2SB)-H(2SD)	0.9900
C(3SB)-C(4SB)	1.477(15)
C(3SB)-H(3SC)	0.9900
C(3SB)-H(3SD)	0.9900
C(4SB)-C(5SB)	1.485(15)
C(4SB)-H(4SC)	0.9900
C(4SB)-H(4SD)	0.9900
C(5SB)-H(5SC)	0.9900
C(5SB)-H(5SD)	0.9900
O(3)-C(10S)	1.36(2)
O(3)-C(13S)	1.46(2)
C(10S)-C(11S)	1.527(17)
C(10S)-H(10A)	0.9900
C(10S)-H(10B)	0.9900
C(11S)-C(12S)	1.603(17)
C(11S)-H(11A)	0.9900
C(11S)-H(11B)	0.9900
C(12S)-C(13S)	1.501(16)
C(12S)-H(12A)	0.9900
C(12S)-H(12B)	0.9900
C(13S)-H(13A)	0.9900
C(13S)-H(13B)	0.9900
N(3)-Ru(1)-N(1)	85.86(11)
N(3)-Ru(1)-N(2)	87.90(11)
N(1)-Ru(1)-N(2)	77.20(11)
N(3)-Ru(1)-C(14)	147.65(18)
N(1)-Ru(1)-C(14)	126.46(18)
N(2)-Ru(1)-C(14)	97.35(15)
N(3)-Ru(1)-C(15)	109.11(17)
N(1)-Ru(1)-C(15)	163.90(16)
N(2)-Ru(1)-C(15)	108.41(16)
C(14)-Ru(1)-C(15)	39.0(2)
N(3)-Ru(1)-C(13)	151.16(16)
N(1)-Ru(1)-C(13)	99.66(14)
N(2)-Ru(1)-C(13)	120.94(15)
C(14)-Ru(1)-C(13)	38.2(2)
C(15)-Ru(1)-C(13)	64.38(18)
N(3)-Ru(1)-C(16)	94.02(13)

N(1)-Ru(1)-C(16)	138.11(16)	N(2)-C(11)-C(12)	116.1(3)
N(2)-Ru(1)-C(16)	144.69(16)	C(7)-C(11)-C(12)	120.2(3)
C(14)-Ru(1)-C(16)	63.79(17)	N(1)-C(12)-C(4)	123.2(3)
C(15)-Ru(1)-C(16)	38.16(19)	N(1)-C(12)-C(11)	116.3(3)
C(13)-Ru(1)-C(16)	63.04(16)	C(4)-C(12)-C(11)	120.5(3)
N(3)-Ru(1)-C(17)	113.48(15)	C(17)-C(13)-C(14)	108.3(4)
N(1)-Ru(1)-C(17)	105.52(14)	C(17)-C(13)-Ru(1)	72.1(2)
N(2)-Ru(1)-C(17)	158.50(15)	C(14)-C(13)-Ru(1)	70.3(2)
C(14)-Ru(1)-C(17)	63.51(18)	C(17)-C(13)-H(13)	125.9
C(15)-Ru(1)-C(17)	63.64(18)	C(14)-C(13)-H(13)	125.9
C(13)-Ru(1)-C(17)	37.73(18)	Ru(1)-C(13)-H(13)	123.3
C(16)-Ru(1)-C(17)	37.21(18)	C(16)-C(15)-C(14)	106.0(4)
C(1)-N(1)-C(12)	117.6(3)	C(16)-C(15)-Ru(1)	71.1(2)
C(1)-N(1)-Ru(1)	127.3(2)	C(14)-C(15)-Ru(1)	70.0(2)
C(12)-N(1)-Ru(1)	115.1(2)	C(16)-C(15)-H(15)	127.0
C(10)-N(2)-C(11)	117.6(3)	C(14)-C(15)-H(15)	127.0
C(10)-N(2)-Ru(1)	127.1(3)	Ru(1)-C(15)-H(15)	123.6
C(11)-N(2)-Ru(1)	115.3(2)	C(17)-C(16)-C(15)	109.8(4)
C(18)-N(3)-Ru(1)	175.1(3)	C(17)-C(16)-Ru(1)	72.3(2)
C(13)-C(14)-C(15)	107.9(4)	C(15)-C(16)-Ru(1)	70.7(2)
C(13)-C(14)-Ru(1)	71.5(2)	C(17)-C(16)-H(16)	125.1
C(15)-C(14)-Ru(1)	71.0(2)	C(15)-C(16)-H(16)	125.1
C(13)-C(14)-H(14)	126.0	Ru(1)-C(16)-H(16)	123.5
C(15)-C(14)-H(14)	126.0	C(16)-C(17)-C(13)	108.0(4)
Ru(1)-C(14)-H(14)	123.1	C(16)-C(17)-Ru(1)	70.5(2)
N(1)-C(1)-C(2)	122.6(3)	C(13)-C(17)-Ru(1)	70.1(2)
N(1)-C(1)-H(1)	118.7	C(16)-C(17)-H(17)	126.0
C(2)-C(1)-H(1)	118.7	C(13)-C(17)-H(17)	126.0
C(3)-C(2)-C(1)	119.8(4)	Ru(1)-C(17)-H(17)	125.0
C(3)-C(2)-H(2)	120.1	N(3)-C(18)-C(19)	178.3(4)
C(1)-C(2)-H(2)	120.1	C(18)-C(19)-H(19A)	109.5
C(2)-C(3)-C(4)	118.9(4)	C(18)-C(19)-H(19B)	109.5
C(2)-C(3)-H(3)	120.5	H(19A)-C(19)-H(19B)	109.5
C(4)-C(3)-H(3)	120.5	C(18)-C(19)-H(19C)	109.5
C(12)-C(4)-C(3)	117.7(3)	H(19A)-C(19)-H(19C)	109.5
C(12)-C(4)-C(5)	117.6(4)	H(19B)-C(19)-H(19C)	109.5
C(3)-C(4)-C(5)	124.7(4)	F(1)-P(1)-F(2)	97.1(3)
C(6)-C(5)-C(4)	121.8(4)	F(1)-P(1)-F(6)	93.0(2)
C(6)-C(5)-H(5)	119.1	F(2)-P(1)-F(6)	91.01(18)
C(4)-C(5)-H(5)	119.1	F(1)-P(1)-F(3)	174.8(3)
C(5)-C(6)-C(7)	121.3(4)	F(2)-P(1)-F(3)	88.1(3)
C(5)-C(6)-H(6)	119.3	F(6)-P(1)-F(3)	87.3(2)
C(7)-C(6)-H(6)	119.3	F(1)-P(1)-F(5)	88.4(2)
C(11)-C(7)-C(8)	116.5(4)	F(2)-P(1)-F(5)	89.17(18)
C(11)-C(7)-C(6)	118.5(4)	F(6)-P(1)-F(5)	178.6(2)
C(8)-C(7)-C(6)	125.0(4)	F(3)-P(1)-F(5)	91.3(2)
C(9)-C(8)-C(7)	119.6(4)	F(1)-P(1)-F(4)	86.8(2)
C(9)-C(8)-H(8)	120.2	F(2)-P(1)-F(4)	175.9(3)
C(7)-C(8)-H(8)	120.2	F(6)-P(1)-F(4)	90.23(18)
C(8)-C(9)-C(10)	120.5(4)	F(3)-P(1)-F(4)	88.0(2)
C(8)-C(9)-H(9)	119.8	F(5)-P(1)-F(4)	89.50(19)
C(10)-C(9)-H(9)	119.8	C(5SB)-O(1S)-C(2SA)	105.7(8)
N(2)-C(10)-C(9)	122.2(4)	C(5SB)-O(1S)-C(5SA)	15.8(10)
N(2)-C(10)-H(10)	118.9	C(2SA)-O(1S)-C(5SA)	106.6(7)
C(9)-C(10)-H(10)	118.9	C(5SB)-O(1S)-C(2SB)	108.6(9)
N(2)-C(11)-C(7)	123.7(3)	C(2SA)-O(1S)-C(2SB)	19.6(8)

C(5SA)-O(1S)-C(2SB)	103.9(8)	C(3SB)-C(4SB)-C(5SB)	106.0(11)
O(1S)-C(2SA)-C(3SA)	110.9(8)	C(3SB)-C(4SB)-H(4SC)	110.5
O(1S)-C(2SA)-H(2SA)	109.5	C(5SB)-C(4SB)-H(4SC)	110.5
C(3SA)-C(2SA)-H(2SA)	109.5	C(3SB)-C(4SB)-H(4SD)	110.5
O(1S)-C(2SA)-H(2SB)	109.5	C(5SB)-C(4SB)-H(4SD)	110.5
C(3SA)-C(2SA)-H(2SB)	109.5	H(4SC)-C(4SB)-H(4SD)	108.7
H(2SA)-C(2SA)-H(2SB)	108.0	O(1S)-C(5SB)-C(4SB)	104.2(10)
C(2SA)-C(3SA)-C(4SA)	105.7(8)	O(1S)-C(5SB)-H(5SC)	110.9
C(2SA)-C(3SA)-H(3SA)	110.6	C(4SB)-C(5SB)-H(5SC)	110.9
C(4SA)-C(3SA)-H(3SA)	110.6	O(1S)-C(5SB)-H(5SD)	110.9
C(2SA)-C(3SA)-H(3SB)	110.6	C(4SB)-C(5SB)-H(5SD)	110.9
C(4SA)-C(3SA)-H(3SB)	110.6	H(5SC)-C(5SB)-H(5SD)	108.9
H(3SA)-C(3SA)-H(3SB)	108.7	C(10S)-O(3)-C(13S)	101.8(15)
C(3SA)-C(4SA)-C(5SA)	106.4(8)	O(3)-C(10S)-C(11S)	113.9(15)
C(3SA)-C(4SA)-H(4SA)	110.4	O(3)-C(10S)-H(10A)	108.8
C(5SA)-C(4SA)-H(4SA)	110.4	C(11S)-C(10S)-H(10A)	108.8
C(3SA)-C(4SA)-H(4SB)	110.4	O(3)-C(10S)-H(10B)	108.8
C(5SA)-C(4SA)-H(4SB)	110.4	C(11S)-C(10S)-H(10B)	108.8
H(4SA)-C(4SA)-H(4SB)	108.6	H(10A)-C(10S)-H(10B)	107.7
O(1S)-C(5SA)-C(4SA)	106.1(8)	C(10S)-C(11S)-C(12S)	98.6(13)
O(1S)-C(5SA)-H(5SA)	110.5	C(10S)-C(11S)-H(11A)	112.0
C(4SA)-C(5SA)-H(5SA)	110.5	C(12S)-C(11S)-H(11A)	112.0
O(1S)-C(5SA)-H(5SB)	110.5	C(10S)-C(11S)-H(11B)	112.0
C(4SA)-C(5SA)-H(5SB)	110.5	C(12S)-C(11S)-H(11B)	112.0
H(5SA)-C(5SA)-H(5SB)	108.7	H(11A)-C(11S)-H(11B)	109.7
C(3SB)-C(2SB)-O(1S)	109.4(10)	C(13S)-C(12S)-C(11S)	98.9(14)
C(3SB)-C(2SB)-H(2SC)	109.8	C(13S)-C(12S)-H(12A)	112.0
O(1S)-C(2SB)-H(2SC)	109.8	C(11S)-C(12S)-H(12A)	112.0
C(3SB)-C(2SB)-H(2SD)	109.8	C(13S)-C(12S)-H(12B)	112.0
O(1S)-C(2SB)-H(2SD)	109.8	C(11S)-C(12S)-H(12B)	112.0
H(2SC)-C(2SB)-H(2SD)	108.2	H(12A)-C(12S)-H(12B)	109.7
C(2SB)-C(3SB)-C(4SB)	105.3(11)	O(3)-C(13S)-C(12S)	104.4(15)
C(2SB)-C(3SB)-H(3SC)	110.7	O(3)-C(13S)-H(13A)	110.9
C(4SB)-C(3SB)-H(3SC)	110.7	C(12S)-C(13S)-H(13A)	110.9
C(2SB)-C(3SB)-H(3SD)	110.7	O(3)-C(13S)-H(13B)	110.9
C(4SB)-C(3SB)-H(3SD)	110.7	C(12S)-C(13S)-H(13B)	110.9
H(3SC)-C(3SB)-H(3SD)	108.8	H(13A)-C(13S)-H(13B)	108.9

7.7.2 Crystallographic data of compound [**3**][BAr_F]

Table 7.4 Crystal data and structure refinement for [**3**][BAr_F]

Identification code	shelxl	
Empirical formula	$C_{51}\ H_{28}\ B\ F_{24}\ N_3\ Ru$	
Formula weight	1250.64	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 13.1001(2) Å	α= 90°.
	b = 12.6405(2) Å	β= 113.0260(10)°.
	c = 33.2285(5) Å	γ = 90°.
Volume	5063.98(13) $Å^3$	
Z	4	
Density (calculated)	1.640 Mg/m^3	
Absorption coefficient	3.682 mm^{-1}	
F(000)	2480	
Crystal size	0.3481 x 0.3057 x 0.2137 mm^3	
Theta range for data collection	2.89 to 73.44°.	
Index ranges	-16<=h<=15, -15<=k<=15, -22<=l<=40	
Reflections collected	21962	
Independent reflections	9973 [R(int) = 0.0322]	
Completeness to theta = 67.00°	100.0 %	
Absorption correction	Analytical	
Max. and min. transmission	0.653 and 0.441	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9973 / 0 / 722	
Goodness-of-fit on F^2	1.443	
Final R indices [I>2sigma(I)]	R1 = 0.0567, wR2 = 0.1696	
R indices (all data)	R1 = 0.0608, wR2 = 0.1751	
Largest diff. peak and hole	1.511 and -1.117 $e.Å^{-3}$	

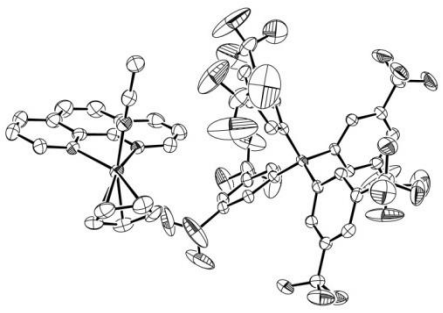


Figure 7.2 ORTEP view of the crystal structure of [**3**][Bar_F].
Thermal ellipsoids are drawn at 50 % probability level.

7.7.3 Crystallographic data of compound [**3**][TRISPHAT-N]

Table 7.5 Crystal data and structure refinement for [**3**][TRISPHAT-N]**.**

Identification code	tra_i_17_corrabs	
Empirical formula	C_{35} H_{17} Cl_{11} N_3 O_6 P Ru	
Formula weight	1097.51	
Temperature	180(2) K	
Wavelength	1.5418 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 15.11619(18) Å	α= 90°.
	b = 18.43420(18) Å	β= 114.7001(14)°.
	c = 15.63521(18) Å	γ = 90°.
Volume	3958.21(8) $Å^3$	
Z	4	
Density (calculated)	1.842 Mg/m^3	
Absorption coefficient	10.866 mm^{-1}	
F(000)	2168	
Crystal size	0.3379 x 0.1287 x 0.0313 mm^3	
Theta range for data collection	3.22 to 74.08°.	
Index ranges	-18<=h<=17, -22<=k<=20, -12<=l<=19	
Reflections collected	16278	
Independent reflections	7836 [R(int) = 0.0884]	
Completeness to theta = 74.08°	97.4 %	
Absorption correction	Analytical	
Max. and min. transmission	0.725 and 0.150	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7836 / 0 / 513	
Goodness-of-fit on F^2	1.353	
Final R indices [I>2sigma(I)]	R1 = 0.0776, wR2 = 0.1928	
R indices (all data)	R1 = 0.0828, wR2 = 0.2020	
Largest diff. peak and hole	3.650 and -2.599 $e.Å^{-3}$	

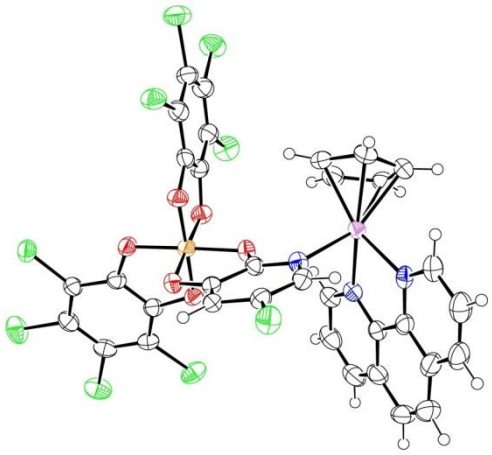


Figure 7.3 ORTEP view of the crystal structure of [**3**][TRISPHAT-N].
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.6 Selected Bond lengths [Å] and angles [°] for [**3**][TRISPHAT-N.

Ru(1)-N(2)	2.087(4)
Ru(1)-N(1)	2.109(4)
Ru(1)-C(5)	2.130(5)
Ru(1)-C(4)	2.144(5)
Ru(1)-N(3)	2.151(4)
Ru(1)-C(2)	2.156(5)
Ru(1)-C(3)	2.161(5)
Ru(1)-C(1)	2.175(5)
P(17)-O(3)	1.707(3)
P(17)-O(5)	1.708(3)
P(17)-O(6)	1.710(3)
P(17)-O(4)	1.714(3)
P(17)-O(2)	1.722(3)
P(17)-O(1)	1.728(3)
N(2)-Ru(1)-N(1)	77.87(16)
N(2)-Ru(1)-C(5)	99.46(18)
N(1)-Ru(1)-C(5)	129.22(19)
N(2)-Ru(1)-C(4)	120.83(18)
N(1)-Ru(1)-C(4)	99.46(18)
C(5)-Ru(1)-C(4)	38.5(2)
N(2)-Ru(1)-N(3)	85.84(15)
N(1)-Ru(1)-N(3)	85.35(14)
C(5)-Ru(1)-N(3)	145.4(2)
C(4)-Ru(1)-N(3)	153.3(2)
N(2)-Ru(1)-C(2)	147.84(18)
N(1)-Ru(1)-C(2)	134.18(19)
C(5)-Ru(1)-C(2)	64.2(2)
C(4)-Ru(1)-C(2)	64.4(2)
N(3)-Ru(1)-C(2)	93.42(18)
N(2)-Ru(1)-C(3)	159.62(18)
N(1)-Ru(1)-C(3)	102.06(19)
C(5)-Ru(1)-C(3)	64.5(2)
C(4)-Ru(1)-C(3)	38.8(2)
N(3)-Ru(1)-C(3)	114.52(19)
C(2)-Ru(1)-C(3)	38.1(2)
N(2)-Ru(1)-C(1)	111.23(19)
N(1)-Ru(1)-C(1)	164.26(19)
C(5)-Ru(1)-C(1)	38.6(2)
C(4)-Ru(1)-C(1)	64.9(2)
N(3)-Ru(1)-C(1)	107.62(18)
C(2)-Ru(1)-C(1)	38.8(2)
C(3)-Ru(1)-C(1)	64.8(2)
O(3)-P(17)-O(5)	87.70(16)
O(3)-P(17)-O(6)	178.60(18)
O(5)-P(17)-O(6)	91.10(16)
O(3)-P(17)-O(4)	91.39(16)
O(5)-P(17)-O(4)	93.99(17)
O(6)-P(17)-O(4)	87.97(17)
O(3)-P(17)-O(2)	92.54(16)
O(5)-P(17)-O(2)	178.14(18)
O(6)-P(17)-O(2)	88.68(17)
O(4)-P(17)-O(2)	87.85(16)
O(3)-P(17)-O(1)	87.83(16)
O(5)-P(17)-O(1)	88.30(16)
O(6)-P(17)-O(1)	92.86(17)
O(4)-P(17)-O(1)	177.55(17)
O(2)-P(17)-O(1)	89.86(16)
C(21)-O(1)-P(17)	111.2(3)
C(22)-O(2)-P(17)	111.1(3)
C(23)-O(3)-P(17)	110.9(3)
C(28)-O(4)-P(17)	111.1(3)
C(29)-O(5)-P(17)	111.4(3)
C(34)-O(6)-P(17)	111.0(3)

7.7.4 Crystallographic data of compound **9e**

Table 7.7 Crystal data and structure refinement for **9e**.

Identification code	shelxl	
Empirical formula	C_{16} H_{20} O_8	
Formula weight	340.32	
Temperature	293(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 18.5685(5) Å	α= 90°.
	b = 6.67667(14) Å	β= 108.928(3)°.
	c = 13.8200(4) Å	γ = 90°.
Volume	1620.70(7) $Å^3$	
Z	4	
Density (calculated)	1.395 Mg/m^3	
Absorption coefficient	0.958 mm^{-1}	
F(000)	720	
Crystal size	0.1957 x 0.1758 x 0.0581 mm^3	
Theta range for data collection	5.04 to 73.15°.	
Index ranges	-22<=h<=21, -8<=k<=8, -15<=l<=16	
Reflections collected	4694	
Independent reflections	1585 [R(int) = 0.0164]	
Completeness to theta = 66.97°	99.6 %	
Absorption correction	Analytical	
Max. and min. transmission	0.949 and 0.865	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1585 / 0 / 111	
Goodness-of-fit on F^2	1.670	
Final R indices [I>2sigma(I)]	R1 = 0.0427, wR2 = 0.1554	
R indices (all data)	R1 = 0.0458, wR2 = 0.1629	
Largest diff. peak and hole	0.246 and -0.162 e.$Å^{-3}$	

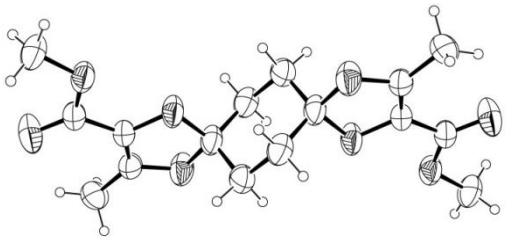


Figure 7.4 ORTEP view of the crystal structure of **9e**.
Thermal ellipsoids are drawn at 50 % probability level.

7.7.5 Crystallographic data of compound **13a**

Table 7.8 Crystal data and structure refinement for **13a**.

Identification code	TRA_V_73_f1	
Empirical formula	C_{18} H_{17} N O_8	
Formula weight	375.33	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.5914(4) Å	α= 83.101(3)°.
	b = 12.7175(5) Å	β= 88.851(3)°.
	c = 16.4484(5) Å	γ = 87.262(3)°.
Volume	1781.95(12) $Å^3$	
Z	4	
Density (calculated)	1.399 Mg/m^3	
Absorption coefficient	0.950 mm^{-1}	
F(000)	784	
Crystal size	0.3096 x 0.2358 x 0.1558 mm^3	
Theta range for data collection	3.50 to 66.59°.	
Index ranges	-8<=h<=10, -14<=k<=15, -19<=l<=19	
Reflections collected	12938	
Independent reflections	6296 [R(int) = 0.0189]	
Completeness to theta = 66.59°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.901 and 0.831	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6296 / 0 / 501	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0740, wR2 = 0.2174	
R indices (all data)	R1 = 0.0855, wR2 = 0.2306	
Largest diff. peak and hole	0.886 and -0.479 $e.Å^{-3}$	

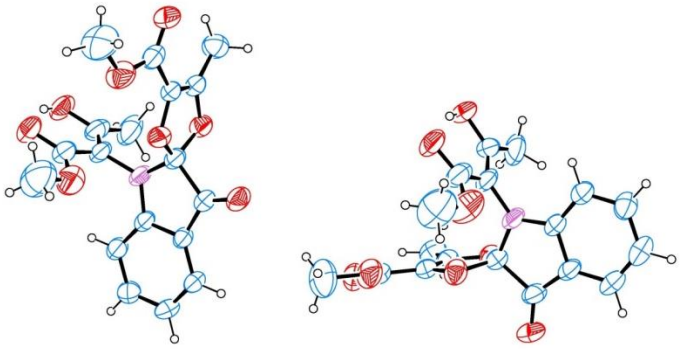


Figure 7.5 ORTEP view of the crystal structure of **13a**.
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.9 Hydrogen bonds for exp_1557_abs [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(26)-H(26)...O(23)	0.85(6)	1.78(6)	2.552(5)	149(6)
O(26B)-H(26B)...O(23B)	0.98(6)	1.63(6)	2.558(5)	157(5)

Symmetry transformations used to generate equivalent atoms:

Table 7.10 Bond lengths [Å] and angles [°] for exp_1557_abs.

O(1)-C(2)	1.200(4)	O(17B)-C(18B)	1.437(5)
O(11)-C(12)	1.384(4)	O(19B)-C(14B)	1.387(4)
O(11)-C(10)	1.434(4)	O(19B)-C(10B)	1.405(4)
O(16)-C(15)	1.206(4)	O(21B)-C(22B)	1.280(5)
O(17)-C(15)	1.329(4)	O(21B)-C(20B)	1.350(7)
O(17)-C(18)	1.444(5)	O(23B)-C(22B)	1.251(4)
O(19)-C(14)	1.389(3)	O(26B)-C(25B)	1.322(4)
O(19)-C(10)	1.410(4)	O(26B)-H(26B)	0.98(6)
O(21)-C(22)	1.305(5)	N(9B)-C(8B)	1.396(4)
O(21)-C(20)	1.358(6)	N(9B)-C(24B)	1.422(4)
O(23)-C(22)	1.258(4)	N(9B)-C(10B)	1.431(4)
O(26)-C(25)	1.316(4)	C(2B)-C(3B)	1.445(5)
O(26)-H(26)	0.85(6)	C(2B)-C(10B)	1.570(4)
N(9)-C(8)	1.392(4)	C(3B)-C(4B)	1.392(4)
N(9)-C(24)	1.424(4)	C(3B)-C(8B)	1.404(4)
N(9)-C(10)	1.429(4)	C(4B)-C(5B)	1.369(5)
C(2)-C(3)	1.454(4)	C(4B)-H(4B)	0.9500
C(2)-C(10)	1.574(4)	C(5B)-C(6B)	1.400(5)
C(3)-C(4)	1.383(4)	C(5B)-H(5B)	0.9500
C(3)-C(8)	1.403(4)	C(6B)-C(7B)	1.382(5)
C(4)-C(5)	1.380(5)	C(6B)-H(6B)	0.9500
C(4)-H(4)	0.9500	C(7B)-C(8B)	1.377(5)
C(5)-C(6)	1.394(5)	C(7B)-H(7B)	0.9500
C(5)-H(5)	0.9500	C(12B)-C(14B)	1.326(4)
C(6)-C(7)	1.387(4)	C(12B)-C(13B)	1.472(5)
C(6)-H(6)	0.9500	C(13B)-H(13D)	0.9800
C(7)-C(8)	1.384(4)	C(13B)-H(13E)	0.9800
C(7)-H(7)	0.9500	C(13B)-H(13F)	0.9800
C(12)-C(14)	1.323(4)	C(14B)-C(15B)	1.460(4)
C(12)-C(13)	1.476(5)	C(18B)-H(18D)	0.9800
C(13)-H(13A)	0.9800	C(18B)-H(18E)	0.9800
C(13)-H(13B)	0.9800	C(18B)-H(18F)	0.9800
C(13)-H(13C)	0.9800	C(20B)-H(20D)	0.9800
C(14)-C(15)	1.464(4)	C(20B)-H(20E)	0.9800
C(18)-H(18A)	0.9800	C(20B)-H(20F)	0.9800
C(18)-H(18B)	0.9800	C(22B)-C(24B)	1.431(6)
C(18)-H(18C)	0.9800	C(24B)-C(25B)	1.370(6)
C(20)-H(20A)	0.9800	C(25B)-C(27B)	1.400(8)
C(20)-H(20B)	0.9800	C(27B)-H(27D)	0.9800
C(20)-H(20C)	0.9800	C(27B)-H(27E)	0.9800
C(22)-C(24)	1.426(6)	C(27B)-H(27F)	0.9800
C(24)-C(25)	1.373(5)	C(12)-O(11)-C(10)	106.9(2)
C(25)-C(27)	1.423(7)	C(15)-O(17)-C(18)	115.3(3)
C(27)-H(27A)	0.9800	C(14)-O(19)-C(10)	106.5(2)
C(27)-H(27B)	0.9800	C(22)-O(21)-C(20)	115.4(4)
C(27)-H(27C)	0.9800	C(25)-O(26)-H(26)	109(4)
O(1B)-C(2B)	1.212(4)	C(8)-N(9)-C(24)	123.9(3)
O(11B)-C(12B)	1.379(4)	C(8)-N(9)-C(10)	110.4(2)
O(11B)-C(10B)	1.432(4)	C(24)-N(9)-C(10)	122.6(2)
O(16B)-C(15B)	1.207(4)	O(1)-C(2)-C(3)	131.8(3)
O(17B)-C(15B)	1.333(4)	O(1)-C(2)-C(10)	122.4(3)

C(3)-C(2)-C(10)	105.8(2)
C(4)-C(3)-C(8)	121.0(3)
C(4)-C(3)-C(2)	131.3(3)
C(8)-C(3)-C(2)	107.8(2)
C(5)-C(4)-C(3)	118.4(3)
C(5)-C(4)-H(4)	120.8
C(3)-C(4)-H(4)	120.8
C(4)-C(5)-C(6)	120.3(3)
C(4)-C(5)-H(5)	119.8
C(6)-C(5)-H(5)	119.8
C(7)-C(6)-C(5)	122.0(3)
C(7)-C(6)-H(6)	119.0
C(5)-C(6)-H(6)	119.0
C(8)-C(7)-C(6)	117.4(3)
C(8)-C(7)-H(7)	121.3
C(6)-C(7)-H(7)	121.3
C(7)-C(8)-N(9)	127.2(3)
C(7)-C(8)-C(3)	120.9(3)
N(9)-C(8)-C(3)	111.9(3)
O(19)-C(10)-N(9)	113.9(3)
O(19)-C(10)-O(11)	105.9(2)
N(9)-C(10)-O(11)	111.9(3)
O(19)-C(10)-C(2)	111.4(2)
N(9)-C(10)-C(2)	104.0(2)
O(11)-C(10)-C(2)	109.8(2)
C(14)-C(12)-O(11)	109.2(3)
C(14)-C(12)-C(13)	133.4(3)
O(11)-C(12)-C(13)	117.4(3)
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(12)-C(14)-O(19)	110.8(2)
C(12)-C(14)-C(15)	129.3(3)
O(19)-C(14)-C(15)	119.8(3)
O(16)-C(15)-O(17)	125.8(3)
O(16)-C(15)-C(14)	123.4(3)
O(17)-C(15)-C(14)	110.7(3)
O(17)-C(18)-H(18A)	109.5
O(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
O(21)-C(20)-H(20A)	109.5
O(21)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
O(21)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
O(23)-C(22)-O(21)	124.5(4)
O(23)-C(22)-C(24)	123.1(4)
O(21)-C(22)-C(24)	112.4(3)
C(25)-C(24)-N(9)	119.1(3)
C(25)-C(24)-C(22)	120.9(3)
N(9)-C(24)-C(22)	120.1(3)
O(26)-C(25)-C(24)	121.2(4)
O(26)-C(25)-C(27)	115.0(4)
C(24)-C(25)-C(27)	123.8(4)
C(25)-C(27)-H(27A)	109.5
C(25)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(25)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(12B)-O(11B)-C(10B)	106.7(2)
C(15B)-O(17B)-C(18B)	115.9(4)
C(14B)-O(19B)-C(10B)	106.5(3)
C(22B)-O(21B)-C(20B)	115.9(4)
C(25B)-O(26B)-H(26B)	102(4)
C(8B)-N(9B)-C(24B)	123.9(3)
C(8B)-N(9B)-C(10B)	110.6(2)
C(24B)-N(9B)-C(10B)	123.6(3)
O(1B)-C(2B)-C(3B)	132.1(3)
O(1B)-C(2B)-C(10B)	121.6(3)
C(3B)-C(2B)-C(10B)	106.3(2)
C(4B)-C(3B)-C(8B)	120.2(3)
C(4B)-C(3B)-C(2B)	131.8(3)
C(8B)-C(3B)-C(2B)	107.9(3)
C(5B)-C(4B)-C(3B)	118.9(3)
C(5B)-C(4B)-H(4B)	120.5
C(3B)-C(4B)-H(4B)	120.5
C(4B)-C(5B)-C(6B)	120.4(3)
C(4B)-C(5B)-H(5B)	119.8
C(6B)-C(5B)-H(5B)	119.8
C(7B)-C(6B)-C(5B)	121.4(3)
C(7B)-C(6B)-H(6B)	119.3
C(5B)-C(6B)-H(6B)	119.3
C(8B)-C(7B)-C(6B)	118.1(3)
C(8B)-C(7B)-H(7B)	120.9
C(6B)-C(7B)-H(7B)	120.9
C(7B)-C(8B)-N(9B)	127.6(3)
C(7B)-C(8B)-C(3B)	120.9(3)
N(9B)-C(8B)-C(3B)	111.4(3)
O(19B)-C(10B)-N(9B)	113.8(3)
O(19B)-C(10B)-O(11B)	106.0(3)
N(9B)-C(10B)-O(11B)	111.2(3)
O(19B)-C(10B)-C(2B)	111.7(3)
N(9B)-C(10B)-C(2B)	103.6(3)
O(11B)-C(10B)-C(2B)	110.6(2)
C(14B)-C(12B)-O(11B)	109.3(3)
C(14B)-C(12B)-C(13B)	133.3(3)
O(11B)-C(12B)-C(13B)	117.4(3)
C(12B)-C(13B)-H(13D)	109.5
C(12B)-C(13B)-H(13E)	109.5
H(13D)-C(13B)-H(13E)	109.5
C(12B)-C(13B)-H(13F)	109.5
H(13D)-C(13B)-H(13F)	109.5
H(13E)-C(13B)-H(13F)	109.5
C(12B)-C(14B)-O(19B)	110.4(3)
C(12B)-C(14B)-C(15B)	129.4(3)
O(19B)-C(14B)-C(15B)	120.2(3)
O(16B)-C(15B)-O(17B)	125.7(3)
O(16B)-C(15B)-C(14B)	123.7(3)
O(17B)-C(15B)-C(14B)	110.6(3)
O(17B)-C(18B)-H(18D)	109.5
O(17B)-C(18B)-H(18E)	109.5
H(18D)-C(18B)-H(18E)	109.5
O(17B)-C(18B)-H(18F)	109.5
H(18D)-C(18B)-H(18F)	109.5
H(18E)-C(18B)-H(18F)	109.5
O(21B)-C(20B)-H(20D)	109.5
O(21B)-C(20B)-H(20E)	109.5
H(20D)-C(20B)-H(20E)	109.5
O(21B)-C(20B)-H(20F)	109.5
H(20D)-C(20B)-H(20F)	109.5
H(20E)-C(20B)-H(20F)	109.5

O(23B)-C(22B)-O(21B)	124.1(4)
O(23B)-C(22B)-C(24B)	124.0(4)
O(21B)-C(22B)-C(24B)	111.8(3)
C(25B)-C(24B)-N(9B)	119.6(4)
C(25B)-C(24B)-C(22B)	121.0(3)
N(9B)-C(24B)-C(22B)	119.4(4)
O(26B)-C(25B)-C(24B)	120.3(4)
O(26B)-C(25B)-C(27B)	115.5(4)
C(24B)-C(25B)-C(27B)	124.3(4)
C(25B)-C(27B)-H(27D)	109.5
C(25B)-C(27B)-H(27E)	109.5
H(27D)-C(27B)-H(27E)	109.5
C(25B)-C(27B)-H(27F)	109.5
H(27D)-C(27B)-H(27F)	109.5
H(27E)-C(27B)-H(27F)	109.5

7.7.6 Crystallographic data of compound **18g**

Table 7.11 Crystal data and structure refinement for **18g**.

Identification code	shelxl	
Empirical formula	$C_{14}\ H_{15}\ Cl\ O_4$	
Formula weight	282.71	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Diffractometer	Supernova	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 15.4195(4) Å	α= 90°.
	b = 6.10154(11) Å	β= 90°.
	c = 28.9632(5) Å	γ = 90°.
Volume	2724.93(9) $Å^3$	
Z	8	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	2.561 mm^{-1}	
F(000)	1184	
Crystal size	0.2493 x 0.1438 x 0.0724 mm^3	
Theta range for data collection	3.05 to 73.33°.	
Index ranges	-12<=h<=18, -7<=k<=4, -35<=l<=34	
Reflections collected	6305	
Independent reflections	2660 [R(int) = 0.0173]	
Completeness to theta = 66.97°	99.8 %	
Absorption correction	Analytical	
Max. and min. transmission	0.850 and 0.656	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2660 / 0 / 173	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.1066	
R indices (all data)	R1 = 0.0431, wR2 = 0.1120	
Largest diff. peak and hole	0.261 and -0.266 $e.Å^{-3}$	

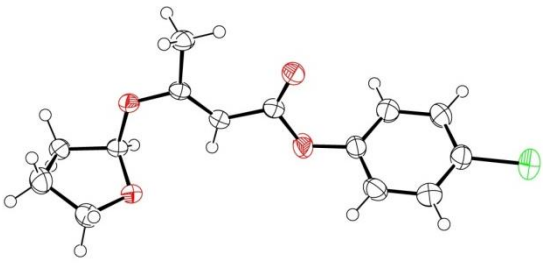


Figure 7.6 ORTEP view of the crystal structure of **18g**.
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.12 Bond lengths [Å] and angles [°] for **18g**.

Cl(1)-C(2)	1.7463(18)
O(8)-C(9)	1.3737(19)
O(8)-C(5)	1.4020(19)
O(10)-C(9)	1.1984(19)
O(14)-C(12)	1.3597(17)
O(14)-C(15)	1.4445(16)
O(16)-C(15)	1.3991(17)
O(16)-C(17)	1.4409(19)
C(2)-C(7)	1.375(3)
C(2)-C(3)	1.377(3)
C(3)-C(4)	1.388(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.375(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.375(3)
C(6)-C(7)	1.389(2)
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
C(9)-C(11)	1.459(2)
C(11)-C(12)	1.342(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.4910(19)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(15)-C(19)	1.513(2)
C(15)-H(15)	1.0000
C(17)-C(18)	1.505(3)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.525(2)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(9)-O(8)-C(5)	118.28(12)
C(12)-O(14)-C(15)	119.41(11)
C(15)-O(16)-C(17)	109.62(12)
C(7)-C(2)-C(3)	121.75(17)
C(7)-C(2)-Cl(1)	118.79(14)
C(3)-C(2)-Cl(1)	119.45(14)
C(2)-C(3)-C(4)	119.07(16)
C(2)-C(3)-H(3)	120.5
C(4)-C(3)-H(3)	120.5
C(5)-C(4)-C(3)	119.30(16)
C(5)-C(4)-H(4)	120.4
C(3)-C(4)-H(4)	120.4
C(4)-C(5)-C(6)	121.50(16)
C(4)-C(5)-O(8)	121.41(16)
C(6)-C(5)-O(8)	116.97(15)
C(5)-C(6)-C(7)	119.38(16)
C(5)-C(6)-H(6)	120.3
C(7)-C(6)-H(6)	120.3
C(2)-C(7)-C(6)	118.99(17)
C(2)-C(7)-H(7)	120.5
C(6)-C(7)-H(7)	120.5
O(10)-C(9)-O(8)	121.57(14)
O(10)-C(9)-C(11)	129.76(14)
O(8)-C(9)-C(11)	108.64(12)
C(12)-C(11)-C(9)	123.31(13)
C(12)-C(11)-H(11)	118.3
C(9)-C(11)-H(11)	118.3
C(11)-C(12)-O(14)	123.68(12)
C(11)-C(12)-C(13)	127.15(14)
O(14)-C(12)-C(13)	109.16(12)
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
O(16)-C(15)-O(14)	111.17(11)
O(16)-C(15)-C(19)	106.80(12)
O(14)-C(15)-C(19)	106.64(11)
O(16)-C(15)-H(15)	110.7
O(14)-C(15)-H(15)	110.7
C(19)-C(15)-H(15)	110.7
O(16)-C(17)-C(18)	107.53(13)
O(16)-C(17)-H(17A)	110.2
C(18)-C(17)-H(17A)	110.2
O(16)-C(17)-H(17B)	110.2
C(18)-C(17)-H(17B)	110.2
H(17A)-C(17)-H(17B)	108.5
C(17)-C(18)-C(19)	103.91(14)
C(17)-C(18)-H(18A)	111.0
C(19)-C(18)-H(18A)	111.0
C(17)-C(18)-H(18B)	111.0
C(19)-C(18)-H(18B)	111.0
H(18A)-C(18)-H(18B)	109.0
C(15)-C(19)-C(18)	102.46(13)
C(15)-C(19)-H(19A)	111.3
C(18)-C(19)-H(19A)	111.3
C(15)-C(19)-H(19B)	111.3
C(18)-C(19)-H(19B)	111.3
H(19A)-C(19)-H(19B)	109.2

7.7.7 Crystallographic data of compound **42aA**

Table 7.13 Crystal data and structure refinement for **42aA.**

Identification code	shelxl	
Empirical formula	$C_{13}H_{14}O_4$	
Formula weight	234.24	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C 2	
Unit cell dimensions	a = 23.8629(7) Å	α= 90°.
	b = 5.02130(9) Å	β= 117.630(4)°.
	c = 22.5822(7) Å	γ = 90°.
Volume	2397.28(11) $Å^3$	
Z	8	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.799 mm^{-1}	
F(000)	992	
Crystal size	0.5616 x 0.0697 x 0.0560 mm^3	
Theta range for data collection	3.71 to 72.44°.	
Index ranges	-19<=h<=29, -6<=k<=5, -27<=l<=27	
Reflections collected	8872	
Independent reflections	4555 [R(int) = 0.0197]	
Completeness to theta = 67.50°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.961 and 0.810	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4555 / 1 / 312	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0477, wR2 = 0.1309	
R indices (all data)	R1 = 0.0526, wR2 = 0.1364	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.791 and -0.271 $e.Å^{-3}$	

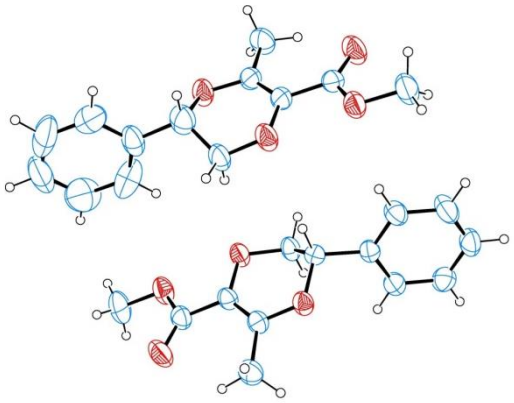


Figure 7.7 ORTEP view of the crystal structure of **42aA**.
Thermal ellipsoids are drawn at 50 % probability level.

Comments:
There are two independent molecules in the asymmetric unit. Absolute structure configuration is C7 S and C7B S.

Table 7.14 Bond lengths [Å] and angles [°] for **42aA**.

O(1)-C(10)	1.369(3)
O(1)-C(7)	1.445(2)
O(2)-C(9)	1.383(2)
O(2)-C(8)	1.433(2)
O(3)-C(12)	1.338(3)
O(3)-C(13)	1.448(3)
O(4)-C(12)	1.208(3)
C(1)-C(6)	1.384(3)
C(1)-C(2)	1.389(3)
C(1)-H(1)	0.9500
C(2)-C(3)	1.373(4)
C(2)-H(2)	0.9500
C(3)-C(4)	1.378(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.388(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.383(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.514(3)
C(7)-C(8)	1.512(3)
C(7)-H(7)	1.0000
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.345(3)
C(9)-C(12)	1.467(3)
C(10)-C(11)	1.500(3)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
O(1B)-C(10B)	1.362(3)
O(1B)-C(7B)	1.476(3)
O(2B)-C(9B)	1.385(3)
O(2B)-C(8B)	1.400(3)
O(3B)-C(12B)	1.337(3)
O(3B)-C(13B)	1.445(3)
O(4B)-C(12B)	1.205(3)
C(1B)-C(6B)	1.357(5)
C(1B)-C(2B)	1.363(5)
C(1B)-H(1B)	0.9500
C(2B)-C(3B)	1.370(6)
C(2B)-H(2B)	0.9500
C(3B)-C(4B)	1.327(7)
C(3B)-H(3B)	0.9500
C(4B)-C(5B)	1.348(6)
C(4B)-H(4B)	0.9500
C(5B)-C(6B)	1.371(5)
C(5B)-H(5B)	0.9500
C(6B)-C(7B)	1.517(4)
C(7B)-C(8B)	1.455(4)
C(7B)-H(7B)	1.0000
C(8B)-H(8BA)	0.9900
C(8B)-H(8BB)	0.9900
C(9B)-C(10B)	1.347(4)
C(9B)-C(12B)	1.469(3)
C(10B)-C(11B)	1.480(3)
C(11B)-H(11D)	0.9800
C(11B)-H(11E)	0.9800
C(11B)-H(11F)	0.9800
C(13B)-H(13D)	0.9800
C(13B)-H(13E)	0.9800
C(13B)-H(13F)	0.9800
C(10)-O(1)-C(7)	117.12(16)
C(9)-O(2)-C(8)	111.59(16)
C(12)-O(3)-C(13)	115.0(2)
C(6)-C(1)-C(2)	120.7(2)
C(6)-C(1)-H(1)	119.6
C(2)-C(1)-H(1)	119.6
C(3)-C(2)-C(1)	120.1(2)
C(3)-C(2)-H(2)	119.9
C(1)-C(2)-H(2)	119.9
C(2)-C(3)-C(4)	119.5(2)
C(2)-C(3)-H(3)	120.3
C(4)-C(3)-H(3)	120.3
C(3)-C(4)-C(5)	120.7(2)
C(3)-C(4)-H(4)	119.7
C(5)-C(4)-H(4)	119.7
C(6)-C(5)-C(4)	120.1(2)
C(6)-C(5)-H(5)	119.9
C(4)-C(5)-H(5)	119.9
C(5)-C(6)-C(1)	118.9(2)
C(5)-C(6)-C(7)	120.36(19)
C(1)-C(6)-C(7)	120.72(19)
O(1)-C(7)-C(8)	109.31(17)
O(1)-C(7)-C(6)	107.65(15)
C(8)-C(7)-C(6)	111.54(17)
O(1)-C(7)-H(7)	109.4
C(8)-C(7)-H(7)	109.4
C(6)-C(7)-H(7)	109.4
O(2)-C(8)-C(7)	110.01(17)
O(2)-C(8)-H(8A)	109.7
C(7)-C(8)-H(8A)	109.7
O(2)-C(8)-H(8B)	109.7
C(7)-C(8)-H(8B)	109.7
H(8A)-C(8)-H(8B)	108.2
C(10)-C(9)-O(2)	121.68(19)
C(10)-C(9)-C(12)	124.1(2)
O(2)-C(9)-C(12)	114.17(19)
C(9)-C(10)-O(1)	122.47(19)
C(9)-C(10)-C(11)	128.1(2)
O(1)-C(10)-C(11)	109.4(2)
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
O(4)-C(12)-O(3)	122.7(2)
O(4)-C(12)-C(9)	125.9(2)
O(3)-C(12)-C(9)	111.43(19)
O(3)-C(13)-H(13A)	109.5
O(3)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(3)-C(13)-H(13C)	109.5

H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(10B)-O(1B)-C(7B)	113.6(2)
C(9B)-O(2B)-C(8B)	113.05(19)
C(12B)-O(3B)-C(13B)	115.65(19)
C(6B)-C(1B)-C(2B)	120.0(3)
C(6B)-C(1B)-H(1B)	120.0
C(2B)-C(1B)-H(1B)	120.0
C(1B)-C(2B)-C(3B)	120.8(4)
C(1B)-C(2B)-H(2B)	119.6
C(3B)-C(2B)-H(2B)	119.6
C(4B)-C(3B)-C(2B)	118.6(3)
C(4B)-C(3B)-H(3B)	120.7
C(2B)-C(3B)-H(3B)	120.7
C(3B)-C(4B)-C(5B)	121.4(4)
C(3B)-C(4B)-H(4B)	119.3
C(5B)-C(4B)-H(4B)	119.3
C(4B)-C(5B)-C(6B)	120.9(4)
C(4B)-C(5B)-H(5B)	119.6
C(6B)-C(5B)-H(5B)	119.6
C(1B)-C(6B)-C(5B)	118.2(3)
C(1B)-C(6B)-C(7B)	125.5(3)
C(5B)-C(6B)-C(7B)	116.3(3)
C(8B)-C(7B)-O(1B)	107.4(2)
C(8B)-C(7B)-C(6B)	114.6(2)
O(1B)-C(7B)-C(6B)	106.8(2)
C(8B)-C(7B)-H(7B)	109.3
O(1B)-C(7B)-H(7B)	109.3
C(6B)-C(7B)-H(7B)	109.3
O(2B)-C(8B)-C(7B)	114.1(2)
O(2B)-C(8B)-H(8BA)	108.7
C(7B)-C(8B)-H(8BA)	108.7
O(2B)-C(8B)-H(8BB)	108.7
C(7B)-C(8B)-H(8BB)	108.7
H(8BA)-C(8B)-H(8BB)	107.6
C(10B)-C(9B)-O(2B)	122.5(2)
C(10B)-C(9B)-C(12B)	124.7(2)
O(2B)-C(9B)-C(12B)	112.8(2)
C(9B)-C(10B)-O(1B)	122.19(19)
C(9B)-C(10B)-C(11B)	127.3(2)
O(1B)-C(10B)-C(11B)	110.5(2)
C(10B)-C(11B)-H(11D)	109.5
C(10B)-C(11B)-H(11E)	109.5
H(11D)-C(11B)-H(11E)	109.5
C(10B)-C(11B)-H(11F)	109.5
H(11D)-C(11B)-H(11F)	109.5
H(11E)-C(11B)-H(11F)	109.5
O(4B)-C(12B)-O(3B)	122.3(2)
O(4B)-C(12B)-C(9B)	126.2(2)
O(3B)-C(12B)-C(9B)	111.49(19)
O(3B)-C(13B)-H(13D)	109.5
O(3B)-C(13B)-H(13E)	109.5
H(13D)-C(13B)-H(13E)	109.5
O(3B)-C(13B)-H(13F)	109.5
H(13D)-C(13B)-H(13F)	109.5
H(13E)-C(13B)-H(13F)	109.5

7.7.8 Crystallographic data of compound **42aC**

Table 7.15 Crystal data and structure refinement for **42aC**.

Identification code	shelxl	
Empirical formula	C_{13} H_{20} O_4	
Formula weight	240.29	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 17.4365(4) Å	α= 90°.
	b = 6.75102(12) Å	β= 90°.
	c = 21.4377(5) Å	γ = 90°.
Volume	2523.52(9) $Å^3$	
Z	8	
Density (calculated)	1.265 Mg/m^3	
Absorption coefficient	0.760 mm^{-1}	
F(000)	1040	
Crystal size	0.3349 x 0.1764 x 0.0623 mm^3	
Theta range for data collection	4.12 to 73.62°.	
Index ranges	-16<=h<=21, -6<=k<=8, -23<=l<=26	
Reflections collected	7926	
Independent reflections	4257 [R(int) = 0.0257]	
Completeness to theta = 66.97°	99.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.959 and 0.883	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4257 / 1 / 312	
Goodness-of-fit on F^2	1.210	
Final R indices [I>2sigma(I)]	R1 = 0.0834, wR2 = 0.2059	
R indices (all data)	R1 = 0.0864, wR2 = 0.2091	
Absolute structure parameter	0.3(4)	
Largest diff. peak and hole	0.745 and -0.358 e.$Å^{-3}$	

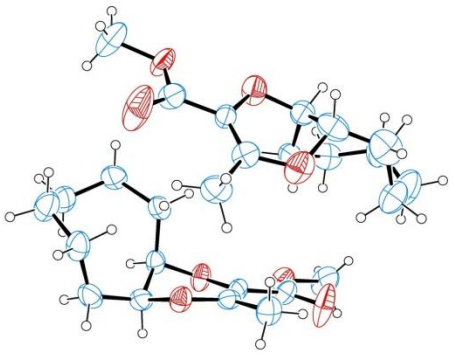


Figure 7.8 ORTEP view of the crystal structure of **42aC**.
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.16 Bond lengths [Å] and angles [°] for integ2_abs.

O(2)-C(3)	1.345(6)
O(2)-C(1)	1.445(7)
O(4)-C(3)	1.208(7)
O(6)-C(5)	1.392(5)
O(6)-C(7)	1.439(6)
O(15)-C(16)	1.380(6)
O(15)-C(14)	1.506(6)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(3)-C(5)	1.448(7)
C(5)-C(16)	1.331(6)
C(7)-C(8)	1.481(8)
C(7)-C(14)	1.524(7)
C(7)-H(7)	1.0000
C(8)-C(9)	1.634(9)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.480(9)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.464(9)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.540(9)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.540(9)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.446(10)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14)	1.0000
C(16)-C(17)	1.473(6)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
O(2B)-C(3B)	1.327(5)
O(2B)-C(1B)	1.421(6)
O(4B)-C(3B)	1.193(6)
O(6B)-C(5B)	1.385(5)
O(6B)-C(7B)	1.434(5)
O(15B)-C(16B)	1.351(6)
O(15B)-C(14B)	1.460(5)
C(1B)-H(1BA)	0.9800
C(1B)-H(1BB)	0.9800
C(1B)-H(1BC)	0.9800
C(3B)-C(5B)	1.476(6)
C(5B)-C(16B)	1.364(6)
C(7B)-C(14B)	1.526(5)
C(7B)-C(8B)	1.531(6)
C(7B)-H(7B)	1.0000
C(8B)-C(9B)	1.540(7)
C(8B)-H(8BA)	0.9900
C(8B)-H(8BB)	0.9900
C(9B)-C(10B)	1.511(7)
C(9B)-H(9BA)	0.9900
C(9B)-H(9BB)	0.9900
C(10B)-C(11B)	1.530(7)
C(10B)-H(10C)	0.9900
C(10B)-H(10D)	0.9900
C(11B)-C(12B)	1.542(7)
C(11B)-H(11C)	0.9900
C(11B)-H(11D)	0.9900
C(12B)-C(13B)	1.535(7)
C(12B)-H(12C)	0.9900
C(12B)-H(12D)	0.9900
C(13B)-C(14B)	1.502(7)
C(13B)-H(13C)	0.9900
C(13B)-H(13D)	0.9900
C(14B)-H(14B)	1.0000
C(16B)-C(17B)	1.504(5)
C(17B)-H(17D)	0.9800
C(17B)-H(17E)	0.9800
C(17B)-H(17F)	0.9800
C(3)-O(2)-C(1)	116.0(5)
C(5)-O(6)-C(7)	115.8(3)
C(16)-O(15)-C(14)	116.3(4)
O(2)-C(1)-H(1A)	109.5
O(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(4)-C(3)-O(2)	122.0(5)
O(4)-C(3)-C(5)	125.6(5)
O(2)-C(3)-C(5)	112.4(4)
C(16)-C(5)-O(6)	123.7(4)
C(16)-C(5)-C(3)	124.8(4)
O(6)-C(5)-C(3)	111.4(3)
O(6)-C(7)-C(8)	106.5(4)
O(6)-C(7)-C(14)	108.0(4)
C(8)-C(7)-C(14)	115.7(4)
O(6)-C(7)-H(7)	108.8
C(8)-C(7)-H(7)	108.8
C(14)-C(7)-H(7)	108.8
C(7)-C(8)-C(9)	111.9(4)
C(7)-C(8)-H(8A)	109.2
C(9)-C(8)-H(8A)	109.2
C(7)-C(8)-H(8B)	109.2
C(9)-C(8)-H(8B)	109.2
H(8A)-C(8)-H(8B)	107.9
C(10)-C(9)-C(8)	116.0(4)
C(10)-C(9)-H(9A)	108.3
C(8)-C(9)-H(9A)	108.3
C(10)-C(9)-H(9B)	108.3
C(8)-C(9)-H(9B)	108.3
H(9A)-C(9)-H(9B)	107.4
C(11)-C(10)-C(9)	117.1(6)
C(11)-C(10)-H(10A)	108.0
C(9)-C(10)-H(10A)	108.0
C(11)-C(10)-H(10B)	108.0
C(9)-C(10)-H(10B)	108.0
H(10A)-C(10)-H(10B)	107.3
C(10)-C(11)-C(12)	118.3(6)
C(10)-C(11)-H(11A)	107.7
C(12)-C(11)-H(11A)	107.7
C(10)-C(11)-H(11B)	107.7
C(12)-C(11)-H(11B)	107.7
H(11A)-C(11)-H(11B)	107.1
C(11)-C(12)-C(13)	115.5(6)
C(11)-C(12)-H(12A)	108.4
C(13)-C(12)-H(12A)	108.4

C(11)-C(12)-H(12B)	108.4
C(13)-C(12)-H(12B)	108.4
H(12A)-C(12)-H(12B)	107.5
C(14)-C(13)-C(12)	119.2(5)
C(14)-C(13)-H(13A)	107.5
C(12)-C(13)-H(13A)	107.5
C(14)-C(13)-H(13B)	107.5
C(12)-C(13)-H(13B)	107.5
H(13A)-C(13)-H(13B)	107.0
C(13)-C(14)-O(15)	108.9(5)
C(13)-C(14)-C(7)	119.2(5)
O(15)-C(14)-C(7)	106.1(4)
C(13)-C(14)-H(14)	107.4
O(15)-C(14)-H(14)	107.4
C(7)-C(14)-H(14)	107.4
C(5)-C(16)-O(15)	119.6(4)
C(5)-C(16)-C(17)	127.3(5)
O(15)-C(16)-C(17)	113.1(4)
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(3B)-O(2B)-C(1B)	116.0(4)
C(5B)-O(6B)-C(7B)	114.6(3)
C(16B)-O(15B)-C(14B)	115.3(3)
O(2B)-C(1B)-H(1BA)	109.5
O(2B)-C(1B)-H(1BB)	109.5
H(1BA)-C(1B)-H(1BB)	109.5
O(2B)-C(1B)-H(1BC)	109.5
H(1BA)-C(1B)-H(1BC)	109.5
H(1BB)-C(1B)-H(1BC)	109.5
O(4B)-C(3B)-O(2B)	122.9(4)
O(4B)-C(3B)-C(5B)	125.6(4)
O(2B)-C(3B)-C(5B)	111.5(4)
C(16B)-C(5B)-O(6B)	121.8(4)
C(16B)-C(5B)-C(3B)	124.3(4)
O(6B)-C(5B)-C(3B)	113.9(3)
O(6B)-C(7B)-C(14B)	107.5(3)
O(6B)-C(7B)-C(8B)	110.3(3)
C(14B)-C(7B)-C(8B)	115.9(3)
O(6B)-C(7B)-H(7B)	107.6
C(14B)-C(7B)-H(7B)	107.6
C(8B)-C(7B)-H(7B)	107.6
C(7B)-C(8B)-C(9B)	113.5(3)
C(7B)-C(8B)-H(8BA)	108.9
C(9B)-C(8B)-H(8BA)	108.9
C(7B)-C(8B)-H(8BB)	108.9
C(9B)-C(8B)-H(8BB)	108.9
H(8BA)-C(8B)-H(8BB)	107.7
C(10B)-C(9B)-C(8B)	117.0(4)
C(10B)-C(9B)-H(9BA)	108.1
C(8B)-C(9B)-H(9BA)	108.1
C(10B)-C(9B)-H(9BB)	108.1
C(8B)-C(9B)-H(9BB)	108.1
H(9BA)-C(9B)-H(9BB)	107.3
C(9B)-C(10B)-C(11B)	115.8(5)
C(9B)-C(10B)-H(10C)	108.3
C(11B)-C(10B)-H(10C)	108.3
C(9B)-C(10B)-H(10D)	108.3
C(11B)-C(10B)-H(10D)	108.3
H(10C)-C(10B)-H(10D)	107.4
C(10B)-C(11B)-C(12B)	116.2(5)
C(10B)-C(11B)-H(11C)	108.2
C(12B)-C(11B)-H(11C)	108.2
C(10B)-C(11B)-H(11D)	108.2
C(12B)-C(11B)-H(11D)	108.2
H(11C)-C(11B)-H(11D)	107.4
C(13B)-C(12B)-C(11B)	115.5(4)
C(13B)-C(12B)-H(12C)	108.4
C(11B)-C(12B)-H(12C)	108.4
C(13B)-C(12B)-H(12D)	108.4
C(11B)-C(12B)-H(12D)	108.4
H(12C)-C(12B)-H(12D)	107.5
C(14B)-C(13B)-C(12B)	117.8(4)
C(14B)-C(13B)-H(13C)	107.8
C(12B)-C(13B)-H(13C)	107.8
C(14B)-C(13B)-H(13D)	107.8
C(12B)-C(13B)-H(13D)	107.8
H(13C)-C(13B)-H(13D)	107.2
O(15B)-C(14B)-C(13B)	106.8(4)
O(15B)-C(14B)-C(7B)	108.0(3)
C(13B)-C(14B)-C(7B)	119.9(4)
O(15B)-C(14B)-H(14B)	107.2
C(13B)-C(14B)-H(14B)	107.2
C(7B)-C(14B)-H(14B)	107.2
O(15B)-C(16B)-C(5B)	121.7(4)
O(15B)-C(16B)-C(17B)	111.4(4)
C(5B)-C(16B)-C(17B)	126.9(4)
C(16B)-C(17B)-H(17D)	109.5
C(16B)-C(17B)-H(17E)	109.5
H(17D)-C(17B)-H(17E)	109.5
C(16B)-C(17B)-H(17F)	109.5
H(17D)-C(17B)-H(17F)	109.5
H(17E)-C(17B)-H(17F)	109.5

7.7.9 Crystallographic data for compound **42aG**

Table 7.17 Crystal data and structure refinement for **42aG.**

Identification code	shelxl	
Empirical formula	C_{12} H_{16} O_4	
Formula weight	224.25	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	*P b c a*	
Unit cell dimensions	a = 12.79235(15) Å	α= 90°.
	b = 9.46091(13) Å	β= 90°.
	c = 18.0888(2) Å	γ = 90°.
Volume	2189.24(5) $Å^3$	
Z	8	
Density (calculated)	1.361 Mg/m^3	
Absorption coefficient	0.842 mm^{-1}	
F(000)	960	
Crystal size	0.6913 x 0.4597 x 0.2000 mm^3	
Theta range for data collection	4.89 to 70.06°.	
Index ranges	-14<=h<=15, -8<=k<=11, -18<=l<=21	
Reflections collected	7107	
Independent reflections	2050 [R(int) = 0.0134]	
Completeness to theta = 67.50°	99.5 %	
Absorption correction	Analytical	
Max. and min. transmission	0.859 and 0.722	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2050 / 0 / 147	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0349, wR2 = 0.0887	
R indices (all data)	R1 = 0.0366, wR2 = 0.0900	
Largest diff. peak and hole	0.230 and -0.168 e.$Å^{-3}$	

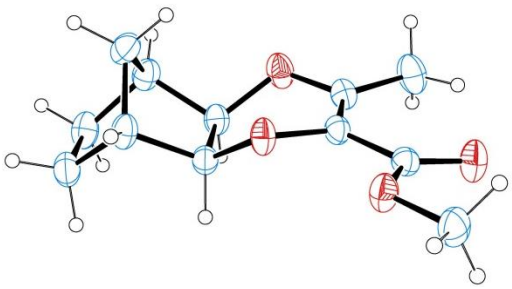


Figure 7.9 ORTEP view of the crystal structure of **42aG**.
Thermal ellipsoids are drawn at 50 % probability level.

7.7.10 Crystallographic data of compound **42eH**

Table 7.18 Crystal data and structure refinement for **42eH**.

Identification code	tra_III_19	
Empirical formula	$C_{15}H_{18}O_4$	
Formula weight	262.29	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 9.53149(19) Å	α= 90°.
	b = 16.5134(3) Å	β= 96.8764(17)°.
	c = 8.44995(15) Å	γ = 90°.
Volume	1320.43(4) $Å^3$	
Z	4	
Density (calculated)	1.319 Mg/m^3	
Absorption coefficient	0.780 mm^{-1}	
F(000)	560	
Crystal size	0.2024 x 0.1579 x 0.1256 mm^3	
Theta range for data collection	4.67 to 72.99°.	
Index ranges	-11<=h<=10, -20<=k<=20, -10<=l<=8	
Reflections collected	9762	
Independent reflections	2608 [R(int) = 0.0223]	
Completeness to theta = 66.97°	100.0 %	
Absorption correction	Analytical	
Max. and min. transmission	0.944 and 0.907	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2608 / 0 / 175	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2sigma(I)]	R1 = 0.0392, wR2 = 0.1141	
R indices (all data)	R1 = 0.0426, wR2 = 0.1182	
Largest diff. peak and hole	0.305 and -0.166 e.$Å^{-3}$	

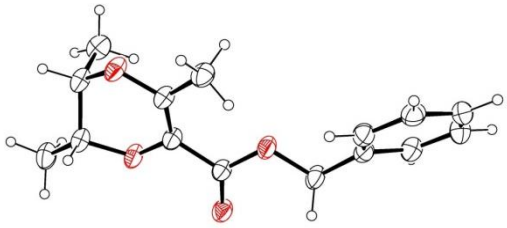


Figure 7.10 ORTEP view of the crystal structure of **42eH**.
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.19 Bond lengths [Å] and angles [°] for **42eH**.

O(8)-C(9)	1.3489(14)
O(8)-C(7)	1.4531(14)
O(10)-C(9)	1.2047(15)
O(13)-C(12)	1.3706(14)
O(13)-C(14)	1.4498(14)
O(16)-C(11)	1.3826(14)
O(16)-C(15)	1.4410(13)
C(1)-C(2)	1.3887(17)
C(1)-C(6)	1.3938(17)
C(1)-H(1)	0.9500
C(2)-C(3)	1.3875(19)
C(2)-H(2)	0.9500
C(3)-C(4)	1.383(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.3900(18)
C(4)-H(4)	0.9500
C(5)-C(6)	1.3885(17)
C(5)-H(5)	0.9500
C(6)-C(7)	1.5008(16)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(9)-C(11)	1.4780(16)
C(11)-C(12)	1.3481(18)
C(12)-C(17)	1.4947(17)
C(14)-C(18)	1.5158(18)
C(14)-C(15)	1.5232(18)
C(14)-H(14)	1.0000
C(15)-C(19)	1.5127(17)
C(15)-H(15)	1.0000
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(9)-O(8)-C(7)	113.63(9)
C(12)-O(13)-C(14)	116.00(9)
C(11)-O(16)-C(15)	113.28(9)
C(2)-C(1)-C(6)	120.32(12)
C(2)-C(1)-H(1)	119.8
C(6)-C(1)-H(1)	119.8
C(1)-C(2)-C(3)	119.94(12)
C(1)-C(2)-H(2)	120.0
C(3)-C(2)-H(2)	120.0
C(4)-C(3)-C(2)	120.05(12)
C(4)-C(3)-H(3)	120.0
C(2)-C(3)-H(3)	120.0
C(3)-C(4)-C(5)	120.01(12)
C(3)-C(4)-H(4)	120.0
C(5)-C(4)-H(4)	120.0
C(6)-C(5)-C(4)	120.42(12)
C(6)-C(5)-H(5)	119.8
C(4)-C(5)-H(5)	119.8
C(5)-C(6)-C(1)	119.24(11)
C(5)-C(6)-C(7)	118.92(11)
C(1)-C(6)-C(7)	121.67(11)
O(8)-C(7)-C(6)	109.65(9)
O(8)-C(7)-H(7A)	109.7
C(6)-C(7)-H(7A)	109.7
O(8)-C(7)-H(7B)	109.7
C(6)-C(7)-H(7B)	109.7
H(7A)-C(7)-H(7B)	108.2
O(10)-C(9)-O(8)	123.11(10)
O(10)-C(9)-C(11)	123.13(11)
O(8)-C(9)-C(11)	113.71(10)
C(12)-C(11)-O(16)	122.86(11)
C(12)-C(11)-C(9)	127.46(11)
O(16)-C(11)-C(9)	109.68(10)
C(11)-C(12)-O(13)	121.31(11)
C(11)-C(12)-C(17)	128.60(11)
O(13)-C(12)-C(17)	110.05(10)
O(13)-C(14)-C(18)	109.15(11)
O(13)-C(14)-C(15)	108.21(9)
C(18)-C(14)-C(15)	114.60(11)
O(13)-C(14)-H(14)	108.2
C(18)-C(14)-H(14)	108.2
C(15)-C(14)-H(14)	108.2
O(16)-C(15)-C(19)	106.90(10)
O(16)-C(15)-C(14)	108.50(10)
C(19)-C(15)-C(14)	114.53(10)
O(16)-C(15)-H(15)	108.9
C(19)-C(15)-H(15)	108.9
C(14)-C(15)-H(15)	108.9
C(12)-C(17)-H(17A)	109.5
C(12)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(12)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(14)-C(18)-H(18A)	109.5
C(14)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(14)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(15)-C(19)-H(19A)	109.5
C(15)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(15)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

7.7.11 Crystallographic data of compound **42aK**

Table 7.20 Crystal data and structure refinement for **42aK**.

Identification code	tra_III_17_82	
Empirical formula	$C_{19}H_{18}O_4$	
Formula weight	310.33	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P\,2_1/c$	
Unit cell dimensions	a = 11.58071(19) Å	α= 90°.
	b = 12.49486(17) Å	β= 94.7309(14)°.
	c = 10.60246(16) Å	γ = 90°.
Volume	1528.94(4) $Å^3$	
Z	4	
Density (calculated)	1.348 Mg/m^3	
Absorption coefficient	0.768 mm^{-1}	
F(000)	656	
Crystal size	0.3002 x 0.1423 x 0.0722 mm^3	
Theta range for data collection	3.83 to 73.33°.	
Index ranges	-14<=h<=13, -15<=k<=15, -13<=l<=13	
Reflections collected	11052	
Independent reflections	3029 [R(int) = 0.0216]	
Completeness to theta = 66.97°	100.0 %	
Absorption correction	Analytical	
Max. and min. transmission	0.947 and 0.858	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3029 / 0 / 210	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0351, wR2 = 0.0941	
R indices (all data)	R1 = 0.0383, wR2 = 0.0978	
Largest diff. peak and hole	0.267 and -0.186 e.$Å^{-3}$	

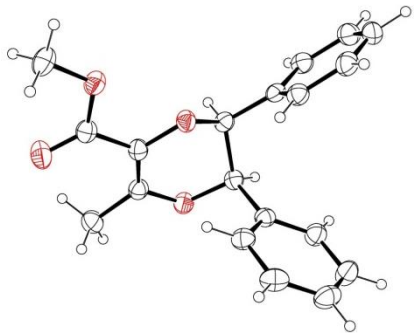


Figure 7.11 ORTEP view of the crystal structure of **42aK**.
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.21 Bond lengths [Å] and angles [°] for **42aK**.

O(2)-C(3)	1.3372(14)
O(2)-C(1)	1.4434(14)
O(4)-C(3)	1.2111(14)
O(8)-C(6)	1.3681(13)
O(8)-C(9)	1.4478(13)
O(11)-C(5)	1.3870(13)
O(11)-C(10)	1.4359(13)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(3)-C(5)	1.4766(15)
C(5)-C(6)	1.3440(16)
C(6)-C(7)	1.4946(16)
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
C(9)-C(18)	1.5113(15)
C(9)-C(10)	1.5366(15)
C(9)-H(9)	1.0000
C(10)-C(12)	1.5057(15)
C(10)-H(10)	1.0000
C(12)-C(17)	1.3912(16)
C(12)-C(13)	1.3963(16)
C(13)-C(14)	1.3871(18)
C(13)-H(13)	0.9500
C(14)-C(15)	1.387(2)
C(14)-H(14)	0.9500
C(15)-C(16)	1.3874(18)
C(15)-H(15)	0.9500
C(16)-C(17)	1.3852(17)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(18)-C(23)	1.3890(16)
C(18)-C(19)	1.3960(16)
C(19)-C(20)	1.3926(17)
C(19)-H(19)	0.9500
C(20)-C(21)	1.3847(19)
C(20)-H(20)	0.9500
C(21)-C(22)	1.3831(19)
C(21)-H(21)	0.9500
C(22)-C(23)	1.3856(18)
C(22)-H(22)	0.9500
C(23)-H(23)	0.9500
C(3)-O(2)-C(1)	114.91(9)
C(6)-O(8)-C(9)	117.93(8)
C(5)-O(11)-C(10)	112.13(8)
O(2)-C(1)-H(1A)	109.5
O(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(4)-C(3)-O(2)	123.58(10)
O(4)-C(3)-C(5)	125.14(11)
O(2)-C(3)-C(5)	111.28(10)
C(6)-C(5)-O(11)	122.38(10)
C(6)-C(5)-C(3)	122.96(10)
O(11)-C(5)-C(3)	114.65(9)
C(5)-C(6)-O(8)	121.77(10)
C(5)-C(6)-C(7)	127.67(11)
O(8)-C(6)-C(7)	110.56(9)
C(6)-C(7)-H(7A)	109.5
C(6)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(6)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
O(8)-C(9)-C(18)	110.22(9)
O(8)-C(9)-C(10)	108.91(9)
C(18)-C(9)-C(10)	116.77(9)
O(8)-C(9)-H(9)	106.8
C(18)-C(9)-H(9)	106.8
C(10)-C(9)-H(9)	106.8
O(11)-C(10)-C(12)	108.80(9)
O(11)-C(10)-C(9)	109.47(9)
C(12)-C(10)-C(9)	113.30(9)
O(11)-C(10)-H(10)	108.4
C(12)-C(10)-H(10)	108.4
C(9)-C(10)-H(10)	108.4
C(17)-C(12)-C(13)	118.95(11)
C(17)-C(12)-C(10)	121.20(10)
C(13)-C(12)-C(10)	119.85(10)
C(14)-C(13)-C(12)	120.42(11)
C(14)-C(13)-H(13)	119.8
C(12)-C(13)-H(13)	119.8
C(15)-C(14)-C(13)	120.20(11)
C(15)-C(14)-H(14)	119.9
C(13)-C(14)-H(14)	119.9
C(14)-C(15)-C(16)	119.57(12)
C(14)-C(15)-H(15)	120.2
C(16)-C(15)-H(15)	120.2
C(17)-C(16)-C(15)	120.38(11)
C(17)-C(16)-H(16)	119.8
C(15)-C(16)-H(16)	119.8
C(16)-C(17)-C(12)	120.44(11)
C(16)-C(17)-H(17)	119.8
C(12)-C(17)-H(17)	119.8
C(23)-C(18)-C(19)	119.00(11)
C(23)-C(18)-C(9)	118.33(10)
C(19)-C(18)-C(9)	122.59(10)
C(20)-C(19)-C(18)	120.17(11)
C(20)-C(19)-H(19)	119.9
C(18)-C(19)-H(19)	119.9
C(21)-C(20)-C(19)	120.16(12)
C(21)-C(20)-H(20)	119.9
C(19)-C(20)-H(20)	119.9
C(22)-C(21)-C(20)	119.79(12)
C(22)-C(21)-H(21)	120.1
C(20)-C(21)-H(21)	120.1
C(21)-C(22)-C(23)	120.27(12)
C(21)-C(22)-H(22)	119.9
C(23)-C(22)-H(22)	119.9
C(22)-C(23)-C(18)	120.61(11)
C(22)-C(23)-H(23)	119.7
C(18)-C(23)-H(23)	119.7

7.7.12 Crystallographic data of compound **42aW**

Table 7.22 Crystal data and structure refinement for **42aW**.

Identification code	shelxl	
Empirical formula	C_{15} H_{16} O_4	
Formula weight	260.28	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.78160(16) Å	α= 90°.
	b = 9.5013(2) Å	β= 90°.
	c = 17.3321(4) Å	γ = 90°.
Volume	1281.45(5) $Å^3$	
Z	4	
Density (calculated)	1.349 Mg/m^3	
Absorption coefficient	0.804 mm^{-1}	
F(000)	552	
Crystal size	0.2589 x 0.2400 x 0.0558 mm^3	
Theta range for data collection	5.10 to 73.08°.	
Index ranges	-9<=h<=7, -7<=k<=11, -14<=l<=21	
Reflections collected	4254	
Independent reflections	2126 [R(int) = 0.0201]	
Completeness to theta = 67.50°	100.0 %	
Absorption correction	Analytical	
Max. and min. transmission	0.957 and 0.848	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2126 / 0 / 175	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0878	
R indices (all data)	R1 = 0.0359, wR2 = 0.0904	
Absolute structure parameter	0.1(2)	
Largest diff. peak and hole	0.165 and -0.154 $e.Å^{-3}$	

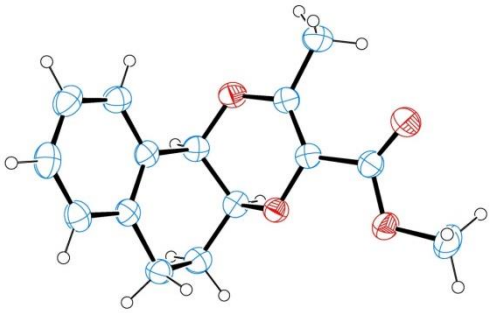


Figure 7.12 ORTEP view of the crystal structure of **42aW**.
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.23 Bond lengths [Å] and angles [°] for **42aW**.

O(2)-C(3)	1.338(2)
O(2)-C(1)	1.445(2)
O(4)-C(3)	1.201(2)
O(6)-C(5)	1.379(2)
O(6)-C(7)	1.439(2)
O(17)-C(18)	1.361(2)
O(17)-C(16)	1.444(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(3)-C(5)	1.469(3)
C(5)-C(18)	1.353(2)
C(7)-C(8)	1.511(2)
C(7)-C(16)	1.525(2)
C(7)-H(7)	1.0000
C(8)-C(9)	1.527(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.514(2)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.397(3)
C(10)-C(15)	1.397(3)
C(11)-C(12)	1.384(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.383(3)
C(12)-H(12)	0.9500
C(13)-C(14)	1.377(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.396(2)
C(14)-H(14)	0.9500
C(15)-C(16)	1.511(3)
C(16)-H(16)	1.0000
C(18)-C(19)	1.486(3)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(3)-O(2)-C(1)	115.57(15)
C(5)-O(6)-C(7)	113.08(13)
C(18)-O(17)-C(16)	117.63(14)
O(2)-C(1)-H(1A)	109.5
O(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(4)-C(3)-O(2)	123.23(18)
O(4)-C(3)-C(5)	125.94(17)
O(2)-C(3)-C(5)	110.84(15)
C(18)-C(5)-O(6)	122.23(16)
C(18)-C(5)-C(3)	122.74(17)
O(6)-C(5)-C(3)	114.98(15)

O(6)-C(7)-C(8)	107.47(14)
O(6)-C(7)-C(16)	109.31(14)
C(8)-C(7)-C(16)	110.37(16)
O(6)-C(7)-H(7)	109.9
C(8)-C(7)-H(7)	109.9
C(16)-C(7)-H(7)	109.9
C(7)-C(8)-C(9)	111.38(15)
C(7)-C(8)-H(8A)	109.4
C(9)-C(8)-H(8A)	109.4
C(7)-C(8)-H(8B)	109.4
C(9)-C(8)-H(8B)	109.4
H(8A)-C(8)-H(8B)	108.0
C(10)-C(9)-C(8)	113.55(16)
C(10)-C(9)-H(9A)	108.9
C(8)-C(9)-H(9A)	108.9
C(10)-C(9)-H(9B)	108.9
C(8)-C(9)-H(9B)	108.9
H(9A)-C(9)-H(9B)	107.7
C(11)-C(10)-C(15)	118.47(16)
C(11)-C(10)-C(9)	119.75(17)
C(15)-C(10)-C(9)	121.74(17)
C(12)-C(11)-C(10)	121.30(19)
C(12)-C(11)-H(11)	119.3
C(10)-C(11)-H(11)	119.3
C(13)-C(12)-C(11)	119.89(19)
C(13)-C(12)-H(12)	120.1
C(11)-C(12)-H(12)	120.1
C(14)-C(13)-C(12)	119.58(18)
C(14)-C(13)-H(13)	120.2
C(12)-C(13)-H(13)	120.2
C(13)-C(14)-C(15)	121.17(18)
C(13)-C(14)-H(14)	119.4
C(15)-C(14)-H(14)	119.4
C(14)-C(15)-C(10)	119.58(17)
C(14)-C(15)-C(16)	119.15(16)
C(10)-C(15)-C(16)	121.25(15)
O(17)-C(16)-C(15)	110.91(14)
O(17)-C(16)-C(7)	110.47(15)
C(15)-C(16)-C(7)	113.24(15)
O(17)-C(16)-H(16)	107.3
C(15)-C(16)-H(16)	107.3
C(7)-C(16)-H(16)	107.3
C(5)-C(18)-O(17)	121.83(17)
C(5)-C(18)-C(19)	127.13(18)
O(17)-C(18)-C(19)	111.00(15)
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

7.7.13 Crystallographic data of compound **42aZ**

Table 7.24 Crystal data and structure refinement for **42aZ.**

Identification code	shelxl	
Empirical formula	C_{12} H_{18} O_4	
Formula weight	226.26	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.8253(8) Å	α= 72.559(9)°.
	b = 9.3502(8) Å	β= 71.869(10)°.
	c = 9.4847(12) Å	γ = 66.471(9)°.
Volume	592.29(11) $Å^3$	
Z	2	
Density (calculated)	1.269 Mg/m^3	
Absorption coefficient	0.779 mm^{-1}	
F(000)	244	
Crystal size	0.5507 x 0.2287 x 0.1210 mm^3	
Theta range for data collection	5.27 to 73.54°.	
Index ranges	-9<=h<=9, -11<=k<=11, -11<=l<=11	
Reflections collected	8119	
Independent reflections	2321 [R(int) = 0.0164]	
Completeness to theta = 67.50°	99.3 %	
Absorption correction	Analytical	
Max. and min. transmission	0.925 and 0.800	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2321 / 0 / 148	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0375, wR2 = 0.1027	
R indices (all data)	R1 = 0.0397, wR2 = 0.1049	
Largest diff. peak and hole	0.252 and -0.213 $e.Å^{-3}$	

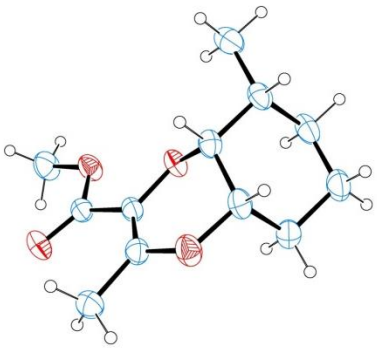


Figure 7.13 ORTEP view of the crystal structure of **42aZ**.
Thermal ellipsoids are drawn at 50 % probability level.

Table 7.25 Bond lengths [Å] and angles [°] for **42aZ**.

O(1)-C(1)	1.3632(14)
O(1)-C(8)	1.4486(14)
O(2)-C(2)	1.3861(12)
O(2)-C(3)	1.4382(13)
O(3)-C(11)	1.3418(14)
O(3)-C(12)	1.4437(14)
O(4)-C(11)	1.2122(13)
C(1)-C(2)	1.3472(16)
C(1)-C(10)	1.4958(15)
C(2)-C(11)	1.4716(15)
C(3)-C(8)	1.5150(17)
C(3)-C(4)	1.5252(15)
C(3)-H(3)	1.0000
C(4)-C(9)	1.5257(18)
C(4)-C(5)	1.5293(16)
C(4)-H(4)	1.0000
C(5)-C(6)	1.522(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.5314(17)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.5170(17)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(1)-O(1)-C(8)	117.00(9)
C(2)-O(2)-C(3)	112.02(8)
C(11)-O(3)-C(12)	115.32(9)
C(2)-C(1)-O(1)	121.86(10)
C(2)-C(1)-C(10)	127.35(11)
O(1)-C(1)-C(10)	110.77(10)
C(1)-C(2)-O(2)	122.21(10)
C(1)-C(2)-C(11)	123.52(10)
O(2)-C(2)-C(11)	114.27(9)
O(2)-C(3)-C(8)	108.67(9)
O(2)-C(3)-C(4)	107.79(9)
C(8)-C(3)-C(4)	112.36(9)
O(2)-C(3)-H(3)	109.3
C(8)-C(3)-H(3)	109.3
C(4)-C(3)-H(3)	109.3
C(3)-C(4)-C(9)	111.24(10)
C(3)-C(4)-C(5)	110.61(9)
C(9)-C(4)-C(5)	113.06(11)
C(3)-C(4)-H(4)	107.2
C(9)-C(4)-H(4)	107.2
C(5)-C(4)-H(4)	107.2
C(6)-C(5)-C(4)	111.41(10)
C(6)-C(5)-H(5A)	109.3
C(4)-C(5)-H(5A)	109.3
C(6)-C(5)-H(5B)	109.3
C(4)-C(5)-H(5B)	109.3
H(5A)-C(5)-H(5B)	108.0
C(5)-C(6)-C(7)	111.05(10)
C(5)-C(6)-H(6A)	109.4
C(7)-C(6)-H(6A)	109.4
C(5)-C(6)-H(6B)	109.4
C(7)-C(6)-H(6B)	109.4
H(6A)-C(6)-H(6B)	108.0
C(8)-C(7)-C(6)	109.64(10)
C(8)-C(7)-H(7A)	109.7
C(6)-C(7)-H(7A)	109.7
C(8)-C(7)-H(7B)	109.7
C(6)-C(7)-H(7B)	109.7
H(7A)-C(7)-H(7B)	108.2
O(1)-C(8)-C(3)	109.71(9)
O(1)-C(8)-C(7)	110.87(10)
C(3)-C(8)-C(7)	112.56(10)
O(1)-C(8)-H(8)	107.8
C(3)-C(8)-H(8)	107.8
C(7)-C(8)-H(8)	107.8
C(4)-C(9)-H(9A)	109.5
C(4)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(4)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(1)-C(10)-H(10A)	109.5
C(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
O(4)-C(11)-O(3)	123.00(10)
O(4)-C(11)-C(2)	125.92(10)
O(3)-C(11)-C(2)	111.07(9)
O(3)-C(12)-H(12A)	109.5
O(3)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(3)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5

Appendix

List of publications

1. "Enol-Acetal Synthesis via Carbenoid C-H Insertions into Tetrahydrofurans Catalyzed by CpRu Complexes" Tortoreto C.; Achard T.; Zeghida W.; Austeri M.; Guénée L.; Lacour J.; *Angew. Chem. Int. Ed.* **2012**, *51*, 5847. DOI: 10.1002/anie.201201541

2. "CpRu-catalyzed carbene insertions into epoxides: 1,4-dioxene synthesis via S_N1-like chemistry with retention of configuration" Achard T.; Tortoreto C.; Pobladór-Bahamonde A. I.; Guénée, L.; Bürgi, T.; Lacour, J.; *Angew. Chem. Int. Ed.* **2014**, *53*, 6140. DOI:10.1002/anie.201402994.

3. "Original Reactivity of α-diazo-β-ketoesters catalyzed by CpRu complexes" Tortoreto C.; Achard T.; Austeri M.; Zeghida W.; Lacour J.; *CHIMIA* **2014**, *68*, 243. DOI:10.2533/chimia.2014.243.

C–O Coupling

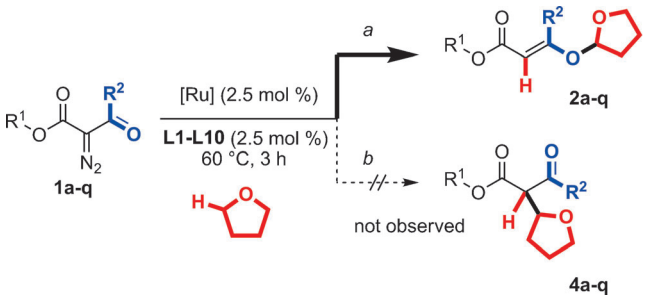
DOI: 10.1002/anie.201201541

Enol Acetal Synthesis through Carbenoid C–H Insertion into Tetrahydrofuran Catalyzed by CpRu Complexes**

*Cecilia Tortoreto, Thierry Achard, Walid Zeghida, Martina Austeri, Laure Guénée, and Jérôme Lacour**

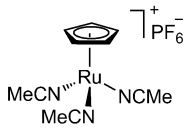
Dedicated to Professor E. Peter Kündig on the occasion of his 65th birthday

Substituted tetrahydrofurans, ubiquitous motifs in biological and natural product chemistry,[1] are accessible by coupling reactions of diazoacetates or aryldiazoacetates with simple tetrahydrofurans.[2,3] These intermolecular carbenoid C–H insertions[4] are efficiently catalyzed by copper, iridium, iron, rhodium, and silver salts or complexes.[2,5] Successful asymmetric versions have also been achieved.[4] In all these instances, a C–C bond is created by insertion of the carbenoid into a C–H bond α to the oxygen ether atom (Scheme 1, route b). Herein, in a new development that uses α-diazo-β-ketoesters **1** as reagents and CpRu (Cp = cyclopentadienyl) moieties as catalysts, we report the kinetically favored formation of C–O instead of C–C bond adducts. The mild reaction conditions yield novel enol acetal motifs **2** through unprecedented 1,3 C–H insertion reactions (Scheme 1, route a).



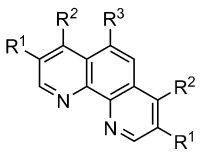
Scheme 1. Favored enol acetal formation through 1,3 C–H insertion of diazocarbonyl compounds into THF. For ligands **L1**–**L10**, see Figure 1.

α-Diazo-β-ketoesters **1**, readily made acceptor/acceptor reagents,[6] are usually characterized by a better chemical stability and a moderate reactivity in comparison to other diazo derivatives.[7] These compounds yet react in the presence of metal catalysts to form electrophilic carbenoid/carbene intermediates. These reactive species undergo many useful transformations, such as cyclopropanation, insertion, dipolar addition, ylide generation, and subsequent rearrangement/macrocyclization reactions.[8] Recently, using combinations of $[CpRu(CH_3CN)_3][PF_6]$ ([**3**][PF_6])[9] and diimine ligands,[10] reagents **1** provided selective O–H insertion and condensation reactions with alcohols, nitriles, ketones, and aldehydes.[11] This result led us to examine the reactivity of other Lewis basic moieties, and THF derivatives in particular, with this catalytic combination.[12]

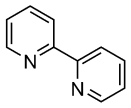


[**3**][PF_6]

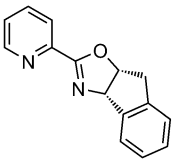
Methyl diazoacetoacetate **1a** ($R^1 = R^2 = Me$, Scheme 1) was thus added to THF solutions of complex [**3**][PF_6] and ligands **L1** to **L10** (Figure 1).[13] Using **L1**, a moderate heating to 60 °C was necessary to induce gas evolution. At that



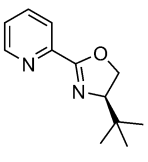
L1: R^1 = H; R^2 = H; R^3 = H; **Conv**: 95 %
L2: R^1 = H; R^2 = Me; R^3 = H; **Conv**: 70 %
L3: R^1 = H; R^2 = OMe; R^3 = H; **Conv**: 48 %
L4: R^1 = H; R^2 = H; R^3 = NO_2; **Conv**: 57 %
L5: R^1 = Me; R^2 = Me; R^3 = H; **Conv**: 50 %
L6: R^1 = H; R^2 = Ph; R^3 = H; **Conv**: 66 %



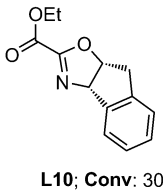
L7; **Conv**: 27 %



L8; **Conv**: 75 %



L9; **Conv**: 22 %



L10; **Conv**: 30 %

Figure 1. Ligands **L1** to **L10**, and conversions of **1a** (0.5 M in THF), using **L** and [**3**][PF_6] (2.5 mol% each), after 2 h (corresponds to 95% conversion for **L1**) at 60 °C (^{1}H NMR, 1,3,5-trimethoxybenzene as internal reference).

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temperature, conversion was complete after 3 h for a relatively high concentration of **1a** (0.5 M).[14] NMR spectroscopic analysis of the reaction mixture indicated the formation of a single product **2a**, composed of fragments of **1a** and THF. Its structure was however incompatible with a C–C bond forming reaction, and it was different from that of already known **4a** (Scheme 1).[15] Based on detailed ^{1}H, ^{13}C, and IR analyses, only an original enol acetal structure involving a C–O linkage was consistent with the data; the motif was confirmed by X-ray diffraction studies of **2g** (see below). Of interest was also that the C=C bond of **2a** is *E*-configured.

We then tested the ligands **L2** to **L10**. To our satisfaction, **2a** was the single product in all these experiments. The conversion of **1a** was however lower in all instances (Figure 1).[16] 1,10-Phenanthroline **L1** was therefore selected for the remainder of the study. The results with other cyclopentadienyl ruthenium(II) salts[17] are summarized in Table 1. Complexes with large lipophilic counterions (SbF_6^-, TRISPHAT (=$P(O_2C_6Cl_4)_3^-$))[18] had a reactivity similar to that of [**3**][PF_6]. Lower conversions were however noticed with anions able to coordinate at the metal center (OTf, TRISPHAT-N).[19] Complex [Cp*Ru(CH_3CN)$_3$][PF_6] (Cp* = pentamethylcyclopentadienyl)[20] was also effective, but the reaction was accompanied by concurrent polymerization of THF. Complex [**3**][PF_6] was therefore used in all further experiments.

Table 1: Metal complex selection.[a]

Entry	[Ru]	Anion	Conv.[b]
1	CpRu(CH_3CN)$_3$	PF_6	95
2	CpRu(CH_3CN)$_3$	SbF_6	95
3	CpRu(CH_3CN)$_3$	TRISPHAT	80
4	CpRu(CH_3CN)$_3$	TRISPHAT-N	43
5	CpRu(CH_3CN)$_3$	OTf	30
6	Cp*Ru(CH_3CN)$_3$	PF_6	90

[a] Reaction conditions: diazo **1a** (0.32 mmol), [Ru] and **L1** (2.5 mol % each), THF (0.6 mL), 2 h, 60 °C. [b] Conversion of **1a** (^{1}H NMR, 1,3,5-trimethoxybenzene as internal reference).

To investigate the scope of the reaction, substrates with different ester groups (alkyl, aryl, allyl) were tested and reactions were allowed to run until full conversion (Table 2). With bulkier alkyl esters, moderate to good yields of **2** were afforded after prolonged reaction time (Table 2, entries 2–5).[21] A series of aryl esters was also studied (Table 2, entries 6–12). In essentially all cases, products of type **2** were obtained. After 24 h, complete conversions were achieved with reagents carrying either electron-donating or electron-withdrawing substituents at the *para* position; this indicates a global lack of electronic effects. Only the highly hindered *o-tert*-butylphenyl reagent did not lead to any insertion reaction (Table 2, entry 12).[22] Product **2g** was found to be moderately soluble in a 4:1 mixture of hexane and Et_2O, which made X-ray-quality crystals accessible. The result of the X-ray analysis is shown in Figure 2. For compounds **2j** and **2k**, although predominant in the crude mixtures, decomposition occurred upon chromatographic purification (on SiO_2 or Al_2O_3). Another substrate, **1m** (R^1 = PhCH=CHCH$_2$, R^2 = Me), was also tested. In this case, the product of intramolecular cyclopropanation (65%) predominated and the corresponding enol acetal **2m** was isolated in 15% yield only (Table 2, entry 13).[23]

Table 2: Substrate scope.[a]

Entry	R^1	R^2	Product	Yield[b]	Time [h][c]
1	Me	Me	**2a**	80	3
2	Et	Me	**2b**	80	3
3	Ph(CH_2)$_2$	Me	**2c**	63	15
4	PhCH$_2$	Me	**2d**	85	20
5	*t*Bu	Me	**2e**	70	20
6	Ph	Me	**2f**	89	24
7	4-ClC_6H_4	Me	**2g**	80	24
8	4-$NO_2C_6H_4$	Me	**2h**	81	24
9	4-*t*BuC_6H_4	Me	**2i**	60	24
10	4-MeOC_6H_4	Me	**2j**	–[d]	24
11	4-$CF_3C_6H_4$	Me	**2k**	–[d]	24
12	2-*t*BuC_6H_4	Me	**2l**	0	24
13	PhCH=CHCH$_2$	Me	**2m**	15[e]	24
14	Et	Pr	**2n**	65	3
15	Me	CH$_2$Ph	**2o**	44	24
16[f]	Et	Ph	**2p**	27	24
17	Et	CF_3	**2q**	–[d]	3

[a] Reaction conditions: diazo **1** (0.32 mmol), [**3**][PF_6] and **L1** (2.5 mol % each), THF (0.6 mL), 60 °C. [b] Yield of isolated product. [c] Reaction time at 100% conversion. [d] Decomposition upon chromatography. [e] Intramolecular cyclopropanation adduct (65%) as major component. [f] Incomplete reaction. Conversion not measurable by ^{1}H NMR spectroscopy.

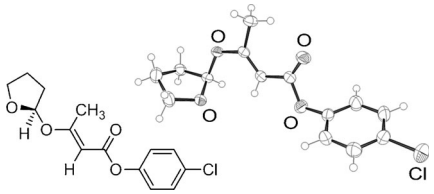
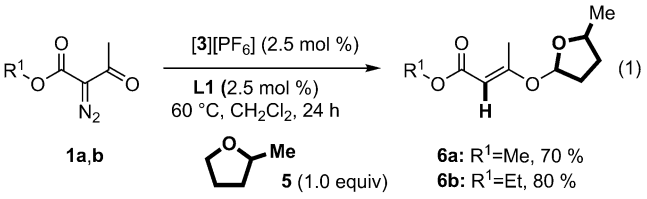


Figure 2. ORTEP view of the structure of (*E*)-**2g** in the crystal. Thermal ellipsoids are drawn at 50% probability level.

With 2-methyltetrahydrofuran (**5**) instead of THF, one equivalent was used as the reaction proceeded well in CH_2Cl_2 as solvent [Eq.(1)]. A longer reaction time was necessary (24 h instead of 3 h), but the isolation of the products (**6a** and



6b) was easier than for reactions performed with **5** as solvent. The C–O bond formation occurred only on the secondary CH_2 carbon atom; no evidence was found in the crude mixture for an insertion on the more hindered tertiary CH site.[25] In line with previous studies, this regioselectivity can be rationalized on steric grounds.[2b] Compounds **6a** and **6b** are obtained as 3.3:1 mixtures of diastereomers due to a lack of discrimination at the anomeric carbon atom.

To gain some insight into the nature of the transformation, a series of experiments was performed using reagents **1a**, **1f**, and **1h** in 1:1 mixtures of THF and [D_8]THF [Eq. (2)]. Mass spectrometry indicated the predominant formation of homocoupling products **HH** and **DD** (>90%) over cross-coupling products **HD** and **DH** (<10%).[26] A larger proportion of **HH** over **DD** was also denoted (Table 3).

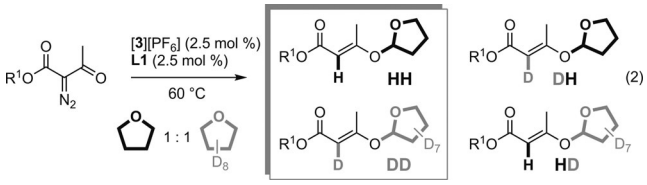


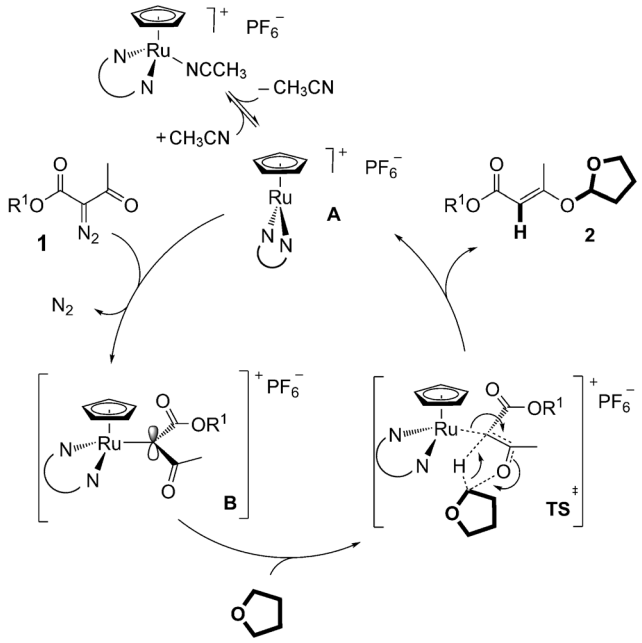
Table 3: Homocoupling and kinetic isotope effects.

Entry	R^1	Product[a]	Ratio **HH**/**DD**[b]
1	Me	**2a**	3.0:1.0
2	Ph	**2f**	3.3:1.0
3	4-$NO_2C_6H_4$	**2h**	3.4:1.0

[a] Reaction conditions: diazo **1** (0.32 mmol), [**3**][PF_6] and **L1** (2.5 mol %), 1:1 THF:[D_8]THF (0.6 mL), 60 °C. [b] Measured by 400 MHz ^{1}H NMR spectroscopy and confirmed by ESI mass spectrometry.

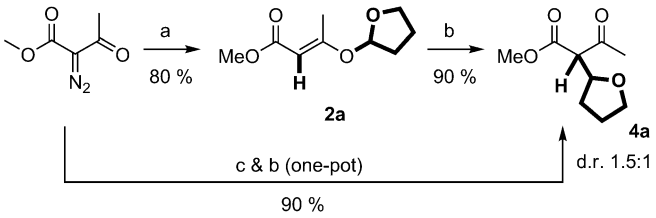
The predominant formation of the homocoupling products **HH** and **DD** advocates for a concerted hydrogen transfer mechanism. The higher proportion of **HH** over **DD** indicates the occurrence of a primary kinetic isotope effect.[27] The measured k_H/k_D values, from 3.0 to 3.4, are in accordance with previously reported results for C–C bond forming reactions.[2b] A mechanistic rationale coherent with these results is proposed in Scheme 2.[28]

In detail, catalyst precursor [**3**][PF_6] reacts with **L1** to generate a [Cp(**L1**)$(CH_3CN)_2$Ru][PF_6] species, which, upon dissociation of the monodentate ligand, forms the catalytically active 16-electron complex **A**.[10] This electron-deficient entity probably reacts with diazo reagent **1** to afford metal carbenoid intermediate **B**. At this stage, in contrast to classical C–H insertions, which proceed via 3-membered transition states,[7] a concerted reaction occurs that involves the keto group of carbenoid **B** and the more accessible C_α–H bond of the ether moiety.[29] A concomitant formation of the novel C–O and C–H bonds occurs in a 5-membered transition state **TS**‡ to release both product **2** and catalyst **A**. This step is stereo-determining as the s-*cis* conformation of the carbonyl group in intermediate **B** is conserved to form the *E*-configured enol.



Scheme 2. Mechanistic rationale. NN corresponds to 1,10-phenatroline (**L1**).

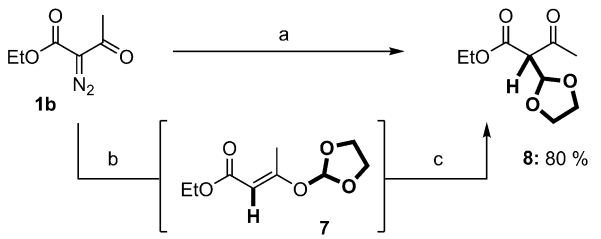
Finally, with compounds **2** in hand, we were able to also synthesize the products of "classical" C–C bond formation. Based on literature precedents,[30] we expected that the enol fragment of **2** would behave as a good leaving group in the presence of Lewis acids. After an induced dissociation, a recombination within the oxocarbenium/enolate ion pair would form adducts **4**. This assumption was validated in the transformation of **2a** into **4a** using catalytic amounts of $Cu(OTf)_2$ or TMSOTf (5 mol%, Scheme 3).[31,32] By using



Scheme 3. a) [**3**][PF_6] (2.5 mol%), **L1** (2.5 mol%), THF, 60 °C, 3 h; b) TMSOTf or $Cu_2(OTf)_2$ (5 mol%), CH_2Cl_2, 0→25 °C, 1 h; c) [**3**][PF_6] (2.5 mol%), **L1** (2.5 mol%), THF (1 equiv), CH_2Cl_2, 60 °C, 24 h.

only one equivalent of THF, the C–H insertion and rearrangement steps can be combined into a single-pot process. In this tandem fashion, a higher yield of **4a** was obtained (90 vs. 72% for two steps).

Using 1,3-dioxolane instead of THF as reactive ether, the classical C–C bond formation occurs under thermal conditions (Scheme 4). At 60 °C, decomposition of **1b** in the presence of the acetal affords **8** as the single adduct. The product of C–O bond forming reaction, **7**, is however observed after 1 hour at 25 °C. Two hours at 60 °C are then sufficient to induce the rearrangement into **8**, and this without



Scheme 4. [**3**][PF_6] (2.5 mol%), **L1** (2.5 mol%), 1,3-dioxolane (solvent): a) 60°C, 3 h; b) 25°C, 1 h; c) 60°C, 2 h.

any added Lewis acid. This result indicates that C–O bond forming is kinetically preferred over C–C bond forming using the current catalyst combination.

In conclusion, we have reported a new reactivity in the CpRu-catalyzed decomposition of diazo compounds and, as a consequence, a novel functionalization of tetrahydrofurans. To our knowledge, it is the first one-step synthesis of enol acetal moieties by direct C–H activation.

Experimental Section

Representative procedure: In a 2 mL screw-cap vial equipped with a magnetic stirring bar, **L1** (1.5 mg, 8 μmol, 2.5 mol%) and [CpRu-$(CH_3CN)_3$][PF_6] (3.5 mg, 8 μmol, 2.5 mol%) were dissolved in 0.60 mL of dry THF. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 min at 25°C and then diazoketoester **1** (0.32 mmol) was added. The solution was stirred at 60°C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Hexane/Et_2O, SiO_2) to afford insertion product **2**.

Crystal structure analysis of **2g**: CCDC 867253 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] a) *Polyether Antibiotics*: *Naturally Occurring Acid Ionophores* (Ed.: J. W. Westley), Marcel Dekker, New York, **1982**; b) D. E. Levy, C. Tang, *The Chemistry of C-Glycosides*, *1st ed.*, Pergamon, Oxford, **1995**; c) F. Q. Alali, X. X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504–540; d) M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407–2473; e) E. J. Kang, E. Lee, *Chem. Rev.* **2005**, *105*, 4348–4378; f) M. Saleem, H. J. Kim, M. S. Ali, Y. S. Lee, *Nat. Prod. Rep.* **2005**, *22*, 696–716.

[2] a) H. M. L. Davies, T. Hansen, *J. Am. Chem. Soc.* **1997**, *119*, 9075–9076; b) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070; c) M. Mar Diaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *J. Am. Chem. Soc.* **2002**, *124*, 896–897.

[3] α-Functionalization of THF derivatives is also feasible through free-radical and other metal-catalyzed processes: a) G. A. Russell, P. Ngoviwatchai, *J. Org. Chem.* **1989**, *54*, 1836–1842; b) V. Gevorgyan, E. Priede, E. Liepins, M. Gavars, E. Lukevics, *J. Organomet. Chem.* **1990**, *393*, 333–338; c) D. P. Matthews, J. R. McCarthy, *J. Org. Chem.* **1990**, *55*, 2973–2975; d) F. Fontana, F. Minisci, Y. M. Yan, L. H. Zhao, *Tetrahedron Lett.* **1993**, *34*, 2517–2520; e) A. J. Clark, S. Rooke, T. J. Sparey, P. C. Taylor, *Tetrahedron Lett.* **1996**, *37*, 909–912; f) J. C. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4486–4487; g) J. S. Xiang, A. Mahadevan, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4284–4290; h) J. Xiang, W. L. Jiang, J. C. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1997**, *119*, 4123–4129; i) A. Inoue, H. Shinokubo, K. Oshima, *Synlett* **1999**, 1582–1584; j) S. Kim, N. Kim, W. J. Chung, C. H. Cho, *Synlett* **2001**, 937–940; k) K. Hirano, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2002**, *43*, 3617–3620; l) H. Inoue, Y. Nagaoka, M. Tomioka, *J. Org. Chem.* **2002**, *67*, 5864–5867; m) K. Yamada, H. Fujihara, Y. Yamamoto, Y. Miwa, T. Taga, K. Tomioka, *Org. Lett.* **2002**, *4*, 3509–3511; n) T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Org. Chem.* **2003**, *68*, 625–627; o) P. P. Singh, S. Gudup, S. Ambala, U. Singh, S. Dadhwal, B. Singh, S. D. Sawant, R. A. Vishwakarma, *Chem. Commun.* **2011**, *47*, 5852–5854.

[4] a) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724; b) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869; c) S. Y. Zhang, F. M. Zhang, Y. Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937–1949.

[5] a) H. M. L. Davies, T. Hansen, D. W. Hopper, S. A. Panaro, *J. Am. Chem. Soc.* **1999**, *121*, 6509–6510; b) J. M. Fraile, J. I. Garcia, J. A. Mayoral, M. Roldan, *Org. Lett.* **2007**, *9*, 731–733; c) H. M. Mbuvi, L. K. Woo, *Organometallics* **2008**, *27*, 637–645; d) H. Suematsu, T. Katsuki, *J. Am. Chem. Soc.* **2009**, *131*, 14218–14219; e) C. J. Lovely, J. A. Flores, X. F. Meng, H. V. R. Dias, *Synlett* **2009**, 129–132; f) J. M. Fraile, J. A. Mayoral, N. Ravasio, M. Roldan, L. Sordelli, F. Zaccheria, *J. Catal.* **2011**, *281*, 273–278.

[6] Diazo reagents of type **1** are readily prepared by using diazo-transfer reagents such as *p*-acetamidobenzenesulfonyl azide (*p*-ABSA): a) G. Maas, *Angew. Chem.* **2009**, *121*, 8332–8341; *Angew. Chem. Int. Ed.* **2009**, *48*, 8186–8195; see also b) W. J. Brehm, T. Levenson, *J. Am. Chem. Soc.* **1954**, *76*, 5389–5391; c) D. F. Taber, R. E. Ruckle, *J. Am. Chem. Soc.* **1986**, *108*, 7686–7693; d) J. S. Baum, D. A. Shook, H. M. L. Davies, H. D. Smith, *Synth. Commun.* **1987**, *17*, 1709–1716; e) M. Hrytsak, T. Durst, *J. Chem. Soc. Chem. Commun.* **1987**, 1150–1151; f) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, M. M. Pearson, *J. Am. Chem. Soc.* **1993**, *115*, 958–964; g) J. R. Davies, P. D. Kane, C. J. Moody, *Tetrahedron* **2004**, *60*, 3967–3977; h) A. M. Harned, W. M. Sherrill, D. L. Flynn, P. R. Hanson, *Tetrahedron* **2005**, *61*, 12093–12099; i) M. E. Meyer, E. M. Ferreira, B. M. Stoltz, *Chem. Commun.* **2006**, 1316–1318; j) K. M. Allan, B. D. Hong, B. M. Stoltz, *Org. Biomol. Chem.* **2009**, *7*, 4960–4964; k) J. L. Chiara, J. R. Suarez, *Adv. Synth. Catal.* **2011**, *353*, 575–579.

[7] M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*: *From Cyclopropanes to Ylides*, Wiley, New York, **1998**.

[8] a) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–269; b) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911–935; c) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903; d) Z. H. Zhang, J. B. Wang, *Tetrahedron* **2008**, *64*, 6577–6605; e) W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem.* **2010**, *122*, 7411–7414; *Angew. Chem. Int. Ed.* **2010**, *49*, 7253–7256; f) D. Rix, R. Ballesteros-Garrido, W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem.* **2011**, *123*, 7446–7449; *Angew. Chem. Int. Ed.* **2011**, *50*, 7308–7311.

[9] a) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067–2096; b) E. P. Kündig, F. R. Monnier, *Adv. Synth. Catal.* **2004**, *346*, 901–904; c) A. Mercier, W. C. Yeo, J. Y. Chou, P. D. Chaudhuri, G. Bernardinelli, E. P. Kündig, *Chem. Commun.* **2009**, 5227–5229.

[10] J. L. Renaud, C. Bruneau, B. Demerseman, *Synlett* **2003**, 408–410.

[11] M. Austeri, D. Rix, W. Zeghida, J. Lacour, *Org. Lett.* **2011**, *13*, 1394 – 1397.
[12] CpRu complexes with cyclooctadiene and diphosphine ligands, known to catalyze the decomposition of certain diazo derivatives, were unreactive in the titled chemistry: W. Baratta, A. DelZotto, P. Rigo, *Chem. Commun.* **1997**, 2163 – 2164; W. Baratta, W. A. Herrman, R. M. Kratzer, P. Rigo, *Organometallics* **2000**, *19*, 3664 – 3669; M. Basato, C. Tubaro, A. Biffis, M. Bonato, G. Buscemi, F. Lighezzolo, P. Lunardi, C. Vianini, F. Benetollo, A. Del Zotto, *Chem. Eur. J.* **2009**, *15*, 1516 – 1526.
[13] The Supporting Information contains optimization studies with **L1** and conversion results with less-performing and even inhibiting ligands.
[14] Without ligand, only 12% conversion is observed and polymerization of THF occurs.
[15] Compound **2a** is characterized by ^{1}H NMR signals at 5.66 (d, $J =$ 4 Hz, OCHO) and 5.32 (s, C=CH) ppm that are at quite higher frequency than the most deshielded proton of **4a** (m, $\delta =$ 4.43 ppm). The configuration of the double bond is readily determined by a NOESY experiment; see: R. Bihovsky, M. U. Kumar, S. Ding, A. Goyal, *J. Org. Chem.* **1989**, *54*, 4291 – 4293; O. Moriya, Y. Urata, Y. Ikeda, Y. Ueno, T. Endo, *J. Org. Chem.* **1986**, *51*, 4708 – 4709.
[16] With enantiopure ligands **L7**, **L9**, and **L10** no enantioselectivity was observed.
[17] Other metal sources were also tested. Whereas copper salts did not induce the formation of **2a**, a small amount (10%) of **2a** is observed in the reaction catalyzed by $[Rh_2(OAc)_4]$. Interestingly, this Rh^{II} complex does not promote the C–O to C–C rearrangement detailed in Scheme 3.
[18] a) J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem.* **1997**, *109*, 660 – 662; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608 – 610; b) J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073 – 7089; c) L. Hintermann, L. Xiao, A. L. Labonne, U. Englert, *Organometallics* **2009**, *28*, 5739 – 5748.
[19] a) For the chemical structure of TRISPHAT-N, see: S. Constant, R. Frantz, J. Müller, G. Bernardinelli, J. Lacour, *Organometallics* **2007**, *26*, 2141 – 2143; b) S. Constant, S. Tortoioli, J. Müller, D. Linder, F. Buron, J. Lacour, *Angew. Chem.* **2007**, *119*, 9137 – 9140; *Angew. Chem. Int. Ed.* **2007**, *46*, 8979 – 8982.
[20] M. D. Mbaye, B. Demerseman, J. L. Renaud, L. Toupet, C. Bruneau, *Angew. Chem.* **2003**, *115*, 5220 – 5222; *Angew. Chem. Int. Ed.* **2003**, *42*, 5066 – 5068.
[21] Moderate yields are often due to the volatility of the compounds.
[22] After 48 h, only 25% conversion of **1l** into the dimer product was observed.
[23] W. Lin, A. B. Charette, *Adv. Synth. Catal.* **2005**, *347*, 1547 – 1552.
[24] Due to the presence of the electron-withdrawing CF_3 group, the leaving-group ability of the enol fragment is strongly increased leading to a probably rapid hydrolysis of the C–O bond during purification.
[25] Preferential C–H insertion on the tertiary carbon atom could be expected based on electronic grounds.
[26] The minimal amounts of products with $M+1$ and $M+7$ masses might be due to the formation of the corresponding cross-coupling products of type **4** according to a dissociation/reassociation mechanism.
[27] M. Gómez-Gallego, M. A. Sierra, *Chem. Rev.* **2011**, *111*, 4857 – 4963.
[28] An alternative hydride abstraction mechanism can be considered: H. T. Bonge, T. Hansen, *Eur. J. Org. Chem.* **2010**, 4355 – 4359.
[29] C. Özen, N. S. Tüzün, *Organometallics* **2008**, *27*, 4600 – 4610.
[30] a) D. J. Dixon, S. V. Ley, E. W. Tate, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2665 – 2667; b) M. F. Buffet, D. J. Dixon, G. L. Edwards, S. V. Ley, E. W. Tate, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1815 – 1827; c) D. J. Dixon, S. V. Ley, E. W. Tate, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2385 – 2394.
[31] Product **4a** is highly volatile and hence the yield of 90% corresponds to a quantitative reaction.
[32] Compound **6a** also rearranges under these Lewis acidic conditions, but the reaction generates a complex mixture of diastereomers that was not deconvoluted.

Synthetic Methods

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[CpRu]-Catalyzed Carbene Insertions into Epoxides: 1,4-Dioxene Synthesis through S_N1-Like Chemistry with Retention of Configuration**

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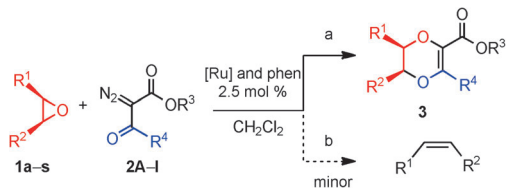
Dedicated to Professor Paul Müller on the occasion of his 75th birthday

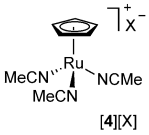
Abstract: *Rather than lead to the usual deoxygenation pathway, metal carbenes derived from α-diazo-β-ketoesters undergo three-atom insertions into epoxides using a combination of 1,10-phenanthroline and [CpRu(CH$_3$CN)$_3$][BAr$_F$] as the catalyst. Original 1,4-dioxene motifs are obtained as single regio- and stereoisomers. A perfect syn stereochemistry (retention, e.r. up to 97:3) is observed for the ring opening, which behaves as an S_N1-like transformation.*

Epoxides (**1**; or oxiranes; Scheme 1) are indispensable synthetic building blocks, which are readily accessible in well-defined stereochemical forms through efficient stereo- and enantioselective functional-group transformations, or otherwise available from commercial sources.[1] Owing to the strain of the three-membered ring, epoxides react with a wide array of nucleophiles and acids, thus leading to ring-opening reactions, often with excellent levels of regioselectivity and/or stereoselectivity.[1] Yet, as a rule, epoxides react differently with (metal) carbenes. Effective deoxygenation processes occur, thus transforming oxiranes into alkenes.[2] For instance, treatment of epoxides with acceptor/acceptor diazo reagents in the presence of a catalytic amount of [Rh$_2$(OAc)$_4$] leads to a quantitative capture of the oxygen atom and a stereospecific formation of the corresponding olefins.[3,4] Herein, in a new development, we report that metal carbenes derived from the α-diazo-β-ketoester reagents **2** undergo three-atom insertions into a large variety of epoxides (Scheme 1). The transformation specifically uses a combination of 1,10-phenanthroline (phen) and the complex [CpRu(CH$_3$CN)$_3$][BAr$_F$] as the catalyst (BAr$_F$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).[5] Original 1,4-dioxene motifs of the type **3** are obtained as single regio- and stereoisomers. A perfect *syn* stereochemistry (retention; e.r. up to 97:3) is observed for the ring opening, which otherwise behaves as an S_N1-like transformation.



Scheme 1. Preferred *syn*-stereoselective 1,4-dioxene formation.

Recently, using combinations of [CpRu(CH$_3$CN)$_3$][PF$_6$] ([**4**][PF$_6$])[6] and diimine ligands as catalysts,[7] the reagents **2** provided selective 1,3-C–H insertions into THF[8] and O–H insertion and condensation reactions with alcohols, nitriles, ketones and aldehydes.[9] These results led us to examine the reactivity of other Lewis basic moieties with the catalytic combination, and epoxides in particular. In practice, the first experiments were performed by treatment of a CH_2Cl_2 solution of the cyclooctene oxide **1a** (1.0 equiv), the complex [**4**][PF$_6$] (2.5 mol%), and phen (2.5 mol%) with the methyl diazoacetoacetate **2A** (R^3 = R^4 = Me, 0.5 M; Scheme 1). At 60 °C, gas evolution was observed and complete consumption of **2A** was achieved in 4 hours. Analysis of the reaction mixture indicated the formation of one major product (**3aA**, 60%)[10] together with some unreacted epoxide. Cyclooctene was only a minor component of the crude reaction mixture. Based on detailed ^{1}H and ^{13}C NMR spectroscopy, and IR analyses, only the original bicyclic structure with a 1,4-dioxene core and a *cis* junction between the two rings (^3J = 9.5 Hz) was



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consistent with the data. The motif was confirmed by X-ray diffraction studies (Figure 1).[11,12]

First, total conversion of **1a** was obtained using an excess of the **2A** (2 equiv). This 1:2 ratio between epoxide and diazo reagent was maintained for the rest of the study. A search for the best catalytic combination was performed. The results are summarized in Table 1 for ruthenium complexes. The phenanthroline is clearly important, because in its absence the reaction leads to larger amounts of the undesired cyclooctene **5a** (entries 2 and 3; up to 30% of **5a**). Most probably, phen acts as a donor chelate ligand which stays on the metal throughout the reaction and the catalytic cycle. Changing the nature of the counterion additionally improved the conversions (entries 4–6). The reactions were faster with lipophilic anions like TRISPHAT [tris(tetrachlorobenzenediolato) phosphate],[13] BAr_F, and SbF_6, when compared to that with PF_6. Not surprisingly, conversions were lower with an anion which is able to coordinate to the metal center (TRISPHAT-N).[14] The complex $[Cp^*Ru(CH_3CN)_3]$[7b] (Cp^* = pentamethylcyclopentadienyl) and its mono-CF_3 analogue did not improve the transformation (entries 8–10). Other metal sources were briefly tested. While copper salts did not induce the formation of the dioxene product, only a small amount (10%) of **3aA** was observed in the reaction catalyzed by $[Rh_2(OAc)_4]$. The 1:1 combination of phen and the salt [**4**][BAr_F] (entry 6) was thus selected and used in further experiments.

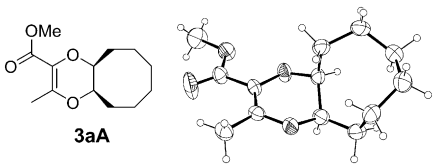
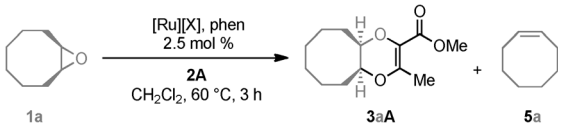


Figure 1. ORTEP view of the crystal structure of the *cis*-configurated **3aA**. Thermal ellipsoids are drawn at 50% probability.

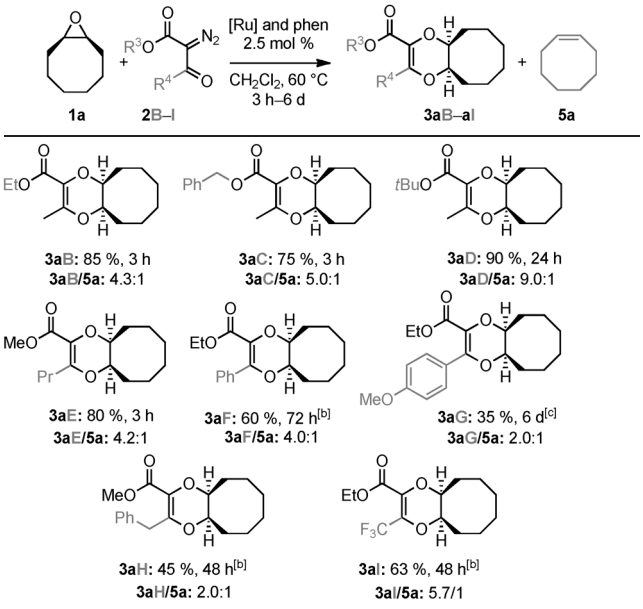
Table 1: Ruthenium complex selection.[a]



Entry	[Ru]	Anion	Conv.[b]	**3/5**[c]
1	$[CpRu(CH_3CN)_3]$	PF_6	86	4.5:1
2[d]	[CpRu(naphthalene)]	PF_6	69[d]	2.5:1
3[d]	$[CpRu(CH_3CN)_3]$	PF_6	85[d]	2.5:1
4	$[CpRu(CH_3CN)_3]$	SbF_6	94	4.4:1
5	$[CpRu(CH_3CN)_3]$	TRISPHAT	95	3.7:1
6	$[CpRu(CH_3CN)_3]$	BAr_F	100	4.4:1
7	$[CpRu(CH_3CN)_3]$	TRISPHAT-N	45	2:1
8	$[Cp^*Ru(CH_3CN)_3]$	PF_6	63	2:1
9	$[Cp^*Ru(CH_3CN)_3]$	SbF_6	42	2.4:1
10	$[(C_{10}H_{12}F_3)Ru(CH_3CN)_3]$	PF_6	44	2.4:1

[a] Reaction conditions: diazo compound **2A** (0.64 mmol), [Ru] and phen (2.5 mol % each), and **1a** (0.32 mmol) in CH_2Cl_2 (0.6 mL) for 3 h at 60°C. [b] Conversions of **1a** monitored by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal reference. [c] Ratio was determined by ^1H NMR analysis of the crude reaction mixture. [d] Without phen ligand.

Table 2: Diazo reagent scope.[a]

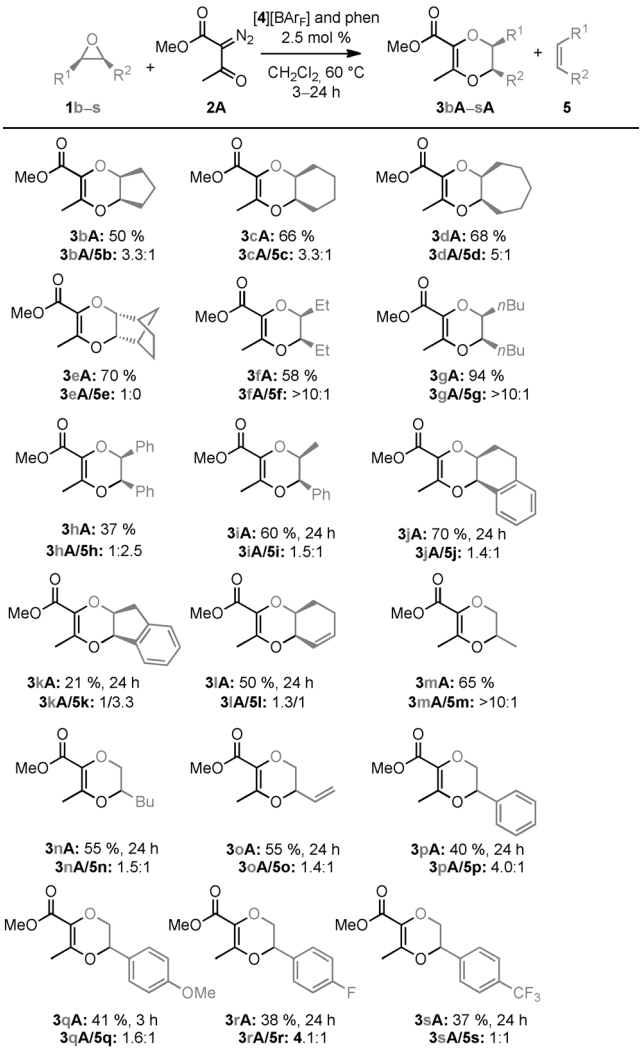


[a] Reaction conditions: diazo compound **2B–I** (0.64 mmol), **1a** (0.32 mmol), [**4**][BAr_F], and phen (2.5 mol % each) in CH_2Cl_2 (0.6 mL) at 60°C. Reaction times and ratios between dioxene and corresponding alkenes are indicated. Yield of isolated compound **3** is an average of at least two reactions. [b] Conv. = 80%. [c] Conv. = 81%.

Diazo reagents with different alkyl ester substituents, **2B–I**, were then tested and reactions with **1a** were allowed to run until full conversion (Table 2). Good yields of the isolated products **3** were afforded with bulkier alkyl esters, sometimes after prolonged reaction times (**3aB–aD**). With the reagents **2B–D**, dioxene formation was clearly favored over the alkene formation. In all cases, *cis* isomers were obtained as determined by NMR spectroscopy. The preference for the *syn*-stereoselective epoxide opening was confirmed with reagents **2E–I**, which bear substituents other than methyl in the α-position of the keto group. In the presence of a propyl chain (**2E**, R^4 = Pr), a similar reactivity was observed (**3aE**). With aryl and benzyl residues, reactions were slower and lower yields were obtained (**3aF–H**). In the case of the CF_3-substituted diazo **2I**, a longer reaction time was also necessary (80% conversion after 48 h) to afford **3aI** as a single stereoisomer (63% yield upon isolation). Such a trifluoromethylated heterocycle is related to known agrochemicals, the preparation of which requires six steps.[15]

The reaction was then tested with a variety of *cis*-configurated epoxides (**1b–l**), using **2A** as the diazo reagent (Table 3). Satisfactorily, the 1,4-dioxene products **3bA–lA** were obtained in all cases as single *cis* isomers irrespective of the cyclic or acyclic nature of the oxiranes.[16,17] Even the sterically crowded epoxide **1e** reacted well under the standard conditions. By using the nonsymmetrical disubstituted oxiranes **1i–l**, reactions proceeded equally well. Importantly, in addition to being *syn* stereoselective, ring openings were fully regioselective as single dioxene products **3iA–lA** were again obtained.[18] Clearly, the substitution reactions occur at the more activated carbon centers bearing aryl or vinyl substitu-

Table 3: Substrate scope.[a]



[a] Reaction conditions: diazo compound **2 A** (0.64 mmol), **1 b–s** (0.32 mmol), [**4**][BAr$_F$], and phen (2.5 mol % each) in CH_2Cl_2 (0.6 mL) at 60 °C. Ratios between dioxene and the corresponding alkenes are indicated. Yield of the isolated compound **3** is an average of at least two reactions. Reaction time 3 h, unless otherwise stated.

ents. Encouraged by these results, reactions were attempted with the monosubstituted substrates **1 m–s**. To our satisfaction, full control over the regioselectivity was again obtained, with the ring opening occurring only at the more substituted carbon atom. These important observations will be discussed in the mechanistic discussion (see below). Interestingly, with vinyl epoxides **1 l–o**, only the 1,4-dioxenes **3 lA** and **3 oA** were isolated. These results contrast with literature precedents for which products of [1,2]-insertion or [2,3]-sigmatropic rearrangements were observed, however such compounds are absent from the current transformation.[2d,j,k] Also, with epoxides carrying aryl substituents, slower reactions and lower yields were globally observed. Possibly, **4** reacts with the aromatic rings, thus leading to a decrease in the effective concentration of the catalyst.[19,20]

To shed light on the process, the styrene oxides **1 p–r** were then used in highly enantioenriched forms (Table 4). Both

Table 4: Chirality transfer.[a]

Entry	X[b]	Substrate	e.r.[c]	Product	e.r.[c]
1	H	(+)-(*R*)-**1 p**	99.5:0.5	(−)-(*R*)-**3 pA**	97:3
2	H	(−)-(*S*)-**1 p**	99.5:0.5	(+)-(*S*)-**3 pA**	97:3
3	OMe	(+)-(*R*)-**1 q**	99.0:1.0	(−)-**3 qA**	77:23
4	F	(+)-(*R*)-**1 r**	98.5:1.5	(−)-**3 rA**	94:6

[a] Reaction conditions: see Table 3, entries 15–17. [b] The *para* substituent on substrates **1 p**, **1 q**, and **1 r**. [c] Determined by CSP-HPLC. Average of at least two reactions.

(*R*)- and (*S*)-**1 p** were tested and the product **3 pA** was obtained with a 97:3 e.r. in favor of the levo- and dextrorotatory enantiomers respectively. With (*R*)-**1 q** and (*R*)-**1 r**, strong and slight decreases in the enantiospecificity of the reaction were noticed (**3 qA**: e.r. 77:23 and **3 rA**: e.r. 94:6). The origin of this variation is discussed in the mechanism section.

Care was taken to determine the absolute configuration of the ring-opened products. It was established by vibrational circular dichroism (VCD).[21,22] IR absorption and VCD spectra were measured for solutions (CD_2Cl_2) of both (−)- and (+)-**3 pA** and compared to the most stable conformer of (*S*)-**3 pA** (Figure 2), thus accounting for about 95 % according

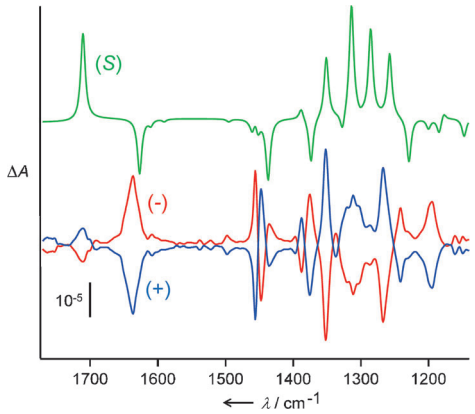
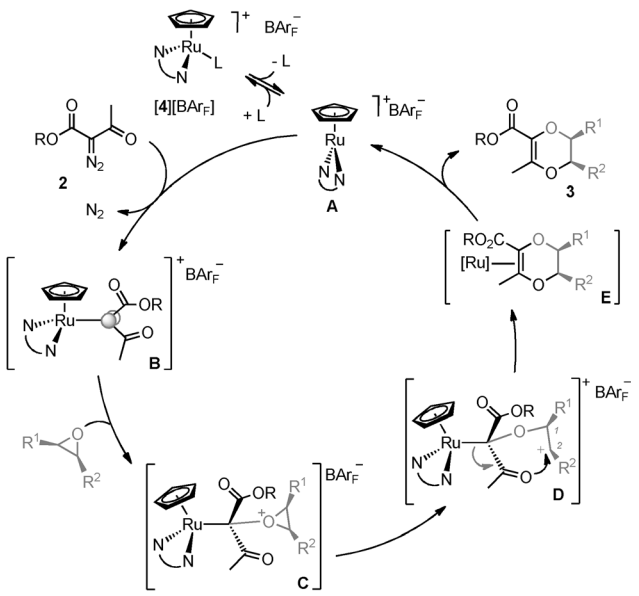


Figure 2. Experimental VCD spectra (CD_2Cl_2, 298 K) of (−)-**3 pA** (red) and (+)-**3 pA** (blue). Calculated spectrum of (*S*)-**3 pA** (green).

to its Boltzmann weight. Overall, a good agreement between the experimental and theoretical spectra was observed, thus allowing the assignment of *S* and *R* configurations for the dioxenes (+)- and (−)-**3 pA**, respectively. This finding was confirmed by an X-ray crystallographic study of (+)-**3 pA**.[23] These results clearly indicate that the formation of **3 pA** occurs with retention of configuration.

A mechanistic rationale, consistent with all the experimental information collected, is proposed in Scheme 2. The catalyst precursor [**4**][BAr$_F$] reacts with phen to generate a [Cp(phen)(CH_3CN)Ru][BAr$_F$] species which, upon dissociation of the monodentate ligand, forms the catalytically active 16-e$^-$ complex **A**. The diazo reagents **2** then react with this electron-deficient species to afford the metal carbene intermediate **B**. At this stage, a nucleophilic attack of the epoxide



Scheme 2. Mechanistic rationale. $\widehat{NN}$ represents the ligand phen. $R^2 > R^1$ in terms of electron-donating ability.

occurs and the metal oxonium ylide intermediate **C** is formed. Promoted by strain and by the electrophilic activation, a C–O bond cleavage occurs in the direction of the carbon atom which better stabilizes the developing positive charge. This step (**C**→**D**) involving an S_N1-like pathway explains the observed regioselectivity.[24] The carbocationic intermediate **D** is then trapped by the keto group to form the cyclic 1,4-dioxene skeleton. To retain the original configuration of the reacting carbon center, this step (**D**→**E**) must be fast, otherwise a racemization/epimerization occurs by a scrambling of the stereotopic faces through an internal rotation around the C1–C2 bond. It is fortunately happening only with **1q** for which the intermediate **D** is strongly stabilized by the *para*-methoxy group. The products **3** are then released and the catalytic cycle continues.[25]

In conclusion, a new reactivity is reported for metal carbene reactions with epoxides owing to the combination of 1,10-phenanthroline and $[CpRu(CH_3CN)_3][BAr_F]$ as the catalyst. Novel 1,4-dioxene motifs of the type **3** are obtained as single regio- and stereoisomers. A *syn* stereochemistry (retention, e.r. up to 97:3) is observed for the ring opening, which behaves as an S_N1-like transformation. Further applications of this approach are looked for.

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[1] A. K. Yudin, *Aziridines and epoxides in organic synthesis*, Wiley, Weinheim, **2006**, pp. 1 online resource (xxi, p. 492).
[2] a) G. Wittig, M. Schlosser, *Tetrahedron* **1962**, *18*, 1023–1028; b) H. Nozaki, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1965**, *6*, 2563–2567; c) H. Nozaki, H. Takaya, R. Noyori, *Tetrahedron* **1966**, *22*, 3393–3401; d) M. Kapps, W. Kirmse, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 75; *Angew. Chem.* **1969**, *81*, 86; e) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**; f) W. Kirmse, R. Lelgemann, K. Friedrich, *Chem. Ber.* **1991**, *124*, 1853–1863; g) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263–309; h) A. Oku, T. Mori, Y. Sawada, *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 934–944; i) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070; j) K. J. Quinn, N. A. Biddick, B. A. DeChristopher, *Tetrahedron Lett.* **2006**, *47*, 7281–7283; k) D. J. Mack, L. A. Batory, J. T. Njardarson, *Org. Lett.* **2012**, *14*, 378–381.
[3] M. G. Martin, B. Ganem, *Tetrahedron Lett.* **1984**, *25*, 251–254.
[4] The high stereospecificity of the reaction is consistent with a concerted fragmentation pathway: See Ref. [2g].
[5] Previously, it was shown that cyclopentadienyle ruthenium(II) complexes are effective catalysts for the decomposition of diazo reagents: a) G. Maas, T. Werle, M. Alt, D. Mayer, *Tetrahedron* **1993**, *49*, 881–888; b) H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223–2224; c) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, *J. Chem. Soc. Jpn.* **1995**, *68*, 1247–1262; d) W. Baratta, A. DelZotto, P. Rigo, *Chem. Commun.* **1997**, 2163–2164; e) A. Del Zotto, W. Baratta, P. Rigo, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3079–3081; f) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067–2096; g) C.-Y. Zhou, W.-Y. Yu, C.-M. Che, *Org. Lett.* **2002**, *4*, 3235–3238; h) C.-M. Che, J.-S. Huang, *Coord. Chem. Rev.* **2002**, *231*, 151–164; i) C.-Y. Zhou, W.-Y. Yu, P. W. H. Chan, C.-M. Che, *J. Org. Chem.* **2004**, *69*, 7072–7082; j) G. Maas, *Chem. Soc. Rev.* **2004**, *33*, 183–190; k) P. Le Maux, T. Roisnel, I. N. Nicolas, G. R. Simonneaux, *Organometallics* **2008**, *27*, 3037–3042; l) W.-W. Chan, S.-H. Yeung, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2009**, *12*, 604–607; m) M. Basato, C. Tubaro, A. Biffis, M. Bonato, G. Buscemi, F. Lighezzolo, P. Lunardi, C. Vianini, F. Benetollo, A. Del Zotto, *Chem. Eur. J.* **2009**, *15*, 1516–1526; n) L. Xia, Y. R. Lee, *Adv. Synth. Catal.* **2013**, *355*, 2361–2374; o) S. Moulin, H. Zhang, S. Raju, C. Bruneau, S. Dérien, *Chem. Eur. J.* **2013**, *19*, 3292–3296.
[6] a) See Ref. [5f]; b) E. P. Kündig, F. R. Monnier, *Adv. Synth. Catal.* **2004**, *346*, 901–904; c) A. Mercier, W. C. Yeo, J. Y. Chou, P. D. Chaudhuri, G. Bernardinelli, E. P. Kündig, *Chem. Commun.* **2009**, 5227–5229.
[7] a) J. L. Renaud, C. Bruneau, B. Demerseman, *Synlett* **2003**, 408–410; b) M. D. Mbaye, B. Demerseman, J. L. Renaud, L. Toupet, C. Bruneau, *Angew. Chem. Int. Ed.* **2003**, *42*, 5066–5068; *Angew. Chem.* **2003**, *115*, 5220–5222; c) M. D. Mbaye, B. Demerseman, J.-L. Renaud, C. Bruneau, *J. Organomet. Chem.* **2005**, *690*, 2149–2158.
[8] C. Tortoreto, T. Achard, W. Zeghida, M. Austeri, L. Guénée, J. Lacour, *Angew. Chem. Int. Ed.* **2012**, *51*, 5847–5851; *Angew. Chem.* **2012**, *124*, 5949–5953.
[9] M. Austeri, D. Rix, W. Zeghida, J. Lacour, *Org. Lett.* **2011**, *13*, 1394–1397.
[10] In product **3xY**, the first and second letters **x** and **Y** relate to the reactive epoxide **1x** and diazo **2Y** respectively.
[11] Product **3aA** was found to be moderately soluble in a 3:1 mixture of hexanes and CH_2Cl_2 at 25 °C. X-ray quality crystals were afforded and a structural analysis was performed (see Table S1 in the Supporting Information for details).
[12] For *syn*-stereoselective epoxide openings, see: a) B. M. Trost, A. Tenaglia, *Tetrahedron Lett.* **1988**, *29*, 2931–2934; b) J. D. Rainier, J. M. Cox, *Org. Lett.* **2000**, *2*, 2707–2709; c) S. Matsubara, H. Yamamoto, K. Oshima, *Angew. Chem. Int. Ed.* **2002**, *41*, 2837–2840; *Angew. Chem.* **2002**, *114*, 2961–2964; d) M. Pineschi, F. Bertolini, R. M. Haak, P. Crotti, F. Macchia, *Chem. Commun.* **2005**, 1426–1428; e) A. J. Cresswell, S. G. Davies, J. A. Lee,

P. M. Roberts, A. J. Russell, J. E. Thomson, M. J. Tyte, *Org. Lett.* **2010**, *12*, 2936 – 2939; f) L. Kohler, E. Schoffers, E. Driscoll, M. Zeller, C. Schmiesing, *Chirality* **2012**, *24*, 245 – 251.

[13] a) J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608 – 609; *Angew. Chem.* **1997**, *109*, 660 – 662; b) L. Hintermann, L. Xiao, A. L. Labonne, U. Englert, *Organometallics* **2009**, *28*, 5739 – 5748; c) G. N. M. Reddy, R. Ballesteros-Garrido, J. Lacour, S. Caldarelli, *Angew. Chem. Int. Ed.* **2013**, *52*, 3255 – 3258; *Angew. Chem.* **2013**, *125*, 3337 – 3340.

[14] a) S. Constant, R. Frantz, J. Müller, G. Bernardinelli, J. Lacour, *Organometallics* **2007**, *26*, 2141 – 2143; b) S. Constant, S. Tortoioli, J. Müller, D. Linder, F. Buron, J. Lacour, *Angew. Chem. Int. Ed.* **2007**, *46*, 8979 – 8982; *Angew. Chem.* **2007**, *119*, 9137 – 9140.

[15] a) H. G. Hahn, K. H. Chang, K. Dal Nam, J. Y. Jun, H. Mah, *Bull. Korean Chem. Soc.* **1999**, *20*, 1218 – 1220; b) H. G. Hahn, K. H. Chang, K. D. Nam, *Bull. Korean Chem. Soc.* **2001**, *22*, 149 – 153; c) H. G. Hahn, K. H. Chang, K. Dal Nam, S. Y. Bae, H. Mah, *Heterocycles* **1998**, *48*, 2253 – 2261; d) H. G. Hahn, K. H. Chang, K. Dal Nam, S. Y. Bae, H. Mah, *J. Heterocycl. Chem.* **2000**, *37*, 1003 – 1008.

[16] Corresponding alkenes were usually observed in most cases as minor products with percentages around 5–15 %.

[17] The *cis* configuration was ascertained by X-ray analysis. The ORTEP diagram of **3hA** is detailed in the Figure S1.

[18] Regio- and stereoselectivity were ascertained by X-ray analysis. The ORTEP diagram of **3jA** is detailed in the Figure S2.

[19] R. Hermatschweiler, I. Fernández, P. S. Pregosin, F. Breher, *Organometallics* **2006**, *25*, 1440 – 1447.

[20] Alternatively, as a result of the the presence of the benzo groups, ansa-ligated Ru^{II} η^6-arene complexes made by ligand exchange between the aryl and cyclopentadienyl moieties could also be formed: a) Y. Miyaki, T. Onishi, H. Kurosawa, *Inorg. Chim. Acta* **2000**, *300 – 302*, 369 – 377; b) P. Pinto, A. W. Goetz, G. Marconi, B. A. Hess, A. Marinetti, F. W. Heinemann, U. Zenneck, *Organometallics* **2006**, *25*, 2607 – 2616; c) B. Therrien, *Coord. Chem. Rev.* **2009**, *253*, 493 – 519.

[21] a) L. A. Nafie, T. A. Keiderling, P. J. Stephens, *J. Am. Chem. Soc.* **1976**, *98*, 2715 – 2723; b) G. Holzwarth, E. C. Hsu, H. S. Mosher, T. R. Faulkner, A. Moscowit, *J. Am. Chem. Soc.* **1974**, *96*, 251 – 252; c) T. B. Freedman, X. L. Cao, R. K. Dukor, L. A. Nafie, *Chirality* **2003**, *15*, 743 – 758.

[22] Calculations of several conformers were done at the DFT B3LYP level of theory using a 6-311++g(d,p) basis set. Frequencies were scaled by 0.98. VCD spectra were constructed from calculated rotational strengths assuming Loretzian band shape with a half-width at half maximum of 5 cm^{-1}. All calculations were performed using Gaussian 09, Revision C.01.

[23] The product (+)-**3pA** was purified up to a 99.5:0.5 e.r. by semipreparative CSP-HPLC and crystallized in a dichloromethane/pentane mixture. Using a single crystal, the Flack parameter was affined to 0.0(2) value indicative of a *S* configuration as well. The ORTEP diagram of (+)-**3pA** is detailed in the Figure S3.

[24] With disubstituted unsymmetrical epoxides, the C–O bond cleavage occurs to preferentially form benzylic carbenium ions. With monosubstituted epoxides, secondary rather than primary carbocations are formed.

[25] Preliminary computational studies starting from the intermediate **B** ($R^1 = H$, $R^2 = Ph$) confirm the proposed mechanism. The rate-limiting step of the reaction is the coordination of the epoxide (+ 9.8 kcal mol^{-1}) en route to the oxonium ylide intermediate **C**. From this species, the formation of intermediate **D** requires only 1.7 kcal mol^{-1}. The final C–O bond formation is a barrier less process (+ 0.4 kcal mol^{-1}), which explains why the retention of configuration is so kinetically favored. Further calculations are in progress.

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Original Reactivity of α-Diazo-β-ketoesters Catalyzed by CpRu Complexes

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§SCS-Metrohm Foundation Award for best oral presentation

Abstract: Using α-diazo-β-ketoesters as reagents and combinations of CpRu fragments and diimine ligands as catalysts, a series of original transformations have been obtained that can be rationalized by the formation of metal carbenes and metal-bound ylide intermediates. Interesting 1,3-dioxole, enol-acetal and 1,4-dioxene motifs are obtained directly when the reactive mixture is reacted in presence of aldehydes or ketones, THF and epoxides.

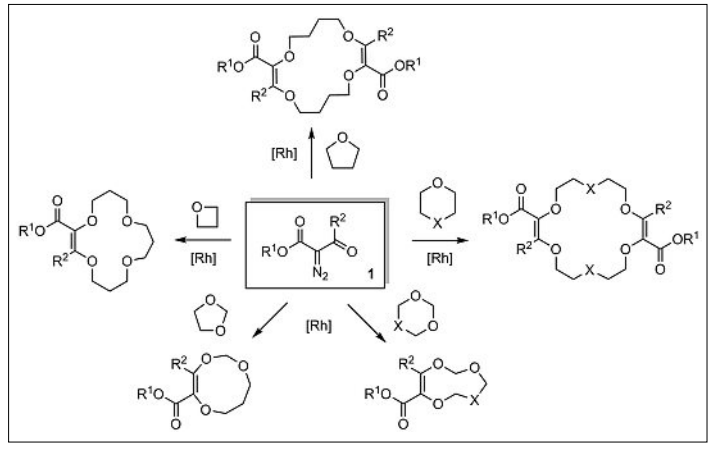
Keywords: Diazo compounds · Insertions · Metal carbenes · Oxonium ylide

Efficient synthesis and catalysis are in continual demand from academic and industrial laboratories. One effective approach to reach this goal is to use, as reaction intermediates, metal carbenes generated by the decomposition of diazo compounds with catalytic amounts of transition metals.[1] The approach is extremely versatile and high levels of selectivity are attained in a large number of transformations (dimerization, metathesis, cyclopropanation, insertion, ylide generation and subsequent rearrangement/macrocyclization reactions).[1–3] The reactivity of the metal carbene intermediates depends strongly on both the substituents on the carbon atom and the associated metal, which can control reactivity and selectivity. While most applications use acceptor and donor/acceptor diazo precursors and metals salts/complexes derived from copper[4] and rhodium,[5] many interesting transformations can be found outside this scheme. Herein, in such a development, the reactivity of metal carbenes obtained by the decomposition of α-diazo-β-ketoesters **1** in the presence of CpRu complexes as catalysts is detailed.

α-Diazo-β-ketoesters are readily prepared and easy-to-handle acceptor/acceptor reagents that are characterized by a better chemical stability and a moderate reactivity compared to other diazo derivatives. These compounds react in presence of certain metal sources to form electrophilic carbene intermediates. In this context, our group recently reported their reaction in presence of Lewis basic cyclic ethers and of dirhodium complexes to yield original 16- and 18-membered macrocycles and medium-sized 8- or 9-membered rings in particular (Scheme 1).[6] The results were rationalized by invoking the formation of metal-free oxonium ylide intermediates.[6a,d] It was then interesting to study if different reactivities could be achieved by using metal catalysts that would form metal-bound ylide intermediates instead, and cyclopentadienyle ruthenium complexes in particular.

In fact, ruthenium complexes,[7] including CpRu derivatives[8] have become an interesting alternative to copper and dirhodium salts or complexes for the decomposition of diazo reagents. For instance, Del Zotto and coworkers have shown that complex $[CpRu(PPh_3)_2Cl]$ reacts with ethyl diazoacetate to promote transformations such as cyclopropanations, N-H and S-H insertions or the reaction of tertiary amines into ammonium ylides that undergo [1,2]-Stevens shifts or sigmatropic rearrangements.[8] Having previously shown that combinations of $[CpRu(CH_3CN)_3][PF_6]$[9] and diimine ligands efficiently catalyze enantioselective Carroll rearrangement[10] and decarboxylic allylic etherification reactions,[11] we decided to examine the influence of this catalytic combination[12] on reactions of α-diazo-β-ketoesters with Lewis basic moieties.

First, simple reactions leading to results in line with the common knowledge in the field were tested to establish the viability of the CpRu/diimine combination as catalyst. For instance, insertions into the O–H bond of alcohols.[1,2d,2e,13] and condensations with nitriles[14] were investi-



Scheme 1. Dirhodium-catalyzed one-pot condensation of α-diazoacetoacetates and cyclic ethers.

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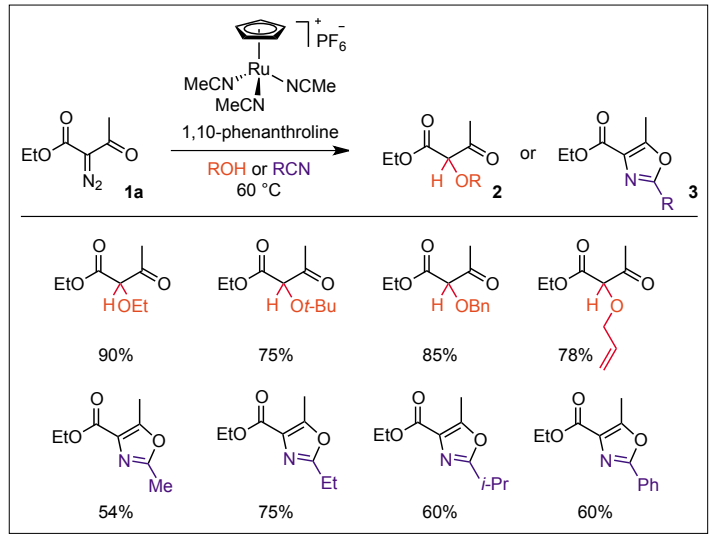
gated. Practically, ethyl diazoacetoacetate **1a** was dissolved in various alcohols and nitriles together with a catalytic amount of $[CpRu(CH_3CN)_3][PF_6]$ and 1,10-phenanthroline (phen, 2.5 mol% each). A moderate heating to 60 °C was necessary to induce a gas evolution. To our satisfaction, complete conversions were achieved in all cases (45–60 min) and the corresponding products of insertion **2** or cyclization **3** were isolated in moderate to good yields (Scheme 2).[15]

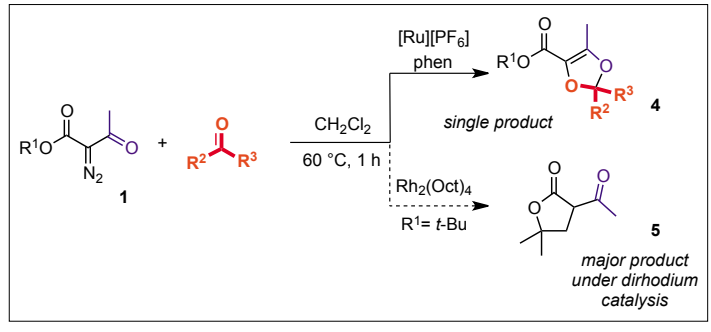
With these results in hand, condensation reactions with carbonyl moieties were examined.[16] Diazocarbonyl compounds are in fact known to react with aldehydes and ketones.[1] In most cases, the carbonyl group acts as a nucleophile, reacting with the electron-deficient carbene center to form carbonyl ylide intermediates that behave as 1,3-dipoles.[17] Several competing pathways are then possible including the formation of epoxides, 1,3-dioxolane and dioxolene moieties through intramolecular rearrangements, intermolecular [3+2]-cycloadditions and condensations.[18]

Interestingly, the use of 1 mol% of CpRu complex and phenanthroline in methylene chloride allowed the reaction to proceed using only one equivalent of the corresponding carbonyl compound (Scheme 3).[15] Reactions were either more selective or faster than with classical dirhodium and copper catalysts as, in this case, only 1,3-dioxole products **4** were obtained and isolated in good yields. These results contrasted with that of $Rh_2(Oct)_4$ catalysis which, under the same conditions using the *tert*-butyl ester as substrate (R^1=*t*-Bu, Scheme 3) afforded predominantly lactone **5** in the crude reaction mixture.[19] Clearly, competition between intramolecular C-H insertions and intermolecular carbonyl ylide formation is avoided by using the combination of $[CpRu(CH_3CN)_3][PF_6]$ and phenanthroline as catalyst. The influence of the diimine ligand was ascertained by using enantiopure pymox (Scheme 4) instead of phen as ligand. Even milder conditions could be used (25 °C, 24 h) to afford an enantioselective condensation forming products **4** with enantiomeric excesses up to 50%.[15] These results advocate for the formation of metal-bound carbonyl ylide intermediates **6** (Scheme 5); subsequent ring closure affording products of type **4**.

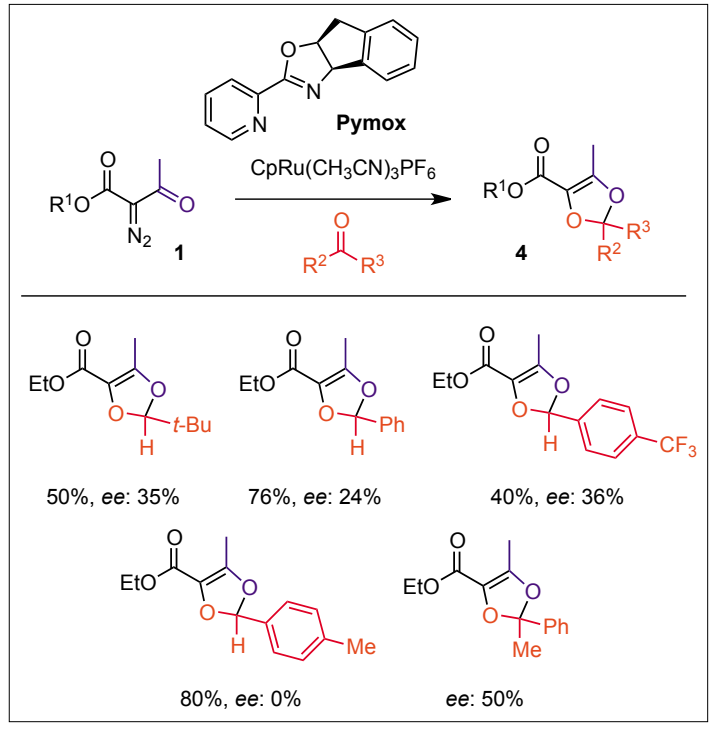
Then, when THF was tested as Lewis basic partner under CpRu/diimine catalysis, an unprecedented 1,3-C-H insertion reaction occurred giving rise to original enol-acetal products of type **7** (Scheme 6).[20,21] Interestingly, in the field of intermolecular metal carbene C–H insertions into THF,[22] only 'classical' derivatives of type **8** were previously reported with a C–C bond formed by insertion of the carbene into a C–H bond α to the oxygen ether atom of THF. Evidence for the formation of macrocyclization adducts could not be found (*e.g.* Scheme 1).[6] In contrast with what had been observed with donor/acceptor carbenes,[22b] the kinetically favored formation of C–O instead of C–C bond adducts is thus attained using the combination of $[CpRu(CH_3CN)_3][PF_6]$ and phen as catalyst. In order to gain some mechanistic insight on the transformation, a series of experiments was performed using a 1:1 mixture of THF and THF-d_8. The absence of cross-over and the occurrence of a primary kinetic isotope effect were noticed. Such experiments suggest a concerted hydrogen transfer as detailed



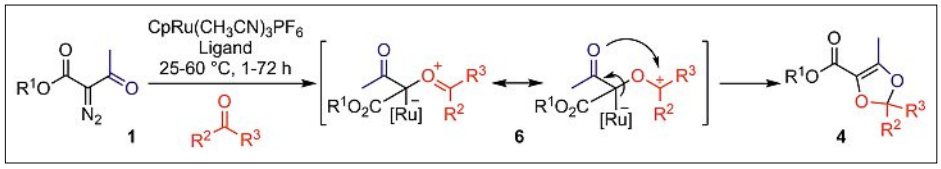
Scheme 2. Insertions and condensation reactions of diazocarbonyls with alcohols and nitriles.



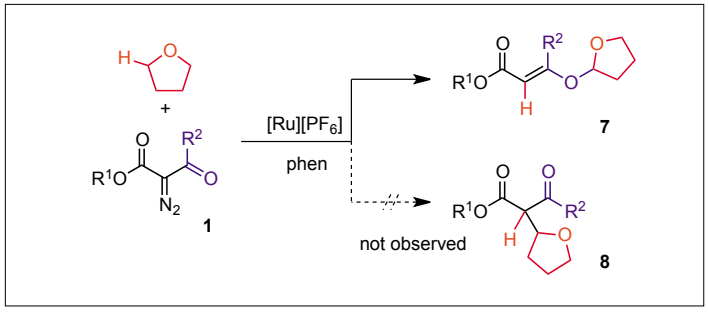
Scheme 3. Preferred condensation over C-H insertion pathway in the CpRu-mediated reactions of diazocarbonyls with aldehydes and ketones. [Ru] indicates complex $[CpRu(CH_3CN)_3]$.



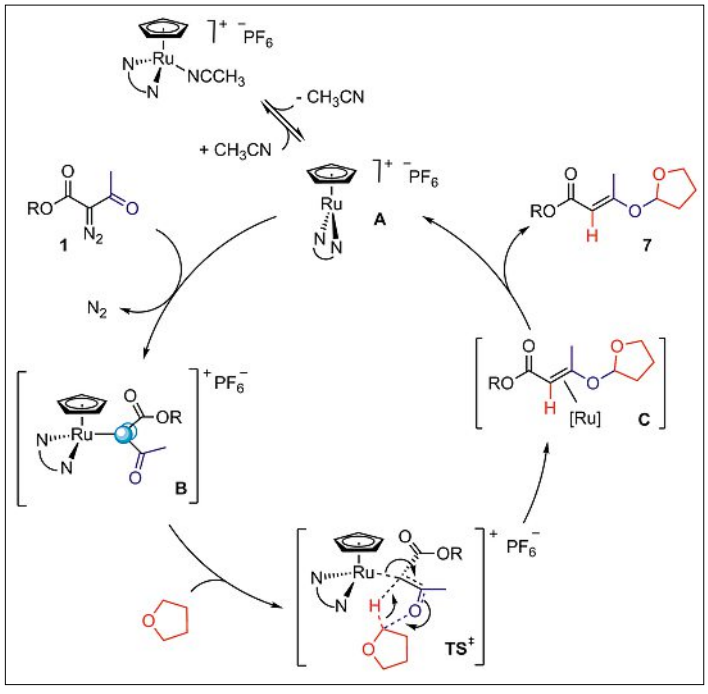
Scheme 4. Enantioselective condensations.



Scheme 5. Mechanistic rationale.



Scheme 6. Preferred 1,3-C-H insertion pathway. [Ru] indicates complex [CpRu(CH$_3$CN)$_3$].

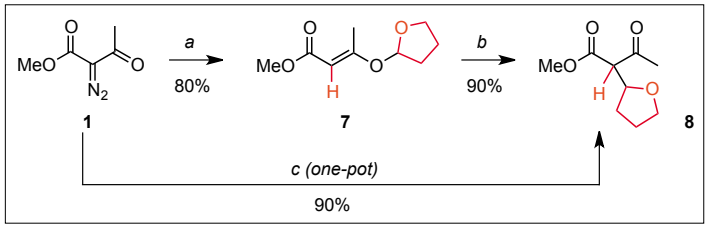


Scheme 7. Mechanistic rationale for the 1,3-C-H insertion into THF.

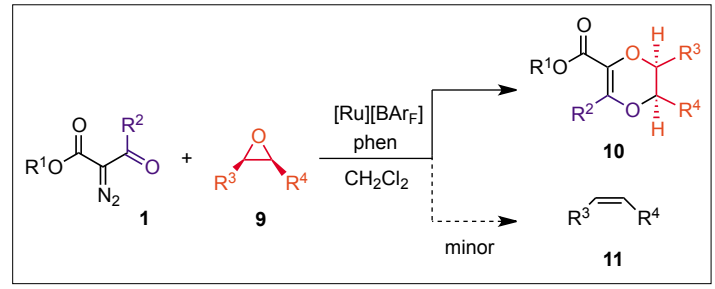
and C–H bonds takes place in a five-membered transition state; this step determines the configuration of enol functional group.

It was further noted that compounds **7** rearrange to the 'classical' products **8** of C–C bond formation when treated with Lewis acids (Scheme 8, step b). For instance, in the presence of Cu(OTf)$_2$ or TMSOTf (5 mol%), a dissociation occurs to form two reactive enolate and oxycarbenium intermediates that recombine. The C–H insertion and the rearrangement steps can be united in a one-pot sequential process; derivatives **8** are then obtained in a higher yield than for the two-step procedure.

Finally, in a recent study,[24] epoxides were used as Lewis basic reactant together with α-diazo-β-ketoesters reagents and the CpRu/diimine catalyst combination. Previously, only few examples of reactions of this type between metal carbenes and epoxides had been reported leading mainly to deoxygenation processes and to the corresponding alkenes by a stereospecific oxygen removal.[25] An unexpected result was again obtained as the treatment of epoxides **9** under the conditions optimized for the reaction with THF led to the prevalent formation of dioxene motifs of type **10** (Scheme 9). In practice, the stereoselective ring opening and three-atom insertion reaction was performed by the simple addition of two equivalents of the α-diazo-β-ketoester reagent to a methylene chloride solution of the epoxide (one equivalent) in the presence [CpRu(CH$_3$CN)$_3$][BAr$_F$] and phen (2.5 mol% each). At 60 °C and under relatively high concentration (0.5 M in **1**), conversion of the diazo reagent is complete in usually 24 h. In the crude reaction mixtures, dioxene adducts of type **10** were always the major components over



Scheme 8. a) [CpRu(CH$_3$CN)$_3$][PF$_6$] (2.5 mol%), phen (2.5 mol%), THF, 60 °C, 3 h; b) TMSOTf or Cu(OTf)$_2$ (5 mol%), CH$_2$Cl$_2$, 0→25 °C, 1 h; c) [CpRu(CH$_3$CN)$_3$][PF$_6$] (2.5 mol%), phen (2.5 mol%), THF (1 equiv.), CH$_2$Cl$_2$, 60 °C, 24 h and then TMSOTf or Cu(OTf)$_2$ (5 mol%), CH$_2$Cl$_2$, 0→25 °C, 1 h.



Scheme 9. Dioxene formation *via* three-atom insertion reactions of diazocarbonyles **1** into epoxides **9**. [Ru] indicates complex [CpRu(CH$_3$CN)$_3$].

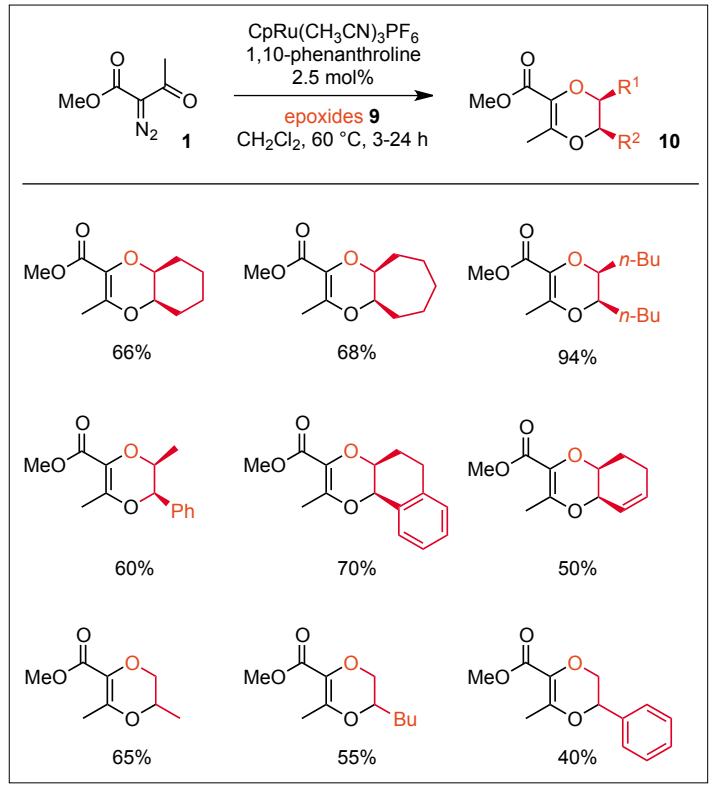
in the mechanistic rationale (Scheme 7). After ligation of the phenanthroline moiety to the CpRu fragment, dissociation of the last acetonitrile leads to the formation of a catalytically active 16-electron species **A**. This electron-deficient entity promotes the decomposition of α-diazo-β-ketoester reagents **1** by a classic addition of the 'enolate' to the Lewis acidic complex and elimination of molecular nitrogen. It affords the metal carbenes intermediates of type **B**. At this stage, it is proposed that a concerted reaction occurs that involves the keto group of the carbene and the less hindered C$_\alpha$–H bond of the ether moiety.[23] Concomitant formation of the new C–O alkenes **11** derived from the deoxygenation pathway.

Noteworthy, dioxenes **10** were formed as single stereoisomers as indicated by ^{1}H NMR spectroscopic and X-ray diffraction analyses; *cis*-epoxides giving rise to *cis*-dioxene derivatives in perfectly *syn*-stereoselective ring opening reactions (Scheme

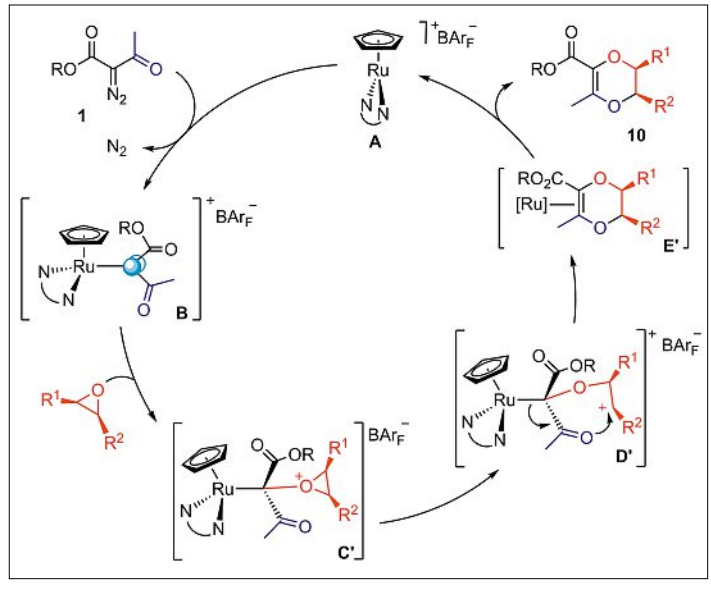
10). Furthermore, when using unsymmetrical *cis*-disubstituted and monosubstituted epoxides, ring-opening products were always obtained as single regioisomers, the substitution reactions occurring at the activated carbon centers (benzylic, allylic or more substituted). To shed some light on the process, both (*R*)- and (*S*)-styrene oxide were tested and the corresponding dioxene product was obtained with a 94% *ee*; X-ray and vibrational circular dichroism analyses clearly indicating the occurrence of a retention of configuration for the ring opening.

A mechanistic rationale coherent with the experimental information is proposed in Scheme 11. It starts with the same species **A** and **B** detailed for the THF functionalization (Scheme 7). Then, a nucleophilic attack of the epoxide occurs on metal carbene **B** and a metal-bound oxonium ylide intermediate **C'** is formed. Promoted by strain and by the electrophilic activation, a C–O bond cleavage occurs in the direction of the carbon that stabilizes better the developing positive charge. This step involving a S_N1-like pathway explains the observed regioselectivity. Carbocationic intermediate **D'** is then trapped rapidly by the keto group at proximity to form the cyclic 1,4-dioxene skeleton – and this with retention of the original configuration of the reacting carbon center in **E'**. Products **10** are then released and the catalytic cycle continues.

In conclusion, by using α-diazo-β-ketoesters as reagents and combinations of CpRu fragments and diimine ligands as decomposition catalysts, a series of original transformations have been obtained that are best rationalized by the formation of metal carbenes and metal-bound ylide intermediates. Interesting 1,3-dioxole **4**, enol-acetal **7** and 1,4-dioxene **10** motifs were obtained in usually good yields by the use of substrates of common Lewis basic moieties such as aldehydes or ketones, THF and epoxides. The reactions proceeded with usually high levels of stereo (and regio) selectivity. Further applications are looked for.



Scheme 10. Stereo- and regioselective ring openings.



Scheme 11. Mechanistic rationale. N⌒N represents ligand phen. R^2>R^1 in terms of electron-donating ability.

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[1] M. P. Doyle, M. A. McKervey, T. Ye, 'Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides', Wiley, New York, **1998**.

[2] a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; c) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911; d) Z. H. Zhang, J. B. Wang, *Tetrahedron* **2008**, *64*, 6577; e) M. M. Diaz-Requejo, P. J. Perez, *J. Organomet. Chem.* **2005**, *690*, 5441; f) C. P. Casey, R. L. Anderson, *J. Organomet. Chem.* **1974**, *73*, C28.

[3] R. H. Grubbs, 'Handbook of Metathesis', Wiley-VCH, **2003**.

[4] a) W. Kirmse, *Angew. Chem. Int. Ed.* **2003**, *42*, 1088; b) R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 3300; c) W. R. Moser, *J. Am. Chem. Soc.* **1969**, *91*, 1141; d) H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, 5239; e) H. Nozaki, S. Moriuti, M. Yamabe, R. Noyori, *Tetrahedron Lett.* **1966**, 59 f) M. P. Doyle, C. S. Peterson, D. L. Parker, *Angew. Chem. Int. Ed.* **1996**, *35*, 1334.

[5] a) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; b) S. Omalley, T. Kodadek, *Tetrahedron Lett.* **1991**, *32*, 2445; c) S. Omalley, T. Kodadek, *Organometallics* **1992**, *11*, 2299; d) J. L. Maxwell, K. C. Brown, D. W. Bartley, T. Kodadek, *Science* **1992**, *256*, 1544; e) R. Paulisse, H. Reimling, E. Hayez, A. J. Hubert, P. Teyssie, *Tetrahedron Lett.* **1973**, 2233; f) H. Brunner, H. Kluschanzoff, K. Wutz, *Bull. Soc. Chim. Belg.* **1989**, *98*, 63; g) M. Kennedy, M. A. Mckervey, A. R. Maguire, G. H. P. Roos, *J. Chem. Soc., Chem. Commun.* **1990**, 361; h) S. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett.* **1990**, *31*, 5173; i) D. Marcoux, A. B. Charette, *Angew. Chem. Int. Ed.* **2008**, *47*, 10155; j) M. P. Doyle, B. D. Brandes, A. P. Kazala, R. J. Pieters, M. B. Jarstfer, L. M. Watkins, C. T. Eagle, *Tetrahedron Lett.* **1990**, *31*, 6613; k) M. P. Doyle, W. R. Winchester, J. A. A. Hoorn, V. Lynch, S. H. Simonsen, R. Ghosh, *J. Am. Chem. Soc.* **1993**, *115*, 9968; l) M. P. Doyle, W. R. Winchester, M. N. Protopopova, A. P. Kazala, L. J. Westrum, *Org. Synth.* **1996**, *73*, 13; m) M. P. Doyle, Q. L. Zhou, C. E. Raab,

G. H. P. Roos, S. H. Simonsen, V. Lynch, *Inorg. Chem.* **1996**, *35*, 6064; n) M. P. Doyle, W. R. Winchester, M. N. Protopopova, P. Muller, G. Bernardinelli, D. Ene, S. Motallebi, *Helv. Chim. Acta* **1993**, *76*, 2227; o) M. P. Doyle, W. H. Hu, I. M. Phillips, C. J. Moody, A. G. Pepper, A. M. Z. Slawin, *Adv. Synth. Catal.* **2001**, *343*, 112.

[6] a) W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2010**, *49*, 7253; b) D. Rix, R. Ballesteros-Garrido, W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2011**, *50*, 7308; c) R. Ballesteros-Garrido, D. Rix, C. Besnard, J. Lacour, *Chem. Eur. J.* **2012**, *18*, 6626; d) M. Vishe, R. Hrdina, L. Guénée, C. Besnard, J. Lacour, *Adv. Synth. Catal.* **2013**, *355*, 3161.

[7] a) G. Maas, T. Werle, M. Alt, D. Mayer, *Tetrahedron* **1993**, *49*, 881; b) H. Nishiyama, Y. Itoh, H. Matsumoto, S. B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223; c) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247; d) C. M. Che, J. S. Huang, *Coord. Chem. Rev.* **2002**, *231*, 151; e) C. Y. Zhou, W. Y. Yu, P. W. H. Chan, C. M. Che, *J. Org. Chem.* **2004**, *69*, 7072; f) G. Maas, *Chem. Soc. Rev.* **2004**, *33*, 183; g) P. Le Maux, T. Roisnel, I. Nicolas, G. Simonneaux, *Organometallics* **2008**, *27*, 3037; h) W. W. Chan, S. H. Yeung, Z. Y. Zhou, A. S. C. Chan, W. Y. Yu, *Org. Lett.* **2010**, *12*, 604.

[8] a) G. Maas, T. Werle, M. Alt, D. Mayer, *Tetrahedron* **1993**, *49*, 881; b) H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223; c) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, *B. Chem. Soc. Jpn.* **1995**, *68*, 1247; d) W. Baratta, A. DelZotto, P. Rigo, *Chem. Commun.* **1997**, 2163; e) A. Del Zotto, W. Baratta, P. Rigo, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3079; f) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067; g) C.-Y. Zhou, W.-Y. Yu, C.-M. Che, *Org. Lett.* **2002**, *4*, 3235; h) C.-M. Che, J.-S. Huang, *Coord. Chem. Rev.* **2002**, *231*, 151; i) C.-Y. Zhou, W.-Y. Yu, P. W. H. Chan, C.-M. Che, *J. Org. Chem.* **2004**, *69*, 7072; j) G. Maas, *Chem. Soc. Rev.* **2004**, *33*, 183; k) P. Le Maux, T. Roisnel, I. N. Nicolas, G. R. Simonneaux, *Organometallics* **2008**, *27*, 3037; l) W.-W. Chan, S.-H. Yeung, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2009**, *12*, 604; m) M. Basato, C. Tubaro, A. Biffis, M. Bonato, G. Buscemi, F. Lighezzolo, P. Lunardi, C. Vianini, F. Benetollo, A. Del Zotto, *Chem. Eur. J.* **2009**, *15*, 1516; n) L. Xia, Y. R. Lee, *Adv. Synth. Catal.* **2013**, *355*, 2361; o) S. Moulin, H. Zhang, S. Raju, C. Bruneau, S. Dérien, *Chem. Eur. J.* **2013**, *19*, 3292.

[9] a) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067; b) E. P. Kündig, F. R. Monnier, *Adv. Synth. Catal.* **2004**, *346*, 901; c) A. Mercier, W. C. Yeo, J. Y. Chou, P. D. Chaudhuri, G. Bernardinelli, E. P. Kündig, *Chem. Commun.* **2009**, 5227.

[10] a) S. Constant, S. Tortoioli, J. Muller, J. Lacour, *Angew. Chem. Int. Ed.* **2007**, *46*, 2082; b) S. Constant, S. Tortoioli, J. Muller, D. Linder, F. Buron, J. Lacour, *Angew. Chem. Int. Ed.* **2007**, *46*, 8979.

[11] a) M. Austeri, D. Linder, J. Lacour, *Chem. Eur. J.* **2008**, *14*, 5737; b) M. Austeri, D. Linder, J. Lacour, *Adv. Synth. Catal.* **2010**, *352*, 3339.

[12] a) J. L. Renaud, C. Bruneau, B. Demerseman, *Synlett* **2003**, 408; b) M. D. Mbaye, B. Demerseman, J. L. Renaud, L. Toupet, C. Bruneau, *Angew. Chem. Int. Ed.* **2003**, *42*, 5066; c) M. D. Mbaye, B. Demerseman, J.-L. Renaud, C. Bruneau, *J. Organomet. Chem.* **2005**, *690*, 2149.

[13] a) E. Aller, D. S. Brown, G. G. Cox, D. J. Miller, C. J. Moody, *J. Org. Chem.* **1995**, *60*, 4449; b) P. Bulugahapitiya, Y. Landais, L. ParraRapado, D. Planchenault, V. Weber, *J. Org. Chem.* **1997**, *62*, 1630; c) J. L. Wood, G. A. Moniz, D. A. Pflum, B. M. Stoltz, A. A. Holubec, H. J. Dietrich, *J. Am. Chem. Soc.* **1999**, *121*, 1748; d) T. C. Maier, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 4594; e) S. F. Zhu, C. Chen, Y. Cai, Q. L. Zhou, *Angew. Chem. Int. Ed.* **2008**, *47*, 932; f) Y. Liang, H. L. Zhou, Z. X. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 17783; g) S. F. Zhu, Q. L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365; h) D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918.

[14] Y, Xu,. Y. L. Wang, S. Z. Zhu, *Synthesis* **2000**, 513.

[15] M. Austeri, D. Rix, W. Zeghida, J. Lacour, *Org. Lett.* **2011**, *13*, 1394.

[16] a) M. E. Alonso, P. Jano, *J. Heterocyclic Chem.* **1980**, *17*, 721; b) M. E. Alonso, A. W. Chitty, *Tetrahedron Lett.* **1981**, *22*, 4181; c) A. E. Russell, J. Brekan, L. Gronenberg, M. P. Doyle, *J. Org. Chem.* **2004**, *69*, 5269; d) V. Nikolaev, L. Hennig, H. Heimgartner, B. Schulze, V. Nikolaev, *Tetrahedron Lett.* **2006**, *47*, 2643; e) A. Padwa, J. Boonsombat, P. Rashatasakhon, *Tetrahedron Lett.* **2007**, *48*, 5938; f) V. V. Nikolaev, H. Heimgartner, A. Linden, I. S. Krylov, V. A. Nikolaev, *Eur. J. Org. Chem.* **2006**, 4737; g) V. V. Nikolaev, B. Schulze, H. Heimgartner, V. A. Nikolaev, *Heterocycles* **2007**, *73*, 433.

[17] D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50.

[18] J. Wang, 'Comprehensive Organometallic Chemistry III', Eds. D. M. P. Mingos, R. H. Crabtree, 'Applications II: Transition metal compounds in organic synthesis 2', Elsevier, Oxford, **2007**, Vol. 11 pp. 151–178.

[19] For related lactone formations, see: a) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, M. M. Pearson, *J. Am. Chem. Soc.* **1993**, *115*, 958; b) A. G. H. Wee, Q. Yu, *J. Org. Chem.* **1997**, *62*, 3324.

[20] C. Tortoreto, T. Achard, W. Zeghida, M. Austeri, L. Guénée, J. Lacour, *Angew. Chem. Int. Ed.* **2012**, *51*, 5847.

[21] Adducts **7** are characterized by ^{1}H NMR signals at 5.66 (d, J = 4 Hz, O-CH-O) and 5.32 (s, C=CH) ppm. The *E* configuration of the double bond was unambiguously determined by NOESY experiment and X-ray diffraction studies.

[22] a) H. M. L. Davies, T. Hansen, *J. Am. Chem. Soc.* **1997**, *119*, 9075; b) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063; c) M. M. Diaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Perez, *J. Am. Chem. Soc.* **2002**, *124*, 896; d) J. M. Fraile, J. I. Garcia, J. A. Mayoral, M. Roldan, *Org. Lett.* **2007**, *9*, 731; e) H. M. Mbuvi, L. K. Woo, *Organometallics* **2008**, *27*, 637; f) H. Suematsu, T. Katsuki, *J. Am. Chem. Soc.* **2009**, *131*, 14218; g) C. J. Lovely, J. A. Flores, X. F. Meng, H. V. R. Dias, *Synlett* **2009**, 129; h) J. M. Fraile, J. A. Mayoral, N. Ravasio, M. Roldan, L. Sordelli, F. Zaccheria, *J. Catal.* **2011**, *281*, 273.

[23] C. Özen, N. S. Tüzün, *Organometallics* **2008**, *27*, 4600.

[24] T. Achard, C. Tortoreto, A. I. Poblador-Bahamonde, L. Guénée, T. Bürgi, J. Lacour, *Angew. Chem. Int. Ed.* **2014**, *53*, doi: 10.1002/anie.201402994R2.

[25] A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263.