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UNIVERSITÉ DE GENÈVE FACULTÉ DES SCIENCES

Département de chimie organique Professeur J. Lacour

Non-Racemic Nitrogen-Based Cations in Asymmetric Chemistry

THÈSE

présentée à la Faculté des sciences de l'Université de Genève

pour obtenir le grade de Docteur ès sciences, mention chimique

par

Jérôme Vachon

de

Feyzin (France)

Thèse N° 3774

GENÈVE

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2006

La Faculté des sciences, sur le préavis de Messieurs J. LACOUR, professeur ordinaire et directeur de thèse (Département de chimie organique), A. ALEXAKIS, professeur ordinaire (Département de chimie organique), et Ch. G. BOCHET, professeur (Université de Fribourg – Département de chimie – Fribourg, Suisse), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

Genève, le 8 septembre 2006

P. Spierer

Thèse - 3774 -

Le Doyen, Pierre SPIERER

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 septembre 2002 au 1er juillet 2006.

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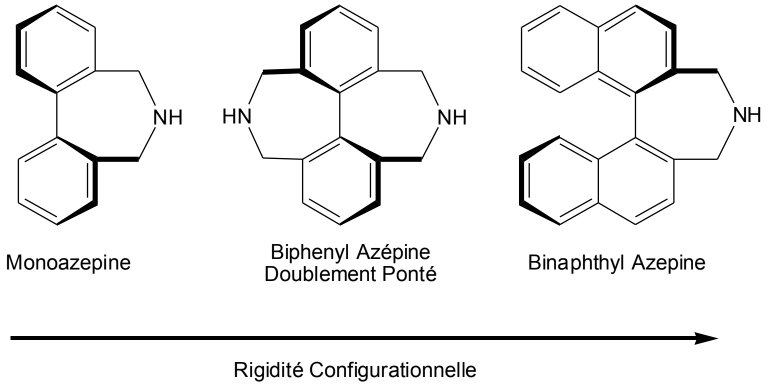
Résumé

De par la demande croissante de composés non racémiques dans les domaines, entre autres, pharmaceutiques et agrochimiques, que ce soit pour l'industrie ou la recherche académique, le développement de procédés énantioselectifs utilisant des composés énantiopures comme catalyseur chiraux connait un intérêt toujours grandissant. Les amines et ammoniums chiraux non racémiques ont souvent été utilisés comme auxiliaires chiraux, comme ligands ou catalyseurs pour la synthèse asymétrique. Par ailleurs, plusieurs exemples dans la littérature nous montrent que des dérivés cycliques de ces composés, présentant une symétrie de type C_2 sont à la base de beaucoup de procédés stéréoselectifs.[1] Parmi ces composés, les diphényles azépines doublement pontés de symétrie D_2 possèdent des propriétés intéressantes car ils présentent un caractère intermédiaire entre les monoazépines et les binaphthyl azépines. En effet, ils sont configurationnellement stable à température ambiante et labile à haute température. Cependant, elles n'ont été que très peu utilisées ainsi qu'étudiées jusqu'à présent.



Le but de ce travail de thèse est de synthétiser de nouveaux catalyseurs chiraux dont la structure sera basée, entre autres, sur ce diphényle azépine doublement ponté. Après une étude configurationnelle de ce type de composés, nous démontrerons qu'il est possible en quelques étapes de synthèse d'obtenir des catalyseurs de type iminium pour l'epoxidation asymétrique d'oléfines ainsi que des catalyseurs de type ammonium pour la catalyse par transfert de phase. Dans les deux cas, le contre ion spécifique des ces cations joue un rôle primordial. Enfin, la

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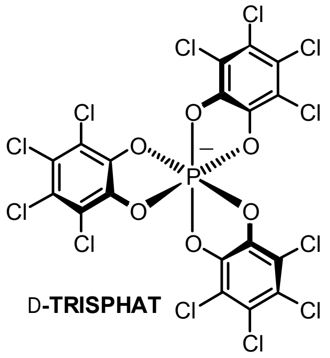
[1] J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581-1590

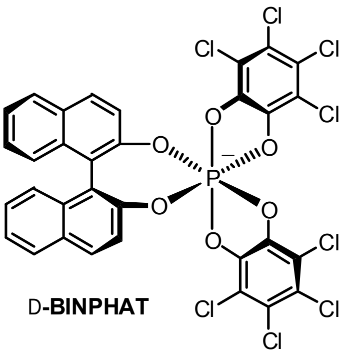
synthèse et la résolution d'une autre classe de composés potentiellement intéressant pour la catalyse par transfert de phase, les diquats, sera présentée.

Description des anions TRISPHAT et BINPHAT

Depuis 1995, le groupe du Prof. Lacour a développé la synthèse et l'utilisation d'anions chiraux phosphore pouvant être d'excellents auxiliaires chiraux à la fois pour des applications analytiques (détermination de la pureté énantiomérique par RMN) et synthétiques (résolution, extraction asymétrique, synthèse stéréosélective).[2] Les énantiomères Δ et Λ de l'anion TRISPHAT peut être facilement synthétisé et dédoublé par association avec un cation ammonium chiral. Les énantiomères Δ et Λ de l'anion BINPHAT sont directement obtenus par une méthode « one-pot » diastéréosélective à partir du (*S*)-BINOL et du (*R*)-BINOL respectivement.



D-TRISPHAT



D-BINPHAT

Associés aux iminiums, le TRISPHAT confère aux sels un caractère lipophile permettant non seulement une simplification considérable de la purification des sels par colonne chromatographique, mais en plus, une solubilité accrue dans les solvants peu polaires tel de le DCM, ce qui s'avèrera primordial pour la réaction d'epoxidation. Pour les ammoniums, le BINPHAT a été préféré au TRISPHAT pour plusieurs raisons. Si le BINPHAT confère les mêmes propriétés de lipophilicité aux cations auxquels il est associé, cet anion de symétrie C_2 est en général plus approprié pour des composés purement organiques.[3] De plus, sa facilité d'accès sous forme énantiopure via le (*S*)-BINOL et la possibilité de remplacer facilement cet anion par d'autres anions (tel que PF_6) présente le BINPHAT comme un anion de choix dans

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[2] S. Constant, J. Lacour, *Top. Curr. Chem.* **2005**, 1-41

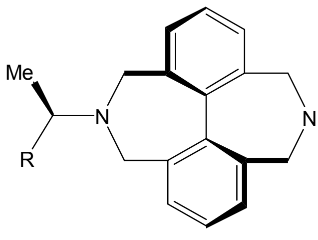
[3] J. Lacour, R. Frantz, *Org. Biomol. Chem.* **2005**, *3*, 15-19; J. Lacour, A. Londez, C. Goujon-Ginglinger, V. Buss, G. Bernardinelli, *Org. Lett.* **2000**, *2*, 4185-4188

notre étude. Il sera particulièrement utilisé pour la résolution de cations azotés chiraux (ammonium et pyridinium).

Synthèse et étude de diphényle azépines doublement pontés

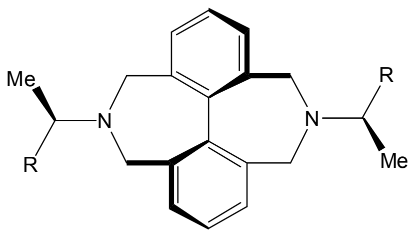
A. Description du projet

De par la non coplanarité des deux phényles, les diphényles azépines doublement pontés sont chiraux et existent sous deux formes atropoisomères de configuration *S*a ou *R*a. Des précédents dans la littérature nous ont montré qu'il était possible, par l'introduction de deux amines chirales sur chaque coté de la molécule, d'obtenir des diastéréoisomères ((*S*a)-**1a-c** et (*R*a)-**1a-c**) isolables sous forme énantioenrichie, voire optiquement pures.[4]



(S_a)-**1a-c**

1a R = Ph
1b R = 1-Naph
1c R = 2-Naph



(R_a)-**1a-c**

Cependant, une faible diastéreosélectivité induite par ces centres stéréogènes exocycliques sur l'axe de type diphényle et la difficulté de séparer les deux diastéréoisomères ont été observés. Il semblait donc que cette chimie puisse devenir intéressante si il était possible de trouver des amines chirales nous permettant, soit de synthétiser ces composés avec de grandes diastéréosélectivités (en particulier thermodynamique) soit d'isoler avec facilité les deux atropoisomères. Ainsi, en plus des amines déjà étudiées précédemment (**a-c**) plusieurs amines chirales (**d-g**) ont été sélectionnées et utilisées pour la préparation de ces composés

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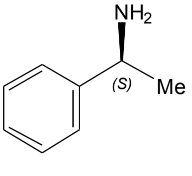
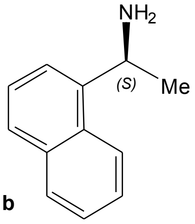
[4] M. Tichy, J. Gunterova, J. Zavada, *Collect. Czech. Chem. Commun.* **1997**, *62*, 1080-1088



a



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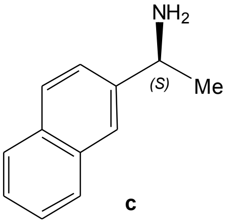
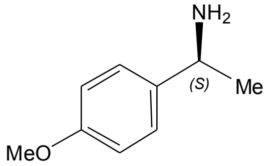
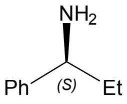


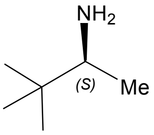
c



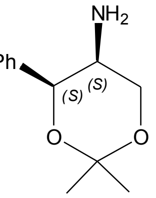
d



e



f



g

B. Résultats

Si la synthèse des composés **1a-g** a été effectuée de manière simple et rapide (deux étapes de synthèse et des rendements > 58%), la séparation des deux atropoisomères s'est révélée plus problématique mais néanmoins possible. De plus, les diastéréosélectivités thermodynamique se sont avérées modeste, la plus élevée ayant été obtenue avec l'amine **b** avec un ratio diastéréomérique de 4.3 : 1. La configuration absolue de chaque atropoisomères a été établie sur la base de leurs spectres de Dichroïsme Circulaire (DC). En effet, de précédents travaux de Mislow et Sandström ont démontré que pour des diphényles pontés en position 2,2', un effet Cotton négatif dans la région comprise entre 250 et 260 nm correspondait a une configuration *S*a et inversement.[5] Une étude configurationnelle a montré que ces composés étaient stables à température ambiante, la barrière d'épimérisation se situant entre 25 et 27 kcal.mol^{-1}.

Pour que cette chimie devienne plus attractive, il fallait cependant améliorer deux points :

- la diastéreosélectivité induite par l'amine chirale
- la séparation physique des deux diastéréoisomères

Ceci a put être réalisé en utilisant le composé **2**, synthétisé en six étapes à partir de produits commerciaux. En effet, en utilisant les amines **a** et **b**, la séparation des deux diastéréoisomères s'est avérée particulièrement aisée par colonne chromatographique. En ce qui concerne les amines **f** et **g**, il semble même que la synthèse ait été complètement diastéréoselctive car il a été impossible de détecter le second diastéréoisomère.

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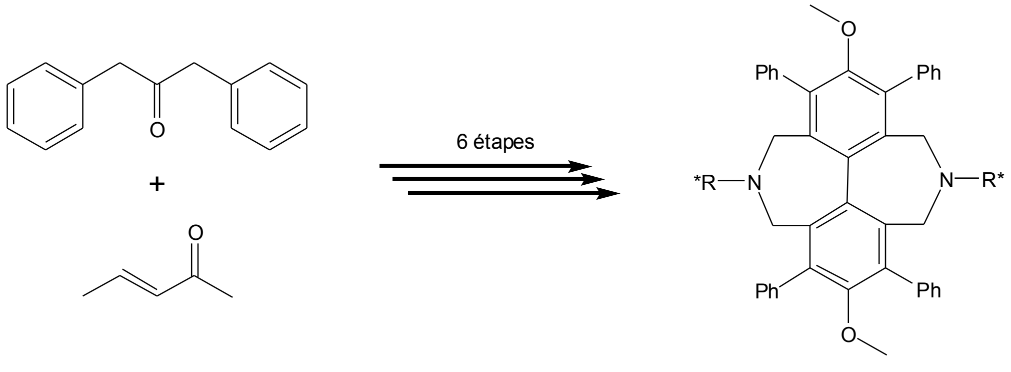
[5] J. Sandstrom, *Chirality* **2000**, *12*, 162-171; L. Loncar-Tomascovic, R. Sarac-Arneri, A. Hergold-Brundic, A. Nagl, M. Mintas, J. Sandstrom, *Helv. Chim. Acta* **2000**, *83*, 479-494; K. Mizlow, M. A. W. Glass, H. B. Hopps, E. Simon, G. H. Wahl, Jr., *J. Am. Chem. Soc* **1964**, *86*, 1710-1783



2

Une étude configurationnelle a montré que ces composés étaient configurationnellement plus stables que les azépines doublement pontées de type **1** avec des barrières d'épimérisation de l'ordre de 32 kcal.mol^{-1}.

Epoxidation asymétrique d'oléfine catalysée par des iminiums chiraux

A. Azépinium configurationnellement labiles

L'epoxidation asymétrique d'oléfines prochirales est un sujet particulièrement porteur car il peut donner accès à des intermédiaires synthétiques particulièrement intéressants pour les chimistes organiciens, car présent dans de nombreux composés naturels et ainsi que pour la production, entre autres, de produits pharmaceutiques potentiels.[6] Parmi les catalyseurs chiraux décrits dans la littérature, les sels d'iminiums s'avèrent particulièrement facile d'utilisation et de préparation, notamment à partir d'azépines cycliques. En effet, ils sont facilement oxydés en présence d'oxone, *in situ*, en sels d'oxaziridinium qui sont des agents de transfert d'oxygène vis-à-vis de substrats nucléophiles tels que les oléfines riches en électron. Dans un premier temps, nous nous sommes particulièrement intéressé au diphényle azépinium simplement ponté (ou monoazépine) de type **4**.

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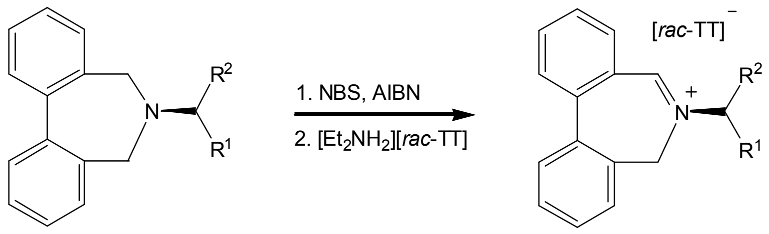
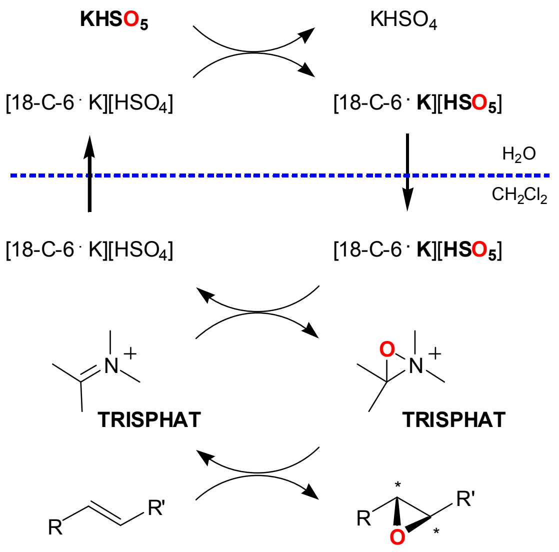
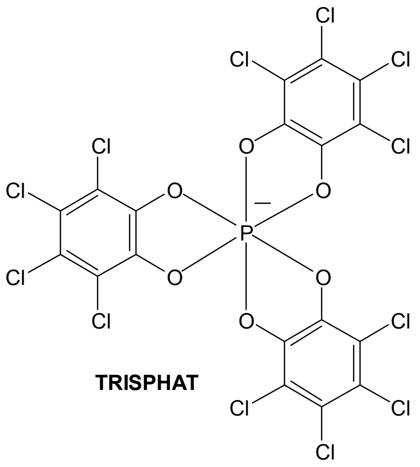
[6] K. B. Sharpless, *Aldrichimica Acta* **1983**, *16*, 67; C. H. Behrens, T. Katsuki, *Coord. Chem. Rev.* **1995**, *140*, 189; J. Gorzynski Smith, *Synthesis* **1984**, 639



3 **4**

Préparés en une seule étape à partir de **3**, différents iminiums portant diverses amines chirales (**b**, **e**, **f**, **g**, **h**) ont été testés pour l'epoxidation asymétrique d'oléfine. Les conditions réactionnelles utilisaient un procédé du type transfert de phase entre le DCM – où sont présents le sel d'iminium et l'oléfine – et l'eau – où sont présents la base ($NaHCO_3$) et l'oxydant (oxone) – un éther couronne (le 18-C-6) permettant le transfert de phase de l'oxydant au catalyseur. Parmi ces catalyseurs, [**4f**][*rac*-TT] et [**4g**][*rac*-TT] étant les sels d'iminiums les plus efficaces avec un excès énantiomérique de ~ 80% sur le phényl-3,4-dihydronaphthalène.[7]





B. Azépinium configurationnellement rigides

Quasiment le même procédé a été appliqué pour la préparation des diphényle azépinium doublement pontés, et ce, à partir des azépines correspondantes de type **1**. Une série de sels d'iminium de type **6** a été préparé et testé dans les mêmes conditions réactionnelles que

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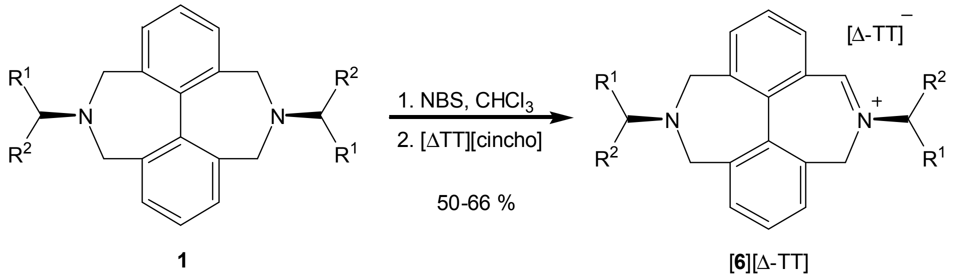
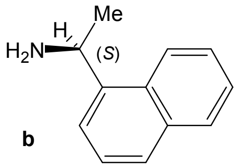
[7] J. Vachon, C. Perollier, D. Monchaud, C. Marsol, K. Ditrich, J. Lacour, *J. Org. Chem* **2005**, *70*, 5903-5911

précédemment. Dans ce cas là, le catalyseur le plus efficace s'avère être [**6e**][Δ-TT] avec un excès énantiomérique de 86% sur le phényl-3,4-dihydronaphthalène.



1 [**6**][Δ-TT]



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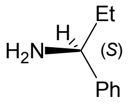

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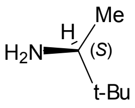

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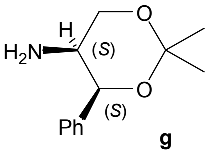
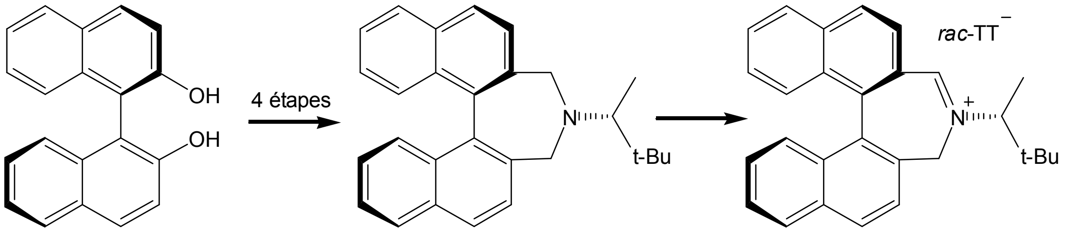


g

Cependant, les meilleurs résultats concernant l'epoxidation d'oléfine catalysée par des iminium a été reporté avec l'iminium (*S*a,L)-**7g** avec un excès énantiomérique de 95% sur le phényl-3,4-dihydronaphthalène.[8] L'amine **f** s'étant avérée d'efficacité comparable à l'amine **g**, il nous semblait intéressant de se pencher sur le catalyseur **7f**. Le sel d'iminium [(*R*a,*R*)-**7f**][*rac*-TT] a été préparé en cinq étapes à partir du (*R*)-BINOL, et dans ce cas là, un excès énantiomérique de 87% a été obtenu sur le phényl-3,4-dihydronaphthalène.



(*R*a)-BINOL (*R*a-*R*)-**8f** (*R*a-*R*)-**7f**

Enfin, des précédents dans la littérature ont montré que des amines pouvaient catalyser des réactions d'epoxidation sur des oléfines. Ainsi, les azépines précurseurs des catalyseurs de type iminium, soit **1f**, **4f** et **8f** ont également été testé dans les mêmes conditions réactionnelles que pour les sels d'iminiums.[9] Dans l'ensemble, ces amines tertiaires présentent des activités et stéréosélectivité comparables à leurs homologues iminiums.

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[8] P. C. B. Page, R. Buckley Benjamin, A. J. Blacker, *Org. Lett.* **2004**, *6*, 1543-1546

[9] M.-H. Gonçalves, A. Martinez, S. Grass, P. C. B. Page, J. Lacour, *Tetrahedron Lett.* **2006**, *47*, 5297 et références citées dedans

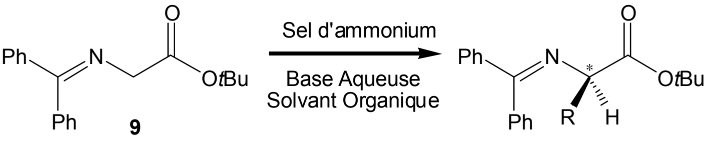
Toutefois, le mécanisme d'action des ces catalyseurs reste encore à déterminer, même si ces résultats laissent penser que ce mécanisme reste identique à celui utilisant des iminiums.

Utilisation d'ammonium chiraux pour la catalyse par transfert de phase

A. Description du projet

Parmi tout les procédés organocatalytiques connus, la catalyse par transfert de phase (CTP) est devenu un sujet d'intérêt grandissant, et ce, depuis les premiers travaux effectués par Makosza il y a environ quarante ans.[10] La CTP met en jeu des conditions réactionnelles permettant le transport actif de réactif polaires d'une phase (liquide en général) à une autre effectué par une quantité sous-stœchiométrique d'une molécule (chargée). C'est actuellement devenu une méthode très pratique et efficace pour avoir accès à des composés synthétique de grande utilité, et ce, avec de grandes puretés énantiomérique.

L'alkylation par transfert de phase de la base de Schiff **9** est un procédé très performant pour l'obtention d'α-amino acides naturels et non naturels. Par ailleurs, ce composé est devenu le substrat de choix comme référentiel quant à l'efficacité d'un système catalytique énantiosélectif. Les conditions réactionnelles « classiques » mettent en jeu un mélange biphasique composé de toluène et d'une solution aqueuse à 50% de KOH avec 5 mol% de catalyseur et s'effectue à 0 °C, l'electrophile étant généralement du bromure de benzyle et la complétion étant atteinte après quelques heures de réactions.



Cependant, les meilleurs catalyseurs décrits dans la littérature jusqu'à présent sont soit issus du pool chiral, soit des composés purement synthétiques. La première catégorie de molécules n'est pas facilement modulable et adaptable à toutes les réactions en CTP et la deuxième catégorie requiert généralement une longue et difficile préparation.[11]

Le but de ce travail est donc de synthétiser de nouveaux catalyseurs dont la structure sera basée sur le diphényle azépine doublement ponté présenté précédemment tout en limitant le

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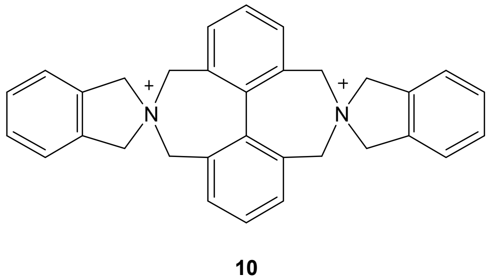
[10] M. Makosza, A. Jonczyk, *Org. Synth.* **1976**, *55*, 91-95; M. Makosza, B. Serafin, *Rocz. Chem.* **1965**, *39*, 1223-1230

[11] B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518-525; M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506-517; K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013-3028

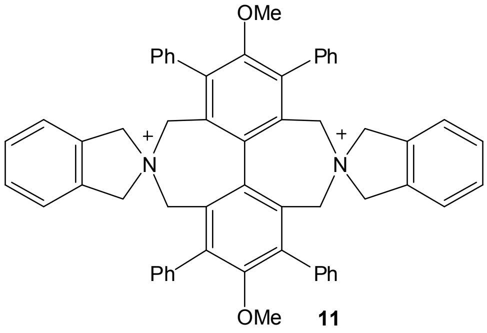
nombre d'étapes synthétiques. Une résolution des ammoniums, chiraux mais racémiques, à l'aide de l'anion BINPHAT sera envisagée.

B. Synthèse et résolution des catalyseurs

Dans un premier temps, nous nous sommes intéressés au composé **10** qui est un *spiro* bis-ammonium de symétrie C_2 combinant deux cycles à cinq chainons externes et deux cycles à sept chainons interne. Comme les diphényle azépines doublement pontés, ce composé est également chiral du à la non coplanarité des deux phényles et existent sous deux formes énantiomères (atropoisomères) de configuration *S*a et *R*a. En termes de synthèse, **10** est facilement accessible en trois étapes à partir du pyrène. Une version encombrée de **10** a été également synthétisée de part l'introduction de quatre groupements phényles en position 3,3' et 5,5' du diphényle central avec l'ammonium **11**. Une version combinant quatre cycles à sept chainons fut aussi préparée avec l'ammonium **12**. Ces deux derniers ammoniums ont été synthétisés en six étapes par la même séquence réactionnelle que pour les azépines de type **2** avec dans ces cas là, l'introduction d'amines secondaires en lieu et place d'amines primaires.



10



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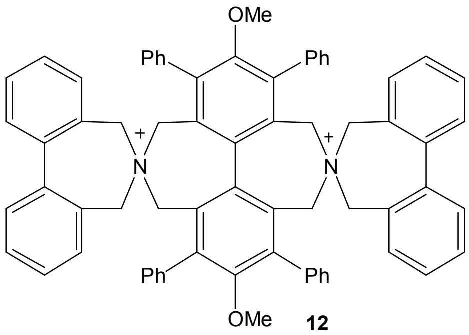

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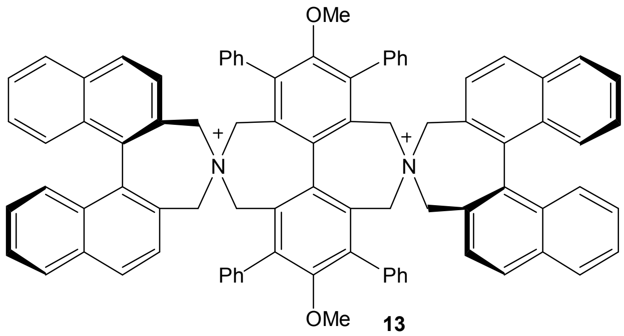

13

Concernant **10**, **11** et **12** un dédoublement des ammoniums a été effectuée grâce au à l'anion BINPHAT. La configuration du diphényle centrale a été également assignée par dichroïsme circulaire par mesure de la nature du signe de l'effet Cotton dans la région 250-260 nm. En ce qui concerne le composé **12**, qui possède deux éléments stéréogènes avec des groupements dinapthyles de configuration *R*a, cet ammonium se présente directement sous forme diastéréomériquement et énantiomériquement pure, de configuration centrale présumée *R*a.[12]

C. Résultat de la CTP sur le substrat 9

Nous nous sommes tout d'abord intéressé à l'ammonium (*R*a)-**10** dans les conditions réactionnelles précédemment décrites. L'effet du contre ion étant inconnu, nous avons effectué deux essais avec comme catalyseurs [(*R*a)-**10**][Δ-BINPHAT]$_2$ et [(*R*a)-**10**][PF_6]$_2$. Dans les deux cas, une conversion totale a été obtenue, mais donnant lieu à un produit racémique. Des précédents dans la littérature nous ayant montré l'importance de groupement volumineux en positions ortho, ortho'.[13] Les catalyseurs **11**, **12** et **13** présentent une telle caractéristique mais les masses molaires de tels composés étant particulièrement élevées et la quantité de produit restreinte, nous nous sommes donc tournés vers une méthode permettant de réduire la quantité de catalyseur à 1 mol% tout en gardant le même temps réactionnel. Cette méthode met en jeu un co-catalyseur achiral (le 18-C-6) favorisant l'extraction de la base inorganique (dans ce cas le KOH) vers la phase organique.[14] Les résultats sont reportés dans le tableau suivant :

Entréé	Catalyseur	quantité	18-C-6 (quantité)	Après 2 h		Après 24 h		
				Conv. %[b]	ee %[b]	Conv. %[b]	ee %[b]	Conf.[b]
1	aucun	-	1 mol%	10	-	90	-	-
2	[(*R*a)-**11**][Δ-BT]$_2$	1 mol%	1 mol%	52	27	nd	nd	(–)-*S*
3	[(*R*a)-**11**][Δ-BT]$_2$	1 mol%	0.1 mol%	15	27	98	14	(–)-*S*
4	[(*R*a)-**11**][PF_6]$_2$	1 mol%	0.1 mol%	nd	nd	95	14	(–)-*S*
5	[(*R*a)-**11**][PF_6]$_2$	1 mol%	-	1	-[c]	2	-[c]	-[c]
6	[(*R*a)-**11**][PF_6]$_2$	5 mol%	-	nd	nd	82	12	(–)-*S*
7	[(*R*a)-**12**][PF_6]$_2$	1 mol%	0.1 mol%	4	30	32	25	(–)-*S*
8	[**13**][Br]$_2$	1 mol%	0.1 mol%	14	48	100	40	(–)-*S*
9	[**13**][Br]$_2$	5 mol%	-	7	51	90	39	(–)-*S*

[a] Conditions 1.2 eq Bromure de benzyle, Toluène/50% aq. KOH (3:2), 18-C-6 (0 à 1 mol%), catalyseur (0 à 5 mol%), 0 °C, 2 à 24 hours. [b] Determinée par CSP-HPLC (Chiralcel OD-H). [c] Conversion trop faible ne permertant pas la determination precise de l'excès énantiomérique ni la configuration absolue du produit.

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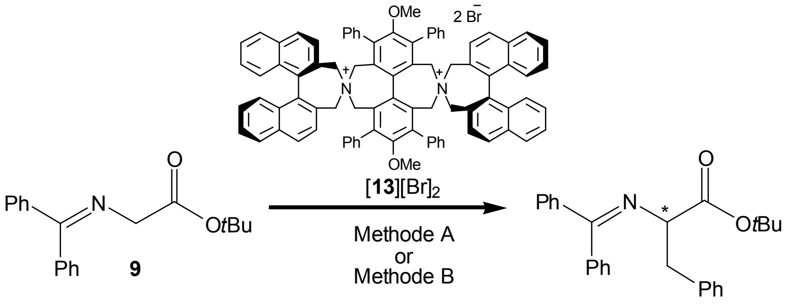
[12] Le spectre de dichroïsme circulaire de **12** ne permet pas la détermination de sa configuration

[13] T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519-6520

[14] S. Shirakawa, K. Yamamoto, M. Kitamura, T. Ooi, K. Maruoka, *Angew. Chem., Int. Ed.* **2005**, *44*, 625-628

En résumé, une diminution de l'excès énantiomérique avec le temps est observée, notamment concernant les réactions catalysées par l'ammonium **11**. Ceci n'est vraisemblablement pas du à une compétition avec le co-catalyseur achiral mais une dégradation du catalyseur dans ces conditions très basique (via un réarrangement intramoléculaire de Stevens[15]) qui semblerait plus marquée pour l'ammonium **11**. Toutefois, dans ces conditions, un excès énantiomérique de 40% à été obtenu avec le catalyseur [**13**][Br]$_2$ avec une conversion totale. Toutefois, il était intéressant de tester d'autres conditions réactionnelles qui pourraient être plus approprié à nos types de catalyseur qui sont relativement peu soluble dans le toluène. Ainsi deux autres méthodes (A et B) ont été testées avec le catalyseur [**13**][Br]$_2$ et les résultats sont reportés dans le tableau suivant :



Catalyseur	Methode	Rend. %[c]	ee %[d]	Conf.[d]
[**13**][Br]$_2$	A[a]	54	41	(–)-*S*
[**13**][Br]$_2$	B[b]	70	7	(–)-*S*

[a] Conditions : 5 mol % catalyseur, 5 eq Bromure de benzyle, 10 eq CsOH.H$_2$O, Toluène / DCM (7:3),-70 °C, 24 heures. [b] Conditions : 5 mol % catalyseur, 5 eq Bromure de benzyle, 10 eq CsOH.H$_2$O, DCM,-78 °C, 24 heures.[c] Rendement isolé après colonne chromatographique. [d] Determinée par CSP-HPLC (Chiralpack IB).

Il apparait clairement que la quantité de DCM joue un rôle primordial dans la stéréosélectivité de la réaction, un milieu trop polaire provoquant vraisemblablement une dissociation trop marquée des paires d'ions (entre l'ammonium **13** et l'énolate de **9**) et diminuant l'efficacité du procédé. Cependant, avec la méthode A, un excès énantiomérique comparable à la méthode précédente a été obtenue. Les limites de notre catalyseur semblent donc atteintes et pour améliorer la sélectivité de nouveaux catalyseurs avec des groupements beaucoup plus encombrants en positions 3,3' et 5,5' doivent être envisagées.

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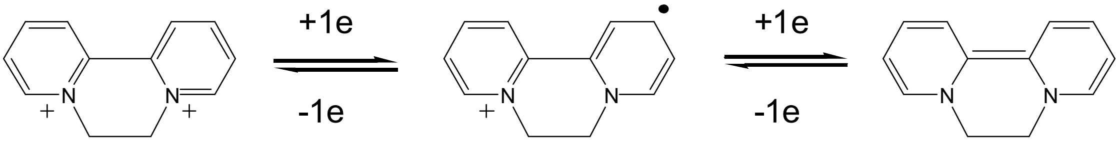
[15] L. Vial, M.-H. Goncalves, P.-Y. Morgantini, J. Weber, G. Bernardinelli, J. Lacour, *Synlett* **2004**, 1565-1568

Synthèse et résolution des premiers diquat non racémiques

A. Description du projet

Les diquats sont une classe importante de composée qui a été considérablement utilisée depuis plus de cinquante ans. Depuis les années cinquante, il sont particulièrement connus pour être de bons herbicides grâce à leur habilité à accepter un électron de façon réversible pour former un cation radical qui peut interférer pendant l'étape de transfert d'électron de la photosynthèse.[16] Plusieurs groupes se sont donc penchés sur cette classe de composé de par leurs propriétés physiques intéressantes, le premier potentiel de réduction étant assez bas et le monocation radicalaire formé étant relativement stable.[17]



Ces composés sont par ailleurs intéressants de part leur chiralité axiale. En effet, la non coplanarité des deux pyridiniums crée un axe de chiralité leur permettant d'exister sous deux formes énantiomériques (et atropoisomériques) de configuration *R*a et *S*a, l'angle dièdre étant dépendant de la taille du cycle non-aromatique. Cependant, il s'avère que ce type de composés a uniquement été reporté comme configurationnellement labile ou alors – pour les molécules qui sont configurationnellement stable – comme mélange racémique. L'accès direct des diquats (une étape de synthèse) et la possibilité de dédoubler ces cations chiraux avec le TRISPHAT et le BINPHAT nous ont conduits à s'intéresser à ses composés qui peuvent potentiellement être utilisés comme catalyseur asymétrique de transfert de phase.

B. Synthèse, dédoublement et étude de diquats à huit chainons

Des précédents dans la littérature nous montrent que les diquats à huit chainons de type **14** sont configurationnellement stables à température ambiante, la valeur exacte de la barrière de racémisation de ces composés étant jusqu'alors inconnue.[18]

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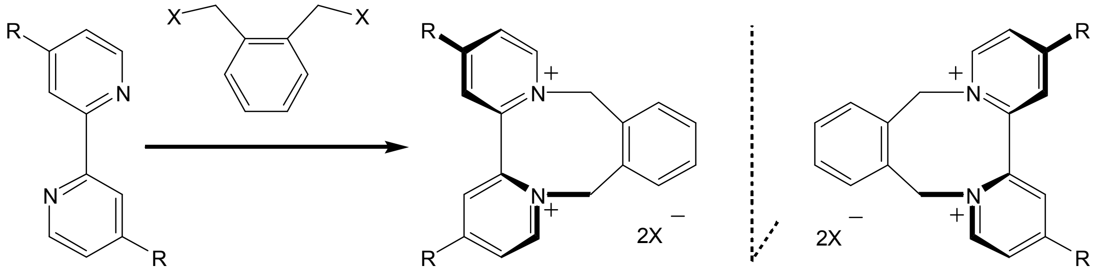
[16] R. C. Brian, G. W. Driver, R. F. Homer, R. L. Jones, (Imperial Chemical Industries Ltd.). DE 1958; W. R. Boon, R. F. Homer, (Imperial Chemical Industries Ltd.). DE 1962, p. 2 pp; R. F. Homer, J. E. Downes, (Imperial Chemical Industries Ltd.). FR 1965, p. 3 pp.; Addn. to Fr. 1,186,992; L. A. Summers, *The Bipyridinium Herbicides* ed., Academic; New York, **1980**

[17] R. F. Homer, T. E. Tomlinson, *Nature (London)* **1959**, *184*, 2012-2013

[18] F. Voegtle, D. Bombach, *Chem. Ber.* **1975**, *108*, 1682-1693



14a (R = H)
14b (R = Me)
14c (R = *t*Bu)

La synthèse de ces composés consiste en une étape de bis-alkylation d'une bipyridine sur un dihalogenoxylène et ce avec de bons rendements (85% pour **14a**, 88% pour **14b** et 66% pour **14c**). Concernant le dédoublement de ces cations, le BINPHAT et le TRISPHAT ont été utilisés, les sels sont solubilisés dans l'acétonitrile et refroidis. Le précipité formé est recueilli et les eaux mères évaporées. Les résultats concernant les diastéréosélectivités obtenues sont rassemblés dans le tableau ci-dessous.

entrée	diquat	d.r.[a] du precipité (configuration)	d.r.[a] des eaux mères (configuration)
1	[**14a**][Δ-BT]$_2$	96% (*S*a)	40% (*R*a)
2	[**14b**][Δ-BT]$_2$	96% (*S*a)	92% (*R*a)
3	[**14c**][Δ-BT]$_2$	88% (*S*a)	40% (*R*a)
4	[**14c**][Δ-TT]$_2$	> 96%[b] (*S*a)	95%[b] (*R*a)

[a] si non mentionné, d.r mesuré par ^{1}H NMR (400MHz, 14% DMSO-d_6 dans CDCl$_3$). [b] d.r mesuré par ^{1}H NMR (400MHz, 3% CD$_3$CN dans CDCl$_3$). [c] Configuration déterminée par diffraction des rayons X. [d] Configuration déterminée par dichroisme ciruculaire et par analogie avec **14c**.

La configuration de **14c** a été établie par diffraction des rayons X et corrélée par dichroïsme circulaire : un effet Cotton négatif vers 250 nm correspond à une configuration *S*a et inversement. Une étude configurationnelle a également été effectuée par dichroïsme circulaire en mesurant la diminution du Δε en fonction du temps et de la température, sur la bande à 250 nm correspondant à l'absorption UV de l'axe biaryle. Les paramètres d'activation de Diquats **14a-c** sont rassemblés dans le tableau ci-dessous.

Entrée	diquat	$\Delta H^{\neq}$ kcal.mol^{-1}	$\Delta S^{\neq}$ cal.mol^{-1}.k^{-1}	$\Delta G^{\neq}$ kcal.mol^{-1}	$t_{1/2}$ (demi-vie)
1	[**14a**][PF$_6$]$_2$	23.89	-5.2	25.43	12 jours
2	[**14b**][PF$_6$]$_2$	26.48	0.0	26.47	71.3 jours
3	[**14c**][PF$_6$]$_2$	22.80	-8.0	25.14	7.25 jours

Comme attendu, ces composés s'avèrent relativement stable à température ambiante avec des temps de demi-vie de plusieurs jours, on peut noter toutefois une légère différence entre les trois diquats quant à leur barrière de racémisation malgré la très grande similitude entre ces composés.

Enfin, le diquat [(*S*a)-**14c**][PF$_6$]$_2$ a été utilisé comme catalyseur de transfert de phase pour l'alkylation de la base de Schiff **9**. Si de bonnes conversions (~ 70%) ont été obtenues, ce diquat a mené à des produits racémiques. Pour envisager de meilleurs résultats avec ces composés en temps que catalyseur, des modifications structurelles doivent être envisagées. Ces diquats constituent toutefois les premiers composés à huit chainons comportant seulement trois contraintes de cycles à avoir été dédoublés. Il paraît ainsi intéressant de pouvoir avoir accès à ce type de composé sous forme optiquement pures et l'on peut raisonnablement penser que d'autres applications peuvent émerger de ces résultats.

Bilan

Ce projet décrit la synthèse, entre autres, de nouveaux composés chiraux et non-racémiques basés sur l'azote cationique autour d'un noyau structurel commun : le diphényle azépine doublement ponté. Après une étude configurationnelle de ce type de composé, nous avons vu que ces molécules pouvaient facilement être transformées en sels d'iminium et appliquées dans l'epoxidation asymétrique d'oléfine prochirales avec des excès énantiomérique allant de modestes à bons (jusqu'à 86%). Par ailleurs, il a été montré que les amines tertiaires elles mêmes, précurseurs des sels d'iminium, pouvaient catalyser la réaction dans les mêmes conditions avec des conversions et des stéréosélectivité semblables. Nous avons également vu qu'il était aussi possible, toujours à partir du même noyau structurel, de synthétiser des ammoniums dans le but de les appliquer pour la catalyse asymétrique par transfert de phase.

Nous avons utilisé l'anion chiral BINPHAT comme agent de dédoublement de ces composés avec succès, les puretés énantiomérique de nos catalyseurs étant toujours supérieures à 96%. Quelques modifications autour du diphényle central avec l'introduction de groupement encombrants en positions 3,3' et 5,5' nous ont permis d'obtenir des excès énantiomérique allant jusqu'à 41% (avec [**13**][Br]$_2$) pour la benzylation de la base de Schiff **9**. Enfin, une autre classe de composés chiraux de l'azote chargée, les diquats, ont été également étudiés. La synthèse et la résolution de diquats tricycliques à huit chainons de type **14** a été effectuée avec succès par l'utilisation du TRISPHAT et du BINPHAT comme agent de dédoublement. La stabilité configurationnelle et les configurations absolue des composés résolus ont été effectué par dichroïsme circulaire, et ce, par corrélation avec un cliché de diffraction de rayon X obtenu sur l'un des sels. Des modifications structurelles sur nos catalyseurs par transfert de phase doivent être néanmoins envisagées afin d'augmenter les stéréosélectivités.

CHAPTER I – DOUBLY BRIDGED BIPHENYL AZEPINES

CHAPTER II - IMINIUM CATALYSTS IN BIPHASIC ENANTIOSELECTIVE OLEFIN EPOXIDATION

CHAPTER III - PHASE TRANSFER CATALYSIS USING CHIRAL AMMONIUM SALTS

CHAPTER IV - SYNTHESIS AND RESOLUTION OF THE FIRST NON-RACEMIC DIQUATS

Abbreviations

Ar: aryl
b: large singlet
TLC: Thin layer chromatography
conc.: concentration
conv.: conversion
CD: Cirucular dichroism
d: doublet
DCM: dichloromethane
Et_2O: Diethyl ether
MeOH: Methanol
iPrOH: isopropanol
ee: enantiomeric excess
eq.: equivalent
hν: light
PTC: Phase transfer Catalysis
m: multiplet
maj.: major
min.: minor
M.p.: melting point
ppm: part per million
q: quartet
quint: quintet
rac: racemic
d.r.: diastereomeric ratio
e.r.: enantiomeric ratio
n.d: not determined
r_f: retardation factor
s: singlet
sept: septuplet
t: triplet
r.t: room temperature

Symbols

δ: chemical shift
ΔG°: Free Gibbs Energy
$\Delta G^{\neq}$: free energy of activation
$\Delta H^{\neq}$: enthalpy of activation
$\Delta S^{\neq}$: entropy of activation
ε: extinction coefficient
λ: wave length
c: concentration
d: bond length
J: coupling constant
l: length
$t_{1/2}$: half life
t_R: retention time
T: temperature

Units

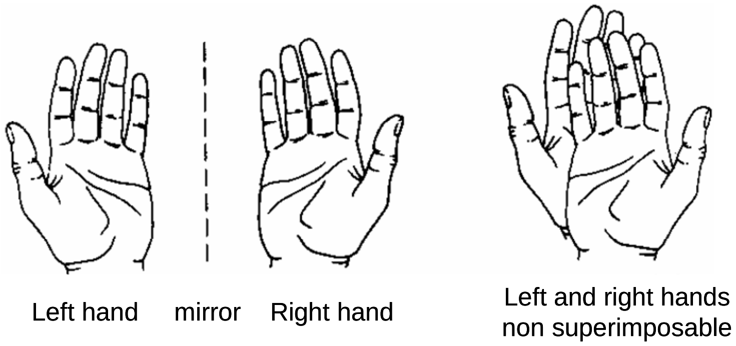
°: degree
°C: degree Celsius
J: joule
K: Kelvin
µl: microliter
mL: milliliter
mmol: millimole
µmol: micromole
M: molarity
s: second
min: minute
h: hour
nm: nanometers

- INTRODUCTION -

NON-RACEMIC NITROGEN-BASED CATIONS IN ASYMMETRIC CHEMISTRY

Importance of Chirality

The word *chiral* comes from the Greek word *cheir,* which means hand and indicates a dissymmetry between an object and its mirror image. Our hands are thus chiral as are most of life molecules.



This term was first introduced by Lord Kelvin during his Baltimore Lectures on Molecular Dynamics and the Wave of Theory of Light (**1904**).*"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."*

Prior to that, the Dutch chemist J. H. van 't Hoff[1] and the French chemist J. A. Le Bel[2], independently, discovered the tetrahedral arrangement of groups around most carbon atom; an arrangement which has deep consequences in terms of chirality. For instance, the common amino acid alanine, can occur in two forms: (*S*)-alanine and (*R*)-alanine, which are mirror images and not superimposable; these structures are called enantiomers. When alanine is produced in a laboratory under normal conditions, a 1:1 mixture of both enantiomers is obtained. The synthesis is symmetrical in the sense that it produces equal amounts of both

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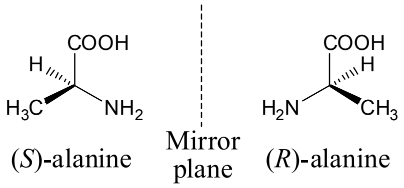
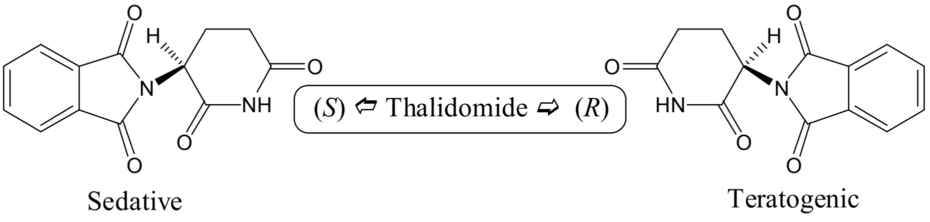
[1] van't Hoff, J. H. *Bull. Soc. Chim. Fr.* **1875**, 295

[2] Le Bel, J. A. *Bull. Soc. Chim. Fr.* **1874**, 337

enantiomers (racemic mixture). Asymmetric synthesis, on the other hand, deals with the production of an excess of one of the two forms.



In **1848**, Pasteur succeeded in separating two sets of crystals of racemic tartaric acid, each of which, in solution, leads to a rotation of planer polarized light of equal intensities but in opposite directions. This difference of physical behavior observed for enantiomers is of importance because these compounds can have completely different chemical and biological properties. Indeed, all living material, mainly uses one of the two possible sets of enantiomers (usually L-amino acids, D-sugars, etc…) so that both forms of chiral molecules present in nature are not equally common. As the receptors of enzymes are extremely specific in their three-dimensional interactions, they prefer binding the enantiomer that better fit the receptor's site "like a key that fits a lock" (Emil Fischer, **1902**). The most famous and tragic example of such selectivity is that of drug Thalidomide. Synthesized in **1953** by the Swiss firm CIBA, it was put into the market in **1956** and sold to pregnant woman as a sedative agent. However, only one enantiomer of Thalidomide helped against nausea, for instance the (*R*)-enantiomer, while the other one could cause fetal damage. This drug has been removed from the market in the early sixties and replaced by an achiral analogue of Thalidomide.



There are other but less dramatic examples of how differently two enantiomers can affect our cells. *Limonene,* for example, is a chiral molecule, and the receptors in our nose are sensitive enough to distinguish the two enantiomers: (*R*)-limonene smells of oranges while its enantiomer (*S*)-limonene smells of lemons.

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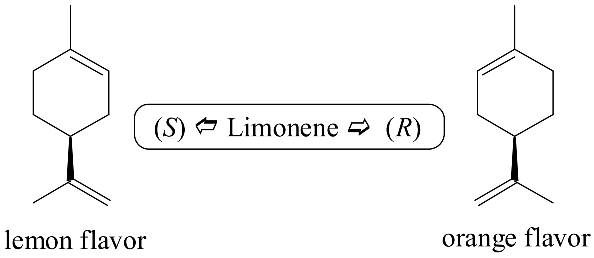
[2] Le Bel, J. A. *Bull. Soc. Chim. Fr.* **1874**, 337



Since the two enantiomers of a chiral molecule may often have totally different physiological effects, it is important to be able to produce each of the two forms pure. During the past few decades intensive research has been devoted into the development of new methods for producing preferentially one of the enantiomers rather than the other. The use of a chiral catalyst is one of the possible tools to achieve this goal.

Stereoselective Organocatalysis

Catalysis is the increase in the rate of a chemical reaction induced by a substoichiometric amount of a compound (catalyst) which is unchanged chemically at the end of the reaction. The term *catalysis* coming from the Greek words for “down”—*kata*—and “loosen”—*lyein* was proposed in **1835** by the Swedish chemist Jöns Jakob Berzelius: *“A catalyst is a substance that promotes a chemical reaction with no net participation in it; it is neither consumed nor replenished”* (J.J. Berzelius, **1836**). Due to the constant demand for non racemic compounds in pharmaceuticals, agrochemicals, synthetic intermediates and for fine chemicals, in both industrial and academic laboratories, many efforts have been devoted to the development of enantioselective processes using enantiopure compounds as chiral catalysts. To a certain extent, catalytic transformations can provide the best “atom economy” because the stoichiometric introduction and removal of the (chiral) auxiliary can often be avoided, or at least minimized.[3] In recent years, much of the work in this area of catalytic asymmetric synthesis has focused on the design and synthesis of organometallic complexes as well as the use of enzymes as stereoselective catalysts. A less studied although equally intriguing field is the use of organic molecules to catalyze reactions and induce dissymmetry into the products. This topic, so-called stereoselective organocatalysis, has received considerable attention in the

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[3] Trost, B. *Science* **1991**, *254*, 1471; Trost, B. *Angew. Chem.* **1995**, *107*, 285

last few years.[4] With the aim of using low molecular weight organic compounds and the desire to understand and mimic enzymes organocatalysis started almost one century ago with the studies of Bredig and Fajans (**1908**).[5] It is only recently that the scientific community begun to appreciate the potential of this useful alternative to well-established (often metal-based) methodologies. The first example of an asymmetric reaction using organocatalysts was reported in **1912** by Bredig, where he noticed that the addition of HCN to benzaldehyde was accelerated by alkaloids. Despite low yields (< 10%), the resulted 2-hydroxy-2-phenylacetonitrile was optically active and of opposite chirality when using quinine and quinidine as catalysts.[6] Amino-acids were used as well as chiral organocatalysts, but before the turn of the century, a limited number of useful applications were described.[7] One of the first successful applications of organocatalysts in asymmetric organic synthesis was the Hajos-Parrish-Wiechert reaction in **1971**. This reaction deals with the desymmetrisation of prochiral triketone by intramolecular aldolisation catalyzed by (*S*)-proline and afforded an indene dione with excellent yield and enantioselectivity (Figure 0-1).[8]

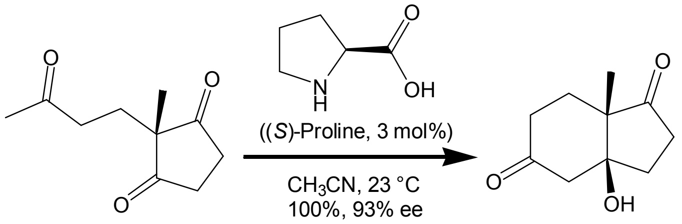

Figure 0-1: Hajos-Parrish-Wiechert reaction (1971)

Phase Transfer Catalysis (PTC)

Among all the organocatalytic processes known, Phase Transfer Catalysis (PTC) has become a topic of great interest since the pioneering work of Makosza almost forty years ago,[9] and the

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[4] For recent reviews on organocatalysis see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. *Acc. Chem. Res.* **2004**, *37*, Issue 8; *Adv. Synth. Catal.* **2004**, *36*, Issues 9 and 10

[5] Bredig, G.; Fajans, K. *Ber.* **1908**, *41*, 752

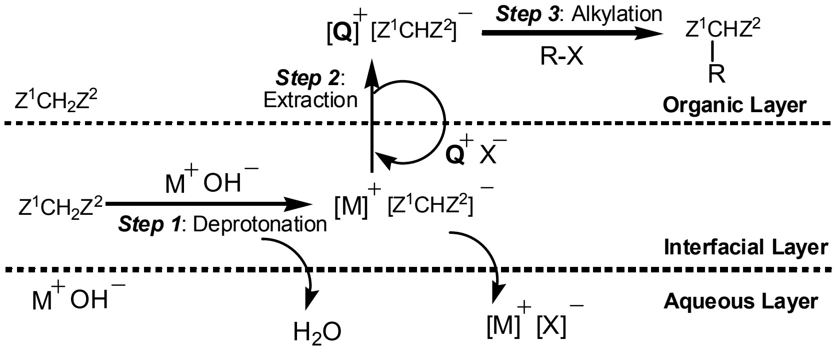
[6] Bredig, G.; Fiske, P. S. *Biochem. Z.* **1913**, *46*, 7

[7] Fischer, F. G.; Marschall, A. *Ber.* **1931**, *64B*, 2825; Langenbeck, W. *Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten*; 2nd ed.; Springer: Berlin, **1949**;

[8] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496; Hajos, Z. G.; Parish, D. R. *J. Org. Chem.* **1974**, *39*, 1615

[9] Makosza, M.; Serafin, B. *Rocz. Chem.* **1965**, *39*, 1223; Makosza, M.; Jonczyk, A. *Org. Synth.* **1976**, *55*, 91

extensive study of Starks in the early 1970s.[10] PTC allows reaction conditions to proceed through the active transport of reactive polar reagents from one phase to another by small sub-stoichiometric amount of (charged) molecules. This method has many advantages over other catalytic (and stoichiometric) processes: simple reaction procedure, mild conditions, safe, inexpensive and environmentally friendly reagents, absence of anhydrous or aprotic solvents, ease of scale-up and (most often) metal-free conditions. Moreover, PTC is compatible with a wide range of solvents (if immiscible with water which contains usually the reactive polar reagents), with ionic liquids,[11] and even without any organic solvent if the substrate plays the role of the organic phase itself.[12] Overall, PTC appears as a "green" alternative to many classical homogeneous reaction conditions.[13]



Scheme 0-1: Proposed Mechanism of the binary phase transfer system ($Q^+ X^-$ = Phase transfer catalyst)

A typical example of a PTC reaction is that of the alkylation of an acidic substrate of type $Z^1CH_2Z^2$ Scheme 0-1). This substrate is deprotonated in the interfacial layer by an inorganic base (M^+OH^-) to form a metallic salt insoluble in the organic layer. An exchange of counter-ion with the phase-transfer catalyst, often a quaternary ammonium cation Q^+, leads to a more lipophilic salt which can be extracted in the organic layer. The carbanion nucleophile associated with Q^+ can react with the electrophile (R-X) contained in the organic layer leading to the desired alkylated product and regenerating the catalyst. If the catalyst is non-racemic

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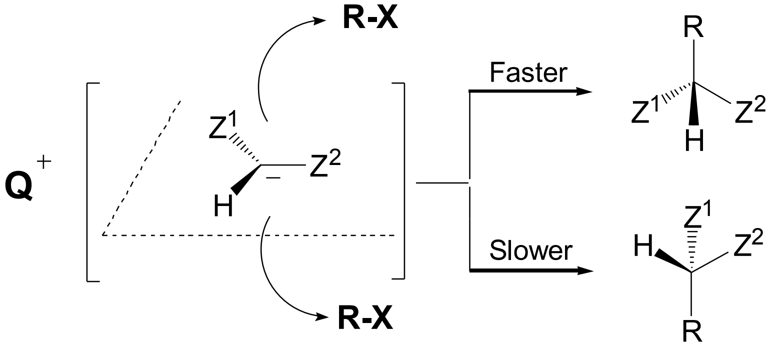
[10] Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195; Starks, C. M.; Owens, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3613

[11] Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351

[12] Mase, N.; Ohno, T.; Morimoto, H.; Nitta, F.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2005**, *46*, 3213; Li, L.; Zhang, Z.; Zhu, X.; Popa, A.; Wang, S. *Synlett.* **2005**, 1873

[13] Yadav, G. D. *Top. Catal.* **2004**, *29*, 145

and the substrate prochiral, the *in-situ* generated reactive intermediate $[Q^+][Z^1CHZ^{2-}]$ has no longer two enantiotopic but two diastereotopic faces (Scheme 0-2). The cationic counter-ion Q^+ acts as a “chiral auxiliary” linked by non-covalent interactions with the prochiral anionic counter-ion. In the case of the formation of tightly associated contact ion pairs between the two species, large chemical and physical differences among the diastereomeric salts can occur. As a consequence, one diastereomeric ion pair will be selected leading to the possibility to induce a stereoselectivity.



Scheme 0-2: Carbanion attack onto RX with its two diastereotopic faces

In **1984**, chemists at Merck were the first to report an efficient enantioselective PTC reaction using a *N*-benzylcinchoninium bromide salt as catalyst for the methylation of a phenyl-indanone substrate (Equation 0-1); the base-induced reaction proceeding with 95% yield and 92% enantiomeric excess (ee).[14] Since then and for many years, the most efficient phase-transfer catalysts were *cinchona* alkaloids derivatives, these compounds being inexpensive and readily available in two diastereomeric, yet pseudo-enantiomeric, forms.[15] However the structural modification for the fine tuning of *cinchona*-alkaloid ammonium catalysts is somewhat limited. In this context, quite a few groups have entered the field of enantioselective PTC by proposing novel structures and geometries for non-racemic ammonium moieties.

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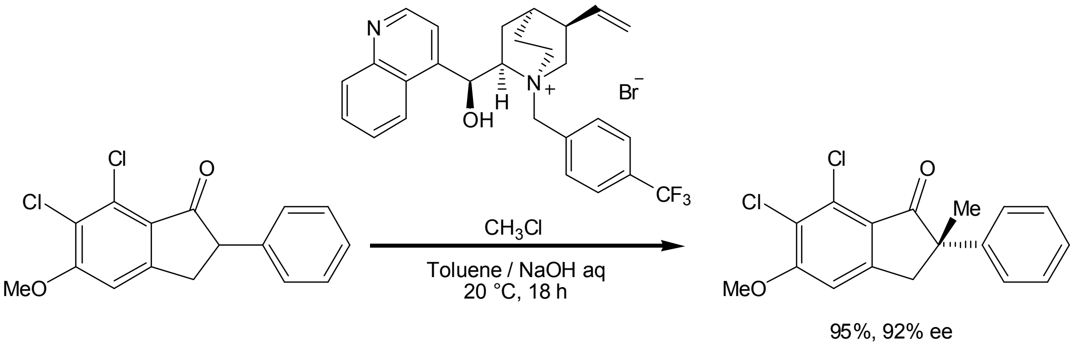
[14] Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446

[15] O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507



Equation 0-1: First efficient enantioselective PTC reaction using *N*-benzylcinchonium bromide as catalyst

As a general trend, the most efficient catalysts developed to date are either coming from the chiral pool as a single enantiomer (*cinchona* alkaloids or tartaric acid derivatives) or purely synthetic ammonium generated from enantiopure BINOL *via* enantiospecific processes.[16] Rather than considering these two approaches a different strategy was developed in the group of Professor Jérôme Lacour that is to synthesize novel non-racemic ammonium structures starting from achiral molecules and to resolve those cations using chiral anions.

Chiral Hexacoordinated Phosphorous Anions

To afford non-racemic or enantiopure cationic products, and benefit from possible new applications, an asymmetric ion pairing with non-racemic anions can be indeed considered. In fact, the association of prochiral or chiral ionic species with enantiopure counterions results in the formation of diastereomeric salts. It is commonly accepted that an ion electrostatically removed from its counterion is never formed in low-polarity solvents but, instead, an *ion pair* is produced. Ion pairing is an essential phenomenon, which has been extensively studied and reviewed.[17] The terms *contact*, *tight*, *intimate or penetrate ion pair* and *solvent-separated* or *loose ion pair* have become well-known in the chemical world.[18] In early approaches, chiral anions issued or derived from the chiral pool have been essentially considered. Numerous applications, especially in the field of enantiomeric resolutions, have been developed and these anions are still used with much success.[19] Today, many applications make also use of purely

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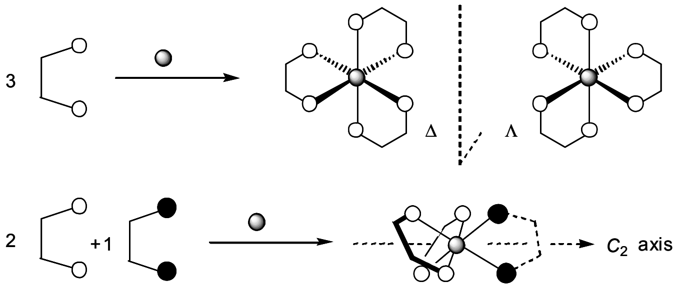
[16] Vachon, J.; Lacour, J. *Chimia* **2006**, *60*, 266

[17] Macchioni, A. *Eur. J. Inorg Chem.* **2003**, 195 and references therein

[18] For an interesting review on this topic see: Macchioni, A. *Chem. Rev.* **2005**, *105*, 2039

[19] Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373 and references therein

synthetic derivatives, and those based on hexacoordinated phosphorus in particular. These compounds are of particular interest as a simple triple chelation of symmetrical bidentate ligands to the octahedral phosphorus is sufficient to create D_3 or C_2-symmetric chiral structures (Scheme 0-3).[20]



Scheme 0-3: Representation of the triple chelation of a bidentate ligand around a phosphorous atom

TRISPHAT ANION

Following the work of Hellwinkel in the 1960s with the synthesis of a tris(biphenyl)phosphate (V) anion, and a tris(benzenediolato)phosphate (V) anion. [21,22] Munoz *et al.* proposed milder conditions to have access to these hexacoordinated phosphorus compounds. It consists in mixing three equivalents of pyrocatechol with one equivalent of PCl_5 followed by the addition of triethylamine leading to a triethylammonium phosphate salt with good yield and excellent purity (Figure 0-2).[23]

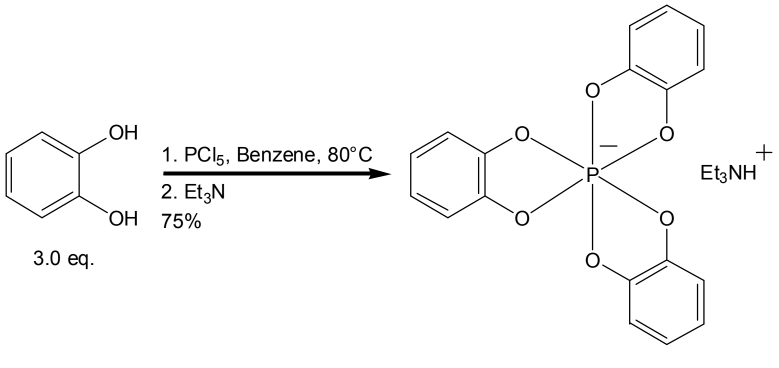


Figure 0-2: Preparation of tris(benzenedioalato)phosphate(v) anion (Munoz, 1979)

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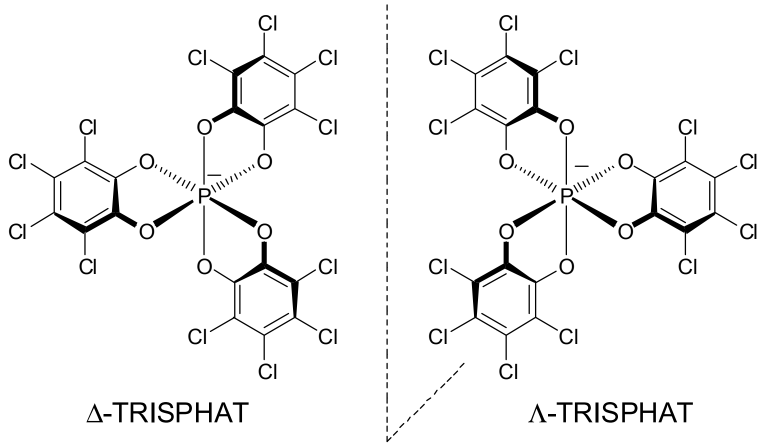
[20] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; 1st ed.; John Wiley & Sons: New York, USA, **1994**;

[21] Hellwinkel, D. *Chem. Ber.* **1965**, *98*, 576; Hellwinkel, D. *Angew. Chem.* **1965**, *77*, 378

[22] Hellwinkel, D. *Chem. Ber.* **1966**, *99*, 3628; Hellwinkel, D.; Wilfinger, H. J. *Phosphorus* **1972**, *2*, 87

[23] Koenig, M.; Klaebe, A.; Munoz, A.; Wolf, R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 40

Unfortunately this particular anion derived from pyrocatechol is configurationally labile as an ammonium salt. Indeed, when obtained in a diastereomericaly enriched form with brucinium as counter-ion, the re-solvatation of this salt led to rapid racemization of the anion, especially in low polar solvents. One hypothesis developed in our laboratory is that the racemization pathway of this anion involves the protonation of one of the oxygen atom of the catecholate ligands by the acidic proton of the ammonium counterion leading to a P-O bond breakage and the opening of the heterocycle to form a spirophosphorane. At this stage, Berry (or other) pseudo-rotation followed by a subsequent random re-cyclisation results in a 1:1 mixture of epimeric salts.



Interestingly, introduction of electron-withdrawing atoms such as chlorines, on the catechol moieties led to configurationally stable anions. The electronic density of the oxygen atom being lower, this decreases their ability to be protonated in acidic medium. Thus, the replacement of the pyrocatechol by tetrachloropyrocatechol, which is commercially available, in the synthesis described by Munoz, confers a better configurational stability to the anion. This particular tris(tetrachlorobenzendiolato)phosphate anion, commonly called TRISPHAT, can be easily synthesized on multigram scales. Concerning the resolution of this anion, classical association with cinchonidine as a chiral resolving agent allows a rapid access to both enantiomers of TRISPHAT with good optical purities and the procedure can also be performed on multigram scale in a quite straightforward manner.[24] The geometry, as well as the absolute configuration of TRISPHAT anion was determined by structural X-ray diffraction

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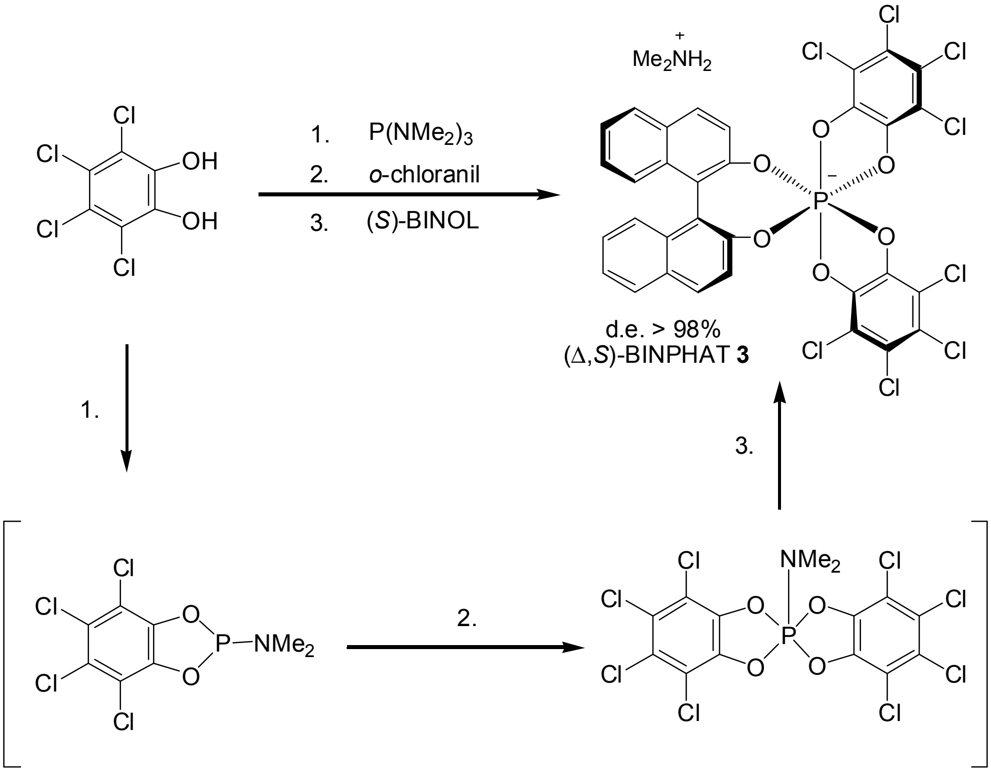
[24] Favarger, F.; Goujon-Ginglinger, C.; Monchaud, D.; Lacour, J. *J. Org. Chem.* **2004**, *69*, 8521

analysis. [25] To confirm this assessment in solution, a circular dichroism analysis, both electronical (ECD) and vibrational (VCD) was recently performed.[26]

BINPHAT ANION

TRISPHAT anion has proven to be a valuable NMR-solvating, resolving and asymmetry inducing agent,[27] with however a generally poor affinity for purely organic cations. To solve this problem, a more electron-rich C_2-symmetric hexacoordinated phosphate anion of configuration controlled by the enantiopure BINOL was prepared. The stereoselective synthesis of this anion named BINPHAT was realized *via* a three steps one-pot process with good yields (usually 65-85%, Scheme 0-4). The resulting anion is diastereomerically pure (>98% d.e. checked by ^{1}H -500 MHz), the (*S*) and (*R*)-BINOL affording anions of Δ and Λ configurations respectively (determined by X-ray diffraction analysis).[28]



Scheme 0-4: Stereoselective synthesis of BINPHAT anion from tetrachlorocatchol

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[25] Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G. *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 608

[26] Bas, D.; Buergi, T.; Lacour, J.; Vachon, J.; Weber, J. *Chirality* **2005**, *17*, S143

[27] Lacour, J.; Frantz, R. *Org. Biomol. Chem.* **2005**, *3*, 15

[28] Lacour, J.; Londez, A.; Goujon-Ginglinger, C.; Buss, V.; Bernardinelli, G. *Org. Lett.* **2000**, *2*, 4185

TRISPHAT and BINPHAT anion’s affinity for N-based cations :

For NMR enantiomeric purity determination of ammoniums

As mentioned above, TRISPHAT is known to be an efficient chiral NMR-solvating agent for, above all, cationic metallo-organic and organometallic substrates. As only few methods are available for the precise determination of optical purity of purely organic cations, it was interesting to see whether BINPHAT anion could display superior chiral solvating properties when associated with chiral ammoniums. Several chiral but racemic ammonium iodide salts have been prepared and put in solution in NMR tubes and were further titrated with a lipophilic tetrabutylammonium Δ-BINPHAT salt. This anion forms tightly associated diastereomeric ion pairs with chiral cations and the short-range interactions that occur lead to efficient ^{1}H NMR enantiodifferentiations. Well-separated signals are usually observed on the spectra of the diastereomeric salts. In Figure 0-3 are represented some ammoniums that have been analyzed with success with the Δδ values (in ppm) underlined of the separated signals of the diastereomeric salts of BINPHAT.[29]

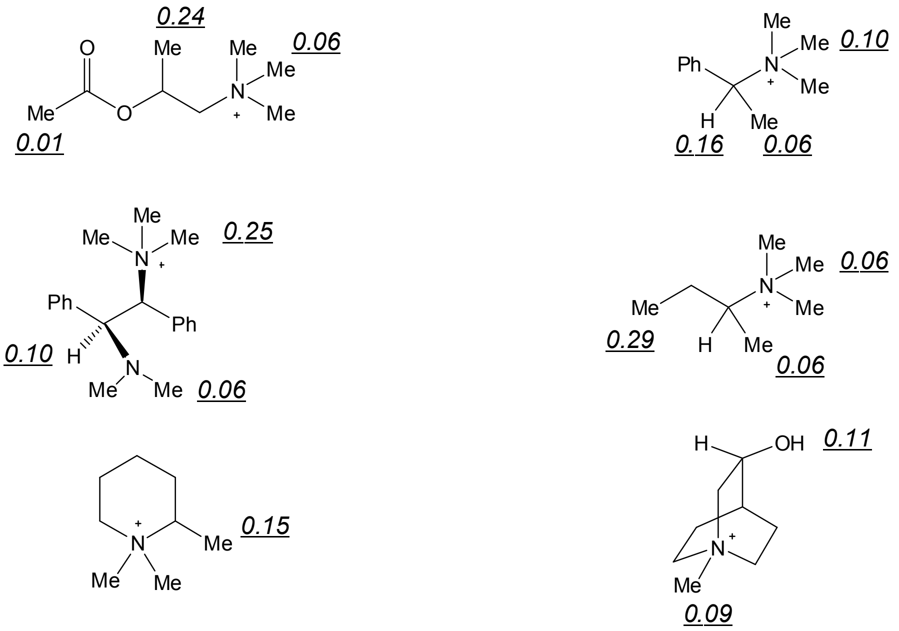

Figure 0-3: Chiral ammonium studied for ^{1}H NMR enantiodifferentiations with the ΔΔδ values (in ppm) underlined of the separated signals of the diastereomeric salts of BINPHAT

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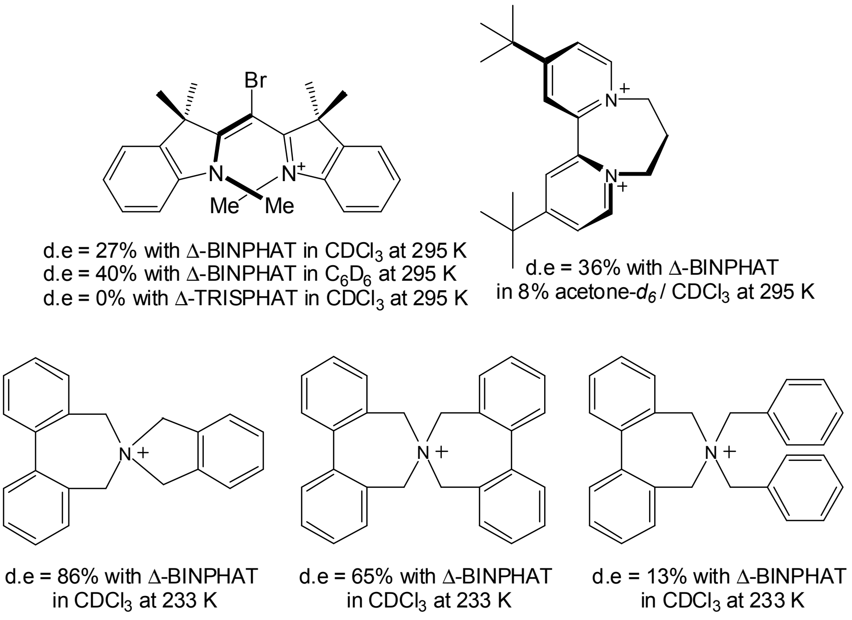
[29] Lacour, J.; Vial, L.; Herse, C. *Org. Lett.* **2002**, *4*, 1351

For Asymmetry induction onto configurationally labile ammoniums

Chiral compounds are sometimes configurationally stable as solids and configurationally labile in solution. When optically active samples of these derivatives are solubilized, a racemization occurs due to the free interconversion of the enantiomers in solution. To obtain these compounds in one predominant configuration over time, one strategy is to add stereogenic elements to their backbone; ***intramolecular*** diastereoselective interactions happen and favor one of the equilibrating diastereomers. If the chiral compounds are charged, an alternative strategy is to consider their ion pairing with chiral counter-ions; ***intermolecular*** rather than intramolecular-diastereoselective interactions then control the stereoselectivity through a supramolecular stereocontrol (Pfeiffer effect).[30] As seen above, the NMR chiral solvating efficiency of TRISPHAT and BINPHAT anions is an excellent analytical tool to provide accurate measurement of the induced selectivity.



d.e = 27% with Δ-BINPHAT in CDCl$_3$ at 295 K
d.e = 40% with Δ-BINPHAT in C$_6$D$_6$ at 295 K
d.e = 0% with Δ-TRISPHAT in CDCl$_3$ at 295 K

d.e = 36% with Δ-BINPHAT
in 8% acetone-d_6 / CDCl$_3$ at 295 K

d.e = 86% with Δ-BINPHAT
in CDCl$_3$ at 233 K

d.e = 65% with Δ-BINPHAT
in CDCl$_3$ at 233 K

d.e = 13% with Δ-BINPHAT
in CDCl$_3$ at 233 K

Figure 0-4: Configurationally labile N-based cations with the d.e of Δ-BINPHAT or Δ-TRISPHAT salts

Care has however to be taken to select cations for which the barrier of interconversion is such that the two enantiomers can be observed at room temperature or accessible at low temperature by NMR. Monomethine dyes, diquats and singly bridged biphenyl ammonium

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[30] Pfeiffer, P.; Quehl, K. *Chem. Ber.* **1931**, *64*, 2667

cations are in these cases and were thus studied with success in conjunction with enantiopure TRISPHAT or BINPHAT anions (Figure 0-4).[31] The NMR signals of the chiral cations were split by the presence of the anions and diastereomeric excesses were measured by integration of the signal corresponding to each diastereomer.

Objectives / Plan

The goal of this thesis was thus to (i) synthesize new axially chiral nitrogen-based cations, (ii) resolve them with, if needed, the chiral anions previously described and (iii) test them in asymmetric phase transfer catalysis.

The first chapter will deal with the study of atropisomeric Doubly Bridged Biphenyl Azepines (DBBA) which will constitute the central structural core of our cationic species. The synthesis and the configurational stability of these derivatives as well as the structural modifications made to enhance the rotational barrier will also be described.

In the second chapter, we will show how the azepines described in the first chapter will be used as efficient precursors to non-racemic iminium salts; those unsaturated cations being effective catalysts for the asymmetric epoxidation of prochiral olefins. A comparison between configurationally labile and configurationally rigid iminium salts will be presented and discussed. Moreover, we will show that theses azepines precursors can, in some cases, be directly used as (*pre*) catalysts for the epoxidation of olefins with similar levels of activity and enantioselectivity.

In the third chapter, we will present that DBBA are also interesting core structures for the synthesis of non-racemic quaternary ammonium salts. The resolution using chiral anions, the configurational stability as well as the use of the resulting dicationic species as phase transfer catalysts for the alkylation of a glycine Schiff base ester will be also treated. Structural modifications of the central core will also be brought to enhance subsequent enantioselectivities.

Finally, in the fourth chapter, another family of non-racemic nitrogen-based cations named diquats will be presented. Their synthesis and their resolution with chiral anions as well as a careful configurational study of these axially chiral bipyridinium dications will be exposed.

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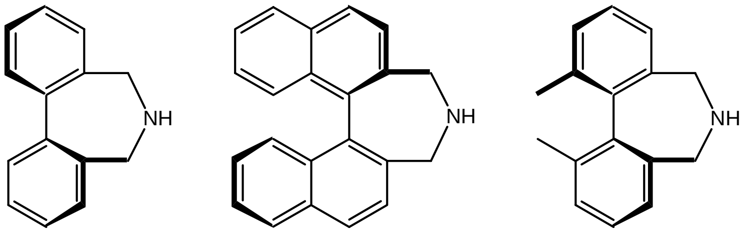
[31] Lacour, J.; Londez, A.; Goujon-Ginglinger, C.; Buss, V.; Bernardinelli, G. *Org. Lett.* **2000**, *2*, 4185; Pasquini, C.; Desvergnes-Breuil, V.; Jodry, J. J.; Dalla Cort, A.; Lacour, J. *Tetrahedron Lett.* **2002**, *43*, 423; Vial, L.; Lacour, J. *Org. Lett.* **2002**, *4*, 3939

Chapter I

DOUBLY BRIDGED BIPHENYL AZEPINES

I-1 Atropisomerism of bridged biaryl compounds

Non-racemic chiral amines and their nitrogen-based cationic derivatives as well, are often used as chiral auxiliaries, ligands or catalysts in asymmetric synthesis. In many instances, C_2-symmetric variants (which are often cyclic derivatives) of these compounds have been used and effective stereoselective processes have been obtained.[1] If pyrrolidine and piperidine frameworks are most often utilized, dibenzoazepine skeletons (Figure I-1 and Figure I-2) have also attracted attention due to the presence of a twisted biaryl bond as a stereogenic element. In these compounds, which include biphenyl **1**,[2] binaphthyl **2**,[3] 1,11-dimethyl-biphenyl **3**,[4] and doubly bridged biphenyl **4** (Figure I-2) moieties,[5] the non planar arrangement of the aromatic units creates an axis of chirality that results indeed in two preferred *S*a or *R*a atropoisomeric conformations (or *P* and *M* configurations respectively).[6]



(S_a)-**1** (R_a)-**2** (S_a)-**3**

Figure I-1: C_2-symmetric seven-membered ring azepines

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[1] Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581; Renfroe, B.; Harrington, C. *Dibenzazepines and other tricyclic azepines*, 1984; Vol. 43

[2] First reports of **1** described as a chiral molecule: Ahmed, S. R.; Hall, D. M. *J. Chem. Soc.* **1958**, 3043

[3] First example of compounds of type **2** used in asymmetric synthesis: Maigrot, N.; Mazaleyrat, J. P.; Welvart, Z. *J. Org. Chem.* **1985**, *50*, 3916; Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820

[4] Fitts, D. D.; Siegel, M.; Mislow, K. *J. Am. Chem. Soc* **1958**, *80*, 480; Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc* **1962**, *84*, 1455

[5] Mizlow, K.; Glass, M. A. W.; Hopps, H. B.; Simon, E.; Wahl, G. H., Jr. *J. Am. Chem. Soc* **1964**, *86*, 1710

[6] Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley-VCH, 1994; p 1142

The term *atropisomerism* coming from the Greek words for “not”—*a*—and “turn”—*tropos* and was firstly introduced by Kuhn in 1933.[7] It is commonly accepted that, as an arbitrary definition, atropisomers are recognized as physically separable species (*i.e.* sufficiently configurationally stable molecules) when, at a given temperature, the a half–life of racemization is at least 1000 seconds (16.7 min). The minimum free energy barrier ($\Delta G^{\neq}$) at room temperature (~300 K) required for the interconversion between the two atropisomers is 22.4 kcal.mol^{-1}.[8]

Studies performed on diphenylazepines of type **1** have revealed that atropisomeric S_a or R_a conformations interconvert freely in solution by rotation around the biphenyl axis with rather low kinetic barriers. Due to the magnetic non-equivalency of the diastereotopic benzylic protons, it has been generally possible to determine the free energy barrier of rotation around the biphenyl axis by VT-NMR experiments. Concerning compound **1**, previous experiments have shown that a sharp singlet for the benzylic protons is still observed even at the lowest attainable temperature of the experiment (– 60 °C in Pyridine-d_5/D_2O 1:1) meaning that the rate of exchange between the two atropisomers is still fast on the NMR time scale even at low temperatures. This indicates a rather lower kinetic barrier ($\Delta G^{\neq}$ < 12 kcal.mol^{-1}).[9] In the same article, it was shown that related quaternary ammonium **1’** displayed a higher racemization barrier ($\Delta G^{\neq}$ ~ 13.4 kcal.mol^{-1}) as separation of the signals could be observed at low temperature NMR so that its stereodynamics could be analyzed (Figure I-2).

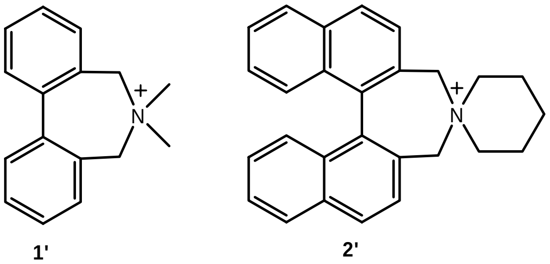

Figure I-2: Configurationally labile (**1’**) and rigid (**2’**) ammoniums described in the literature

In comparison, compounds of type **2** and **3** are configurationally stable at 20 °C and rotation around the biaryl axis (if possible) occurs only at very elevated temperature. For compound **3**, the inversion process cannot be entirely ruled out (due to decomposition at

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[7] Kuhn, R. *Moleculare Asymmetrie*; Franz Deuticke: Leipzig, 1933;

[8] Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384

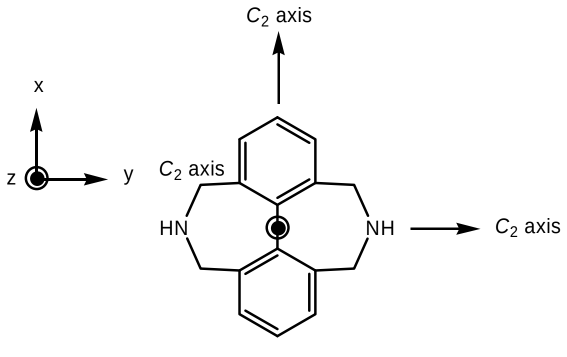
[9] Sutherland, I. O.; Ramsay, M. V. J. *Tetrahedron* **1965**, *21*, 3401

elevated temperature) but theoretical calculations provide strong support for the rotational pathway.[10] For compound **2'** (Figure I-2), an half-life of 26 hours has been determined at 172 °C in boiling ethanol (which correspond to a $\Delta G^{\neq}_{(445K)} \sim 37$ kcal.mol^{-1}).[11] In accordance to recent denomination, derivatives of type **1** and **2**/**3** can be considered as being *tropos* and *atropos* respectively.[12]

I-2 Doubly Bridged Biphenyl Azepines (DBBA): an intermediate situation

I-2.1 Introduction and preliminary results

Biphenyls bearing four identical substituants in the positions 2, 2', 6 and 6' are achiral (provided there are no other substituants attached to the aromatic rings). On the other hand, biphenyl systems with two identical 2,6- and 2',6'-bridges are chiral, being exceptional in that they possess, instead of a plane of symmetry, three mutually perpendicular C_2 axes (D_2 point group, Figure I-3).



4

Figure I-3: D_2-symmetric doubly bridged biphenyl azepine **4**

In term of configurational stability, derivatives of type **4** present an intermediate situation between compounds **1** and **2**/**3**. Previously, Tichy, Gunterova and Zavada have described the synthesis of diastereomeric doubly bridged diamines **4a**, **4b** and **4c** (Figure I-4).[13] But apart

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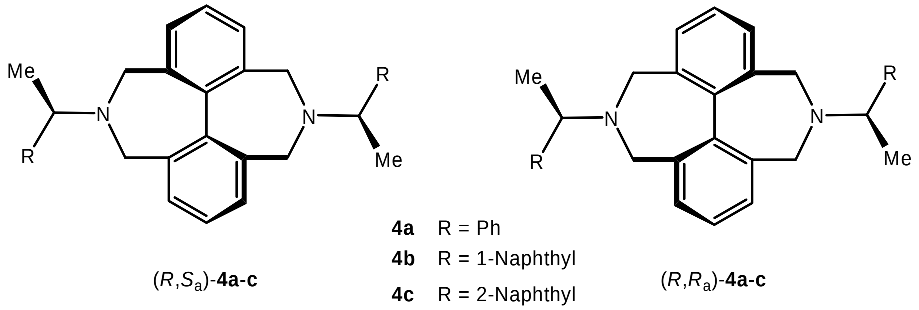
[10] Rademacher, P.; Stoelevik, R. *Acta Chem. Scand.* **1969**, *23*, 660; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219; Cooney, J. D.; Brownstein, S. K.; ApSimon, J. W. *Can. J. Chem.* **1974**, *52*, 3028; Battiste, D. R.; Davis, L. P.; Nauman, R. V. *J. Am. Chem. Soc* **1975**, *97*, 5071

[11] Beaven, G. H.; Bird, G. R.; Hall, D. M.; Johnson, E. A.; Ladbury, J. E.; Lesslie, M. S.; Turner, E. E. *J. Chem. Soc.* **1955**, 2708

[12] Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561; Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369

[13] Tichy, M.; Gunterova, J.; Zavada, J. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1080

from these examples, no attempts to prepare **4** in an optically active form have been reported.[14] In the original paper of Zavada, these compounds were prepared by direct alkylation of 2,2',6,6'-tetrakis(bromomethyl)biphenyl with centrally chiral (*R*)-1-phenylethylamine **a**, (*R*)-1-(1-naphthyl)ethylamine **b** and (*R*)-1-(2-naphthyl)-ethylamine **c** respectively. The diastereomeric ratios of the resulting (R, R_a) and (R, S_a) atropisomers were moderate (d.r. 55:45 in CH_3CN for the three compounds **4a-c**) and quite dependant of the solvent nature (d.r. up to 37:63 for **4c** in dioxane). The diastereomers of **4a** and **4c** were nevertheless separated by semi-preparative HPLC and/or crystallization.



(R,S_a)-**4a-c**

4a R = Ph
4b R = 1-Naphthyl
4c R = 2-Naphthyl

(R,R_a)-**4a-c**

Figure I-4: DBBA **4a-c** described by Zavada and coworkers

The absolute configuration of the biphenyl twist in the products was assigned on the basis of CD spectra and comparison with singly bridged biphenyl models (of type **3**) of known sense of twist. Indeed, Mislow and Sandström had observed and rationalized for 2,2'-bridged biphenyls that a negative Cotton effect in the region of 250-260 nm corresponds to a *S*a configuration for the biphenyl moiety.[15] According to Zavada, the key step for the determination of the final configuration adopted by the molecule of type **4** is the first cyclisation step **A** to **B** as detailed in Figure I-5. The intermediate **A** is unique in that it represents a "*nonplanar, conformationally frozen species with a stereochemically undefined (prostereogenic[16]) biaryl axis"*. The stereochemical definition is attained in the diastereoselective cyclization step **A** → **B**. The diastereoselectivity of the cyclisation is given by differing reactivities of the two alternative conformers of **A** arising by rotation about the $ArCH_2$–N bond, underlying the axial chirality induction by a centrally chiral element.

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[14] Mizlow, K.; Glass, M. A. W.; Hopps, H. B.; Simon, E.; Wahl, G. H., Jr. *J. Am. Chem. Soc* **1964**, *86*, 1710; Kovac, B.; Klasinc, L.; Vukosa, E.; Loncar-Tomaskovic, L.; Mintas, M. *Croat. Chem. Acta* **1999**, *72*, 43

[15] Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc* **1962**, *84*, 1455; Mizlow, K.; Glass, M. A. W.; Hopps, H. B.; Simon, E.; Wahl, G. H., Jr. *J. Am. Chem. Soc* **1964**, *86*, 1710; Sandstrom, J. *Chirality* **2000**, *12*, 162; Loncar-Tomascovic, L.; Sarac-Arneri, R.; Hergold-Brundic, A.; Nagl, A.; Mintas, M.; Sandstrom, J. *Helv. Chim. Acta* **2000**, *83*, 479

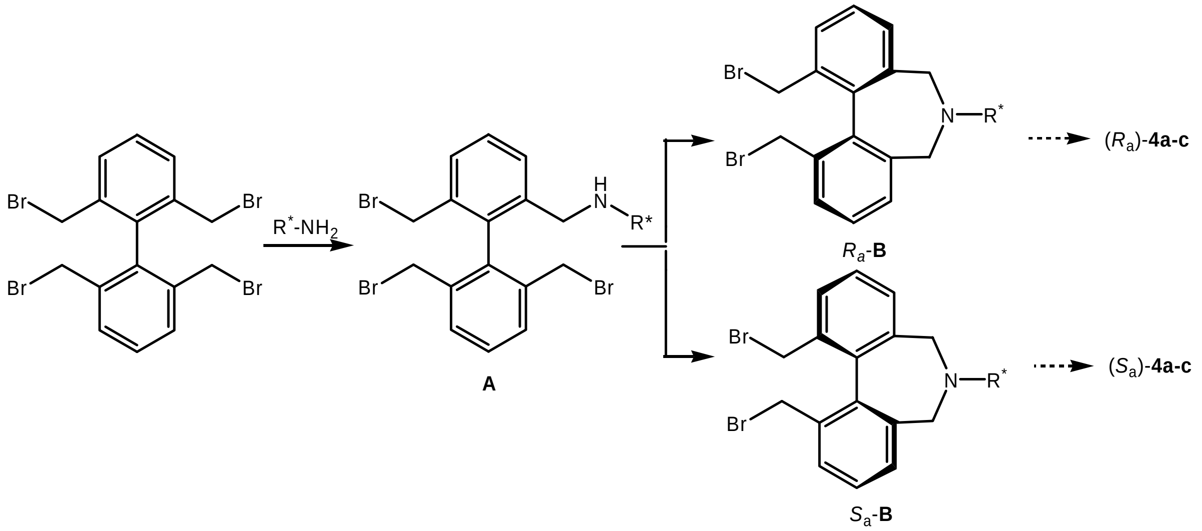

Figure I-5: Mechanism of formation of DBBA **4a-c** *via* intermediate **A** and **B**

Interestingly, upon heating at 80 °C, it was noticed that the atropisomers of **4a**, **4b** and **4c** epimerize in favor of the (*R*, R_a) isomer with relatively high diastereomeric ratios (d.r. up to 4.3 to 1). Enantio- and diastereomerically pure derivatives of type **4** can thus be readily prepared. These compounds present, at room and elevated temperature, *atropos* and *tropos* character respectively.

Surprisingly, unlike derivatives **2** and **3**, compounds of type **4** have been rarely used in asymmetric synthesis; the reason being – possibly – the moderate level of stereocontrol induced by the exocyclic stereocenters onto the biaryl axis. We reasoned that such chemistry might become attractive if effective chiral exocyclic appendages could be found that would lead to

(i) high diastereomeric ratios – under thermodynamic control in particular – and/or

(ii) easy physical separation of the atropisomers.

We thus envisioned the synthesis and the isolation of new diastereomeric doubly bridged compounds (**4d** to **4g)** made from a selection of novel chiral amines (**d** to **g**, Figure I-6); the stereoinduction onto the biaryl axis by the new stereocenters being studied under thermodynamically controlled conditions. To afford a systematic comparison of the influence of exocyclic stereogenic elements onto singly and doubly bridged biphenyls, the *tropos* equivalents (**1a** to **1g**) of compounds **4a** to **4g** were prepared and analyzed.

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[16] Bringmann, G.; Reuscher, H. *Tetrahedron Lett.* **1989**, *30*, 5249

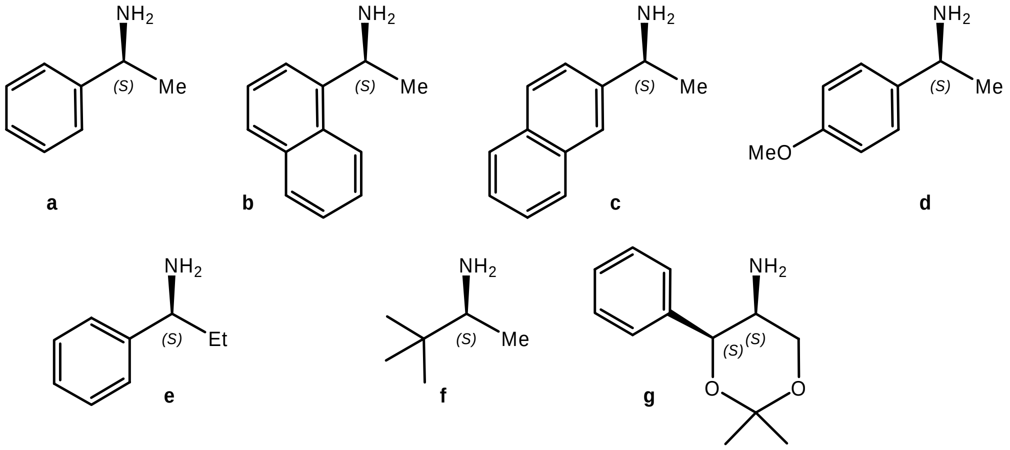

Figure I-6: (*S*)-configured enantiopure amines **a-g** used for the preparation of DBBA of type **4**

I-2.2 Configurational analysis

The synthesis of derivatives of type **4** is relatively straightforward and consists in two steps (Figure I-7). Ozonolysis of commercially available pyrene leads to the biphenyl-2,2',6,6'-tetracarbaldehyde with moderate yield (55%).[17] After reductive amination of the latter compound in presence of a chiral amine **a**, **b**, **d**, **e**, **f** and **g** and sodium cyanoborohydride, azepines **4a**, **4b**, **4d**, **4e**, **4f** and **4g** respectively were obtained with relatively good yields (58 to 100%).[18]

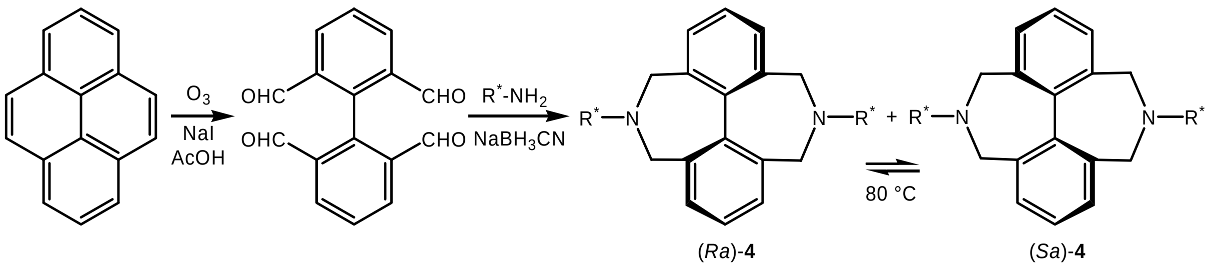

Figure I-7: Preparation of DBBA of type **4** *via* ozonolysis of pyrene and subsequent reductive amination

Separations of the two diastereomers were first tried by column chromatography on silica gel. It appears that in all cases, the first eluted diastereomer can be obtained with moderate yields (15 to 30%) but unfortunately, the second eluted diastereomer is contaminated with the other

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[17] Agranat, I.; Rabinovitz, M.; Shaw, W. C. *J. Org. Chem.* **1979**, *44*, 1936

[18] Kawaguchi, M.; Ohashi, J.; Kawakami, Y.; Yamamoto, Y.; Oda, J. *Synthesis* **1985**, 701; Fray, A. H.; Augeri, D. J.; Kleinman, E. F. *J. Org. Chem.* **1988**, *53*, 896

diastereomer so that low yields, for the better cases, are obtained (4 to 13%). For **4d** and **4e,** where it was not possible to recover the second diastereomer with good diastereoselectivity, a few milligrams were obtained for the analysis using semi-preparative HPLC.

Circular Dichroism (CD) measurement of each diastereomer was performed to assign the configuration of the biphenyl axis. Methanol was chosen as solvent for all experiments except for **4b** which is essentially insoluble in this solvent; in this case DCM has been preferred. In order to compare data more easily, care was taken in this study to select amines of same (*S*) configuration at the carbon α to the nitrogen atom. All CD spectra are gathered in Figure I-8. To the exception of **4f** and **4g**, all the most eluted (major, as determined by NMR on the crude product, see § I-2.3) diastereomer show a negative Cotton effect ($\Delta\varepsilon < 0$, Table I-1) around 255 nm indicating a preferred *P* (or *S*a) configuration for the biphenyl moiety.[19]

			First Eluted Diastereomer [a]				Second Eluted Diastereomer [a]			
entry	DBBA	$[\alpha]_D$ amine	Rdt (%)	$[\alpha]_D$	Conf. [b]	$\Delta\varepsilon$ cm^2·mmol^{-1} [b] (250-260 nm)	Rdt (%)	$[\alpha]_D$	Conf. [b]	$\Delta\varepsilon$ cm^2·mmol^{-1} [b] (250-260 nm)
1	**4a**	-39	30	-240.0	*S*a	-21.12	13	27.5	*R*a	10.42
2	**4b**	-59	16	-11.2	*S*a	-4.12	4	3.4	*R*a	4.50
3	**4d**	-26	22	-263.5	*S*a	-31.30	0[d]	62.1	*R*a	18.21
4	**4e**	-19.8	28 [c]	-298.2	*S*a	-33.90	0[d]	51	*R*a	19.30
5	**4f**	2.5	20	256.0	*R*a	16.44	6	-0.1	*S*a	-11.38
6	**4g**	29.6	26	235.5	*R*a	37.68	10	-22.1	*S*a	-25.02

[a] yield after flash chromatography unless otherwise stated. [b] Conformation and $\Delta\varepsilon$ determined by circular dichroism; the reported value for $\Delta\varepsilon$ (cm^2·mmol^{-1}) corresponds to the maxima in the region 250-260 nm. [c] Obtained by selective precipitation in methanol. [d] obtained by semi-preparative HPLC (SP 250/10 Nucleosil 50-7) on mg scale.

Table I-1: Results of the separation of the two diastereomers of DBBA **4a**, **4b**, **4d**, **4e**, **4f** and **4g** with isolated yield, optical rotation, configuration with corresponding $\Delta\varepsilon$ at 250 nm in circular dichroism of each diastereomer

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[19] With **4f** and **4g**, (*S*) configurated amines **f** and **g** lead to preferred diastereomer kinetic and thermodynamic of (*S*, *R*a) configuration (*vide infra*).

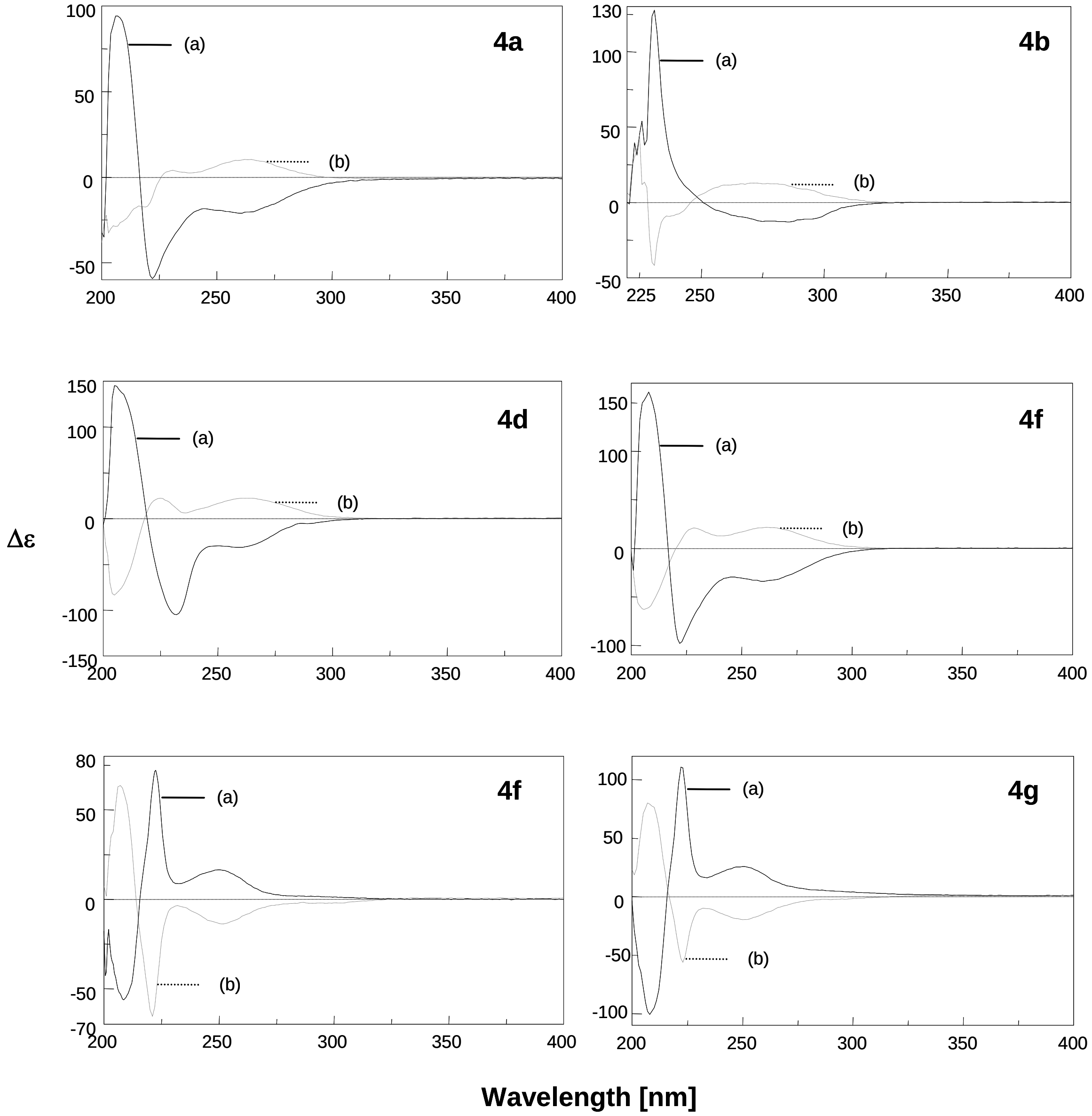

Figure I-8: : CD spectra of DBBA **4a**, **4b**, **4d**, **4e**, **4f** and **4g**, (*c* 1.10^{-5} M, MeOH except for **4b** done in DCM): (a, plain) first eluted (major) diastereomer and (b, dashed) second eluted (minor) diastereomer

From this table we can depict some tendencies:

(i) A dextrorotatory amine induces a dextrorotatory azepine for the first eluted diastereomer and a levorotatory azepine for the second eluted diasteromer and the other way round.

(ii) An amine with a (*S*) configuration induces an (*S*a) atropisomer for the first eluted diastereomer and an (*R*a) atropisomer for the second eluted diasteromer except for amines **f** and **g** (Table I-1, entry 5 and 6).

(iii) A dextrorotatory azepine has a negative Cotton effect around 255 nm (*P* configuration) on circular dichroism and the other way round.

I-2.3 Kinetics and Thermodynamics

To study the stereoinduction of these amines onto the biaryl axis of the biphenyl azepines, kinetic and thermodynamic diastereomeric ratios were measured by ^{1}H NMR as the two diastereomers have different chemical shifts (usually, protons α to the nitrogen were good probes, Figure I-9). Kinetic ratios were measured from the crude mixture of diastereomers obtained after the synthesis (spectrum *a*, Figure I-9). Care was taken to verify that this ratio remains unchanged over time at room temperature and that, during the workup, no heat had been applied to removed solvents. Thermodynamic ratios were calculated after heating separately each diastereomer (first eluted (spectrum *b*) and second eluted (spectrum *c*), Figure I-9) for 20h at 80 °C in benzene. Under those conditions, a total equilibration was achieved as identical ratios were obtained starting from both diastereomer (spectrum *d*, Figure I-9). Initially, we thought that bulkier amines **f** and **g** ought to afford greater diastereomeric excess through greater steric interactions. But results indicated that it is not the case as the best thermodynamic ratios were obtained with amines **b** and **e** with 4.3:1 and 4.2:1 ratios respectively (Table I-2, entry 2 and 4). Interestingly, in all the cases, the kinetically favored diastereomer is also the thermodynamically one.

Entry	DBBA	d.r Kinetic [a]	d.r Thermodynamic [b]	Major Configuration (Kinetic diastereomer)	Major Configuration (Thermodynamic diastereomer)
1	**4a**	1.2 : 1	3.4 : 1	*S*a	*S*a
2	**4b**	1.4 : 1	4.3 : 1	*S*a	*S*a
3	**4d**	1.1 : 1	3.0 : 1	*S*a	*S*a
4	**4e**	1.1 : 1	4.2 : 1	*S*a	*S*a
5	**4f**	2.4 : 1	2.5 : 1	*R*a	*R*a
6	**4g**	1.8 : 1	1.6 : 1	*R*a	*R*a

[a] d.r. determined by ^{1}H RMN on the crude material. [b] d.r. determined by ^{1}H RMN after heating at 80°C for 20h in benzene.

Table I-2: Kinetic and thermodynamic diastereomeric ratio obtained for DBBA **4a**, **4b**, **4d**, **4e**, **4f** and **4g** with the corresponding configuration of the major diastereomer

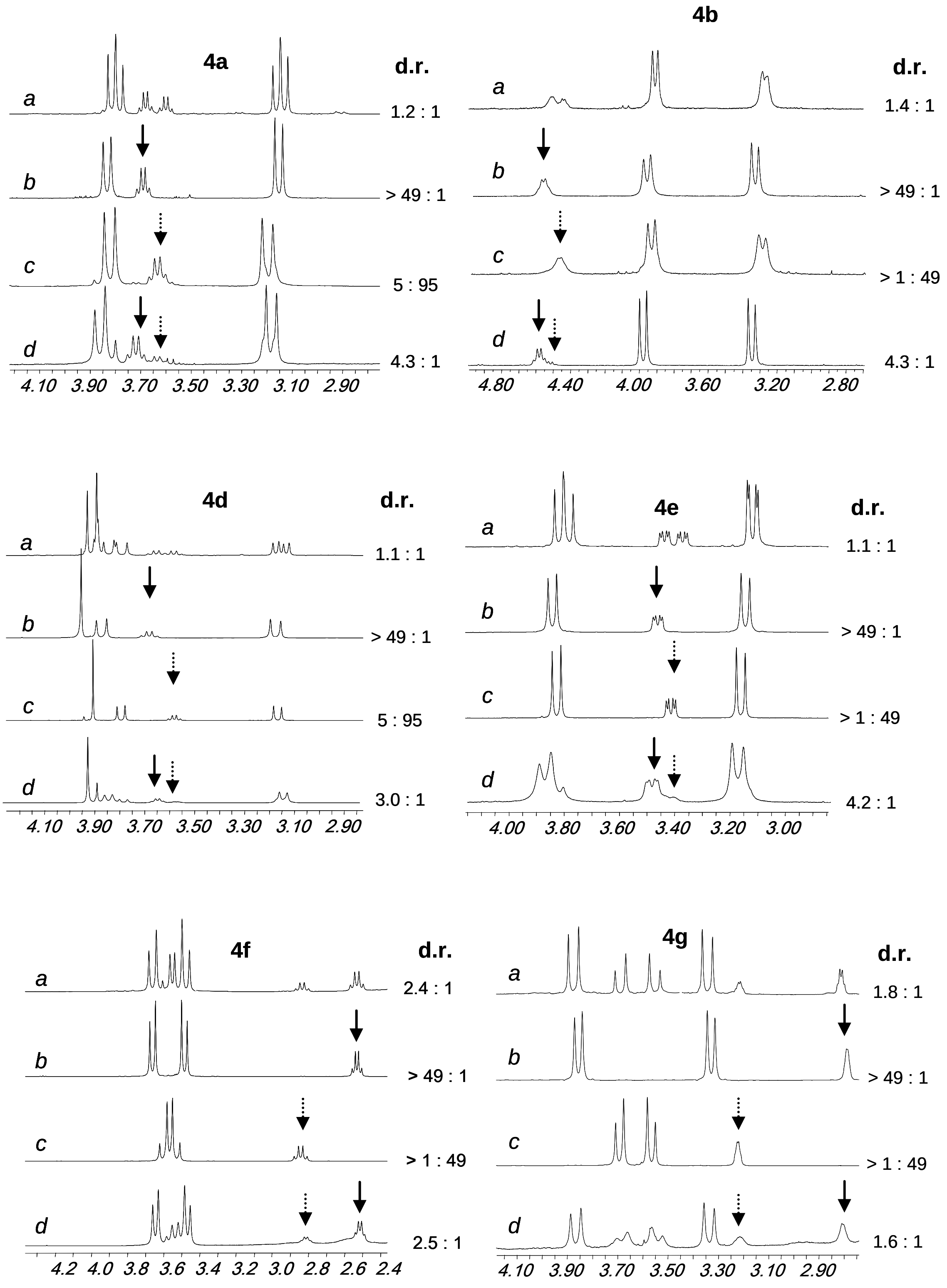

Figure I-9: NMR (400 MHz, $CDCl_3$) of **4a**, **4b**, **4d**, **4e**, **4f** and **4g** with *a*: crude mixture; *b*: first eluted diasteromer; *c*: second eluted diastereomer; *d*: thermodynamic equilibrium

I-3 Syntheses and Study of Dibenzoazepines

I-3.1 Configurational analysis

To determine if the presence of two exocyclic stereogenic elements was leading to better stereoselectivity than just one – a trivial question that had however no answer – a comparative study was performed with the analogous tropos biphenyl azepine of type **1** (Table I-3). The synthesis of these compounds follows the same route, just replacing pyrene by phenanthrene affording the desired azepines **1a-1g** with good yields (from 77 to 97%, Figure I-10).

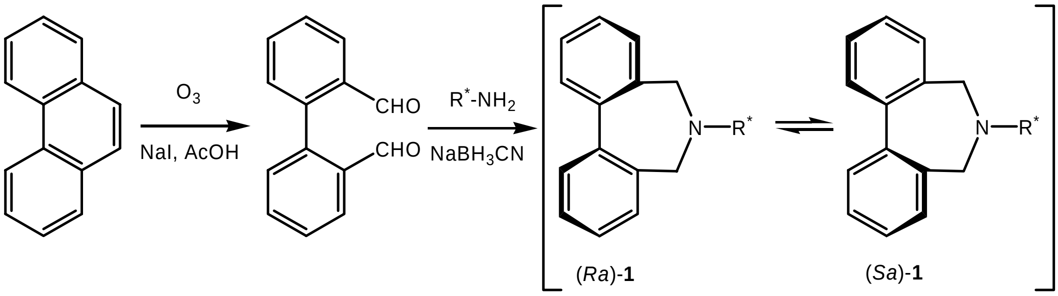

Figure I-10: Preparation of DBBA of type **1** *via* ozonolysis of phenanthrene and subsequent reductive amination

As for the DBBA, optical rotation and CD measurements were performed. Positive and negative Cotton effects were observed for these derivatives around 255 nm, demonstrating the occurrence of preferred conformations in solution. The results are summarized in Table I-3 along with the free energies of rotation around the biphenyl axis determined by VT-NMR experiments.

As mentioned before, rather low kinetic barriers were found for these compounds and little influence of the exocyclic appendage was depicted on kinetics (10.3 to 11.7 $kcal.mol^{-1}$). In conformity with the DBBA series, one of the best chiral appendage in terms of stereoinduction onto the biaryl axis of the biphenyl is amine **e** with a d.r of 6.7:1 at 193K (Table I-3, entry 4). However, an unexpected resulted was obtained with amine **g** (Table I-3, entry 6). Indeed, the configuration of the thermodynamically favored diastereomer of **1g** seems to be in this case (*S*a), like for the other amines (**a**, **b**, **d**, **e**). However, unlike derivatives of type **4** that present a configurational stability at room temperature and for which the absolute configuration can be assigned at that temperature (by CD), compounds **1** are labile and there is thus no proof that the preferred diastereomer at 193 K is the same at 293 K. Indeed, there are quite a few such exceptions in the literature of that type.[20] Only a VT-CD experiment could answer that question, but unfortunately, we do not have this set-up available in Geneva.

Entry	Azepine	$[\alpha]_D$ amine	$[\alpha]_D$ azepine	$\Delta\varepsilon$ $cm^2{\cdot}mmol^{-1}$ CD (254 nm) [a] (293 K)	Configuration. Azepine [a] (293 K)	d.r [b] (193 K)	$\Delta G°$ ($Kcal.mol^{-1}$) (193 K)	$\Delta G^{\neq}$ [c] ($Kcal.mol^{-1}$) (193 K)
1	**1a**	-39	-45.0	-5.8	*S*a	4.5 : 1	-0.58	11.2
2	**1b**	-59	-72.0	-5.8	*S*a	4.0 : 1	-0.53	10.7
3	**1d**	-26	-61.5	-8.1	*S*a	5.9 : 1	-0.68	11.1
4	**1e**	-19.8	-49.0	-5.8	*S*a	6.7 : 1	-0.73	11.3
5	**1f**	2.5	38.7	+3.4	*R*a	5.5 : 1	-0.66	10.3
6	**1g**	29.6	95.5	-1.4	*S*a	3.2 : 1	-0.45	11.7

[a] Configuration and $\Delta\varepsilon$ determined by circular dichroism. [b] Diastereomeric ratio determined by ^1H RMN. [c] $\Delta G^{\#}$ determined by ^1H NMR using the equation $\Delta G^{\neq} = R.Tc.(22.96+\ln(Tc/(\Delta\mu^2+6J^2)^{1/2}))$ with Tc (K) as the coalescence temperature, $\Delta\mu$ (Hz) as the separation frequency of the peaks and J (Hz) as the constant coupling between the nuclei.

Table I-3: Optical rotation, configuration with corresponding $\Delta\varepsilon$ at 254 nm in circular dichroism, diastereomeric ratio at 193 K with Gibbs free energy $\Delta G°$ and $\Delta G^{\neq}$ of dibenzoazepines **1a**, **1b**, **1d**, **1e**, **1f** and **1g**

I-3.2 Thermodynamic Comparison between DBBA 4 and Dibenzoazepines 1

As mentioned before, we were wondering whether the presence of two chiral auxiliaries would be leading to better selectivity than just one, the doubling of the source of induction being possibly translated into quantitative terms into a doubling of the equilibrium constant; this being of course impossible to measure experimentally. To sort the issue, we decided to measure the ΔG° values for the thermodynamic equilibriums of compounds **4** at 80 °C that saw ratios ranging from 1.6:1 to 4.3:1 between the diastereomers. With these values in hand and considering a temperature independency, theoretical equilibrium constants were calculated at -80 °C (193 K) using Van't Hoff equation. The results are detailed in Table I-5 and are compared to that of experiments with **1**. If there is clearly a trend for compounds **a**, **b**, **d** and **e** to see a larger induction on DBBA that on monoazepines ($3.6 > K_4/K_1 > 1.3$, Table I-4, entries 1 to 4), derivatives **4f** and **4g** are "exceptions" ($K_4/K_1 < 1$, Table I-4, entries 5 and

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[20] Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 1551; Fukazawa, Y.; Usui, S.; Tanimoto, K.; Hirai, Y. *J. Am. Chem. Soc.* **1994**, *116*, 8169; Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277

6). However, due to the incertitude on the experiment measurements as well as approximations in the mathematical treatment, care should be taken to consider this as a qualitative assessment.

		DBBA **4**			Monoazepine **1**
Entry	R*-NH$_2$	$\Delta G°$ (Kcal.mol^{-1}) T= 293 K	Equilibrium constant K (353 K)	Equilibrium constant K (193°C)	Equilibrium constant K (193°C)
1	**a**	-0.86	3.4	9.4	4.5
2	**b**	-1.02	4.3	14.3	4.0
3	**d**	-0.77	3.0	7.5	5.9
4	**e**	-1.01	4.2	13.9	6.7
5	**f**	-0.64	2.5	5.3	5.5
6	**g**	-0.07	1.6	2.4	3.2

Table I-4: Comparisons of equilibrium constant K at 193 K for between compounds of type **4** and **1**

I-3.3 Kinetic comparison of 4 and 1

To fully characterize compounds **4**, it was decided to perform a kinetic analysis and to determine precisely the activation barrier for derivatives of type **4**. Diastereomerically pure samples were heated at four different temperatures (60, 70, 80, 90 °C) and aliquots taken at given time were immediately “frozen” at room temperature; the ratio between (*S*, *R*a) and (*S*, *S*a) diastereomers being measured on analytical HPLC (Chiralcel OD-H).

		DBBA **4**			Monoazepine **1**
Entry	R*-NH$_2$	$\Delta G^{\neq}$ (Kcal.mol^{-1}) T= 293 K	$\Delta H^{\neq}$ (Kcal.mol^{-1}) T= 293 K	$\Delta S^{\neq}$ (cal/(mol.K) T= 293 K	$\Delta G^{\neq}$ (Kcal.mol^{-1}) T= 193 K
1	**a**	n.d.	n.d.	n.d.	11.2
2	**b**	26.8	24.8	-6.6	10.7
3	**d**	n.d.	n.d.	n.d.	11.1
4	**e**	25.9	18.1	-26.6	11.3
5	**f**	24.7	17.0	-26.2	10.3
6	**g**	25.8	24.5	-4.6	11.7

Table I-5: Comparisons of first order kinetics $\Delta G^{\neq}$ free energy barrier between Monoazepine **1a,b,d-g** and DBBA **4a,b,d-g**

With these data in hands, kinetic constants were measured at four temperatures, and hence, the possible determination of all thermodynamic parameters. Results are indicated in Table I-5 along with those of derivative **1** mentioned for just comparison. A direct comparison of the kinetic barriers $\Delta G^{\neq}$ of **1** and **4** shows a difference of at least 15 kcal.mol^{-1} in favor of the DBBA which confers to them a noticeable configurational stability at room temperature.

However, with an half-life in the range of a few days (82 hours for **4f**, Table I-5, entry 5), these compound are prone to epimerization in solution at room temperature and care should be taken not to keep these compounds for too long in solution.

I-4 Hindered Doubly Bridged Biphenyl Azepine (HDBBA)

I-4.1 Synthesis

To possibly increase the configurational stability of these systems (and the stereoselectivity in subsequent application, see chapter III), it was decided to introduce phenyl groups in 3,3' and 5,5' position of the central biphenyl unit. The steric hindrance generated in these positions leading possibly to slower kinetics of epimerization and higher stereocontrol. The synthesis of these Hindered Doubly Bridge Biphenyl Azepines (HDBBA) require 7 steps (Figure I-11). Aldolisation and crotonisation between 1,3-diphenylacetone and 3-penten-2-one in presence of freshly prepared sodium methoxide afforded **5** in a good yield (73%); a yield quite improved when compared to that reported in the literature (y= 41%).[21] The latter compound was further dehydrogenated quantitatively by treatment as a neat substance in presence of palladium on charcoal at 250°C to give **6** was used without any need of purification.[21] A phenolic coupling using manganese (III) acetate was performed on **6**, in glacial acetic acid, giving access to **7** with rather low yield (36%) due to orthoquinone formation during this reaction.[22] Indeed, the ^{1}H NMR of the crude reaction mixture shows, after the consumption of all the starting material, a 1.7 to 1 ratio between orthoquinone (precisely the 2,6-dimethyl-3,5-diphenylcyclohexa-2,5-diene-1,4-dione) and compound **7**. Due to similar retention time on silica gel, these compounds were barely separable by column chromatography. However clean separation of **7** was afforded by recrystallisation in Et_2O/Hexane.

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[21] Vilardo, J. S.; Lockwood, M. A.; Hanson, L. G.; Clark, J. R.; Parkin, B. C.; Fanwick, P. E.; Rothwell, I. P. *J. Chem. Soc., Dalton Trans.* **1997**, 3353

[22] Nishino, H.; Itoh, N.; Nagashima, M.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 620; Galan, A.; Sutherland, A. J.; Ballester, P.; Rebek, J., Jr. *Tetrahedron Lett.* **1994**, *35*, 5359

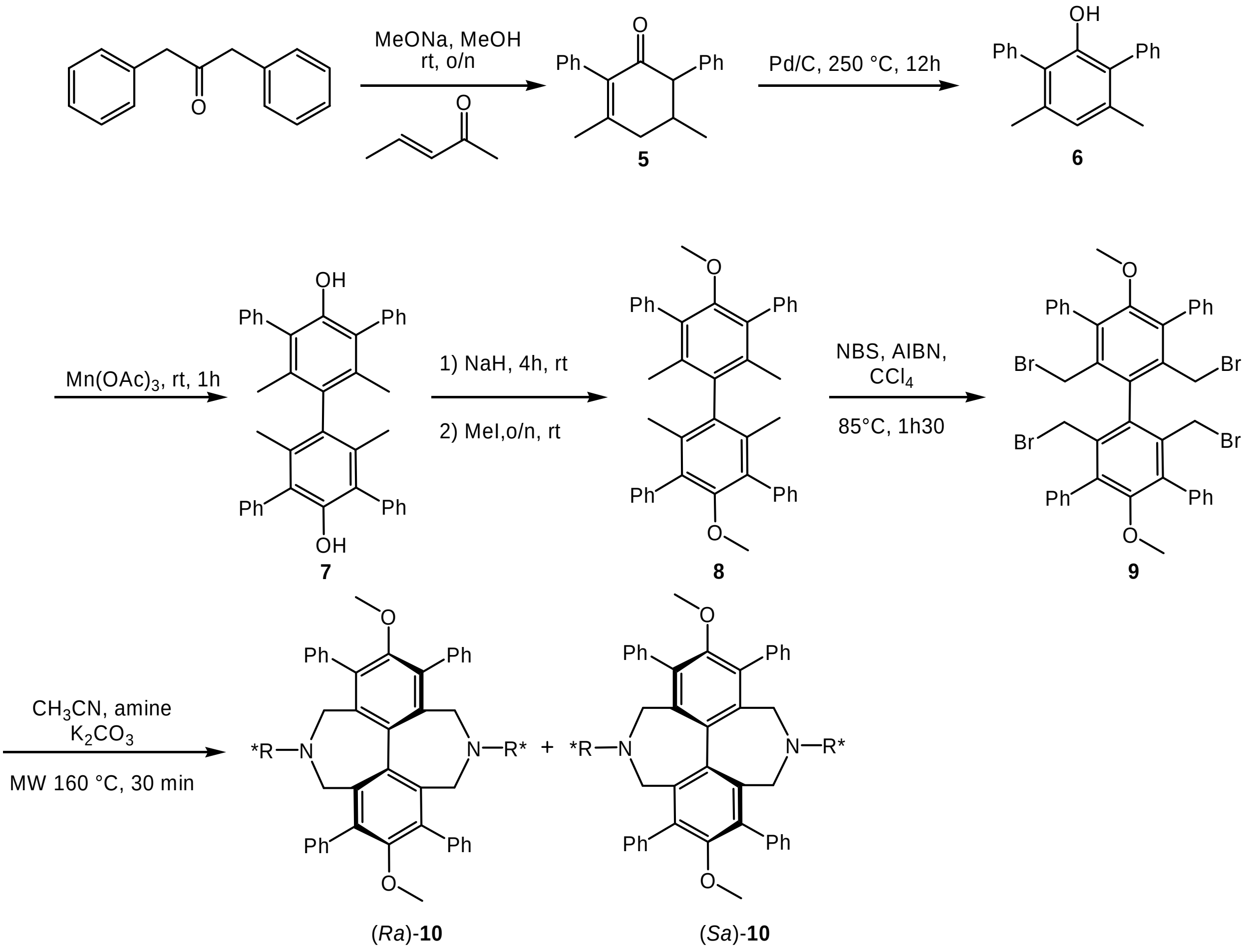

Figure I-11: Synthesis of Hindered Doubly Bridged Biphenyl Azepines of type **10**

Concerning the bis-methylation of the bis-alcohol **7**, the use of a strong base such as sodium hydride was required and **8** was obtained with 95% yield. Several attempts to use weaker bases (K_2CO_3, Cs_2CO_3) were unsuccessful. The latter compound was then converted into the 2,2',6,6'-tetrakis(bromomethyl)biphenyl derivative **9** in presence of NBS and a catalytic amount of AIBN (5 % mol) under light bulb irradiation, in reflux of CCl_4 with again a 95% yield, which is quite remarkable for a tetrahalogenation reaction (>98% each). Finally, a nucleophilic substitution on **9**, using amines **a**, **b**, **f** and **g**, all of (*S*) configuration, were performed at reflux of acetonitrile overnight or using microwave apparatus during 30 minutes at 160 °C; identical ratios were obtained under both conditions. The synthesis sequences yielded for **a** and **b** a diastereomeric mixture of (*R*a)-**10** and (*S*a)-**10**. For **10a**, a 6:1 d.r. was determined in favor of the second eluted diastereomer. For **10b**, the diastereomeric ratio could not be determined with precision due to presence of impurities in the crude reaction mixture but the isolated yields obtained for each diastereomer could be a good indication of it (Figure I-12). Each diastereomer was easily separated by column chromatography. The first eluted diastereomer is also in this case the minor isomer with 15% recovered yield compared to the second eluted diastereomer which has been obtained in 65% yield. This corresponds approximatively to a 4.3:1 ratio in favor of the second eluted diastereomer.

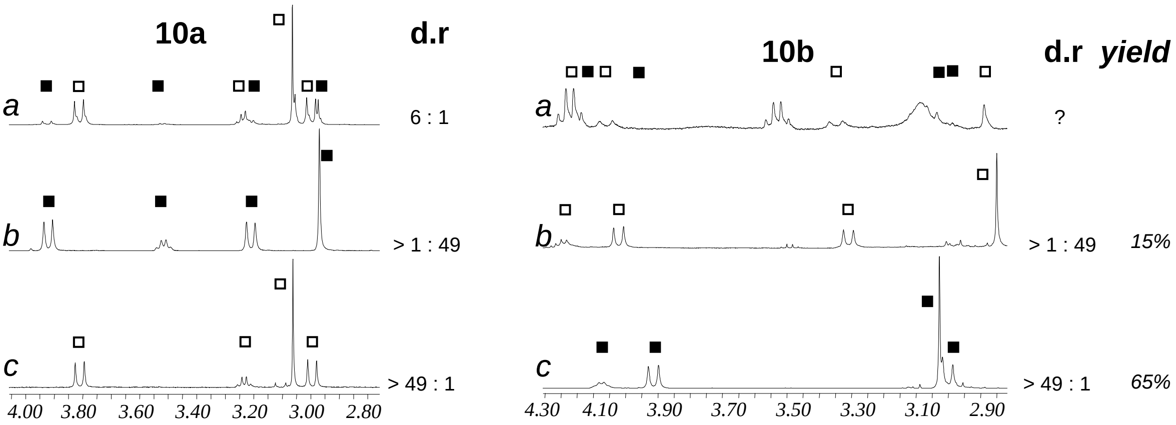

Figure I-12: NMR (400 MHz, $CDCl_3$) of 10a-b with *a*: crude mixture; *b*: first eluted diasteromer (■); *c*: second eluted diastereomer (□)

Concerning compounds **10f** and **10g**, broad signals were obtained in ^1H NMR when $CDCl_3$ was used as solvent so that we could not see two pairs of diastereomers. However, only one spot was observed in chromatography (r_f ~ 0.77 for **10f** and 0.71 for **10g**, silica gel, DCM/EtOAc 9:1) and we could not see a second peak when injected on HPLC using various conditions (Column IB; 0.5 $mL.min^{-1}$; Hexane/iPrOH 90:10 or 95:5 or 99:1). While performing ^1H NMR experiment in acetone-d_6 for **10f** and DMSO-d_6 for **10g**, slightly better resolved signals were observed (except for the benzylic protons which are still broad), showing only one set of signals for some specific groups. Either the two diastereomers are isochronous, or more likely the synthesis of **10f** and **10g** is completely diastereoselective.

I-4.2 Configurational analysis

As for the DBBA, CD measurements were performed in order to assign configurations for each isolated diastereomer (Figure I-13). However, even though these HDBBA are structurally related to the known DDBA, there is no evidence that these compounds should behave are regular biphenyls in presence of circular polarized light. Due to the presence of extra aromatic substituents, correlation between a negative Cotton effects in the region of 250-260 nm with a *P* (or *S*a) configuration of the central biphenyl is not trivial.

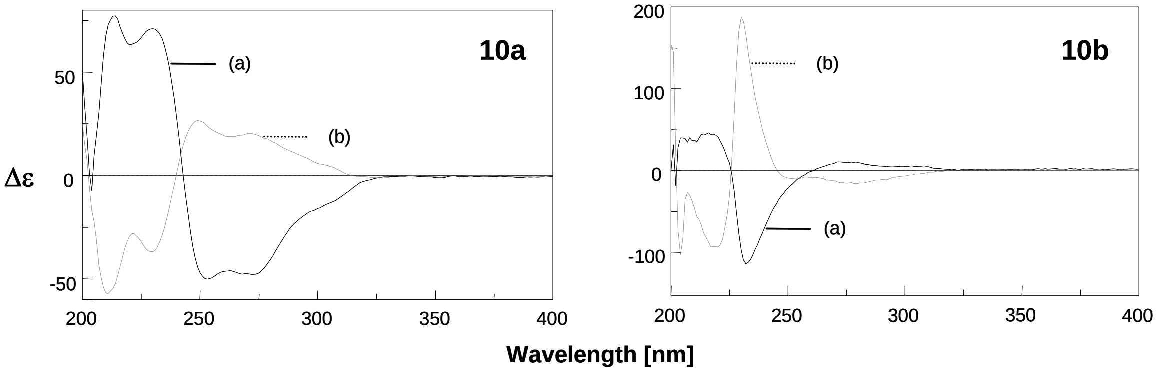

Figure I-13: CD spectra of **10a** (left) and **10b** (right), (*c* 5.10^{-6} M, MeOH) with (a) first eluted (minor) diastereomer and (b) second eluted (major) diastereomer

If the rule applies, then, similarly to **4a** and **4b**, the first eluted diastereomers for **10a** and **10b** ((a), Figure I-13) would have a negative Cotton effect in the region of 250-260 nm which tends to prove that these specific diastereomers have a *S*a configuration and conversely for the second eluted diastereomers ((b), Figure I-13). However in these two cases, the first eluted diastereomers are the minor ones whereas the second eluted are the major diastereomers. Interestingly, CD experiments performed on **10f** and **10g** showed similar spectra for both compounds and a strong negative Cotton effect in the region 250-260 nm is also observed. Based on the assumption that **10f** and **10g** are diastereopure, it seems that their configurations are both *P*

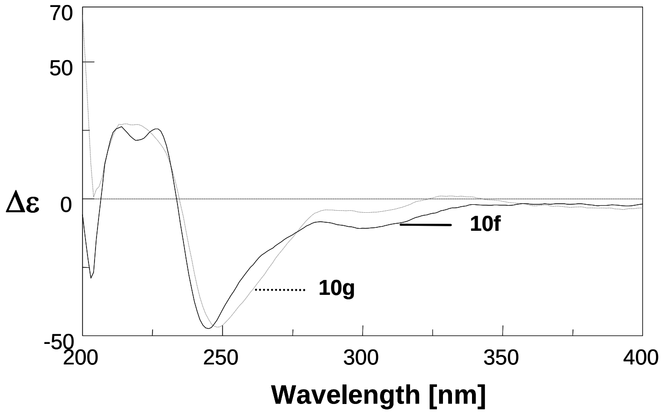

Figure I-14: CD spectra of **10f** (continuous line) and **10g** (dotted line), (*c* 5.10^{-6} M, MeOH)

I-4.3Configurational stability

In order to epimerize these hindered doubly bridged biphenyl azepines and get some kinetic informations, similar experiments to that of **4** were performed. However, contrary to DBBA, heating overnight in reflux of benzene either diastereomer of **10b** only a few percents of the other diastereomer was observed, whereas these conditions were sufficient to epimerize completely compounds of type **4**. In consequence, a solvent with a higher boiling point (toluene) was required for the study as well as longer reaction time. The result of this experiment is shown in Figure I-15.

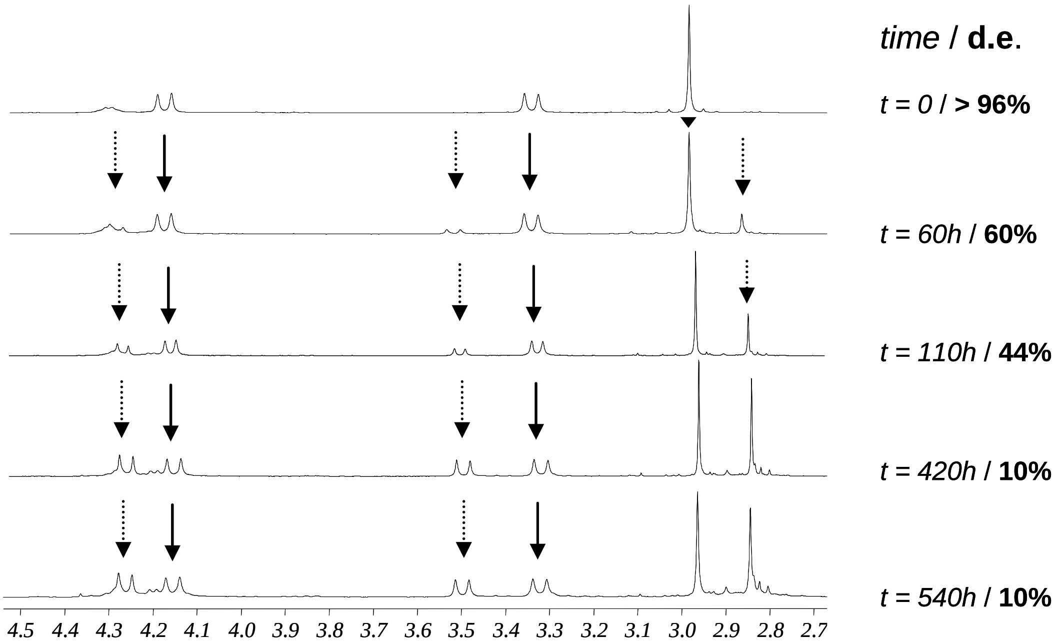

Figure I-15: Epimerization of one pure diastereomer of **10b** in toluene-d_8 at 110 °C followed by ^{1}H NMR (400 MHz)

We notice that a quite long time of heating is needed for the complete epimerization of **10b** as it took a few days to reach the thermodynamic equilibrium of the two diastereomers (*ca* 420h). Moreover this thermodynamic ratio is relatively low (55/45) and in favor of the second eluted diastereomer, which correspond to a Gibbs free energy $\Delta G°$ of -0.152 kcal.mol^{-1} at 110 °C. In order to determine precisely the energy barrier of rotation of the biphenyl axis, the variation through time of the diastereomeric ratio of a heated solution of one of the two diastereomers was measured at four different temperatures; the measurement being done by HPLC. A $\Delta G^{\neq}$ value of 31.7 kcal.mol^{-1} was determined for **10b** which shows how stable these HDBBA are. This corresponds to an increase of 5 kcal.mol^{-1} compared to its DBBA homologous **4b**, as a consequence of the presence of phenyl substituent in 3,3’ and 5,5’ positions of the central biphenyl core.

I-4.4 Conclusion

Trying to find a good balance between decent configurational stability at room temperature and concomitant stereocontrol at elevated temperature of the central biphenyl axis by exocyclic stereogenic elements, doubly bridged biphenyl azepines (DBBA) of type **4** were shown to be interesting compounds for that purpose. Moreover, a larger induction onto the equilibrium constants were, to a certain extent, noticed in presence of two exocyclic stereogenic elements instead of one. However it appeared to be quite difficult to separate both diastereomers in good yields for simple derivatives, and the diastereoselectivity obtained, either during the synthesis (kinetic diastereoselectivity) or after complete epimerization at high temperatures of these compounds (thermodynamic diastereoselectivity) is quite low (d.r up to 4.3:1). On the whole, these problems have been solved by introducing phenyl substituent in 3,3’ and 5,5’ positions of the central biphenyl core. Indeed, these newly synthesized hindered doubly bridged biphenyl azepines (HDBBA) appeared easier to purify and isolate in a diastereomerically pure form in the cases were another diastereomer is formed. Epimerization of these amines was feasible though much higher temperature and reaction times were required. In the following chapters we will see that these compounds could be easily derivatized in order to form new organocatalysts for asymmetric reactions.

Chapter II

IMINIUM CATALYSTS IN BIPHASIC ENANTIOSELECTIVE OLEFIN EPOXIDATION

II-1 Organocatalyzed processes for asymmetric olefin epoxidation

In the previous chapter we have detailed the synthesis as well as the structural aspects (configurational stability, absolute configuration) of dibenzoazepines (singly and doubly bridged). This chapter will show that these compounds could be successfully used as precursors of iminium salts which are known to be efficient catalysts for the asymmetric epoxidation of non-functionalized olefins. This topic has received considerable attention these last 20 years as chiral epoxides are not only useful precursors for organic chemists as synthetic intermediates in the production of enantiomerically pure pharmaceuticals,[1] but also frequently met structures in natural products.[2] As such, triptolide, epothilones and cryptophycin possess epoxide units as essential structural moieties for their biological activities (Figure II-1).[3]

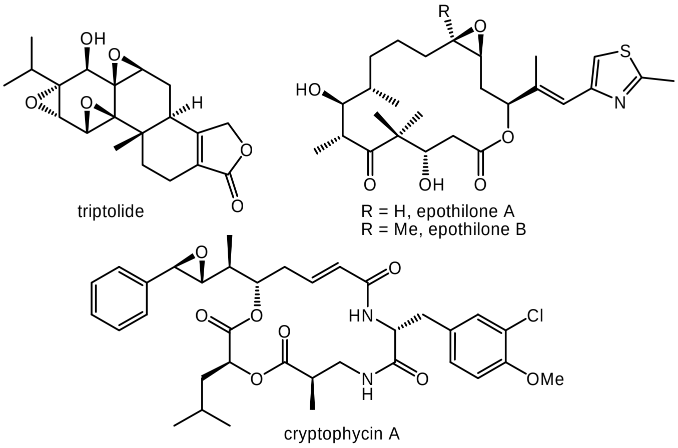

Figure II-1: Examples of natural products containing epoxide groups

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[1] Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67; Gorzynski Smith, J. *Synthesis* **1984**, 639; Behrens, C. H.; Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189

[2] See for example: Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543; Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205; Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857

[3] Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497

Moreover, epoxides are believed to be key intermediates in the biosynthesis of many natural products such as brevetoxin-B (Figure II-2), monensin and glabrescol.[3]

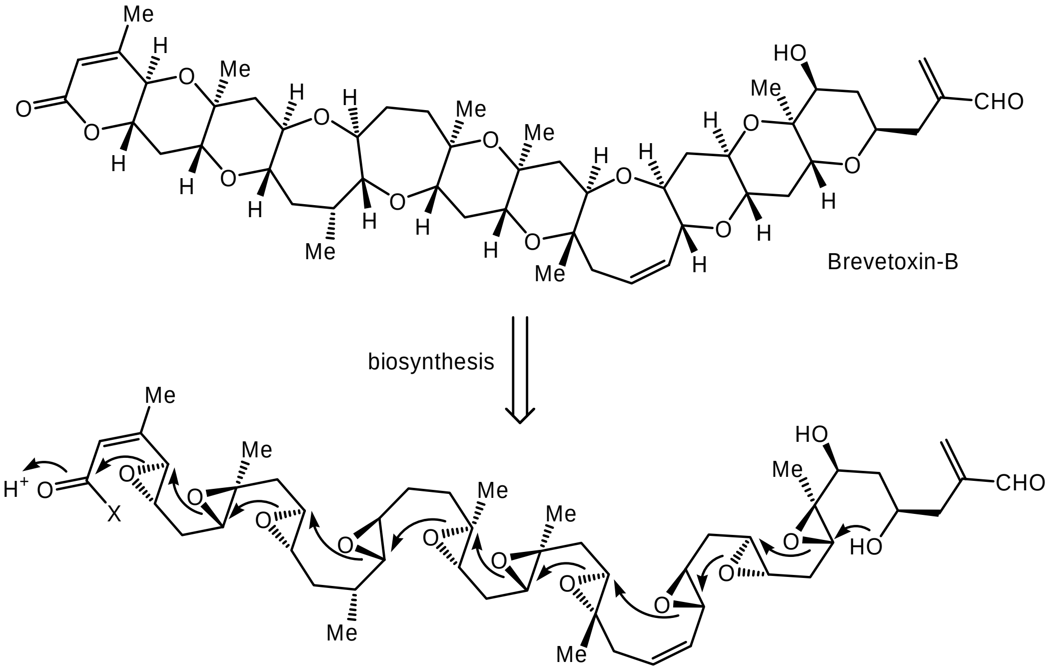

Figure II-2: Biosynthesis of Brevetoxin-B from epoxides

Quite a few efficient methods exist for their preparation from olefins and many of them use transition metal catalysts.[4] The Sharpless epoxidation is a powerful tool for the asymmetric epoxidation of allylic alcohols; the hydroxyl group directing oxygen-atom transfer to the olefin in an enantioselective fashion.[5] For non-functionalized olefins, the chiral Mn-salen catalysts developed independently by the groups of Jacobsen[6] and Katsuki[7] are particularly effective for *cis*-olefins. In the recent years, much effort has been devoted to the development of organocatalyzed epoxidation conditions that afford metal-free procedures; the catalysts being perhydrates, ketones, oxaziridine moieties, amines or ammoniums as well as iminium

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[4] For recent reviews see: Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603; Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457

[5] Katsuki, T. In *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford University Press, UK: Oxford, 2001; p 244 pp; Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N.;Pfaltz, A.;Yamamoto, H., Eds.; Springer ed.: New York, 1999; Vol. 2, p 503 pp.

[6] Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801; Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063; Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378; Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937; Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123

[7] Katsuki, T. *J. Mol. Catal. A: Chem.* **1996**, *113*, 87; Katsuki, T. *Curr. Org. Chem.* **2001**, *5*, 663

salts.[8] Without minimizing the importance of the other catalysts, this chapter will mainly detail the recent advances made in this latter area which concerns essentially:

(i) Chiral ketones for the dioxirane mediated epoxidations
(ii) Chiral iminiums salts for oxaziridinium mediated epoxidations

These two systems are recognized to be, by far, the best for the organocatalytic asymmetric epoxidation of *trans*-disubstituted or trisubstituted olefins. This chapter will mainly deal with the results obtained during this PhD thesis using novel chiral iminium salts as catalysts for the biphasic phase transfer asymmetric epoxidation of non-functionalized olefins. Finally a third subtopic which is the use of chiral amines as precatalysts will be presented in the last part of this chapter with the latest results obtained in the group as well as other laboratories.

II-1.1 Dioxirane mediated epoxidation using chiral ketones

Ketone catalyzed epoxidation of olefins is one of the most studied organocatalytic process. Isotopic labeling studies performed by Curci in 1979 showed that using Oxone® triple salt ($KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a stoichiometric oxidant, dioxirane species were generated *in situ* from ketones *via* the Criegee intermediate and that these intermediaries were responsible of the decomposition of Oxone® (Figure II-3).[9]

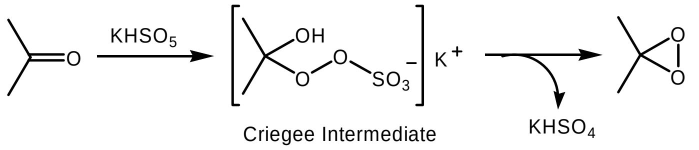

Figure II-3: Formation of dioxirane from ketone oxyadation by Oxone *via* the Criegee intermediate

The use of chiral dioxiranes was also initiated by Curci in the middle of the 1980s, but modest enantioselectivities were obtained (e.e. < 20%) and the use of a large excess of ketone as a precursor of the dioxirane (from 2 to 30 eq.) was necessary (Figure II-4).[10]

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[8] Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499; Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596; Ho, C. Y.; Chen, Y. C.; Wong, M. K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898

[9] Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63; Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758

[10] Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155; Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831

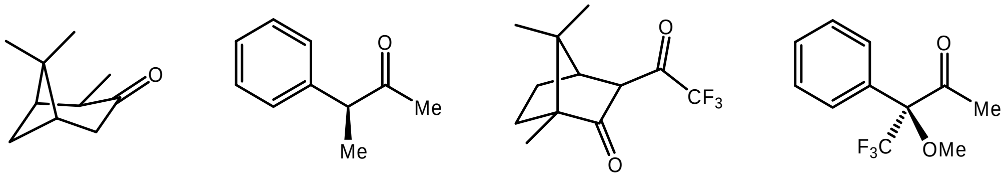

Figure II-4: Curci’s chiral ketone catalysts

More recently, the process has been particularly improved to achieve rather high levels of enantioselectivity using, for instance, [11]-membered ring C_2-symmetric α,α’-diacyloxyketone (Figure II-5).[11] This catalyst relies on a rigid symmetric structure lying on a C_2 axis. The electron withdrawing ester moieties are believed to activate the ketone group and it also adds further rigidity to the chiral framework which may help for reaching higher ee values. When the 1st generation catalyst was used (X = H), moderate to good enantiomeric excesses were obtained on *trans*-disubstituted and trisubstituted olefins (ee up to 87% on *trans*-stilbene derivatives). On the other hand, this ketone catalyst was particularly inefficient on terminal olefins or cyclic olefins where very low ee were obtained. To explore the effect of steric hindrance in 3,3’ positions, the authors designed a series of ketones bearing different “steric sensors”. They found that the need of an appropriate size is required as two small (H) or too big ($SiMe_3$) groups leads to a decrease in enantioselectivity, the best balance being for instance a chloride or a bromide (ee up to 95% on *trans*-stilbene derivatives). Though efficient, these catalysts present several drawbacks: high catalysts loadings (> 10% mol), expensive starting material and the need of several steps for their preparation is required as well as strong substrate dependence in terms of enantioselectivities.

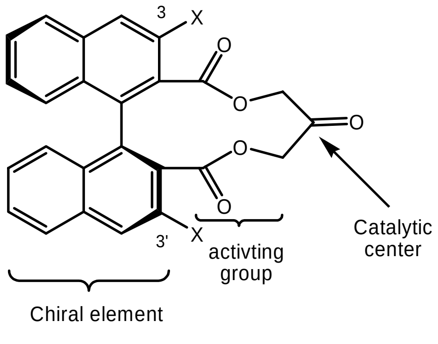

Figure II-5: Yang’s C_2-symmetric binaphthyl ketone catalysts

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[11] Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491

D-Fructose derived cyclohexanones behave also as effective catalysts due to their ease of access (2 steps form the D-glucose) and their more general efficiency towards (*Z*,*E*) olefins (Figure II-6), making them valuable derivatives.[12] These efficient ketone mediated reactions need often to be carefully monitored as moving a few tenths of a unit away from a 7.5-8 pH region may lead to a rapid decomposition of the hydrogenpersulfate oxidant in basic conditions (pH > 8). While, on the contrary, lower pH conditions (pH < 7.5) are used or obtained during the course of the reaction, then a rapid decomposition of the ketone is observed *via* Baeyer-Villiger like oxidation of the carbonyl moieties.[13]

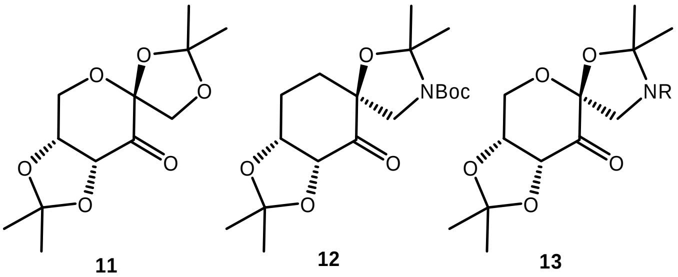

Figure II-6: Shi's D-Fructose derived ketone catalysts

However, if enantioselectivities are excellent with ketone **11** (Figure II-6), (>90% on a variety of *trans* and trisubstituted olefins) working in this range of pH leads essentially to poor conversion (< 10%) so that an excess amount of ketone catalysts is needed. Interestingly, when conducted at pH 10.5 (controlled by addition of K_2CO_3 or KOH as the reaction proceeds), very high ee were still observed (90-92%) with good conversions (> 80%) and the quantity of ketone catalysts can be reduced to 20 mol % as the catalyst is reactive enough to compete with the Oxone® auto destruction in high pH.[14] This ketone catalyst has been successfully applied for the kinetic resolution and desymmetrisation of 1,4-cyclohexadienes.[15] A carbocyclic analog catalyst has also been prepared for the epoxidation of styrene derivatives with ketone **12** (Figure II-6). In this case, the catalyst displays better efficiency than **11** with styrene derivatives (e.e up to 93%).[16] However, its lengthy synthesis (13 steps

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[12] Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806

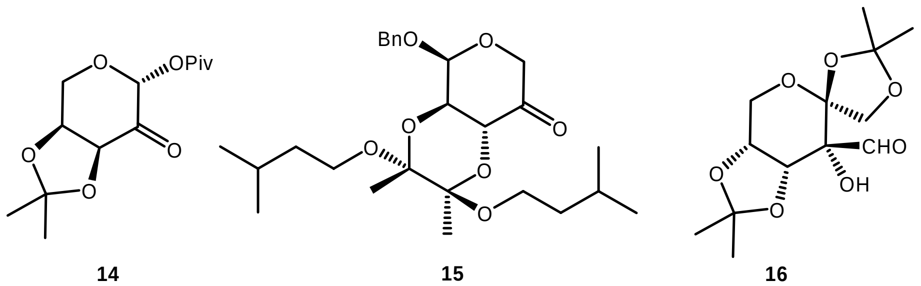
[13] Denmark, S. E.; Forbes, D. C.; Hays, D. S.; Depue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. For more technical details on Oxone see Internet site: http://www.dupont.com/oxone/techinfo/.

[14] Shi, y. *Acc. Chem. Res.* **2004**, *37*, 488

[15] Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904

[16] Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5794

starting from quinic acid with 1.1% overall yield) precludes its practical use. In that context, several ketones of type **13** (Figure II-6) have been readily prepared from D-glucose and various anilines in four steps. A screening of various styrene derivatives with different electronic properties showed that the best ketone catalysts of type **13** was the one prepared from *p*-Ethylaniline with 92% ee on the *p*-CF_3-vinylbenzene.[17] Recently, Shi and co-workers showed that this particular catalyst was also very efficient on chromene olefins with ee up to 93%.[18] Other uloses derived from D-arabinose, D-mannose, D-glucose and L-sorbose were also reported by Shi, but they afforded poor chemical yields on epoxidation (0-57% yield).[19] The use of arabinose-derived uloses instead of fructose was also described by Shing and co-workers. Indeed, L-fructose is not commercially available and its synthesis in an easy way is still a remaining problem to be solved.[20] On the other hand the abundance of arabinose in the chiral pool and its commercial availability in large quantities for both enantiomers made these compounds of particular interest. Using 10 mol% of catalyst **14** (Figure II-7) good yields were obtained (77-89%) but with moderate enantioselectivities (40-68% ee).[21] Interestingly, by introducing "steric blockers" in the tunable butane-2,3-diacetal moiety of ketone **15** (Figure II-7), the epoxidation reaction still proceeds with good yields (> 81% on a wide range of olefins, catalyst loading:10 mol%) and an increase in enantioselectivity (up to 90% ee on triphenylethylene) was observed.[22]



14 **15** **16**

Figure II-7: Catalysts derived from ulose derivatives

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[17] Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715

[18] Wong, O. A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973

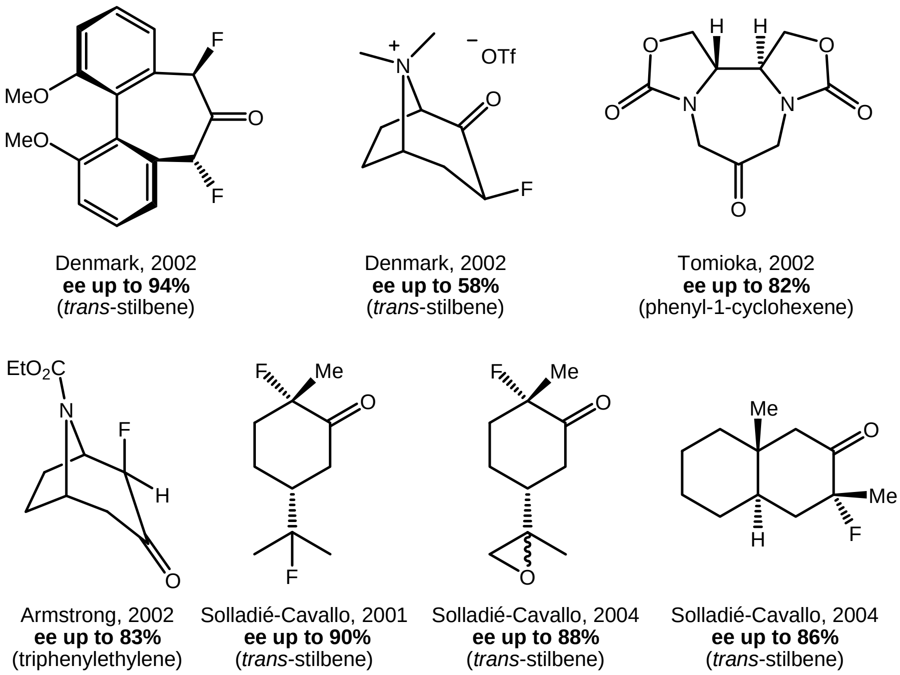
[19] Tu, Y.; Wang, Z. X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475

[20] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224

[21] Shing, T. K. M.; Leung, Y. C.; Yeung, K. W. *Tetrahedron* **2003**, *59*, 2159

[22] Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904

Fructose derived catalyst **16** reported by Zhao and co-workers, which is the aldehyde analog of **11** (Figure II-7), displayed the first highly enantioselective epoxidation of alkenes with aldehyde as a catalyst (ee up to 93.5% on *trans*-stilbene). In the same manner, a dioxirane is assumed to be generated *in situ* by Oxone®.[23]



Denmark, 2002
ee up to 94%
(*trans*-stilbene)

Denmark, 2002
ee up to 58%
(*trans*-stilbene)

Tomioka, 2002
ee up to 82%
(phenyl-1-cyclohexene)

Armstrong, 2002
ee up to 83%
(triphenylethylene)

Solladié-Cavallo, 2001
ee up to 90%
(*trans*-stilbene)

Solladié-Cavallo, 2004
ee up to 88%
(*trans*-stilbene)

Solladié-Cavallo, 2004
ee up to 86%
(*trans*-stilbene)

Figure II-8: Chiral ketones as precursors of dioxirane with systems of Denmark (2002),[24] Tomioka (2002),[25] Armstrong (2002)[26] and Solladié-Cavallo (2001),[27] (2004)[28,29]

Yang's ketone and ulose derivatives are not the only catalysts reported in the literature and in this context, several groups have entered the field by proposing novel structures and geometries for the ketone moieties. Among all the reported catalysts, here are summarized the most recent efficient ketone derived catalysts; the best enantiomeric excesses obtained with them as well as the nature of the olefin are indicated close to the structures (Figure II-8).

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[23] Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* **2003**, *44*, 7403

[24] Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479

[25] Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* **2002**, *43*, 631

[26] Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610

[27] Solladie-Cavallo, A.; Bouerat, L.; Jierry, L. *Eur. J. Org. Chem.* **2001**, 4557

[28] Solladie-Cavallo, A.; Jierry, L.; Norouzi-Arasi, H.; Tahmassebi, D. *J. Fluor. Chem.* **2004**, *125*, 1371

[29] Solladie-Cavallo, A.; Jierry, L.; Klein, A.; Schmitt, M.; Welter, R. *Tetrahedron: Asymmetry* **2004**, *15*, 3891

To conclude on this part, it is noteworthy that very promising results were also obtained with the α-fluorotropinone of Armstrong (Figure II-8) immobilized on silica. This chiral-supported catalyst promoted the stereoselective epoxidation of several trans-disubstituted and trisubstituted olefins with ee values up to 80% and were perfectly reusable with the same performance for at least three catalytic cycles.[30]

II-1.2 Oxaziridinium mediated epoxidation using chiral iminium salts

II-1.2.a Reported non-racemic iminium salt catalysts for asymmetric epoxidations

Iminium salts are an interesting alternative to ketones. There are easily oxidized *in situ* into oxaziridinium salts which are rather effective oxygen transfer reagents towards nucleophilic substrates. Their use as an oxidant has to be mentionned for the particular transformations of (i) thioethers to sulfoxides, (ii) amines and pyridine to their N-oxide derivatives, (iii) imine to oxaziridine and (iv) electron-rich unfunctionalized olefins to epoxides. Moreover, the propensity of oxaziridinium species to be readily prepared by the reaction of iminium ions with Oxone® in a slightly acidic media ($NaHCO_3$) renders the development of catalytic processes possible (Figure II-9).[31]

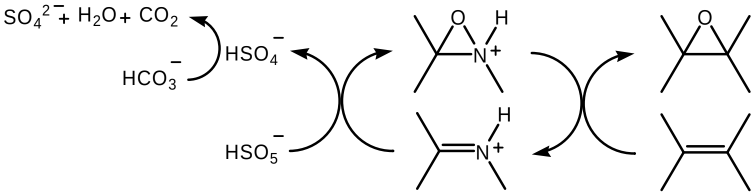

Figure II-9: Catalytic epoxidation of olefins *via* iminium oxidation by Oxone into oxaziridinium

The first example of an asymmetric oxaziridinium catalyzed reaction was reported in 1993 using dihydroisoquinolinium cation **17** as a catalyst.[32] This compound synthesized in four

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[30] Sartori, G.; Armstrong, A.; Maggi, R.; Mazzacani, A.; Sartorio, R.; Bigi, F.; Dominguez-Fernandez, B. *J. Org. Chem.* **2003**, *68*, 3232

[31] Hanquet, G.; Lusinchi, X.; Milliet, P. *C. R. Acad. Sci., Ser. II: Mec., Phys., Chim., Sci. Terre Univers* **1991**, *313*, 625; Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727

[32] Bohe, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271; Bohe, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141

steps from ephedrine was directly inspired by the studies of the Orsay group since 1976 (Figure II-10).[33]

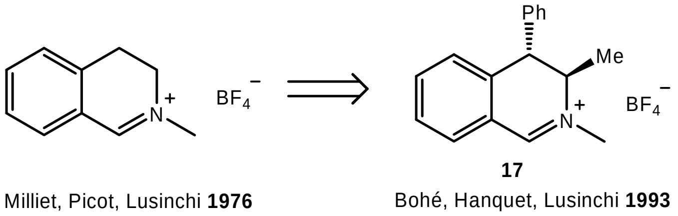

Figure II-10: First reported achiral and chiral dihydroisoquinolinium catalysts

The reaction conditions (solvent, temperature) were later optimized and the mechanism was furthermore studied.[34] Since this pioneering work, several groups have proposed successful enantioselective variants of this oxaziridinium-catalyzed reaction as reported below (Figure II-11). There are essentially two classes of non-racemic iminium ion catalysts. One class is constituted of exocyclic chiral iminium salts such as compounds [**18**][BF_4],[35] [**19**][ClO_4],[36] and [**20**][X][37] made by the condensation of enantiopure pyrrolidine moieties with aldehydes or ketones. Decent levels of stereoselective induction were obtained using these cations (e.e up to 59% with compound **20** on *trans*-stilbene). Rather high catalyst loading is unfortunately required (10 mol% for **18**, 100 mol% for **19** and between 20 and 50% for **20**), probably due to *in-situ* hydrolysis of the iminium moieties under the aqueous reaction conditions. The second class involves endocyclic chiral iminium salts. As mentioned before, the first non-racemic example was salt [**17**][BF_4]. Using this derivative, modest level of selectivity was achieved (ee up to 35%). In 1996, Aggarwal and coworkers reported axially chiral, configurationally stable, binaphthyl derived catalyst [**21**][BF_4]; this compound being particularly efficient for the epoxidation of 1-phenyl-cyclohexene (71% e.e.).[38] A mechanistic rationale was proposed by the authors to explain the absolute sense of configuration of the resulting epoxides.[39] In

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[33] Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1573

[34] Bohe, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 155; Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727

[35] Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810

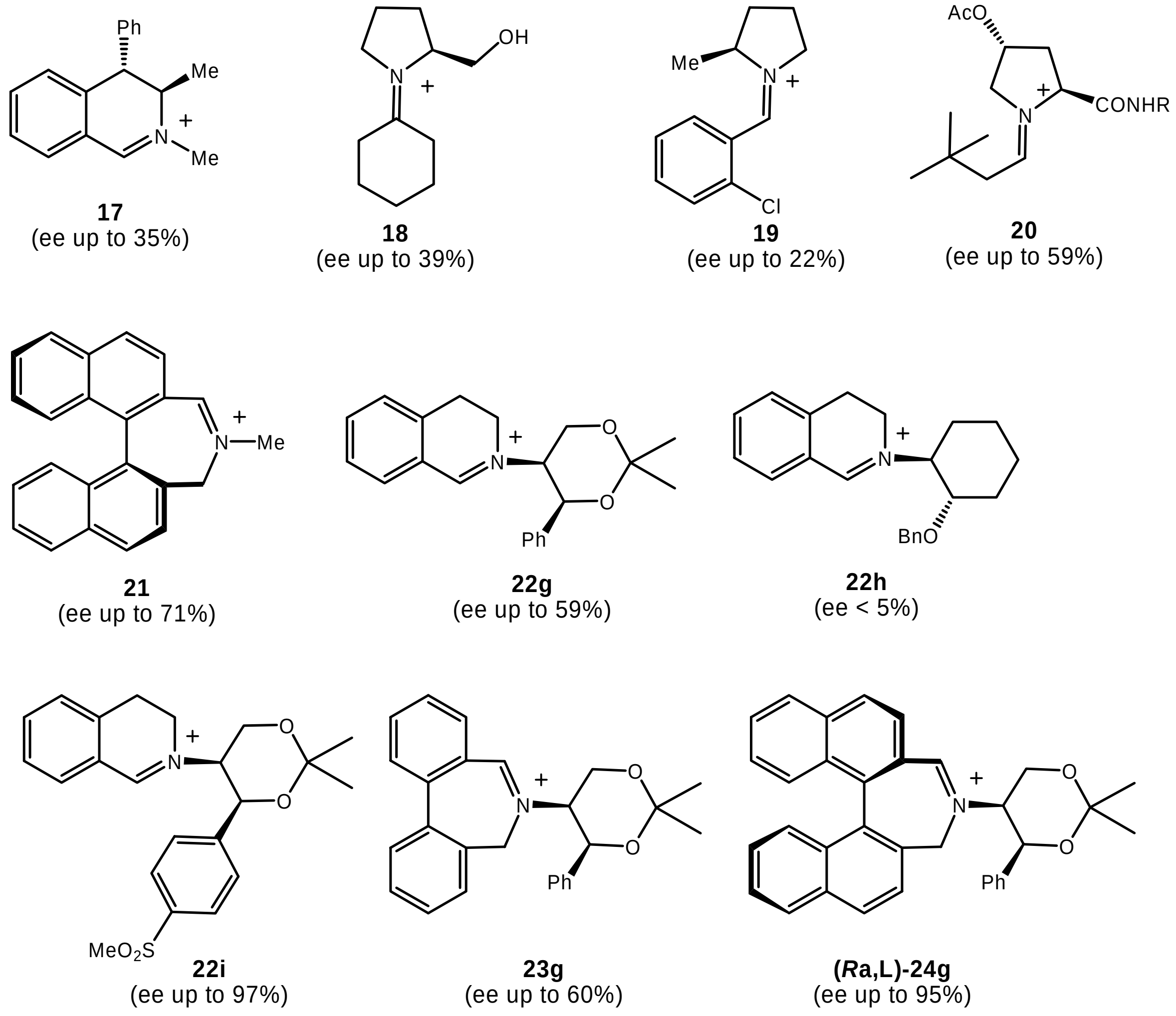
[36] Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341

[37] Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587

[38] Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191

[39] Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 2948

1998, Page and coworkers modified the core structure of catalyst **17** by introducing stereogenic elements outside rather than inside of the [6]-membered ring heterocycles.[40]



17
(ee up to 35%)

18
(ee up to 39%)

19
(ee up to 22%)

20
(ee up to 59%)

21
(ee up to 71%)

22g
(ee up to 59%)

22h
(ee < 5%)

22i
(ee up to 97%)

23g
(ee up to 60%)

(*R*a,L)-24g
(ee up to 95%)

Figure II-11: Known exocyclic and cyclic iminium non-racemic catalysts **17** to **24**

A strong influence of the chiral appendage was noticed as L-(+)-acetonamine[41] derived iminium **22g** displayed a quite higher selectivity than **22h** made from (1*S*,2*S*)-2-benzyloxycyclohexylamine (ee 41% and <5% respectively with 1-phenyl-cyclohexene). Very recently, Page and co-workers reported a modification of catalyst **22g** carrying a *para*-

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[40] Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774; Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3325; Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Buckley, B.; Bethell, D.; Smith, T. A. D.; Slawin, A. M. Z. *J. Org. Chem.* **2001**, *66*, 6926

[41] L-(+)-acetonamine corresponds (4S,5S)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane

methylsulfonyl group (iminium **22i**) that behaves as a very efficient asymmetric catalyst, for benzopyran derivatives in particular.[42]

A second generation of iminium catalysts with exocylic chiral appendages was independently developed by the group of Loughborough[43] and the Lacour's group.[44] These catalysts utilize the same diphenylazepinium cation **1** derived from L-(+)-acetonamine and differ only by the nature of the counterion – BPh_4 and TRISPHAT [(tris(tetrachlorobenzendiolato) phosphate (V)] respectively. Unlike derivatives **22g**, compound **23g** possesses a biphenyl skeleton, which is chiral and configurationally labile. As mentioned in chapter I, literature precedents show that biphenyl species of this type exist as two atropisomers (*R*a and *S*a) that interconvert freely in solution, just by rotation around the stereogenic axis. Direct comparison of the BPh_4 salts of [7]-membered **23g** and [6]-membered **22g** rings showed that most of the reaction rates, conversions and enantioselectivities are enhanced by the use of the larger ring size catalysts. Recently Page and coworkers were able to synthesize and isolate three enantiopure forms of the four possible diastereomers of **24g** which combine Aggarwal's conformationally rigid dinaphthazepinium skeleton (*R*a and *S*a atropisomers) with Page's L-(+)- or D-(–)-acetonamine.[45] Only one pair of enantiomeric catalysts, (*R*a,L) (drawn in Figure II-11) and (*S*a,D), displayed high reactivity and selectivity (up to 95% e.e. for the epoxidation of the 1-phenyl-3,4-dihydronaphthalene); the mismatched diastereomers leading to essentially poor conversions under the same reaction conditions.

II-1.2.b Transition states and origins of stereoselctivities

Despite the large number of articles dealing with the asymmetric epoxidation catalyzed by oxaziridinium salts, only a few things are known about the mechanism of the reaction. So far, the Lusinchi group is the only one to be able to isolate the oxaziridinium salt (of iminium **17**) and demonstrate that this is the catalytic active species. Thus, the catalytic cycle proposed (Figure II-9) has been widely adapted to the whole iminium salt catalysts without being demonstrated systematically. Page and co-workers also proposed a mechanism for the synthesis of oxaziridinium salts in which, the rate determinating step is believed to be either

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[42] Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005**, *7*, 375

[43] Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, 580

[44] Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8257

[45] Page, P. C. B.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2004**, *6*, 1543

the attack of the iminium unit by persulfate or the subsequent expulsion of HSO_4^- to form the oxaziridinium salt, which can transfer oxygen to a substrate in the subsequent step (Figure II-12).[46]

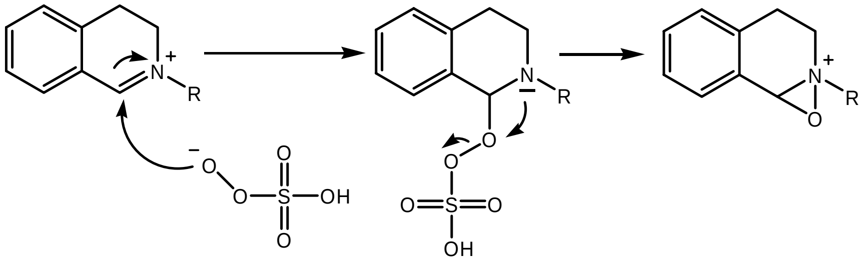
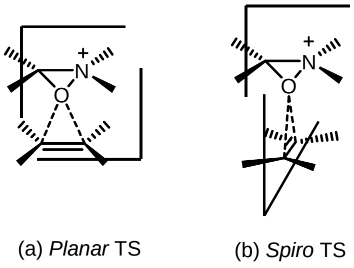


Figure II-12: Proposed mechanism for the synthesis of oxaziridinium salts

Concerning the epoxidation mechanism, we can say undoubtedly that this reaction is stereospecific, in the sense that *trans* and *cis*-olefins lead to a *trans* and *cis*-epoxides respectively. The epoxidation reactions of non-particularly activated olefins by electrophilic oxygen atom transfer reagents are assumed to be S_N2-type displacements[47] and are usually rationalized in terms of two energetically preferred transition states (TS).

(i) a *planar* transition state ((a), Figure II-13)

(ii) a *spiro* transition state ((b), Figure II-13)



(a) *Planar* TS (b) *Spiro* TS

Figure II-13: Two possible transition states with (a) a planar TS and (b) a spiro TS

In the *planar* TS, the electrophilic oxygen containing functional group of the reagent and the developing epoxides lay within a plane (as in the classic Bartlett's "butterfly" arrangement for the TS of the epoxidation by peracides[48]). In the *spiro* TS the electrophilic oxygen containing

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[46] Page Philip, C. B.; Buckley Benjamin, R.; Appleby, L. F.; Alsters, P. A. *Synthesis* **2005**, 3405 and references cited therein

[47] Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1410

[48] March, J.; Wiley-Interscience: New York, 1992;

functional group of the reagent and the developing epoxides are mutually perpendicular. Theoretical studies (M.O calculations) revealed that this *spiro* TS seems preferred over *planar* TS in the epoxidations catalyzed by performic acid, dioxirane, dimethyldioxirane and trifluoromethyldioxirane. More accurate computational methods have then allowed to show a preference for an asynchronous spiro TS in the epoxidation catalyzed by oxaziridine and for a synchronous TS in the epoxidation catalyzed by performic acid and dioxirane.[49] The terms synchronous and asynchronous describe equal or unequal C − O bond formation respectively in the TS. Concerning epoxidation mediated by iminium catalyst **17**, the authors claimed that a *planar* TS better explained the stereochemistry obtained for the epoxides. More recently, Houk and coworkers showed by B3LYP/6-31G calculations that epoxidation catalyzed by iminium catalysts **17** and **21** are rather *spiro* and synchronous.[50]

II-1.2.c Gain in selectivity by solvent and temperature modifications

Traditionally, the epoxidation reactions are performed in mixtures of CH_3CN and water. This combination is often a good solvent for all reagents, the lipophilic olefins as well as the polar BF_4^- or PF_6^- salts of iminium cations. Previously, using salt [**23g**][TRISPHAT], strict biphasic CH_2Cl_2/water conditions could be used and an enhancement of the selectivity of the epoxidation reaction as well as a good recovery of the epoxides was demonstrated. In fact, the lipophilicity of TRISPHAT anion confers to its salts an affinity for organic solvents and, once dissolved, the ion pairs do not partition in aqueous layers. Consequently, a tight containment of the reagents in two liquid phases occurs; the organic TRISPHAT salts in the organic layer and Oxone® in the aqueous phase. Addition of a catalytic amount of 18-Crown-6 (2.5 mol%) establishes a transport mechanism of $KHSO_5$/$KHSO_4$ between aqueous and organic phases and permit the oxidation in CH_2Cl_2 of the iminium cation into the reactive oxaziridinium form (Figure II-14).

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[49] Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147 and references cited therein

[50] Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 2948

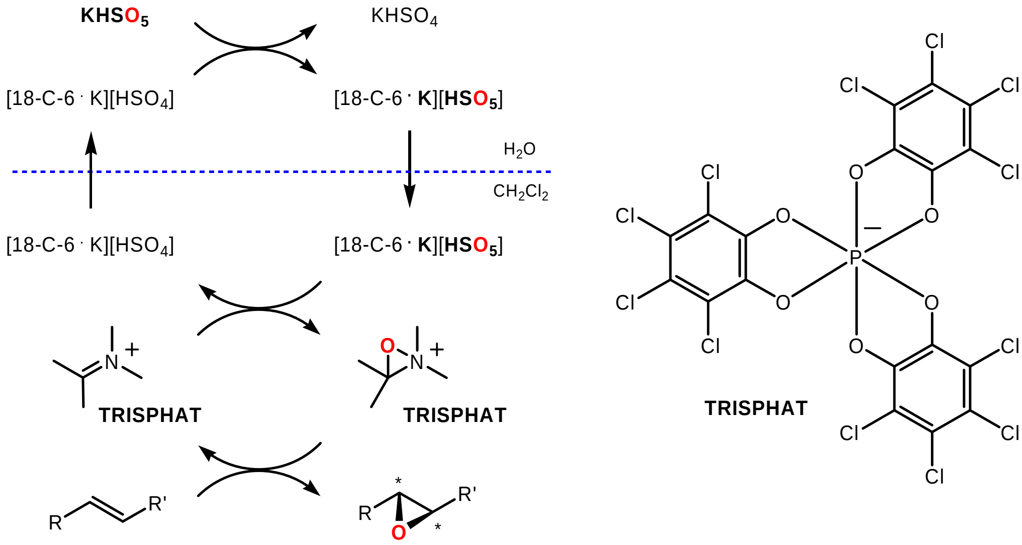

Figure II-14: Proposed catalytic cycle of biphasic epoxidation reaction

As mentioned, slightly better results were obtained using these conditions in which the oxidation occurs only in the CH_2Cl_2 phase. One can wonder whether the increased stereoselectivity of the epoxidation reaction in the less polar CH_2Cl_2 compared to CH_3CN results from a “destabilization” of the cationic spiro diastereomeric transition states and hence, in more discriminating stereoselective interactions.

A similar observation was recently reported by Page and coworkers who developed strict anhydrous conditions using pure CH_2Cl_2 as solvent and tetraphenylphosphonium monoperoxybisulfate (TPPP) as a stoichiometric oxidant. The reactions can now be performed at −40 °C and a further increase in selectivity was observed for some substrates.[42,51] Using these conditions in combination with catalyst **22i**, allowed them to perform the enantioselective synthesis of Levcromakalim with 97% ee.[52]

For the initial selection of non-racemic catalyst of type **22**, a rather extensive screening of chiral exocyclic appendages was performed by Page and coworkers. Several enantiopure primary amine precursors were attached to the dihydroisoquinolinium skeleton and the resulting compounds tested. For the diphenylazepinium systems, with the exception of (-)-isopinocamphenylamine which leads to a less selective catalyst than L-(+)-acetonamine **g**, no further modification of the chiral backbone has been reported to date. The twisted [7]-membered ring of **23g** being sufficiently different from the “planar” dihydroisoquinolinium

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[51] Page Philip, C. B.; Barros, D.; Buckley, B. R.; Ardakani, A.; Marples Brian, A. *J. Org. Chem.* **2004**, *69*, 3595

[52] Page Philip, C. B.; Buckley Benjamin, R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005**, *7*, 375

framework of **22g**, it was debatable whether L-(+) acetonamine was also in this case the best auxiliary. As a first approach, we were interested in preparing a series of novel diphenylazepinium moieties prepared from commercially available non-racemic primary amines and to test their efficiency in biphasic TRISPHAT-mediated epoxidation reactions.

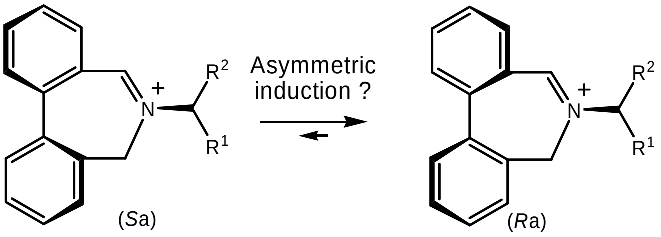

Figure II-15: Possible stereocontrol by chiral exocyclic appendages

As already mentioned, two atropisomeric conformations exist for the [7]-membered ring backbone of catalysts **23b, 23e, 23f, 23g** and **23h**. The presence of the chiral appendages results in the formation of diastereomeric structures that equilibrate rapidly in solution with – possibly – a drift of the conformational equilibrium towards one preferred (*R*a) or (*S*a) diastereomer as a consequence of intramolecular discriminating interactions (Figure II-15).[53] Care was thus taken in this study to characterize the structure of the diphenylazepinium cations by variable temperature NMR spectroscopy (VT-NMR) and circular dichroism (CD) in search of a correlation between good enantioselectivity in the products and high diastereomeric control of the biphenyl axial configuration of the catalysts. Part of this section was realized in collaboration with Dr. Céline Pérrolier, a post-doctorate associate of the group.

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[53] Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369

II-2 Biphasic Enantioselective Olefin Epoxidation Using Tropos Dibenzoazepinium Catalysts

II-2.1 Synthesis of the catalyst and results

II-2.1.a Synthesis of the iminium salts

One of our goals was thus to vary the nature of the chiral appendages linked to the diphenylazepinium catalytic framework. Care was taken to select, in addition to L-(+) acetonamine **g**, acyclic and cyclic amines commercially available in both enantiomeric forms; only the (*S*) enantiomers of the selected amines are shown on Figure II-16. Only compound **23f** was prepared in both enantiomeric forms for reasons that will be detailed later.

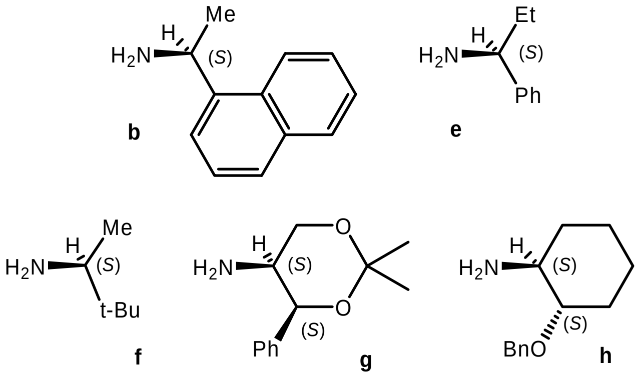

Figure II-16: Selected amines for the formation of catalysts **23b** and **23e-h**

Synthesis of the derived diphenylazepinium catalysts ot type **23** was realized in one step starting from the already described dibenzoazepines of type **1** following a general and reproducible protocol (that is to say a total of 3 steps starting from phenanthrene). Oxidation of the azepines with NBS and a catalytic amount of AIBN in CCl_4 at room temperature afforded the diphenylazepinium ions as their bromide salts;[54] this milder room-temperature protocol being preferred to I_2/KOAc procedure.[55] The crude reaction mixtures were directly submitted to ion exchange metathesis with 1.2 equivalent of racemic [Et_2NH_2][TRISPHAT] salt. The lipophilicity of TRISPHAT (TT) anion modifies profoundly the chromatographic properties of the cations associated with it and the resulting ion pairs, [**23b**][*rac*-TT],

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[54] Mary, A.; Renko, D. Z.; Guillou, C.; Thal, C. *Bioorg. Med. Chem.* **1998**, *6*, 1835

[55] Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3408

[**23e**][*rac*-TT], [**23f**][*rac*-TT], [**23g**][*rac*-TT] and [**23h**][*rac*-TT] were poorly retained on polar chromatographic phase (Al_2O_3, pH 9.9, CH_2Cl_2) allowing their isolation in modest to decent yields (Figure II-17).[56]

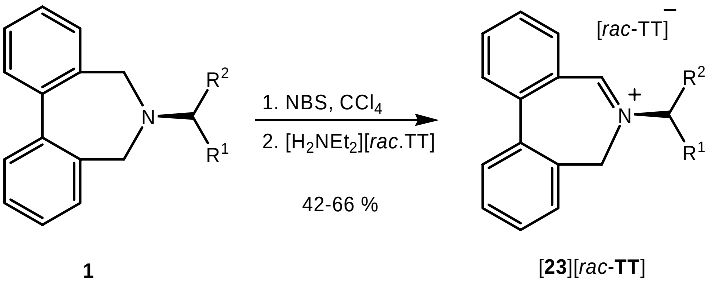

Figure II-17: Synthesis of catalysts of type **23** from azepines of type **1**

II-2.1.b Catalysis performed at 20 °C

Catalysts [**23b**][*rac*-TT], [**23e**][*rac*-TT], [**23f**][*rac*-TT], [**23g**][*rac*-TT] and [**23h**][*rac*-TT] were then tested using the biphasic CH_2Cl_2/water/18-C-6 protocol detailed previously. Prochiral di- and tri substituted unfunctionalized alkenes **25** to **29** (Figure II-18) were used as substrates and the results are reported in Table II-1. Significantly, catalyst [**23f**][*rac*-TT], in which (*S*)-1,2,2-trimethyl-propylamine **f** has replaced the *L*-(+)-acetonamine moiety, shows results comparable with those of iminium [**23g**][*rac*-TT] salt in conversions and enantioselectivity. With olefins **25-29**, these two catalysts afford epoxides with the same absolute configurations. As it can be expected, opposite sense of induction was obtained when the catalyst made from the (*R*)-1,2,2-trimethyl-propylamine was used. Compound [**23h**][*rac*-TT] leads to slightly lower enantioselectivities (from 70 to 62 % ee from olefin **26**).

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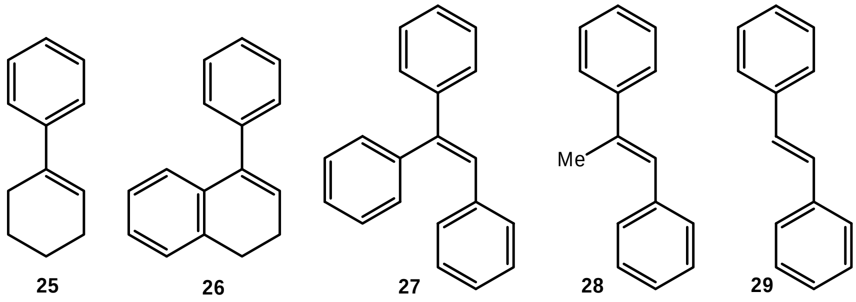
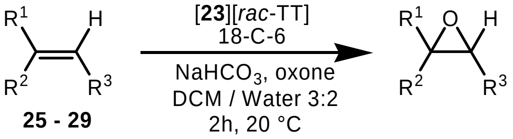
[56] Lacour, J.; Barchéchath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567



25 **26** **27** **28** **29**

Figure II-18: Olefins **25-29** tested in epoxidation reactions



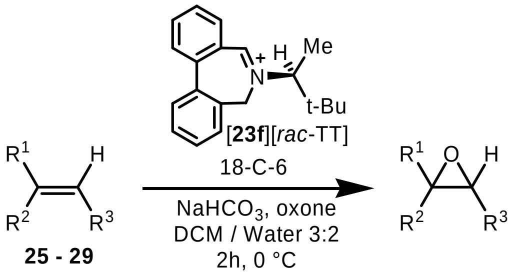
Catalyst	Results	**25**	**26**	**27**	**28**	**29**
[**23b**][*rac*-TT]	ee. %[c]	5[d]	3	7	10	3
	Conv. %[b]	50[f]	62	58	70	57
	Configuration	-[e]	-[e]	(+)-(*S*)	(-)-(1*S*,2*S*)	-[e]
[**23e**][*rac*-TT]	ee. %[c]	21[d]	29	2	5	4
	Conv. %[b]	87[f]	66	57	53	48
	Configuration	(+)-(1*R*,2*R*)	(-)-(1*S*,2*R*)	-[e]	-[e]	-[e]
[**23f**][*rac*-TT]	ee. %[c]	65[d]	70	29	41	14
	Conv. %[b]	100[f]	72	69	84	62
	Configuration	(-)-(1*S*,2*S*)	(+)-(1*R*,2*S*)	(+)-(*S*)	(-)-(1*S*,2*S*)	(-)-(*S*,*S*)
[*ent*-**23f**][*rac*-TT]	ee. %[c]	-	70	28	40	-
	Conv. %[b]	-	63	79	94	-
	Configuration	-	(-)-(1*S*,2*R*)	(-)-(*R*)	(+)-(1*R*,2*R*)	-
[**23g**][Λ-TT][g]	ee. %[c]	69[d]	76	23	42	17
	Conv. %[b]	100[f]	85	82	80	67
	Configuration	(-)-(1*S*,2*S*)	(+)-(1*R*,2*S*)	(+)-(*S*)	(-)-(1*S*,2*S*)	(-)-(*S*,*S*)
[**23h**][*rac*-TT]	ee. %[c]	55[d]	62	17	25	6
	Conv. %[b]	100[f]	68	70	81	61
	Configuration	(-)-(1*S*,2*S*)	(+)-(1*R*,2*S*)	(+)-(*S*)	(-)-(1*S*,2*S*)	(-)-(*S*,*S*)

[a] Conditions : 5 mol % catalyst, 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 20 °C, 2 hours. Average of at least two runs. [b] Conversion calculated using naphthalene as internal standard unless otherwise stated. [c] Determined by CSP-HPLC (Chiralcel OD-H) unless otherwise stated. [d] Determined by CSP-GC (Chiraldex Hydrodex β–3P). [e] Enantiomeric excesses too low to allow a precise determination of the absolute configuration. [f] Conversion calculated with dodecane as an internal reference. [g] Control experiments led to similar results using *rac*-TT as counter ion.

Table II-1: Epoxidation of Olefins at 20 °C using catalysts of type **23**

This catalyst derived from (1*S*,2*S*)-2-benzyloxycyclohexylamine **h**, is, however, quite more efficient than the previously reported **22h**. Catalysts [**23e**][*rac*-TT] and [**23b**][*rac*-TT] that contain stereogenic centers α to the nitrogen atom bearing a small alkyl chain (Me, Et) and an aromatic group (1-Naphthyl, Phenyl) afford epoxides with a drastic decrease of the enantioselectivity (for olefin **26**, 29 and 3% ee respectively) although with decent amount of conversions. Generally the best results were obtained with 1-phenyl-3,4-dihydronaphthalene **26** as a substrate. Finally, catalysts [**23f**][*rac*-TT] and [**23e**][*rac*-TT], albeit both prepared from *S*-configured acyclic α-branched amines, afford the epoxides of olefin **12** with opposite configurations, (–)-(1*S*,2*S*) and (+)-(1*R*,2*R*)-1-phenylcyclohex-1-ene oxide, respectively (Table II-1).[57] The same observation can be made for the oxidation product of **26**.

II-2.1.c Catalysis performed at 0 °C



Olefin	0 °C		20 °C	
	ee %[c]	Conv. %[b]	ee %[c]	Conv. %[b]
25	66[d]	68[e]	65[d]	100[e]
26	80	100	70	72
27	31	61	29	69
28	46	75	41	84
29	17	64	14	62

[a] Conditions : 5 mol % catalyst [**23f**][rac-TT], 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 2 hours. Average of at least two runs. [b] Conversion was calculated using an internal standard (naphthalene) unless otherwise stated. [c] Determined by CSP-HPLC (Chiralcel OD-H) unless otherwise stated. [d] Determined by CSP-GC (Chiraldex Hydrodex β–3P). [e] Conversion calculated with dodecane as an internal reference.

Table II-2: Low temperature (0 °C) epoxidation of **25** to **29** in the presence of [**23f**][*rac*-TT][a]

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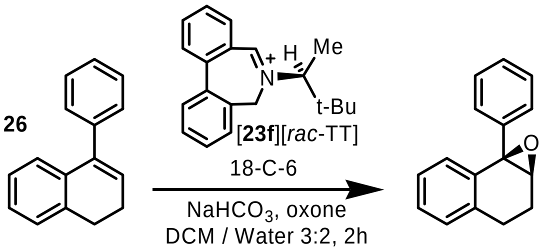
[57] Such an observation has been previously reported, although in an other context : Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Ito, S. *Tetrahedron Lett.* **1992**, *33*, 1651

The effect of the temperature was studied with all the prepared catalysts as Page and co-workers have observed that a lower temperature can lead to an increase in the enantioselectivity of the epoxidation reaction.

Due to the presence of water in the biphasic CH_2Cl_2/water/18-C-6 protocol, we could not reach very low temperatures. The presence of 4 equivalents of $NaHCO_3$ (1.0 M) and 1.1 equivalent of Oxone® (0.27 M) saturating the aqueous phase, the experiments could be performed at –5 °C as a lower limit.[58] However, for practical reasons, most experiments were carried out at 0 °C; all reagents being soluble in both phases. Catalyst [**23**][*rac*-TT] was selected for the initial test and the results of the reactions of olefins **25-29** with Oxone in its presence are summarized in Table II-2. Using the same time frame (2 h) as for the reactions at room temperature, we observed in the particular case of 1-phenyl-3,4-dihydronaphthalene **26**, quite better conversions (100% *vs.* 72% at 20 °C) and enantiomeric excess (80% *vs.* 70%). No significant improvement was noticed on the other olefins tested.

With these results in our hands, the study was continued at four different temperatures using the better substrate **26** and precatalyst [**23f**][*rac*-TT] (Table II-3). Good conversions were always obtained using temperatures from 4 to -5 °C. For the enantioselectivity, a moderate but definite increase in asymmetric induction was obtained at each decreasing-temperature step.



temperature	25°C	4°C	0°C	-5°C
ee. %[b]	70	76	80	81
Conv. %[c]	72	100	100	100
Configuration	(+) (1*R*, 2*S*)	(+) (1*R*, 2*S*)	(+) (1*R*, 2*S*)	(+) (1*R*, 2*S*)

[a] Conditions : 5 mol % catalyst [**23f**][*rac*-TT], 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 2 hours. Average of at least two runs. [b] Determined by CSP-HPLC (Chiralcel OD-H). [c] Conversion was calculated using an internal standard (naphthalene).

Table II-3: Temperature effect on the epoxidation of **26** by Oxone® in the presence of [**23f**][*rac*-TT][a]

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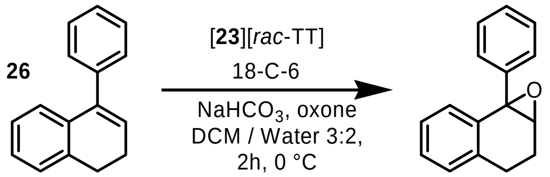
[58] Solubilities in water : (a) $NaHCO_3$ at 0 and 20 °C, 0.82 and 1.14 $mmol.mL^{-1}$ respectively ; (b) Oxone at 20 °C, 0.42 $mmol.mL^{-1}$.

Finally, all iminium catalysts were tested using substrate **26** under the biphasic conditions at 0 °C and the results are reported in Table II-4. In general, conversions were better at 0 °C than at room temperature. Better enantiomeric excesses were measured in all cases. Interestingly, catalyst [**23f**][*rac*-TT] leads to essentially the same ee at 0 °C as [**23g**][*rac*-TT] whereas a noticeable difference was observed at room temperature.



Catalyst	0 °C		20 °C	
	ee %[b]	Conv. %[c]	ee %[b]	Conv. %[c]
[**23b**][*rac*-TT]	7	100	3	62
[**23e**][*rac*-TT]	35	92	29	66
[**23f**][*rac*-TT]	80	100	70	72
[**23g**][*rac*-TT]	79	91	76	84
[**23h**][*rac*-TT]	70	94	62	68

[a] Conditions : 5 mol % catalyst, 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 2 hours. Average of at least two runs. [b] Determined by CSP-HPLC (Chiralcel OD-H). [c] Conversion was calculated using an internal standard (naphthalene).

Table II-4: Low temperature (0 °C) epoxidation of **26** by Oxone®. Catalyst study.[a]

II-2.2Towards a rationalization of the results

As already mentioned in chapter I, diphenylazepines of type **1,** precursors to compounds **23**, undergo rapid conformational equilibrium in solution with rather low energy barriers ($\Delta G^{\neq} \sim$ 10-12 $kcal.mol^{-1}$). Slightly faster equilibration can be envisioned for iminium derivatives **23** in view of the literature precedents, indicating that a change of hybridization of atoms from sp^3 to sp^2 within seven-membered diphenyl ring frameworks usually enhance the rate of rotation around the biaryl bond.[59] Because the presence of the chiral appendages resulting in the formation of diastereomeric structures, a possible nonequal distribution of (*R*a) and (*S*a) diastereomers was considered. Care was thus taken in this study to characterize the structure

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[59] Tichy, M.; Ridvan, L.; Holy, P.; Zavada, J.; Cisarova, I.; Podlaha, J. *Tetrahedron: Asymmetry* **1998**, 9, 227 and references therein

of the diphenylazepinium cations by variable temperature NMR spectroscopy (VT-NMR) and circular dichroism (CD) in search of a correlation between good enantioselectivity in the products and high diastereomeric control of the biphenyl axial chirality of the catalysts.

II-2.2.a Variable Temperature ^{1}H NMR experiments

^{1}H NMR analysis of salts [**23h**][*rac*-TT], [**23e**][*rac*-TT], and [**23b**][*rac*-TT] confirmed the postulated assumption of a fast equilibrium among diastereomeric (*R*a) and (*S*a) structures as single (broad) and double (sharp) sets of signals were observed for these systems at 298 and 233 K, respectively. The signal of the iminium proton (δ 8.7-10.0-ppm region) was particularly useful to monitor the stereodynamics (Figure II-19). Two signals appeared at 233 K due to a relatively slow interconversion of the atropisomers on the NMR time scale and collapse with increasing temperature.

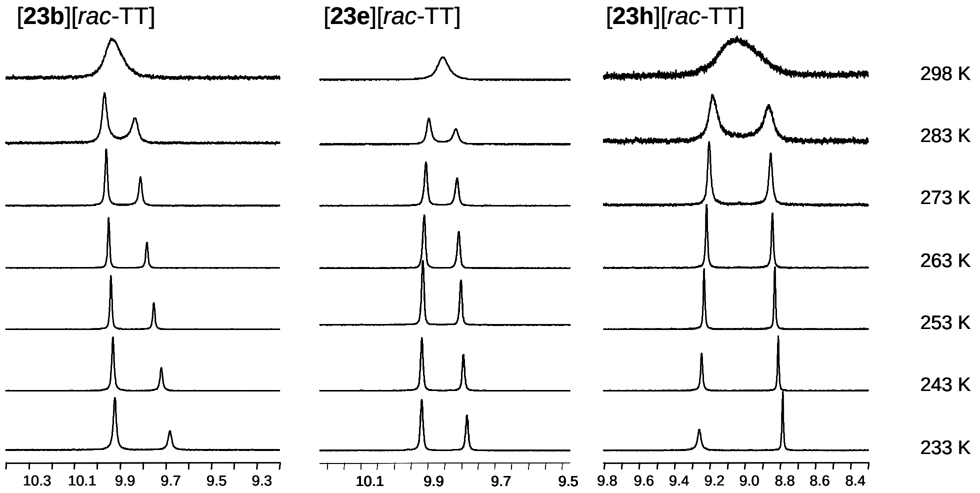

Figure II-19: VT-NMR (500 MHz, CD_2Cl_2) of salts [**23b**][*rac*-TT], [**23e**][*rac*-TT], [**23h**][*rac*-TT] and resulting diastereoselectivity (233 K, d.r. 50:50; 59:41; 69:31 respectively

Compounds [**23h**][*rac*-TT], [**23e**][*rac*-TT], and [**23b**][*rac*-TT] thus behaved as expected. Low diastereomeric enrichment (dr from 50:50 to 69:31) was observed because ratios between the (*S*a) and (*R*a) atropisomers could be measured by integration of the signals at 233 K and these are reported in Table II-5. If one considers that NMR coalescence is reached at 298 K for these three systems, then approximate energy barriers around of 12 kcal.mol^{-1} can be rapidly estimated.[60]

Salts [**23g**][*rac*-TT] and [**23f**][*rac*-TT] presented a more complex behavior and, at first sight, a rather puzzling NMR situation (Figure II-20). At 298 K, both spectra presented two broad signals in the iminium region, whereas only one is observed for salts of cations **23h**, **23e**, and **23b**. When the temperature was lowered, one signal became sharp whereas the others broaden or split in two. A total of three signals was observed for [**23f**][*rac*-TT] at 233 K. This behavior was not accountable by the previous analysis of just two diastereomeric structures occurring at 233 K.

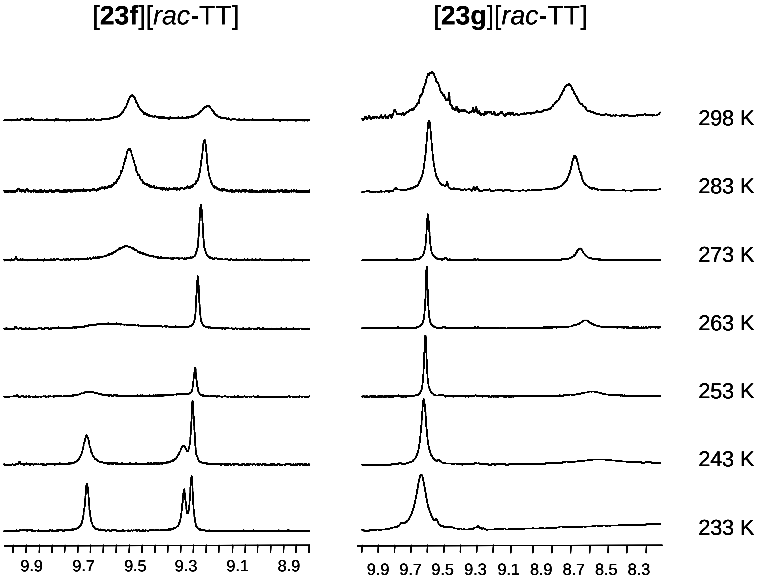

Figure II-20: VT-NMR (CD_2Cl_2,) of salts [**23g**][*rac*-TT] (500 MHz) and[**23f**][*rac*-TT] (400 MHz).

Previously, the group of Pr. Lacour as well as others have shown that slow rotation around N(sp2)-C(sp3, tertiary) bonds can occur when bulky substituents (R_1, R_2 (Figure II-21)) are attached to the carbon.[61,62] For some acridinium derivatives, rotation barriers of 18.2, 20.1,

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[60] The relationship $\Delta G^{\neq} = RT_c\ (22.96 + \ln(T_c/\Delta\nu))$ was used to determine the activation energy, $\Delta G^{\neq}$, from the coalescence temperature, T_c (K), and the frequency of separation of the peaks, $\Delta\nu$ (Hz).

[61] Uncuta, C.; Paun, I.; Deleanu, C.; Plaveti, M.; Balaban, A. T.; Roussel, C. *New. J. Chem.* **1997**, *21*, 1055; Balaban, T. S.; Gheorghiu, M. D.; Roussel, C.; Balaban, A. T. *Z. Naturforsch., B* **1985**, *40B*, 1555; Balaban, A. T.; Dinculescu, A. *Tetrahedron* **1984**, *40*, 2547; Balaban, A. T.; Gheorghiu, M. D.; Balaban, T. S. *J. Mol. Struct.* **1984**, *114*, 363; Seeman, J. I.; Schug, J. C.; Viers, J. W. *J. Org. Chem.* **1983**, *48*, 2399; Katritzky, A. R.; Vassilatos, S. N.; Alajarin Ceron, M. *Org. Magn. Reson.* **1983**, *21*, 587; Seeman, J. I.; Galzerano, R.; Curtis, K.; Schug, J. C.; Viers, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 5982; Balaban, A. T.; Uncuta, C.; Dinculescu, A.; Elian, M.; Chiraleu, F. *Tetrahedron Lett.* **1980**, *21*, 1553

[62] Laleu, B.; Herse, C.; Laursen, B. W.; Bernardinelli, G.; Lacour, J. *J. Org. Chem.* **2003**, *68*, 6304

and 16.7 kcal.mol^{-1} were measured for the derivatives of amines **g**, **f**, and **h**, respectively; the structures derived from amines **g** and **f** displayed the slowest motions. Although the NMR behavior of the acridinium salt derived from amine **e** was not studied, one can estimate its rotation barrier is in the range of 12 kcal.mol^{-1}; a value that has been determined for the (*S*)-phenylpropan-1-amine.

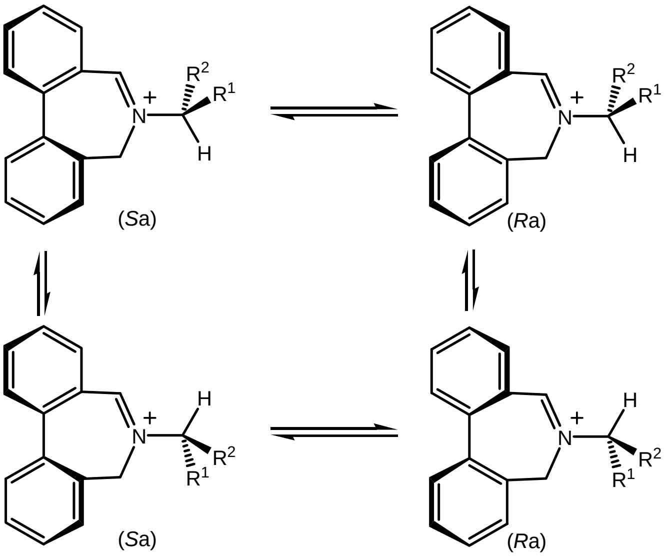

Figure II-21: Conformations of catalyst **23** as a combination of rotameric and atropisomeric geometries

In view of these results, it is likely that such hindered rotation around the N(sp2)-C(sp3) bond also occurs for salts [**23g**][*rac*-TT] and [**23f**][*rac*-TT], leading to a maximum of four atropisomers (Figure II-21). Because it is improbable that the barrier of interconversion between the biaryl atropisomers changes upon a modification of the exocyclic appendage, the two signals observed at 298 K must correspond to rotamers with 52:48 and 60:40 ratios in the case of salts [**23g**][*rac*-TT]and [**23f**][*rac*-TT], respectively. For salt [**23f**][*rac*-TT], as the sample is cooled to 233 K, one of the signals is split and the ratio between the (*R*a) and (*S*a) conformers reaches a 67:33 value. The other signal only sharpens as the temperature is decreased. For this rotamer it seems that the signals of the iminium proton of the (*R*a) and (*S*a) conformers are isochronous. The analysis of the signals of salt [**23g**][*rac*-TT] could not be pursued due to the “disappearance” of one of the signals at 233 K caused, most probably, by a very large difference of the chemical shifts of the diastereomeric iminium proton signals at low temperature. The selectivity ratios and excesses measured in these NMR experiments are summarized in Table II-5.

II-2.2.b Circular Dichroism measurements

Conformational studies of biphenyl moieties can also be performed by CD, as the predominance of one equilibrating atropisomer leads to the appearance of Cotton effects in the UV region. As mentioned in chapter I, non-conjugated bridged biphenyls with a (*S*) configuration (*P* helicity) and a inter-ring angle of approximatively 45° will have a negative Cotton effect centered around 250 nm.[63] For series of compounds with the same inter-ring angle, the intensity of the Cotton effect is proportional to the enantiomeric or diastereomeric excesses in solution. For the studied iminium salts, the presence of the conjugated iminium moiety extends the absorbance of the cations to the 300-400-nm region in which the chiral exocyclic appendages are CD silent (Figure II-22). The use of racemic TRISPHAT also ensures a lack of participation of tetrachlorocatecholate chromophores.

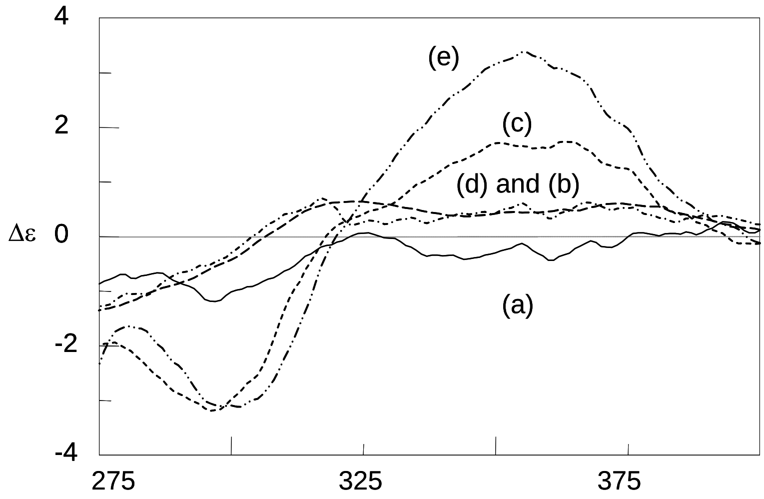

Figure II-22: CD spectra of (a) [**23b**][*rac*-TT] (—),(b) [**23e**][*rac*-TT] (- · -), (c) [**23f**][*rac*-TT] (- - -), (d) [**23g**][*rac*-TT] (– – –) and (e) [**23h**][*rac*-TT] (– · · –) in CH_2Cl_2 (10^{-5} M, 20 °C)

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[63] Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1455; Borecka, B.; Cameron, T. S.; Linden, A.; Rashidy-Ranjbar, P.; Sandström, J. *J. Am. Chem. Soc.* **1990**, *112*, 1185

To our surprise, only compounds [**23h**][*rac*-TT] and [**23f**][*rac*-TT] displayed measurable negative and positive Cotton effects at 300 and 350 nm, respectively (10^{-5} M, CH_2Cl_2, 20 °C). This was unexpected in view of the NMR results for which low diastereomeric excesses were observed for the other samples (with the exception of [**23g**][*rac*-TT]). Only a concentration dependence of the stereoselective induction can be invoked to explain these results because the NMR samples were measured in quite higher concentration (10^{-3} M) than the CD samples. Because good biaryl twisting was expected for the more effective catalysts [**23f**][*rac*-TT] and [**23h**][*rac*-TT], the lack of induction for compound [**23g**][*rac*-TT] is surprising.

Compound	d.r.	d.e.	r.r.	Δε (357nm)	epoxide from **26**	
					e.e.	Configuration
[**23g**][*rac*-TT]	-	-	52:48	0.5	79	(+)-(1*R*,2S)
[**23f**][*rac*-TT]	56:44	8%	60:40	1.7	80	(+)-(1*R*,2S)
[**23h**][*rac*-TT]	50:50	0%	-	3.4	70	(+)-(1*R*,2S)
[**23e**][*rac*-TT]	59:41	18%	-	0.5	35	(—)-(1*S*,2R)
[**23b**][*rac*-TT]	69:31	28%	-	0.0	6	(+)-(1*R*,2S)

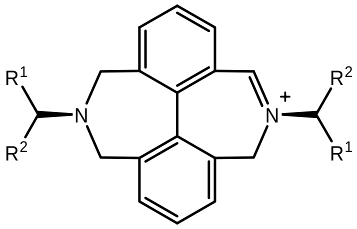
Table II-5: Diastereomeric ratios and excesses (233 K), rotamer ratios (298 K), Cotton effects (Δε) and enantiomeric excesses for the oxidation of **13** with catalysts [**23b**][*rac*-TT], [**23e**][*rac*-TT], [**23f**][*rac*-TT], [**23g**][*rac*-TT]and [**23h**][*rac*-TT] at 0 °C

II-2.2.c Conclusion

In conclusion, no direct or obvious correlation was found between the enantioselectivity of the epoxidation reactions and a stereocontrol of the twisted biaryl bond of the seven-membered ring by exocyclic chiral appendages. Catalysts of type **23** exist as complex mixtures of biaryl (*R*a) and (*S*a) atropisomers and rotamers around the $N(sp^2)$-$C(sp^3)$ bond. Most probably, the barriers of interconversion between these conformers have low energies in comparison with the transition-state energies leading to oxaziridinium intermediates or epoxide products. The reaction mechanism most probably follows the *Curtin-Hammet* principle and, as shown, a conformational analysis of the initial catalysts yields little information for the understanding of the selectivity. However, the results have also shown that (*S*)-1,2,2-trimethylpropylamine derived iminium catalyst **23f** can be essentially as efficient as derivative **23g**. As this bulky amine is commercially available in both enantiomeric forms, which is not the case for acetonamine, its use in the formation of **23f** seems to be an interesting development in this iminium catalyzed chemistry.[64] Furthermore, temperature experiments have shown that a decrease of only 20 °C can have a positive impact on enantiomeric excesses. This latter catalyst has been successfully used in a scaled up epoxidation reaction on 5.0 g of olefin **26** with similar yields and enantioselectivities.[65]

II-3 Biphasic Enantioselective Olefin Epoxidation Using Atropos Doubly Bridged Biphenyl Azepinium Catalysts

As mentioned previously, very high degrees of enantioselectivities were obtained for the epoxidation reactions using Aggarwal‘s configurationally stable binaphthyl derived catalyst [**21**][BF_4] (e.e up to 71% on olefine **25**) and, above all, Page's configurationally stable binaphthyl subunit combined to a chiral exocyclic appendage [(*R*a,L)-**24g**][BF_4] (e.e up to 95% on olefine **26**). Taking into account that doubly bridged biphenyl derivatives of type **4** are configurationally stable at room temperature (cf. Chapter I) - which is not the case of dibenzoazepinium of type **23** - we thought that these compounds could be effective precursors to the preparation of efficient mixed [azepine/azepinium] catalysts of type **30**.



30

Figure II-23: mixed [azepine/azepinium] catalysts of type **30**

At that stage many issues have to be solved:

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[64] Vachon, J.; Perollier, C.; Monchaud, D.; Marsol, C.; Ditrich, K.; Lacour, J. *J. Org. Chem* **2005**, *70*, 5903

[65] Vachon, J.; Pérollier, C.; Martinez, A.; Lacour, J. *Catalysts for Fine Chemical Synthesis*; VCH-Wiley, 2006; Vol. 5

(i) Could we use that same procedure for the oxidation of azepine to iminium as for compounds of type **1**?

(ii) If yes, will the newly formed mixed [azepine/azepinium] salt formed epimerize during the reaction?

(iii) Will the doubly bridged biphenyl azepinium be as configurationally stable as the doubly bridged biphenyl azepine (DBBA) **4**?

(iv) Will these compounds be efficient catalysts for the epoxidation of olefins?

In this perspective, a study of the synthesis, the isolation and the catalytic activity of new doubly bridged mixed [azepine/azepinium] salts was started with compounds bearing the same chiral appendage as for the *tropos* compounds of type **23** previously described. Part of this section was realized in collaboration with Dr. Alexandre Martinez, a post-doctorate associate of the group.

II-3.1 Catalyst preparation

The synthesis of the Doubly Bridged Biphenyl mixed [azepine/azepinium] catalysts **30b**, **30e**, **30f** and **30g** was performed in one step starting from the already described DBBA of type **4** with amines – all (*S*) configured - **b**, **e**, **f** and **g** (Figure II-16), following a general and reproducible protocol (that is to say a total of 3 steps starting from pyrene). In the cases of DBBA **4b** and **4e** only the (*S*a) -diastereomer was submitted to the oxidation step. Concerning DBBA **4f** and **4g** both (*S*a) and (*R*a) - diastereomer were isolated and submitted to oxidation, because these two chiral amines led to the higher asymmetric induction when used as the monoazepinium catalyst of type **23**. As a first try, the same oxidation procedure (1.3 eq. of NBS with a catalytic amount of AIBN in CCl_4 at 20 °C overnight) that was previously used for the oxidation of diphenylazepines of type **1**, was tested. Interestingly, the reaction did provide the desired iminium bromide salt of type **30** but a slight epimerization of the compound was observed. Indeed, as previously mentioned, a change of hybridization of atoms from sp^3 to sp^2 within seven-membered diphenyl ring frameworks usually enhances the rate of rotation around the biaryl axis. As the half life of DBBA **4f** is for example is only 53h at 23 °C this could explain the epimerization during the reaction. To find a faster oxidation process the reaction conditions were changed. CCl_4, which doesn't solubilize completely the

NBS was replaced by a better solvent ($CHCl_3$). Surprisingly this modification increased dramatically the reaction rate and no addition of AIBN was required. In these conditions only few seconds were needed (compared to 12 hours) to reach completion of the reaction (checked by the consumption of the starting material by TLC). Then, the crude reaction mixtures were directly submitted to ion exchange metathesis with 1.2 equivalent of [cinchonidinium][Δ-TT]. Similarly to iminium salts of type **23**, the lipophilicity of TRISPHAT anion allows the compounds to be purified by column chromatography (Al_2O_3, pH 9.5, CH_2Cl_2) allowing their isolation in modest to decent yields (50-66%). Using this procedure, 6 catalysts were obtained : [(*S*a)-**30b**][Δ-TT], [(*S*a)-**30e**][Δ-TT], [(*R*a)-**30f**][Δ-TT], [(*S*a)-**30f**][Δ-TT], [(*R*a)-**30g**][Δ-TT] and [(*S*a)-**30g**][Δ-TT] (Figure II-24).[66]

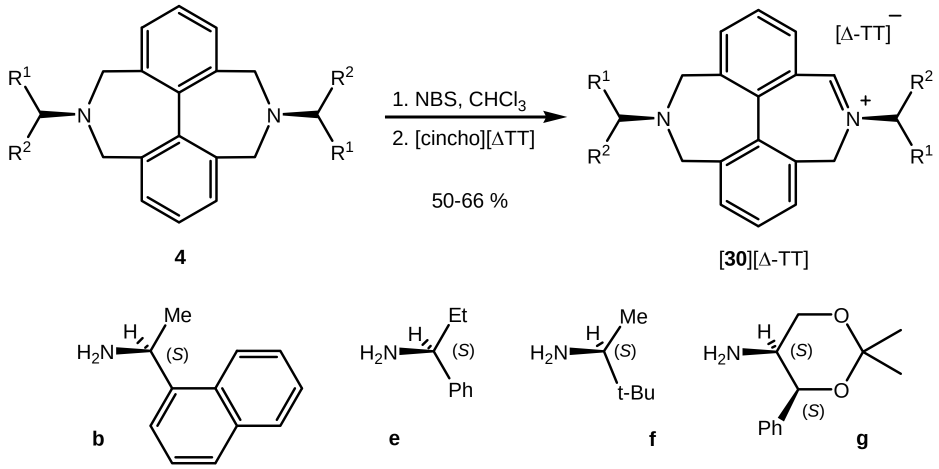

Figure II-24: Synthesis of iminiums [**30b**][Δ-TT], [**30e**][Δ-TT], [**30f**][Δ-TT] and [**30g**][Δ-TT] bearing the corresponding amines **b**, **e**, **f** and **g**

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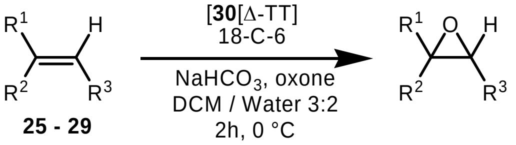
[66] In those experiments, for ease of synthesis, enantiopure Δ-TRISPHAT was used as counterion although its non-racemic nature has no influence on the stereoselectivity of the reaction, see ref 44

II-3.2 Catalysis performed at 0 °C

Epoxidation reaction on olefins **25** to **29** with the previously mentioned catalysts were carried out using the biphasic CH_2Cl_2/water protocol in the presence of 18-C-6 (2.5 mol%) as the phase transfer agent as detailed previously. The results are reported in Table II-6.



Catalyst	Results	**25**	**26**	**27**	**28**	**29**
[(*S*a)-**30b**][Δ-TT]	ee. %[c]	58[d]	67	26	49	42
	Conv. %[b]	26[f]	69	25	44	46
	Configuration	(+)-(1*R*,2*R*)	(-)-(1*S*,2*R*)	(-)-(*R*)	(+)-(1*R*,2*R*)	(+)-(*R*,*R*)
[(*S*a)-**30e**][Δ-TT]	ee. %[c]	71[d]	85	24	55	27
	Conv. %[b]	82[f]	60	21	51	27
	Configuration	(+)-(1*R*,2*R*)	(-)-(1*S*,2*R*)	(-)-(*R*)	(+)-(1*R*,2*R*)	(+)-(*R*,*R*)
[(*R*a)-**30f**][Δ-TT]	ee. %[c]	76	76	31	59	31
	Conv. %[b]	56	80	26	61	26
	Configuration	(-)-(1*S*,2*S*)	(+)-(1*R*,2*S*)	(+)-(*S*)	(-)-(1*S*,2*S*)	(+)-(*R*,*R*)
[(*S*a)-**30f**][Δ-TT]	ee. %[c]	-	49	-	41	-
	Conv. %[b]	-	76	-	75	-
	Configuration	-	(+)-(1*R*,2*S*)	-	(-)-(1*S*,2*S*)	-
[(*R*a)-**30g**][Δ-TT]	ee. %[c]	34[d]	53	17	48	30
	Conv. %[b]	95[f]	95	75	80	95
	Configuration	(-)-(1*S*,2*S*)	(+)-(1*R*,2*S*)	(+)-(*S*)	(-)-(1*S*,2*S*)	(-)-(*S*,*S*)
[(*S*a)-**30g**][Δ-TT]	ee. %[c]	22[d]	27	-	45	-
	Conv. %[b]	75[f]	89	-	95	-
	Configuration	(+)-(1*R*,2*R*)[e]	(+)-(1*R*,2*S*)	-	(-)-(1*S*,2*S*)	-

[a] Conditions : 5 mol % catalyst, 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 0 °C, 2 hours. Average of at least two runs. [b] Conversion calculated using naphthalene as internal standard unless otherwise stated. [c] Determined by CSP-HPLC (Chiralcel OD-H) unless otherwise stated. [d] Determined by CSP-GC (Chiraldex Hydrodex β–3P). [e] Enantiomeric excesses too low to allow a precise determination of the absolute configuration. [f] Conversion calculated with dodecane as an internal reference.

Table II-6:. Epoxidation of olefins at 0 °C using catalysts of type [**30**][Δ-TT].[a]

In almost all cases, moderate to good conversions were obtained, in particular on olefins **25** and **26**. Enantiomeric excesses were only slightly improved compared to the tropos series **23**. It is for instance the case, for instance with catalyst [(*S*a)-**30e**][Δ-TT] where ee up to 86% on olefin **26** was obtained *vs.* 29% ee previously with [**23e**][*rac*-TT]. Unfortunately due to a limited access to diastereomeric precursor, [(*R*a)-**30e**][Δ-TT] could not be prepared and no information on the matched/mismatched nature of diastereomer [(*S*a)-**30e**][Δ-TT] can be provided.[67] A full comparison was however feasible with the derivatives of amine **f**. Salts [(*R*a)-**30f**][Δ-TT] and [**23e**][*rac*-TT] behaved with remarkable analogy as enantiomeric excess and absolute configurations of the resulting epoxides were essentially identical; only conversions being lower with the larger system. Poorer results were obtained with diastereomeric [(*S*a)-**30f**][Δ-TT] indicating clearly the "mismatched" nature of this reagent. Bizarrely, both diastereomers [(*R*a)-**30g**][Δ-TT] and [(*S*a)-**30g**][Δ-TT] were found to be poorly selective catalysts. This was quite surprising as amine **g** has proven to be the best chiral appendage for both catalyst bearing biphenyl moiety (with **23g**) and binaphthyl moiety (with **24g**).

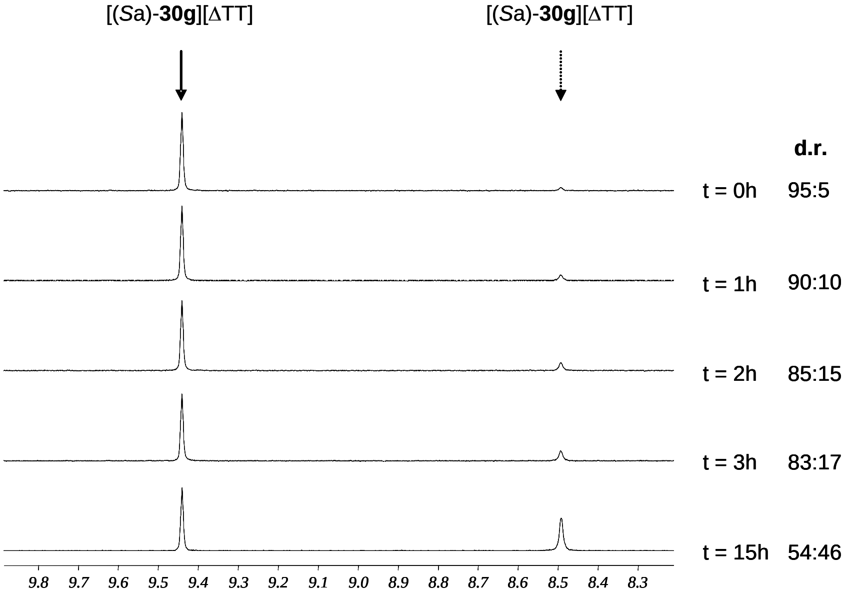


Figure II-25: Epimerization of [(*S*a)-**30g**][Δ-TT] at 20°C in CD_2Cl_2

To explain these rather disappointing overall results, a few hypotheses can be suggested. First of all, we imagined that the catalysts could epimerize during the course of the reaction. To verify this, we followed the kinetic of epimerization by ^{1}H NMR by integration of the signals of the iminium proton (δ 8.7–10.0 ppm region) of each diastereomer within few hours period of time (Figure II-25). Interestingly, we observed that an epimerization occurs but this

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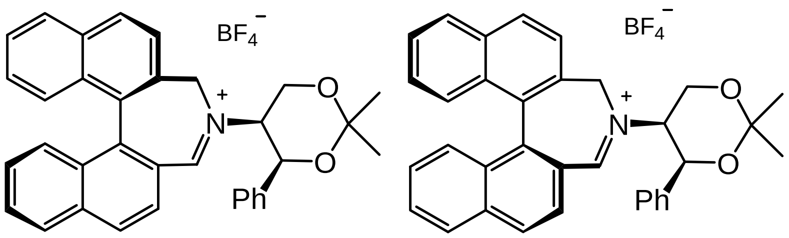
[67] Only few mg of the (*R*a)-**4e** diastereomer have been isolated by semi-perparative HPLC

phenomenon is rather slow compared to the reaction time (less than 2h) so that this could not be the only explanation for the modest level of enantioselectivities observed. Another explanation could be the dihedral angle of the doubly bridged biphenyl structure and the lack of extended aromatic structure as compared to binaphthyl moieties. This parameter seems to be crucial regarding the results obtained by Page and coworkers. In this case, the configuration of the binaphthyl axis directs the final configuration of the epoxide as changing from *R*a-binaphthyl to *S*a-binaphthyl moieties and keeping the same L-acetonamine chiral appendage leads to the reverse configuration of the epoxide (Figure II-26). In terms of dihedral angle, binaphthyl frameworks are known to be around 65° which is quite more than the doubly bridged biphenyl skeleton with a dihedral angle ~ 45°,[59] and obviously the central core of compounds 30 have also a less extended aromatic nature in the doubly bridged biphenyl mixed [azepine/azepinium] series, providing – maybe – less room for interactions with olefins. Another hypothesis which cannot be verified is that maybe, the second chiral appendage is somehow involved in the epoxidation reaction, something to be considered in view of the later results.



[(R_a,L)-**24g**][BF_4]
ee = 91% on olefin **25**
configuration: (+)-(1*R*,2*R*)

[(S_a,*L*)-**24g**][BF_4]
ee = 78% on olefin **25**
configuration:(-)-(1*S*,2*S*)

Figure II-26: Match ((*R*a,L)-**24g**) and mismatch ((*S*a,L)-**24g**) catalysts for the epoxidation of olefin **25**

II-4 Amine or Ammonium salts as catalysts for epoxidation of non-functionalized olefins

II-4.1 Chiral secondary amine catalysts reported in the literature

Whereas the epoxidation of olefins catalyzed by iminium salts has been known for quite some time, the mediation of the reaction by amines and/or ammonium salts is still a new topic. Following the work of Yang, while studying the *in situ* formation of an iminium salt with the appropriate combination of a carbonyle and an amine partner, Aggarwal and co-workers found by control experiments that epoxidation reaction could occur by the amine alone, and asymmetric induction was observed when a chiral amine such as **31** was used (Figure II-27).[68]

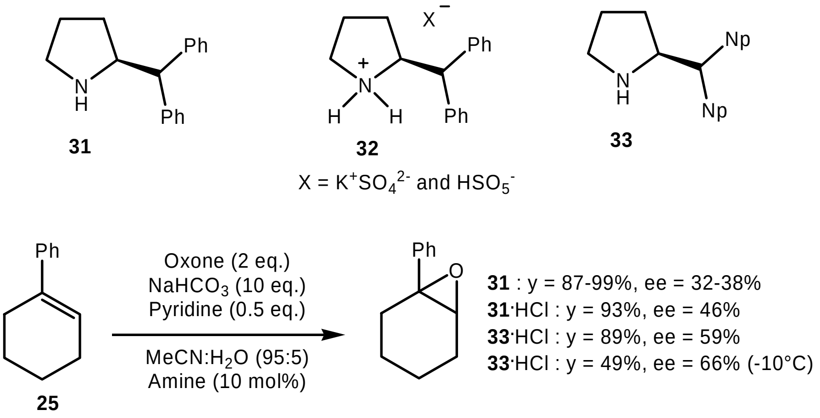


Figure II-27: Amine catalyzed Oxone epoxidation of 1-phenylcyclohexene **25**

A first hypothesis proposed by Aggarwal suggested the involvement of an amine radical cation as the alkene oxidating species. However, difficulties in reproducing the key comparative control experiments led the authors to look more closely to the mechanism of the process.[69] In the epoxidation conditions described in Figure II-27, they found that the HCl salt of **31** was even more efficient than the free base **31** in terms of activity and enantioselectivity; the pyridine playing the role of a "proton shuttle" to limit epoxide hydrolysis and the subsequent formation of a diol.[70] The more bulky catalyst **33** was also tested and led to a better enantioselectivity while performing the reaction at -10 °C (ee = 66%). By trying to

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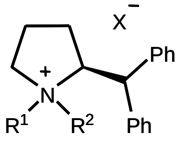
[68] Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317

[69] Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 11223

recover the amine at the end of the reaction, they found that, when performed at room temperature, the amine was completely oxidized in its N-oxide derivative. However this oxidation product was found not to promote the epoxidation reaction. By performing the same reaction at -10 °C, the epoxidation still took place and the amine could be recovered in good yields. It was discovered that the reaction of the amine **31** with Oxone led to the formation of the salt **32** which contains a mixture of the potassium sulfate and peroxymonosulfate anions (Figure II-27). While performing the same reaction with the complex **32**, identical enantioselectivity was obtained indicating that this compound was the active epoxidizing species.



R^1	R^2	X	Yield (%)	ee of epoxide (%)
H	H	Cl	93	46
Me	H	Cl	58	5
Me	Me	BF_4	13	0

Table II-7: Variation of yield and enantioselectivity with the ammonium-salt structure in the oxone epoxidation of 1-phenycyclohexene 25

As highlighted by Armstrong, the reason why the complex **32** is more reactive than oxone itself maybe that the ammonium couterion acts as a phase-transfer catalyst.[71] Moreover, as shown in Table II-7, the fact that the reactivity dropped with the methylated version of catalyst **31** led Aggarwal to propose a novel mode of activation involving hydrogen bonding from HSO_5^- and the ammonium (Figure II-28).

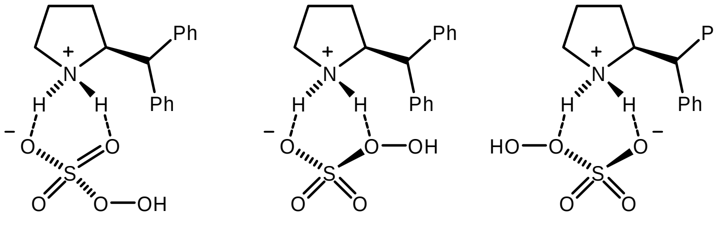


Figure II-28: Possible modes of interaction between a secondary ammonium salt and HSO_5^-

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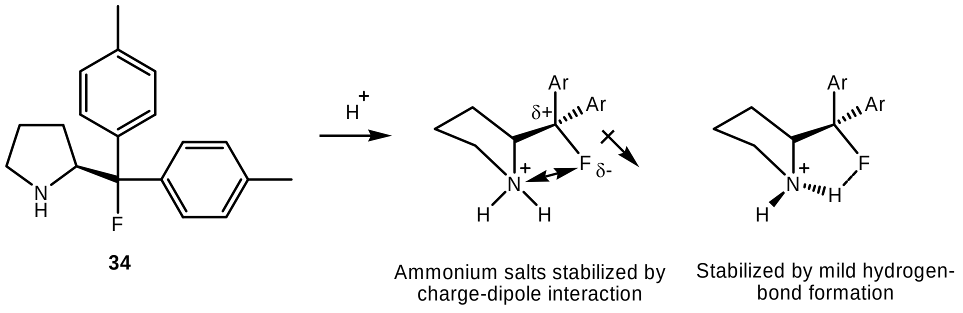
[70] Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596

[71] Armstrong, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1460

Similarly, Yang and coworkers found that amines themselves could promote epoxidation under slightly acidic reaction conditions. A broad range of amine (cyclic, acyclic, primary and secondary) was tested in their reaction conditions which consists in adding a mixture of Oxone (4 eq.) and $NaHCO_3$ (10 eq.) to a solution of amine (1 eq.) and *trans*-stilbene (1 eq.) in a CH_3CN/H_2O (10:1) solution at room temperature for 5h.[72] They found that cyclic secondary amines are better catalysts than acyclic primary and secondary amines in terms of activity. Electron-withdrawing substituents (O, F) were found to be useful when placed at a β-position of the amino group as better conversions were obtained in these cases. They reported also a series of chiral cyclic secondary amines based on the same pyrrolidine moiety as Aggarwal, having different substitution patterns. The highest enantiomeric excess (61%) occurred for the epoxidation of 1-phenylcyclohexene catalyzed by amine **34** (Figure II-29) bearing a fluorine atom at the β-position relative to the amino center. According to the authors, the presence of electronegative fluorine atoms may stabilize the positively charged ammonium salts through favorable charge-dipole interactions or mild hydrogen bond formation with an ammonium proton (Figure II-29). The slightly acidic reaction conditions employed (no pyridine was used in this case) obviate the need to use ammonium salts which, as Aggarwal mentioned it, are the actual catalysts that mediate the epoxidation with the dual role of (i) phase transfer catalyst and (ii) Oxone activator.



Ammonium salts stabilized by charge-dipole interaction

Stabilized by mild hydrogen-bond formation

Figure II-29: Stabilization of the ammonium salts by the fluorine substituent

Until recently, the only amine based catalyst for olefin epoxidation reported in the literature were the α-substituted pyrrolidine moieties for which no-stable iminium analogues can be found. Indeed, most of these species, in particular the most hindered ones, are prone to

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[72] Ho, C. Y.; Chen, Y. C.; Wong, M. K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898

solvolysis in the reaction conditions. Though Aggarwall has demonstrated that the methylated pyrrolidine was less efficient than the corresponding secondary amine (Table II-7) Lacour and coworkers showed that azepine derived tertiary amines can also mediate epoxidation reactions.[73] Three different amines were prepared for the study (Figure II-30). Amine 1g and diastereomers in the binaphthyl derived (*R*a,L)-35g and (*S*a,L)-35g (Figure II-30), directly related to iminium cations 23g, (*R*a,L)-24g and (*S*a,L)-24g respectively. All six compounds were tested as catalysts for olefin epoxidation in (i) homogeneous CH_3CN/water conditions and (ii) biphasic CH_2Cl_2/water conditions with 18-crown-6 as a phase transfer agent.

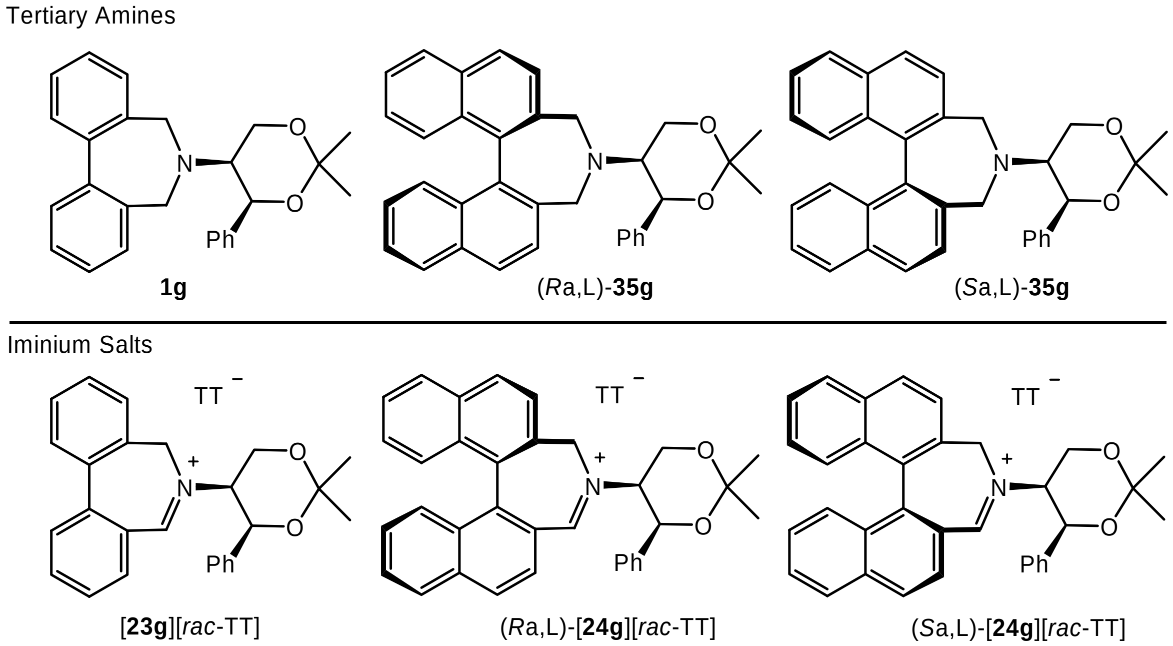

Figure II-30: Non-racemic tertiary amines and their corresponding iminium salts derived from amine **g**

In short, the tertiary amines perform essentially as well as their corresponding iminium salts as catalysts for the enantioselective epoxidation of some prochiral olefins – in particular in the acetonitrile / water conditions (ee up to 80% on olefin **26** with catalyst (*R*a,L)-**35g**). The enantioselectivities obtained have not gone beyond the 95% ee obtained with [**24g**]$[BF_4]$. However, as making the amines requires less synthetic steps than the preparation of the iminium salts, it was therefore interesting to study other azepines synthesized – and those reported in this thesis in particular – in the context of the enantioselective epoxidation.

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[73] Gonçalves, M.-H.; Martinez, A.; Grass, S.; Page, P. C. B.; Lacour, J. *Tetrahedron Lett.* **2006**, *47*, 5297

II-4.2 Direct use of DBBA as catalysts for epoxidation reactions

As already mentioned, the mixed [azepine/azepinium] salts derived from DBBA **30b**, **30e**, **30f** and **30g** were not better catalysts than the iminiums of type **23** for the epoxidation of some prochiral olefins. Despite this fact, eight dibenzoazepines of type **4** (Figure II-31) were nevertheless tested. All the epoxidation reactions were carried out in biphasic DCM/water conditions as this method is better suited for screenin. Indeed, contrary to acetonitrile/water, DCM is a very good solvent for all the olefins as well as all the catalysts so that everything can be put in solution for parallel injection rather than weighting systematically all the compounds. The results are listed in Table II-8.

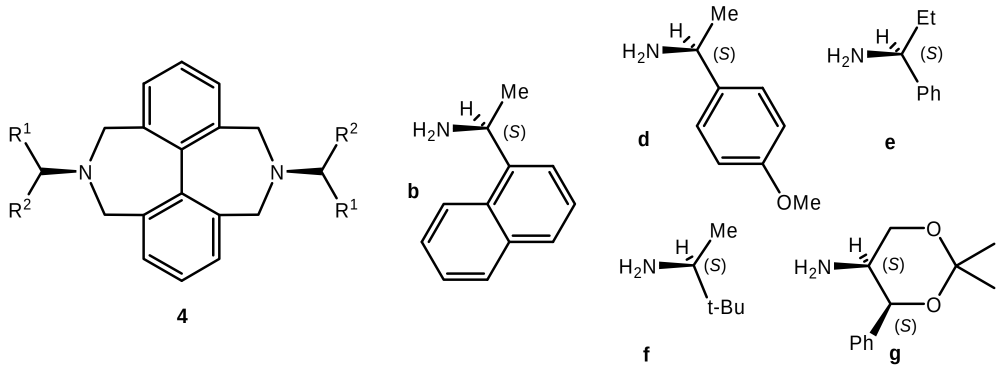
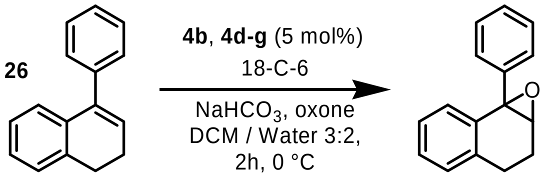


Figure II-31: Doubly Bridged Biphenyl Azepines **4d-g**



Results	(*S*a)-**4b**	(*S*a)-**4d**	(*S*a)-**4e**	(*R*a)-**4e**	(*R*a)-**4f**	(*S*a)-**4f**	(*R*a)-**4g**	(*S*a)-**4g**[b]
ee. %[c]	-	-	-	-	77	79	52	11
Conv. %[b]	2	1	1	0	55	69	51	77
Conf.	-	-	-	-	(+)-(1*R*,2*S*)	(+)-(1*R*,2*S*)	(+)-(1*R*,2*S*)	(-)-(1*S*,2*S*)

[a] Conditions : 5 mol % catalyst, 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 0 °C, 2 hours. Average of at least two runs. [b] Conversion calculated using naphthalene as internal standard. [c] Determined by CSP-HPLC (Chiralcel OD-H).

Table II-8: Asymmetric epoxidation using catalysts **4b, 4d-g**

Two classes of catalysts can be drawn. First, the azepines derived from benzylic chiral primary amines (**b**, **d**, **e**) lead a complete lack of epoxidation. The second class is constituted of diastereomeric derivatives (*R*a)-**4f**, (*S*a)-**4f**, (*R*a)-**4g** and (*S*a)-**4g**. Significantly, compounds **4f** derived from 1,2,2-trimethylpropylamine are catalysts and are as reactive as compounds **4g** but leading to higher levels of ee. This was not obvious as it was expected that the lack of electron-withdrawing atoms on the exocyclic appendages of **4f** would be detrimental in view of Yang's hypothesis for both reactivity and selectivity of catalytic active amines. As iti is obviously not the case, one suspects that the Aggarwal mechanism is not at play in our case and that the tertiary amines are oxidized *in-situ* to – possibly – the iminium ions, the good correlation between the results of the epoxidation with (*R*a)/(*S*a)-**4f** and [(*R*a)/(*S*a)-**30f**][Δ-TT] being another indication. In view of this novel hypothesis, a reason for the lack of epoxidation in presence of amines **4b**, **4d** and **4e** is then, possibly, the exocyclic oxidation of the nitrogen atom (favored in the presence of aromatic groups) and subsequent hydrolysis of the strained tetra-substituted iminium ion destroying the catalyst. Finally, comparison of the results of (*R*a)-**4f** and (*S*a)-**4f** indicates that the configuration of the epoxides is controlled by the exocyclic appendage and not by the biaryl twist of the core, an situation opposite to that of (*R*a,L)-**35g** and (*S*a,L)-**35g**.

II-4.3 Direct comparison of homologous amine catalysts and iminium catalysts

To our knowledge, for these dinaphthylazepinium systems, to the exception of (-)-isopinocamphenylamine which leads to less selective catalysts than those derived from L-(+)-acetonamine, no other chiral exocyclic appendage has been reported to date. In view of our results with [**23f**][*rac*-TT] and [**23g**][*rac*-TT], it was debatable whether binaphthyl iminium ions [(*R*a,*S*)-**24f**][*rac*-TT] and [(*R*a,*R*)-**24f**][*rac*-TT] derived from 1,2,2-trimethyl-propylamine **f** would display similar or better levels of selectivity to that of salts [(*R*a,L)-**24g**][*rac*-TT] and [(*S*a,L)-**24g**][*rac*-TT] and whether the biaryl core would still predominate in the stereocontrol.

Furthermore and maybe more importantly, as we have recently demonstrated that azepines precursors to iminium ions [**23g**][*rac*-TT], [(*R*a,L)-**24g**][*rac*-TT] and [(*S*a,L)-**24g**][*rac*-TT], are essentially as effective catalysts for the enantioselective epoxidation of prochiral olefins than their unsaturated derivatives,[73] we wondered whether azepines **1f**, (*R*a,*S*)-**35f** and (*R*a,*R*)-**35f** (Figure II-32) would behave similarly and display also effective enantioselective oxidation abilities.

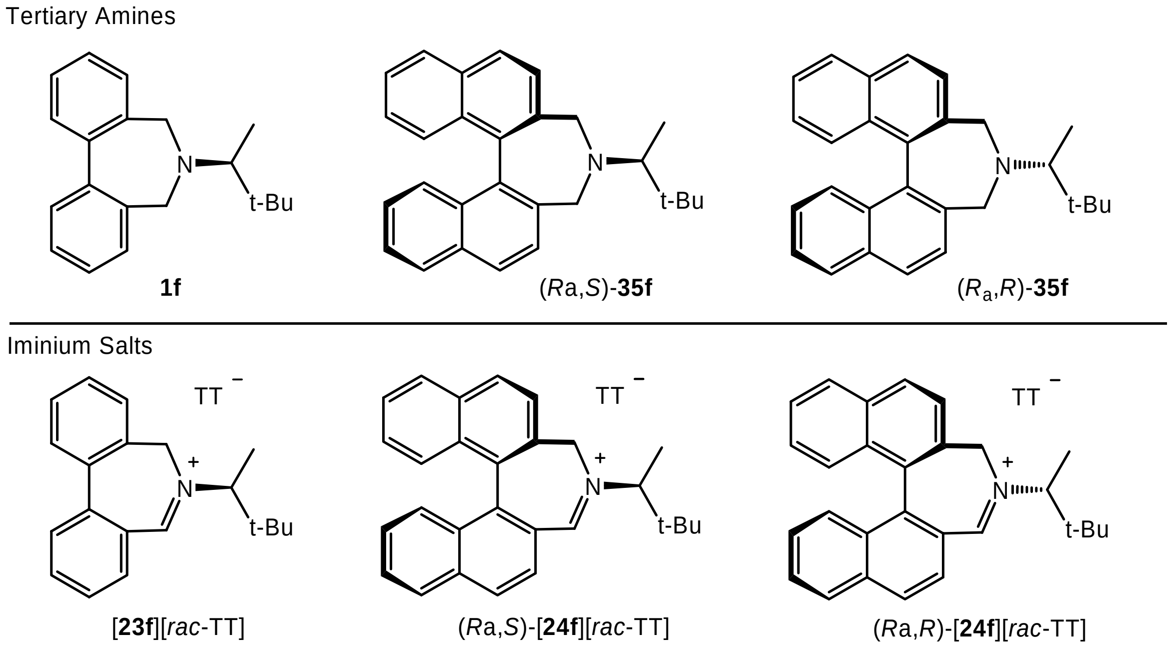


Figure II-32: Non-racemic tertiary amines and their corresponding iminium salts with their absolute configuration, derived from amine **f**

II-4.3.a Preparation of the catalysts

The preparation of azepine **1f** and its derived iminium salt [**23f**][rac-TT] has been shown previously. For the making of the novel binaphthyl derivatives (*R*a,*S*)-**35f**, (*R*a,*R*)-**35f**, [(*R*a,*S*)-**24f**][*rac*-TT] and [(*R*a,*R*)-**24f**][*rac*-TT], a short three steps protocol was developed using known (R_a)-2,2'-bis(bromomethyl)-1,1'-binaphthyl as starting material and standard reactions (Figure II-33): (i) an alkylation with (*S*)-**f** or (*R*)-**f** to afford diastereomeric amines (*R*a,*S*)-**35f** and (*R*a,*R*)-**35f** (72 and 76% respectively); (ii) subsequent eliminations with *N*-bromosuccinimide to form the iminium salts; and (iii) ion pair metatheses with an ammonium TRISPHAT salts to afford the final products [(*R*a,*S*)-**24f**][*rac*-TT] and [(*R*a,*R*)-**24f**][*rac*-TT] (86 and 88% respectively, two steps).

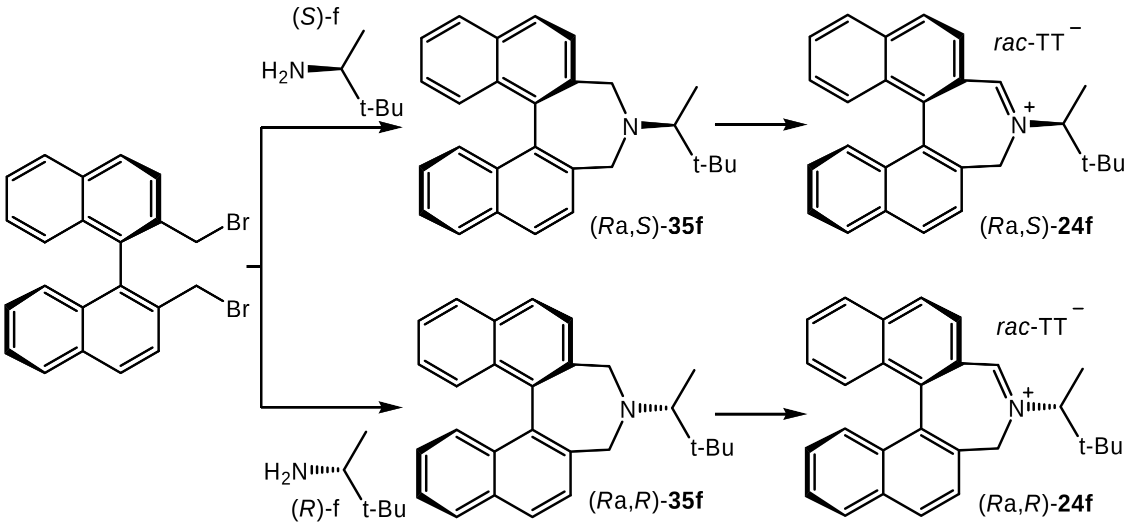
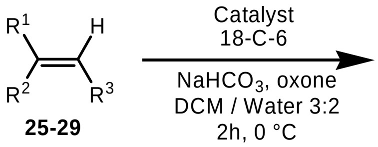


Figure II-33: Synthesis of azepines **35f** and iminium TRISPHAT salts **24f**

II-4.3.b Results for the epoxidation reaction

One set of epoxidation conditions (CH_2Cl_2 / $NaHCO_3$ / 18-crown-6 / H_2O) and five different prochiral di- and tri substituted unfunctionalized alkenes (**25-29**) were selected for the study. The results are reported in Table II-9 and Table II-10 for the biphenyl (**1f** and **23f**) and binaphthyl ((*R*a,*S*)-**35f**, (*R*a,*R*)-**35f**, [(*R*a,*S*)-**24f**][*rac*-TT] and [(*R*a,*R*)-**24f**][*rac*-TT]) catalysts respectively. Significantly, amine **1f** behaves as an effective catalyst performing essentially as well as iminium **23f** in terms of conversions; enantiomeric excesses being however globally lower with the azepine moiety. Ee values up to 70 and 80% were nevertheless obtained with olefin **26** as substrate and catalysts **1f** and [**23f**][rac-TT] respectively. To the exception of alkene **29**, non-racemic epoxides of analogous absolute configurations were isolated from the reactions with **1f** and [**23f**][rac-TT]; the result with *trans*-stilbene that sees an inversion in the sense of induction is, at the moment, unexplained.

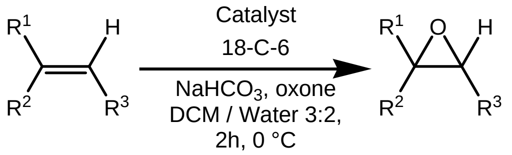


Alkene	Amine **1f**			Iminium [**23f**][*rac*-TT]		
	Conv. %[b]	e.e. %[c]	Conf.	Conv. %[b]	e.e. %[c]	Conf.
25	58	39[d]	(–)-(1*S*,2*S*)	68	66[d]	(–)-(1*S*,2*S*)
26	100	70	(+)-(1*R*,2*S*)	100	80	(+)-(1*R*,2*S*)
27	60	15	(+)-(*S*)	61	31	(+)-(*S*)
28	74	22	(–)-(1*S*,2*S*)	75	46	(–)-(1*S*,2*S*)
29	61	22	(+)-(1*R*,2*R*)	64	17	(–)-(1*S*,2*S*)

[a] Conditions : 5 mol % catalyst, 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 0 °C, 2 hours. Average of at least two runs. [b] Conversion calculated using naphthalene as internal standard. [c] Determined by CSP-HPLC (Chiralpack IB) unless otherwise stated. [d] Determined by CSP-GC (Chiraldex Hydrodex β–3P)..

Table II-9: Asymmetric epoxidation of olefin **25-29** with catalysts **1f** and [**23f**][*rac*-TT]

As mentioned, olefins **25-29** were also treated with substoichiometric amounts (5 mol %) of ((*R*a,*S*)-**35f**, (*R*a,*R*)-**35f**, [(*R*a,*S*)-**24f**][*rac*-TT] and [(*R*a,*R*)-**24f**][*rac*-TT]. The results are reported in Table II-10; all four derivatives behave as catalysts. Careful analysis of the data reveals a number of subtleties but some general trends can be found. If one compares the selectivity of the diastereomeric catalysts together – that is (*R*a,*S*)-**35f** with (*R*a,*R*)-**35f** and [(*R*a,*S*)-**24f**][*rac*-TT] with [(*R*a,*R*)-**24f**][*rac*-TT] – one generally observes analogous levels of stereoinduction in the (*R*a,*S*) and (*R*a,*R*) series with, to the exception of olefin **27**, slightly better ee with the (*R*a,*R*)-configurated catalysts. Identical sense of induction is obtained for the non-racemic epoxides in all examples. It indicates that the binaphthyl framework is (again[45,73]) a more effective chiral auxiliary than 1,2,2-trimethyl-propylamine **f** since the configuration of the epoxides does not change with opposite absolute configuration of the chiral appendage. This general lack of "matched" / "mismatched" distinction, as far as enantiomeric excesses are concerned, do not apply to conversions. Catalyst [(*R*a,*S*)-**24f**][*rac*-TT] performed better than [(*R*a,*R*)-**24f**][*rac*-TT]. Amine (*R*a,*S*)-**35f** also catalyzed the reaction better than (*R*a,*R*)-**35f** (e.g. olefin **26**, (*R*a,*S*)-**35f**: 100% *vs.* (*R*a,*R*)-**35f**: 44%). As such, the "matched" catalysts in terms of selectivity (ee values) are "mismatched" in terms of conversions. If one now compares the selectivity of the homologous amine and iminium salts– that is **35f** with **24f**, one notices that the amines and iminium salts induce the same sense of stereoselective induction into the non-racemic epoxides; the iminium cations leading to (slightly) better enantiomeric excesses, in particular in the case of olefin **26** (e.g. ee: [(*R*a,*S*)-**24f**][*rac*-TT]: 30% *vs.* (*R*a,*S*)-**35f**: 3%).



	Amines				Iminiums				
Catalysts	(*R*a,*S*)-**35f**		(*R*a,*R*)-**35f**		[(*R*a,*S*)-**24f**] [*rac*-TT]		[(*R*a,*R*)-**24f**] [*rac*-TT]		
	Conv. %[b]	e.e. %[c]	Conv. %[b]	e.e. %[c]	Conv. %[b]	e.e. %[c]	Conv. %[b]	e.e. %[c]	Conf.[e]
25	70	74[d]	43	86[d]	67	84[d]	48	86[d]	(–)-(*S*,*S*)
26	100	81	44	86	85	86	61	87	(+)-(1*R*,2*S*)
27	56	37	50	26	82	38	62	29	(+)-(*S*)
28	70	49	23	59	75	61	54	61	(–)-(1*S*,2*S*)
29	87	3	28	14	98	30	75	30	(–)-(*S*,*S*)

[a] Conditions : 5 mol % catalyst, 2.5 mol % 18-C-6, 1.1 eq Oxone®, 4.0 eq $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 0 °C, 2 hours. Average of at least two runs. [b] Conversion calculated using naphthalene as internal standard. [c] Determined by CSP-HPLC (Chiralpack IB) unless otherwise stated. [d] Determined by CSP-GC (Chiraldex Hydrodex β–3P). [c] The configurations of the epoxides are all the same for the four catalysts

Table II-10: Asymmetric epoxidation of olefin **25-29** with catalysts (*R*a,*S*)-**35f**, (*R*a,*R*)-**35f**, [(*R*a,*S*)-**24f**][*rac*-TT] and [(*R*a,*R*)-**24f**][*rac*-TT]

It is remarkable that the amines and iminium ions lead to such similar enantiomeric excess values. It is therefore reasonable to consider a single mechanistic pathway for the two processes which may involve the *in situ* transformation of the tertiary amine into the reactive iminium species in these highly oxidative conditions.[74] Investigations are currently underway to understand the mechanism of the catalytic process with these particular tertiary azepines and azepinium salts

II-4.4 Conclusion

In this last part we have seen that tertiary amines precursors of the iminium salt catalysts could be effective precatalysts for the asymmetric epoxidation of some prochiral olefins; their efficiency being almost similar in terms of activity and enantioselectivity. Again the chiral

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[74] It is, in that sense, very different from the recent studies of Aggarwal and Yang on the epoxidation of olefins mediated by catalytic aliphatic secondary ammonium salts

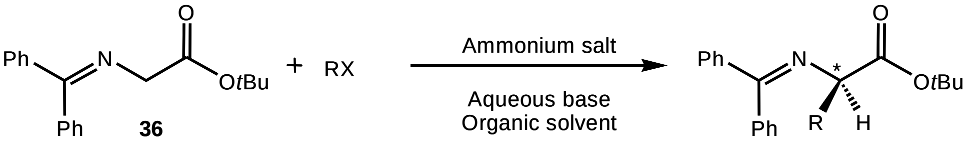
appendage **f** seems a good alternative to L-acetonamine **g** as better enantioselectivities were obtained in catalysts of type **4** or **30**. The 95% ee have obtained by Page with iminium catalyst [(*S*a,L)-**24g**][BF_4] have not been exceeded but iminium catalyst **25f** and amine catalyst **35f** showed promising results. However, many issues are still not solved concerning the mechanism with these tertiary amines catalysts. Many clues tend to prove that, these compounds do not behave like amine catalysts described by Aggarwal and Yang which are derived form pyrrolidine. In their case, tertiary amine are poorly efficient as the need of N-H groups to form hydrogen bonding with Oxone is required. Control experiments using catalyst **1f** showed complete consumption of the amine into oxidized species so that we were not able to recover the free amine at the end of the reaction. Some other experiments have to be pursued to determine the exact nature of the active species that catalyze the epoxidation reaction.

Chapter III

PHASE TRANSFER CATALYSIS USING CHIRAL AMMONIUM SALTS

Due to the constant demand for non racemic molecules in both industrial and academic laboratories, many efforts have been devoted in the last 25 years to the development of enantioselective phase transfer catalyzed (PTC) processes. At the time we entered the field (2003-2004), much of this chemistry was well reviewed with recent articles dating of 2003 / 2004 which treated essentially of the synthesis of non racemic α-amino acid.[1] After a short historical introduction on this topic, we will detail enantioselective PTC reactions reported in the last three years (2003-2006) and demonstrate how broad and active the field is (~90 references) – and this considering ammonium catalyzed reactions only. This chapter will end with the results obtained during this PhD thesis which deals with the synthesis of novel chiral ammonium structures that can be applied as phase transfer catalysts.

III-1 Milestones of enantioselective PTC before 2003



Equation III-1: Asymmetric synthesis of α-amino acids via the Schiff base ester alkylation

Non-racemic ammoniums allow asymmetric PTC processes, and the isolation of optically active products by simple reactions in biphasic media of charged intermediates with electrophilic compounds. As mentioned in the introduction of this PhD thesis, the Merck group in 1984 was able to synthesis a non-racemic bioactive molecule, (+)-indacrinone, through an asymmetric PTC alkylation using N-benzylcinchonium bromide as phase transfer

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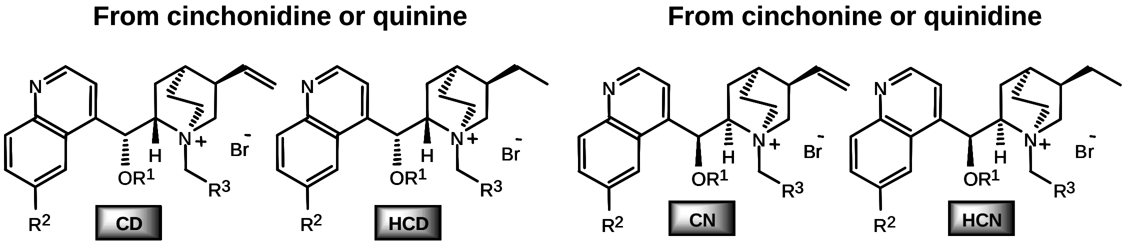
[1] Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518; Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013; O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506

catalyst.[2] Five years later, this type of catalyst was successfully used for the asymmetric synthesis of α-amino acids using the Schiff base ester **36** as substrate (Equation III-1), with promising enantioselectivities (ee up to 66%).[3] In 1997, a "breakthrough" in enantioselective PTC was reported independently by the groups of Corey and Lygo. Using *N*-(9-anthracenylmethyl)ammonium halide salts of cinchonine **37a** and cinchonidine **37c** (Figure III-1), Lygo could achieve the alkylation at 20 °C of imino ester **36** with enantiomeric excesses up to 94%.[4] With the more soluble *O*-allyl derivative **37b,** CsOH•H_2O as a base and lower temperature (-78 °C), (Figure III-1), Corey performed the same reactions with a higher selectivity (ee up to 99.5%).[5]


From cinchonidine or quinine **From cinchonine or quinidine**

37a: R^1 = H, R^2 = H
R^3 = 9-anthracenyl

37c: R^1 = H, R^2 = H
R^3 = 9-anthracenyl

37b: R^1 = allyl, R^2 = H
R^3 = 9-anthracenyl

Figure III-1: *Cinchona* alkaloids derived catalysts

The above results led to a surge of new interest in enantioselective PTC which has been, as mentioned before, reviewed up to 2003-2004. In short, quite a few structural variations of the alkaloid framework were tested using the four classical *cinchona* natural products that are cinchonine / quinidine (CN), cinchonidine/quinine (CD) and their dihydro equivalents (HCN and HCD respectively); the above abbreviations being used throughout the chapter. Various appendages were linked to the bridgehead nitrogen and to the benzylic oxygen atoms. Catalyst optimization studies led Lygo to perform the reaction of **36** with improved enantioselectivity up to 98% ee (0 °C).[6] Dimeric dicationic catalysts with different chemical spacers in between two *cinchona* ammonium moieties were prepared by the groups of Jew,

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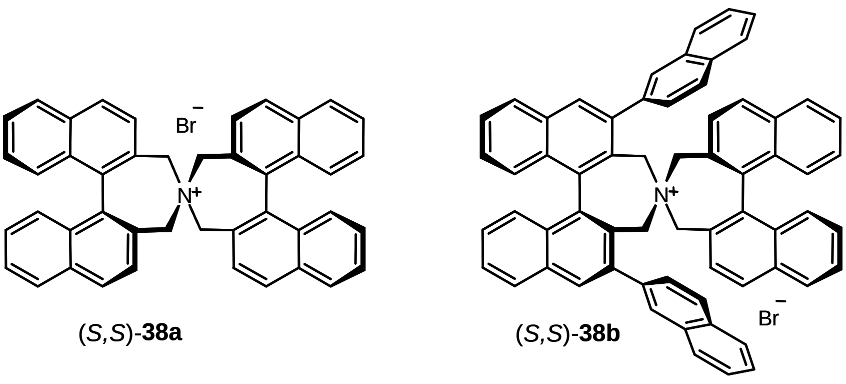
[2] Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446
[3] O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353
[4] Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595
[5] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414

Park and Najera, which gave very convincing results (ee up to 99%);[7] a trimeric catalyst was reported as well (up to 97% ee).[8] *N*-Linked polymer supported *cinchona*-alkaloid derivatives were also synthesized using Merrifield resins;[9] *O*-linked Merrifield polymers performing equally well.[10]

However, fine tuning of *cinchona*-alkaloid ammonium catalysts is somewhat limited to the above described structural modifications and, in this context, quite a few groups have entered the field of enantioselective PTC by proposing novel structures and geometries for the ammonium moieties. For instance, in 1999, Maruoka and collaborators have shown that purely synthetic C_2-symmetrical bis(binaphthyl)ammonium salts of type **38** (Figure III-2), available from (*S*) or (*R*)-BINOL in several steps, are effective chiral phase transfer catalysts. The reactions of ester **36** with alkyl halides occurred with decent selectivity using the "naked" ammonium cation **38a** (up to 79% ee); better results being obtained with salts of cation **38b** that contains *β*-naphthyl substituents at 3,3' positions of the binaphthyl core (ee = 96%).[11]



(*S*,*S*)-**38a** (*S*,*S*)-**38b**

Figure III-2: C_2-symmetric spiro ammonium developed by Maruoka and coworkers (1999)

After this voluntarily short and limited summary of the situation up to 2003, care will now be taken to detail novel catalytic ammonium salts – without excluding the "old faithful" ones that still find new and effective uses. To give a quick perception of the efficiency of the

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[6] Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015

[7] Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244; Chinchilla, R.; Mazon, P.; Najera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927

[8] Park, H. g.; Jeong, B. s.; Yoo, M. s.; Park, M. k.; Huh, H.; Jew, S. s. *Tetrahedron Lett.* **2001**, *42*, 4645

[9] Chinchilla, R.; Falvello, L. R.; Galindo, N.; Najera, C. *J. Org. Chem.* **2000**, *65*, 3034; Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2001**, *12*, 983

[10] Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synthesis* **2001**, 1742

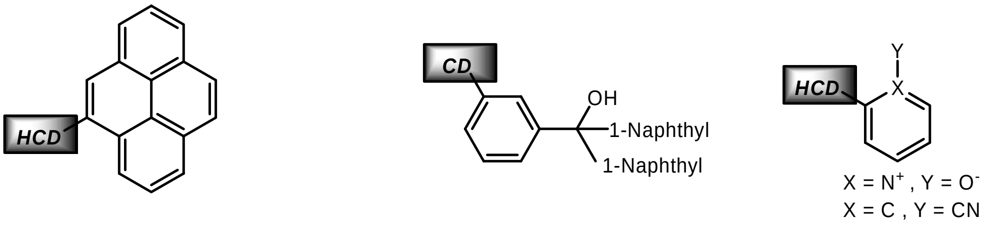
[11] Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519

catalytic moieties, the best enantiomeric excesses obtained with them will be indicated close to the structures with a few words describing the chemical context of their use – the reactions being detailed later in the chapter according to the substrate nature, reagents and conditions.

III-2 Non Racemic Ammonium Cations Catalysts: Recent Advances

Chiral ammonium phase transfer catalysts can be divided in three main classes that are (i) molecules derived from *cinchona* alkaloids (Figure III-3 and Figure III-4), (ii) those made from other *chiral pool* moieties (Figure III-5),[12] and (iii) purely synthetic ammonium cations (Figure III-6 and Figure III-7). A fourth class will be briefly presented which is the group of the readily recyclable (including polymer supported) catalysts.

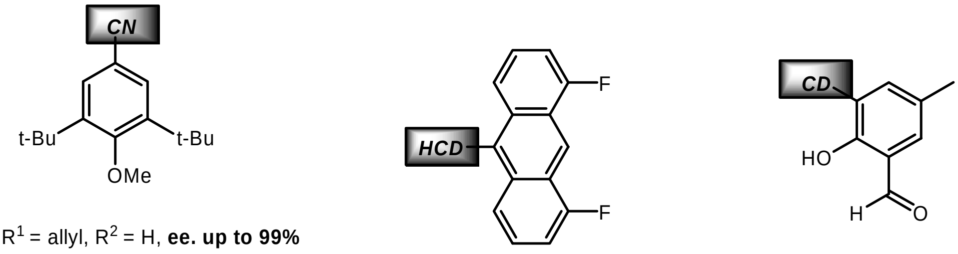
III-2.1 Cinchona based ammonium cations



39: R^1 = H, R^2 = H, **ee up to 94%** (Schiff base ester alkylation)

40: R^1 = allyl, R^2 = H, **ee up to 99%** (Schiff base ester alkylation)

41: R^1 = allyl, R^2 = H, **ee up to 99%** (Schiff base ester alkylation)



42a: R^1 = allyl, R^2 = H, **ee. up to 99%** (alkylation of α,β-keto esters)

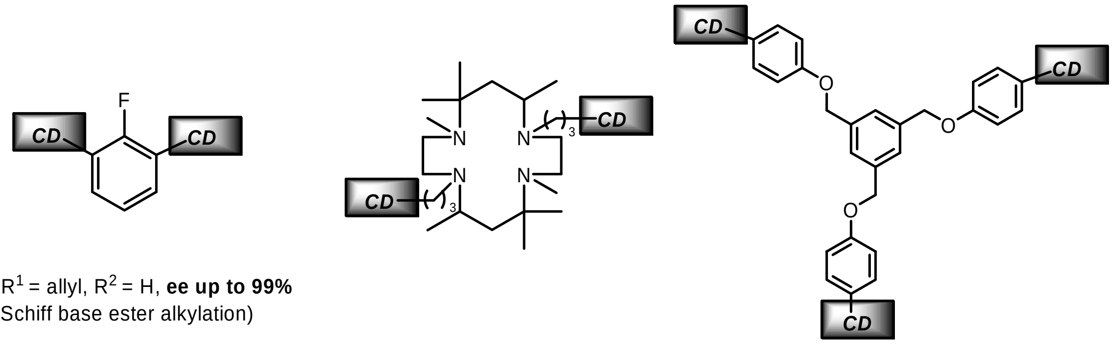
42b: R^1 = propargyl, R^2 = H,
ee up to 76% (fluorination of α-cyano esters)
ee up to 69% (fluorination of α,β-keto esters)

43: R^1 = allyl, R^2 = H, **ee up to 98%** (Schiff base ester alkylation)

44: R^1 = *p*-Tosyl, R^2 = H, **ee up to 95%** (aziridination of olefins)

Figure III-3: Monomeric *cinchona* ammonium catalysts – structural variation of the R^3 group in reference to structures detailed in Figure III-1

As mentioned, several modifications of the *cinchona* alkaloid core have been proposed that involve, in general, introduction of substituents (i) at the bridgehead nitrogen atom, (ii) at the benzylic hydroxyl group or (iii) at position 6 of the quinoline. The efficiency of the catalysts relies mostly on the substituent added on the bridgehead nitrogen atom. Various benzylic groups have been introduced to study the influence of steric effects (e.g., compounds **39** and **40**),[13] of electronic effects (molecule **41**),[14] and a combination of both (**42** and **43**).[15,16] Taking into account these factors, it is possible to elaborate the right catalyst for the desired reaction; compound **44** being for instance designed for the aziridination of electron deficient olefins.[17]



45a: R^1 = allyl, R^2 = H, **ee up to 99%**
(Schiff base ester alkylation)

45b: R^1 = H, R^2 = OMe, **ee up to 99%**
(epoxidation of chalcone)

46: R^1 = allyl, R^2 = H, **ee up to 99%**
(Schiff base ester alkylation)

47: R^1 = allyl, R^2 = H, **ee up to 98**%
(Schiff base ester alkylation)

Figure III-4: Dimeric and trimeric *cinchona* ammonium catalysts – structural variation of the R^3 group in reference to structures detailed in Figure 1.

As mentioned, effective dimeric and trimeric catalysts combining two or three *cinchona* ammonium cations were elaborated before 2003. Structural improvements were recently reported by extensive variations of the chemical nature of the linker (length, size, electronics) affording novel dimeric (**45, 46**) and trimeric (**47**) moieties; very high enantiomeric excesses being obtained in many of the studied reactions.[18,19]

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[12] Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935

[13] Kumar, S.; Ramachandran, U. *Tetrahedron* **2005**, *61*, 7022; Elango, S.; Venugopal, M.; Suresh, P. S.; Eni *Tetrahedron* **2005**, *61*, 1443

[14] Yoo, M.-S.; Jeong, B.-S.; Lee, J.-H.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1129

[15] Park, E. J.; Kim, H. R.; Joung, C. U.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2004**, *25*, 1451

[16] Andrus, M. B.; Ye, Z.; Zhang, J. *Tetrahedron Lett.* **2005**, *46*, 3839

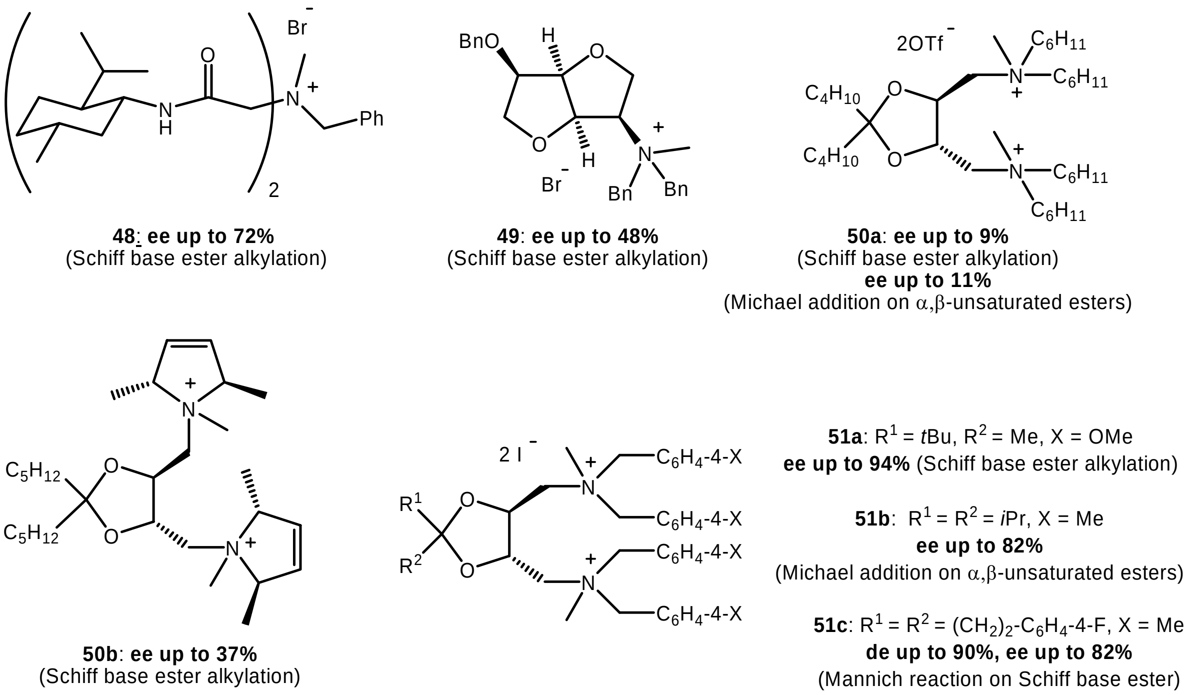
[17] Murugan, E.; Siva, A. *Synthesis* **2005**, 2022

[18] Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497; Siva, A.; Murugan, E. *J. Mol. Catal. A: Chem.* **2005**, *241*, 111; Siva, A.; Murugan, E. *Synthesis* **2005**, 2927

[19] Jew, S.-s.; Lee, J.-H.; Jeong, B.-S.; Yoo, M.-S.; Kim, M.-J.; Lee, Y.-J.; Lee, J.; Choi, S.-h.; Lee, K.; Lah, M. S.; Park, H.-g. *Angew. Chem., Int. Ed.* **2005**, *44*, 1383

III-2.2 Other ammonium cations derived from chiral pool moieties

As one might suspect, the structural diversity of the chiral pool was exploited to generate non racemic ammonium catalysts of structures different from those of the *cinchona* alkaloids. For instance, quaternary ammonium cations **48** and **49** (Figure III-5) were synthesized respectively from L-menthol and isosorbide, which is a byproduct of the starch industry coming respectively from the dehydration of D-sorbitol.[20]



48: ee up to 72%
(Schiff base ester alkylation)

49: ee up to 48%
(Schiff base ester alkylation)

50a: ee up to 9%
(Schiff base ester alkylation)
ee up to 11%
(Michael addition on α,β-unsaturated esters)

50b: ee up to 37%
(Schiff base ester alkylation)

51a: R^1 = *t*Bu, R^2 = Me, X = OMe
ee up to 94% (Schiff base ester alkylation)

51b: $R^1 = R^2$ = *i*Pr, X = Me
ee up to 82%
(Michael addition on α,β-unsaturated esters)

51c: $R^1 = R^2 = (CH_2)_2\text{-}C_6H_4\text{-4-F}$, X = Me
de up to 90%, ee up to 82%
(Mannich reaction on Schiff base ester)

Figure III-5: Other ammonium cations derived from the chiral pool

Modest to decent levels of selectivity were obtained when these cations were engaged in PTC. Ammonium cations derived from *tartaric acid* were also prepared (e.g., **50** and **51**) and used successfully (*vide infra*). The nature of the substituents on the ammonium moieties is primordial to reach high level of enantioselectivity – this is particularly noticeable when comparing the efficiency of salts **50** and **51**.[21,22,23]

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[20] Kumar, S.; Sobhia, M. E.; Ramachandran, U. *Tetrahedron: Asymmetry* **2005**, *16*, 2599; Kumar, S.; Ramachandran, U. *Tetrahedron* **2005**, *61*, 4141

[21] Rueffer, M. E.; Fort, L. K.; MacFarland, D. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3297; Kowtoniuk, W. E.; MacFarland, D. K.; Grover, G. N. *Tetrahedron Lett.* **2005**, *46*, 5703; Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206; Fukuta, Y.; Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Nemoto, T.; Kisugi, T.; Okino, T.; Shibasaki, M. *Proc. Natl. Acad. Sci. U. S. A* **2004**, *101*, 5433

[22] Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743

III-2.3 Purely synthetic ammonium cations

As mentioned, very high levels of enantioselectivity were obtained before 2003 when using spiro C_2-symmetrical bis(binaphthyl) ammonium salts of type **38a** or **38b**. Further modifications of the nature of the aryl substituents at 3,3’ positions (compounds **38c** to **38f,** Figure III-6) were studied by the Kyoto group.[24,25] The major drawback of molecules of type **38** – if any – is that more than 10 steps are classically required to synthesize the appropriate binaphthyl subunits. In order to simplify the preparation of the compounds, Maruoka and coworkers developed a new synthetic procedure; one of the improvements being that metallation of the binaphthyl core with magnesium bis(2,2,6,6-tetramethylpiperamide) as a base which facilitates the scale-up of the overall process.[26] Introduction of aryl substituents at the 4,4’ and 6,6’ positions of the bis-binaphthlyl core was also carried out (e.g., **52** and **53**);[27] compound **53**, which presents a D_2-symmetry, is interesting as its preparation requires essentially half the amount of synthetic preparative steps than C_2-symmetrical analogues. Catalyst **54** based on a rigid 6,6’-dimethyl biphenyl skeleton was also described.[28] For **53** and **54**, bulkier aromatic moieties could be introduced on the biaryl core due to the reduction in steric hindrance around the central nitrogen atom. Quite a few other cyclic biaryl ammonium cations were reported recently by the groups of Maruoka and Lygo which include (i) configurationally rigid (*atropos*)[29] monobinaphthyl ammonium structures (**55** and **56**),[30,31] (ii) *atropos* monobiphenyl adducts (e.g., **57**),[32] (iii) configurationally labile (*tropos*) biphenyl moieties with either stereogenic (a) exocyclic appendages (e.g., **58**)[33] or (b) *atropos* biaryl moieties (**59**).[34] A polycationic variant (**60**) of catalyst **56** was furthermore described.[35]

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[23] Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564

[24] Maruoka, K. *Pure Appl. Chem.* **2005**, *77*, 1285

[25] Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139

[26] Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576

[27] Hashimoto, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3313; Hashimoto, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1599

[28] Ooi, T.; Kubota, Y.; Maruoka, K. *Synlett.* **2003**, 1931

[29] Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561; Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369

[30] Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548

[31] Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549

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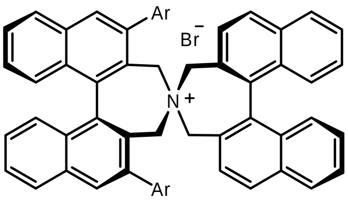
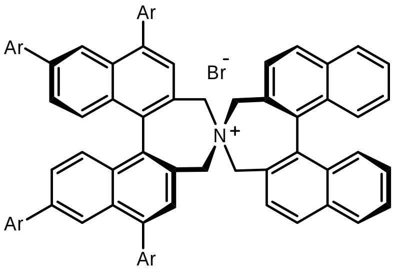
[33] Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629

[34] Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844

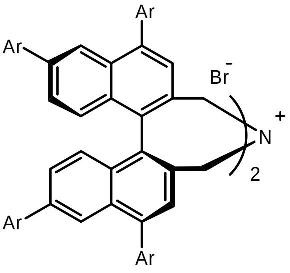
[35] Kano, T.; Konishi, S.; Shirakawa, S.; Maruoka, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1243



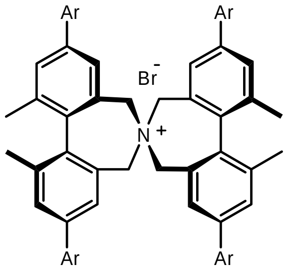
(*S*,*S*)-**38c** (Ar = 3,4,5-F_3-Ph)
(*S*,*S*)-**38d** (Ar = 3,5-bisCF_3-Ph)
(*S*,*S*)-**38e** (Ar = 3,5-bis(3,5-bisCF_3-Ph)-Ph)
(*S*,*S*)-**38f** (Ar = 3,5-bis(3,5-bis*t*Bu-Ph)-Ph)



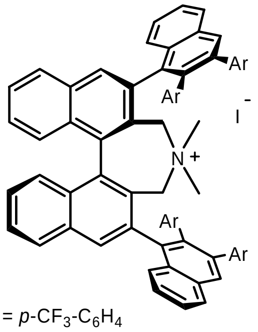
(*S*,*S*)-**52** (Ar = 3,5-diphenylphenyl)
ee up to 96%
(Schiff base ester alkylation)



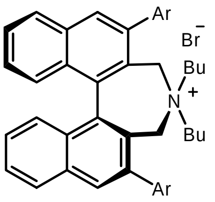
(*S*,*S*)-**53** (Ar = 3,5-diphenylphenyl)
ee up to 97%
(Schiff base ester alkylation)



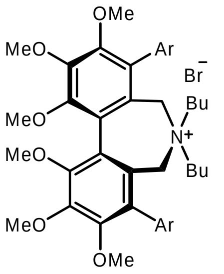
(*R,R*)-**54** (Ar = C(Me_2)Ph)
ee up to 97%
(Schiff base ester alkylation)



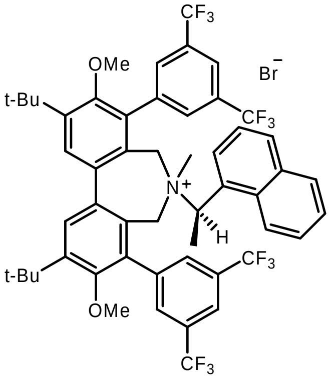
(*R*)-**55**: Ar = *p*-CF_3-C_6H_4
ee up to 98%
(Strecker reaction)



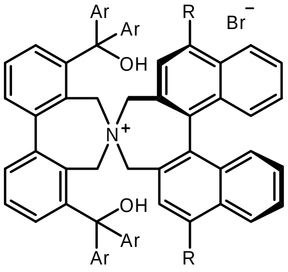
(*S*)-**56** (Ar = 3,4,5-F_3-Ph)
ee = 97-99%
(Schiff base ester alkylation)



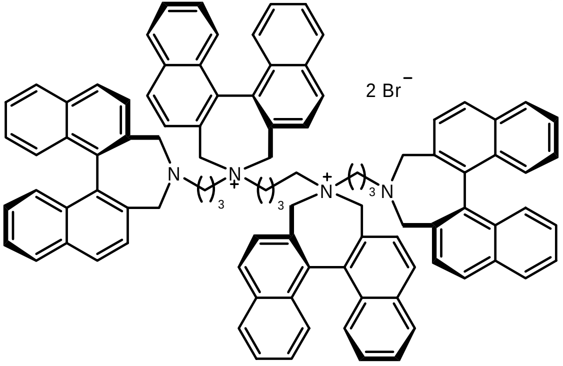
(*S*,*S*)-**57** (Ar = 3,4,5-F_3-Ph)
ee = 94 - 98%
(Schiff base ester alkylation)



58: **ee up to 97%**
(Schiff base ester alkylation)



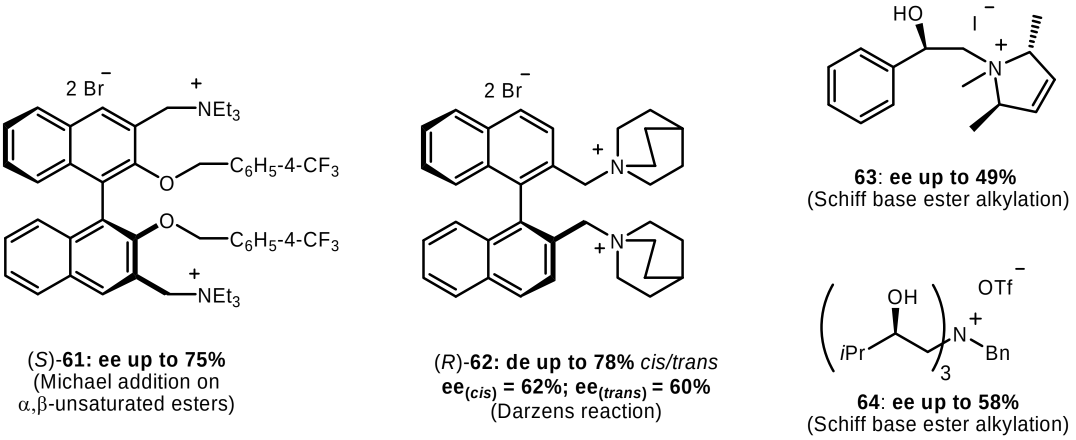
(*S*)-**59a** (Ar = Ph, R = H),
(*S*)-**59b** (Ar = R = 3,5-diphenyl-phenyl)
ee up to 96%
(epoxydation of chalcone)
ee up to 97%
(Michael addition of malonates on chalcones)



60: **ee up to 83%**
(Schiff base ester alkylation)

Figure III-6: Purely synthetic cyclic ammonium catalysts

Finally, geometrically related yet structurally different dicationic bisammonium catalysts based on a binaphthyl core were also reported recently (**61** and **62**, Figure III-7).[36,37] Pyrolinium salt **63** and C_3-symmetrical ammonium **64** made from enantiopure epoxides precursors were also described. All these moieties displaying moderate to decent levels of selectivity (*vide infra*).[38]



(S)-61: ee up to 75%
(Michael addition on α,β-unsaturated esters)

(R)-62: de up to 78% *cis/trans*
ee$_{(cis)}$ = 62%; ee$_{(trans)}$ = 60%
(Darzens reaction)

63: **ee up to 49%**
(Schiff base ester alkylation)

64: **ee up to 58%**
(Schiff base ester alkylation)

Figure III-7: Purely synthetic acyclic ammonium catalysts

III-2.4 Readily recyclable ammonium catalysts

Further work on polymer supported phase transfer ammonium catalysts have recently appeared;[39] these catalysts presenting several advantages over homogeneous ones such as simplified work-up for product purification, easy recovery of the catalyst for potential recycling, good stability and reduced toxicity. As before, the novel catalysts are *cinchona*-based. Several positions for the anchoring of the polymers were tested (see Figure III-8) as well as different spacers (size, length) and polymer supports (Merrifield, PEG or SynPhase lantern).

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[36] Arai, S.; Tokumaru, K.; Aoyama, T. *Chem. Pharm. Bull.* **2004**, *52*, 646

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[39] Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Mol. Diversity* **2005**, *9*, 277

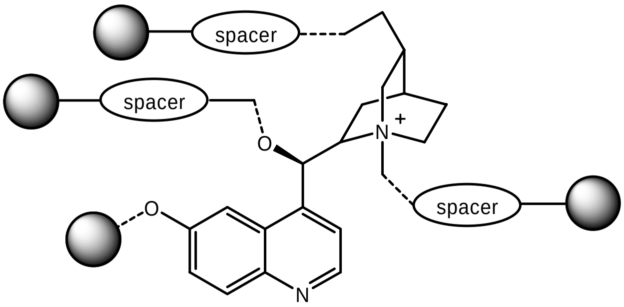
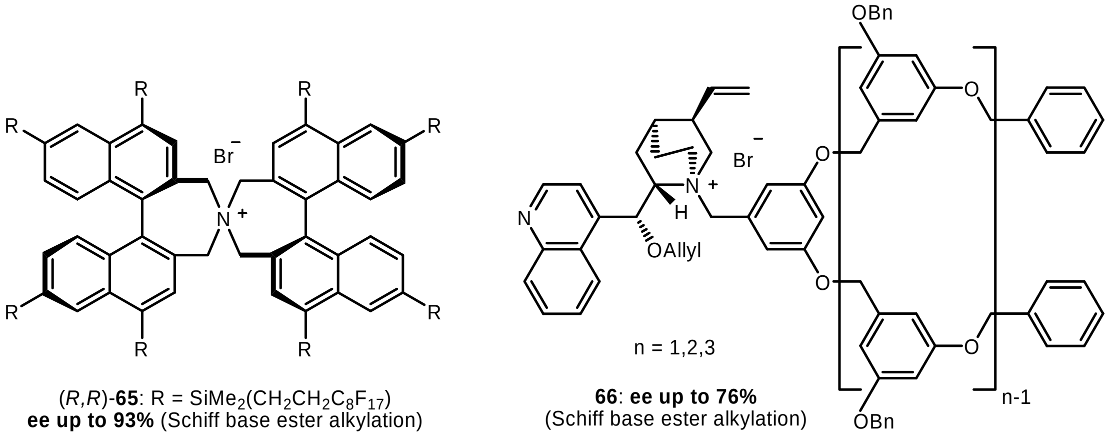


Figure III-8: various anchoring possibilities for polymer supported *cinchona* based ammonium catalysts

Other recyclable catalysts have been reported in the literature such as fluorous-phase compatible D_2-symmetric ammonium salt **65** (Figure III-9) and dendritic cinchona-based salt **66** (Fréchet type wedges up to generation three); applications of these catalysts being described later in the article.[40,41]



(R,R)-**65**: R = $SiMe_2(CH_2CH_2C_8F_{17})$
ee up to 93% (Schiff base ester alkylation)

66: **ee up to 76%**
(Schiff base ester alkylation)

Figure III-9: Recyclable ammonium catalysts

After this summary of the variety of the ammonium cations prepared for a use in enantioselective PTC, the reactions that were studied will now be detailed.

III-2.5 Reactions on Schiff Base Glycine 36

As described, phase transfer catalyzed alkylation of glycine ester derivatives is a powerful method for the preparation of natural and unnatural α-amino acids (Equation III-1). As such,

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[40] Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429

[41] Guillena, G.; Kreiter, R.; Van de Coevering, R.; Klein Gebbink, R. J. M.; Van Koten, G.; Mazon, P.; Chinchilla, R.; Najera, C. *Tetrahedron: Asymmetry* **2003**, *14*, 3705

most reported studies have used this process as an "acid test" to measure and compare the efficiency of their enantioselective catalyst system. The most used substrate in this reaction is the glycine Schiff base *tert*-butyl ester **36** that usually affords the best reactivity / selectivity profile – although some other substrates have been used (*vide infra*).[42] Typical conditions are those of reactions performed at 0 °C with 1 mol% of catalyst in a toluene / 50% aqueous KOH mixture as biphasic solvent medium; completion being reached within a few hours of reaction.

III-2.5.a Alkylation reactions with ammonium cations coming from the chiral pool

As mentioned, good level of enantioselectivity was reached prior to 2003 with ammonium cations of type **37**. Trying to provide the most complete view on substituent effects, a general screening of *cinchona*-based catalysts with various appendages linked to the nitrogen bridgehead atom and/or the hydroxyl group was performed using a parallel synthesizer and an on-line HPLC monitoring of both rate and enantiomeric excess.[43] Among the eighty eight catalysts tested, four of them displayed enantiomeric excesses above 90% with good reproducibility. With such a large data collection, a computational rationalization could then be attempted. Based on twelve structures, comparison of experimental and theoretical enantiomeric excesses was performed and showed good level of agreement using 3D-QSSR models. This provides a rationalization and a guide to synthetic efforts towards the elaboration of the most efficient catalysts of type **37**.[44]

Tartrate derivatives of type **51** are new to the period of 2003-2006. Concerning the alkylation reaction on **36**, the best catalyst in this series is compound **51a** that provides high level of enantioselectivity (up to 94% ee). As these compounds are advantageous in terms of catalyst accessibility (only five steps amenable to large-scale production using inexpensive reagents and simple operations) and versatility (tunable ketal substituents and aryl groups), a bright future can be envisioned for them.

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[42] O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; Lygo, B.; Allbutt, B. *Synlett.* **2004**, 326

[43] Lygo, B.; Andrews, B. I.; Hirst, J. D.; Melville, J. L.; Peterson, J. A.; Slack, D. *Chimica Oggi* **2004**, *22*, 8

[44] Melville, J. L.; Andrews, B. I.; Lygo, B.; Hirst, J. D. *Chem. Commun.* **2004**, 1410

III-2.5.b Alkylation reactions with purely synthetic ammonium cations

With purely synthetic ammonium catalysts that often require several steps for their making, care was taken recently to find conditions affording high reactivity and selectivity using truly minimal amounts of catalysts (<0.1 mol%). With compounds of type **38**, a screening of various aryl moieties at the 3,3'-positions revealed that the bis(3,4,5-F_3-Ph) derivative **38c** is one of the best catalyst for the alkylation of **36** since essentially enantiopure natural and unnatural α-amino acids can be afforded. Using anaerobic conditions, it was shown that the overall efficiency of **38c** remains when decreasing its loading to 0.2 mol% only. Further improvements could be enacted when the rather lipophilic nature of compounds of type **38** was acknowledged. It disfavors the first step of the catalytic process that is the interfacial deprotonation of the glycine Schiff base ester **36** by the aqueous base – the cationic ammonium counterion remaining in the organic layer rather than moving to the more polar interface or even aqueous layer. Maruoka and coworkers showed that the process can be accelerated using an achiral co-catalyst, 18-crown-6, which helps extract the inorganic base (usually KOH) to the interface or the organic layer. The catalyst and co-catalyst loadings can then be both decreased to 0.05 mol% without loss of yield and selectivity (3 hours reaction time).[45] Rather than adding a co-reagent, it is also possible to decrease the catalyst loading by increasing the polarity (decreasing the lipophilicity) of the ammonium cation. Using compound **56** and **57**, amounts as low as 0.01 mol% could be used and resulted in high yields and enantioselectivity.[31,32]

Further studies were performed with compounds of type **38**. One of them was an inquiry on the "multiplier effect of chiral auxiliaries" using polycationic derivative **60**. The length of alkyl chains linking the various ammonium binaphthyl units has a distinct influence on the enantioselectivity (up to 83%) and – more surprisingly – also on the absolute configuration of the alkylated product.

It was also shown that the presence of an *atropos* biaryl moiety is not mandatory for reaching high enantioselectivity in the alkylation of **36**; reactions in the presence of ammonium ions of type **58** proceeding in some instances with high enantiomeric excess. Compounds of type **58** combine a *tropos* biphenyl 7-membered ring and a stereogenic acyclic appendage; Lygo and coworkers showing that the most efficient catalyst is a combination of a stereogenic 1-

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[45] Shirakawa, S.; Yamamoto, K.; Kitamura, M.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 625

(naphthalen-1-yl)ethanamine appendage and two bis(3,5-trifluoromethyl)phenyl moieties at the 3,3’ positions of the biphenyl. A computational QSSR experiment was also performed on 40 different catalysts of type **58**. Again, good agreement between experimental and theoretical enantiomeric excesses was observed.[46]

III-2.5.c Alkylation reactions using recyclable ammonium catalysts or practical reaction conditions

Studies on the enantioselective alkylation reactions of **36** with recyclable ammonium catalysts were further performed in the recent years and promising results were obtained on various fronts. For instance, with non racemic polymer supported catalysts, enantiomeric excesses as high as 81% were reported using an organic-layer soluble non-cross linked PEG *N*-bound cinchonidinium salt.[47] An *O*-bound Merrifield polymer with an *N*-(9-anthracenylmethyl)cinchonidinium unit displayed very high selectivity (ee up to 96%) and recyclability (3x with almost no loss of activity). Further examples showing similar results in terms of selectivity and reactivity were also reported.[48]

Fluorous-phase compatible D_2-symmetric ammonium salt **65** was also used in the enantioselective alkylation reaction of **36**. The reactions were performed using standard biphasic conditions (toluene / 50% KOH aq.) and the catalyst was readily recovered by simple extraction in FC-72 as a fluorous solvent. Enantiomeric excesses up to 90% were obtained and the catalyst could be recycled three times with no loss of activity.

Dentritic molecules of type **66** were also used due to their easy recovery by means of ultra filtration, nanofiltration or size exclusion techniques. Under slightly modified conditions (toluene / $CHCl_3$ / 50% KOH aq., –20 °C), good yields and decent selectivity levels (up to 76%) were obtained. Reactions performed under “tea bag” dialysis membrane conditions required longer reaction times and a loss of selectivity was also noticed after each run (from 64 to 40% ee after the third run).

Recently, Jew, Park and coworkers showed that practical reaction conditions could be performed by changing the nature of the substrate rather than modifying the catalyst. Polymer

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[46] Melville, J. L.; Lovelock, K. R. J.; Wilson, C.; Allbutt, B.; Burke, E. K.; Lygo, B.; Hirst, J. D. *J. Chem. Inf. Comput. Model.* **2005**, *45*, 971

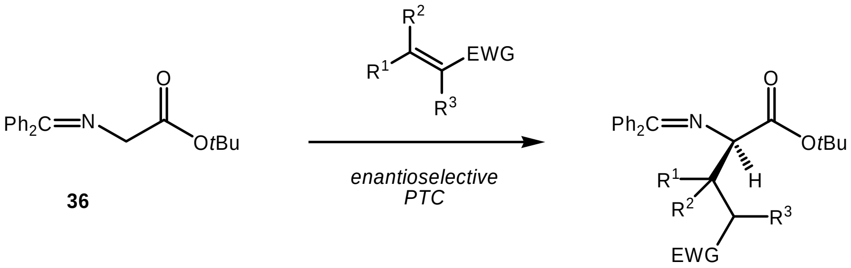
[47] Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2003**, *14*, 1671

[48] Chinchilla, R.; Mazon, P.; Najera, C. *Adv. Synth. Catal.* **2004**, *346*, 1186; Chinchilla, R.; Mazon, P.; Najera, C. *Molecules* **2004**, *9*, 349

supported glycine Schiff base substrates were used.[49] The anchoring of the substrate on Merrifield resins was performed through the imine moiety. The phase transfer alkylation reaction proceeded almost quantitatively with very good enantiomeric excess (up to 99%) using catalyst **37b**.[50]

III-2.5.d Conjugate addition reactions

In the above mentioned reactions, the electrophilic reagents used in combination with substrate **36** and the non racemic ammonium catalysts have been traditional alkyl halides as well as allylic and benzylic moieties. To extend the scope of this chemistry, other electrophiles were used and electron-deficient olefins in particular (Equation III-2, EWG: electron-withdrawing group).[51]



Equation III-2: Michael addition reaction of enolate of **36** to electron deficient olefins

For instance, using catalyst **58**, Lygo and coworkers were able to perform the conjugate addition of the enolate of **36** to various methyl vinyl ketones; the reaction proceeding with surprisingly modest selectivity (up to 60% ee). However, a simple modification of the substrate nature (use of a benzhydryl ester instead of a *tert*-butyl ester) afforded much higher selectivity (up to 94%) and, after a simple hydrogenation reaction (H_2, Pd/C), the synthesis of non-racemic 2,5-disubstituted pyrrolidines was readily achieved.[52]

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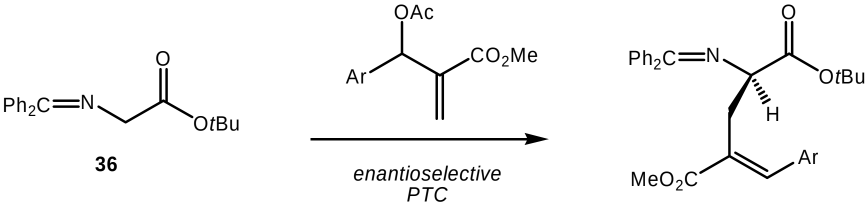
[49] Park, H.-G.; Kim, M.-J.; Park, M.-K.; Jung, H.-J.; Lee, J.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Ku, J.-M.; Jew, S.-s. *Tetrahedron Lett.* **2004**, *46*, 93

[50] Park, H.-g.; Kim, M.-J.; Park, M.-K.; Jung, H.-J.; Lee, J.; Choi, S.-h.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Ku, J.-M.; Jew, S.-s. *J. Org. Chem.* **2005**, *70*, 1904

[51] Chinchilla, R.; Mazon, P.; Najera, C.; Ortega, F. J.; Yus, M. *ARKIVOC (Gainesville, FL, United States)* **2005**, 222; Siebum, A. H. G.; Tsang, R. K. F.; van der Steen, R.; Raap, J.; Lugtenburg, J. *Eur. J. Org. Chem.* **2004**, 4391

[52] Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461

Michael addition reactions onto α,β-unsaturated esters were also realized and ammonium salts **51b** and **61** proved to be quite efficient catalysts for this process as enantiomeric excess of 82 and 75% were obtained respectively.[42, 59] Another interesting example was reported which concerns the tandem conjugate addition / elimination of activated allylic acetate aimed at synthesizing non-racemic derivatives of glutamic acid (Equation III-3). Enantiomeric excesses up to 97% were obtained using catalyst **37b**.[53]



Equation III-3: Tandem conjugate addition / elimination of enolate of **36** to allylic acetate

III-2.5.e Aldol and Mannich reactions

Enantioselective PTC is not limited to the alkylation or conjugate addition reactions of glycine esters of type **36** and any reaction proceeding through the formation of a prochiral anionic intermediate upon reaction with a base of the strength of hydroxide OH^- is amenable to it. In that context, asymmetric *aldol* reactions of glycine ester derivatives with aldehydes moieties were tested; these reactions affording a straightforward route to β-hydroxy-α-amino acids which are compounds of great importance in natural product and industrial chemistry (Equation III-4). Using the right combination of aldehydes and catalyst (**38e**), Maruoka and coworkers were able to obtain high diastereomeric excesses in favor of anti-*aldol* adducts (up to 92%); the major diastereomers being almost enantiopure (ee ~ 98%).[54]

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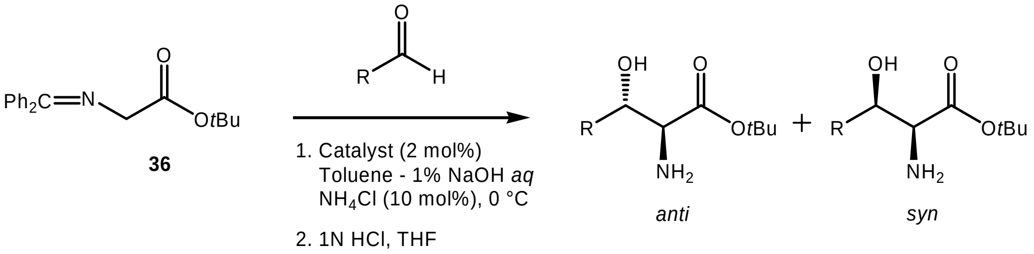
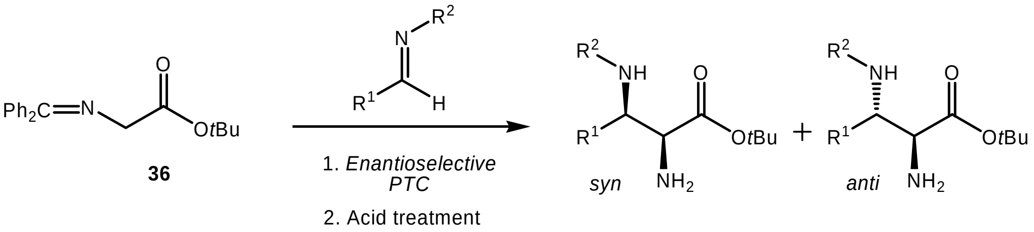
[53] Ramachandran, P. V.; Madhi, S.; Bland-Berry, L.; Reddy, M. V. R.; O'Donnell, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 13450

[54] Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685



Equation III-4: Asymmetric aldol reaction of enolate of **36** to aldehydes

Similarly, *Mannich* reactions of glycine ester **36** were performed under enantioselective PTC conditions with imine derivatives as electrophiles. α,β-Diamino acids were readily afforded (Equation III-5). Two different reports detail this chemistry.



Equation III-5: Asymmetric Mannich reaction of enolate of **36** to imines

In one instance, using imino esters as electrophiles (Equation III-5, $R^1 = CO_2Et$, $R^2 =$ PMP), it was possible to synthesize the nitrogen analogues of diethyl tartrates which are useful building blocks in modern asymmetric chemistry. Performing the reaction with 2.5 mol% of catalyst **38c** under optimized conditions (mesitylene / 17% NaOH *aq*., -20 °C, 6 h), the *syn* diastereomer was obtained as the major product with decent diastereomeric (de 64%) and high enantiomeric excesses (ee 91%).[55] In the second case, a solid-liquid PTC protocol was utilized with 10 mol% of catalyst **51c** and various aromatic imines (Equation III-5, $R^1 =$ Ar, $R^2 =$ Boc). The *syn* diastereomer was also obtained predominantly with, again, high levels of selectivity (de 90-99%, ee 58-82%).

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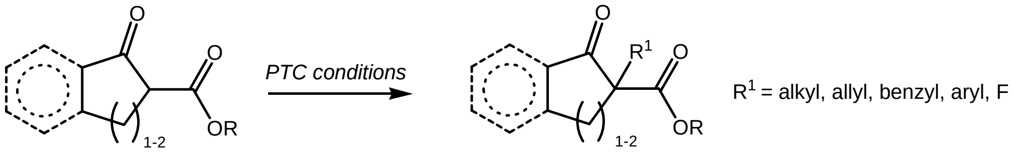
[55] Ooi, T.; Kameda, M.; Fujii, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397

III-2.6 Other enantioselective PTC using non racemic ammonium salts

III-2.6.a Reactions of β-keto esters

β-Keto esters are also ready candidates for phase-transfer catalyzed reactions due to the relatively high acidity of the α proton(s) (pKa ~11 in H_2O). Quite a few cyclic variants have been tested in enantioselective reactions; the moieties being aromatic or not, and often 5- or 6-membered rings (Equation III-6).



Equation III-6: Various Phase Transfer Catalyzed reactions on β-keto esters

For instance, using indanone ester derivatives and 1 mol% of catalyst **38d**, very good yields and enantioselectivity (up to 95%) were obtained in alkylation reactions. In the same report, it was shown that cyclopentanone and cyclohexanone esters were also capable to perform alkylation reactions and Michael additions onto α,β-unsaturated aldehydes and ketones with good yields and enantiomeric excesses.[56] Similar results were obtained with various *β*-keto esters using catalyst **42a** (ee up to 99%).[57] Interesting examples of fluorination (catalyst **42b**, e.e up to 69%), and S_NArylation (catalyst of type **37**, e.e up to 92%) of β-Keto ester have also been reported.[58] Cyclic α-amino-β-keto esters were also tested in enantioselective PTC to give access to azacyclo-α-amino acids (Equation III-7); catalyst **38d** being highly selective in that process.[59]

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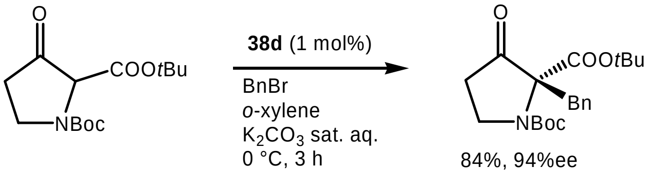
[56] Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796

[57] Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897

[58] Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545; Bella, M.; Kobbelgaard, S.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670

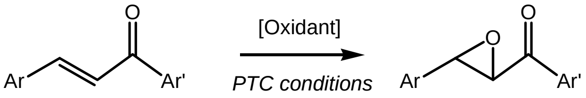
[59] Ooi, T.; Miki, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 191



Equation III-7: Benzylation of cyclic α-amino-β-keto ester catalyzed by **38d**

III-2.6.b Epoxidation reactions on chalcone derivatives

The epoxides of chalcone derivatives are frequently met structures in natural product chemistry.[60] Since the pioneering work of Wynberg who first performed enantioselective phase transfer epoxidation reactions of electron deficient olefins (Equation III-8),[61] a number of useful variants of this reaction have been elaborated.[62] For instance, Lygo (using sodium hypochlorite as oxidant) and Corey (using freshly prepared potassium hypochlorite) were able to perform the reaction with increased level of selectivity using ammonium salts of type **37** as catalysts.[63]



Equation III-8: Epoxidation in PTC conditions of chalcone derivatives

Since then, a variety of other oxidants have been used in biphasic or triphasic conditions such as hydrogen peroxide, alkyl hydroperoxide, combinations of urea and H_2O_2, sodium perborate or percarbonate, as well as trichloroisocyanuric acid.[64]

Recently, bifunctional ammonium catalysts **59a** and **59b** were used to improve further the enantioselectivity of the reactions; these cations being design to interact simultaneously with

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[60] Carde, L.; Davies, D. H.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2455; Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3501; Cappi, M. W.; Chen, W.-P.; Flood, R. W.; Liao, Y.-W.; Roberts, Y.-W. M.; Skidmore, J.; Smith, J. A.; Williamson, N. M. *Chem. Commun.* **1998**, 1159; Chen, W.-P.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1999**, 103

[61] Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, 1831

[62] Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215; Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94

[63] Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599; Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287

[64] Ye, J.; Wang, Y.; Liu, R.; Zhang, G.; Zhang, Q.; Chen, J.; Liang, X. *Chem. Commun.* **2003**, 2714; Ye, J.; Wang, Y.; Chen, J.; Liang, X. *Adv. Synth. Catal.* **2004**, *346*, 691

both nucleophile and electrophile using electrostatic and H-bonding interactions. A screening of several enones gave systematically excellent yields and enantioselectivity with sodium hypochlorite as the oxidant.

In many of these examples, it is necessary to perform the reactions at lower temperature and slower kinetics often results. To recover some of the reactivity, it is possible to add surfactants that increase the surface area between the separated phases by micellar formation.[65] For instance, catalytic amounts of TRITON X-100 or SPAN 200 are sufficient to promote such an effect and, in the presence of dimeric catalyst of type **45**, quantitative epoxidation of *trans*-chalcone was observed rapidly with quantitative yields and almost complete stereocontrol.

III-2.6.c Michael additions on enone derivatives

As only few reports have appeared on phase-transfer catalyzed enantioselective C-C bond forming reactions using chalcones as electrophiles,[66] a recent study tackled the issue using bifunctional catalysts of type **59**; the presence of the alcohol moiety of the ammonium ions being crucial to obtain high levels of selectivity. For instance, using **59b** and diethyl malonate as nucleophile, the products of addition onto a variety of chalcones could be isolated with high enantiomeric excesses (from 85 to 94% ee).[67] In an independent study, it was shown that cyclopentenones can also be used as electrophiles; addition of malonate esters in presence of catalysts of type **2** occurring with decent selectivity (up to 74%).[68]

With the aim of synthesizing non racemic γ-keto acids which are important intermediates for the preparation of peptide isosteres, the dimerization of α,β-enones under enantioselective PTC was recently reported using a Michael – double bond – transposition sequence (Equation III-9). With the right combination of enone structure (X = electron-donating group, R = bulky substituent) and catalyst (**37c**), good yields (>79%) and high level of selectivity (83 to 98% ee) were obtained.[69]

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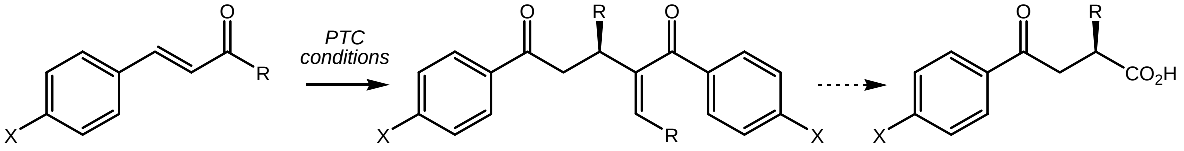
[65] Shaw, D. J. *Introduction to Colloid and Surface Chemistry*; Butterworth-Heinemann, 1992;

[66] Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351; Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *34*, 473; Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299

[67] Ooi, T.; Ohara, D.; Fukumoto, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 3195

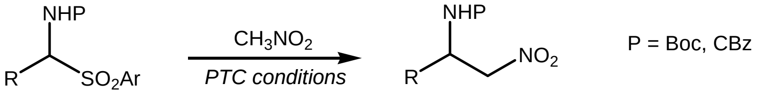
[68] Donnoli, M. I.; Scafato, P.; Nardiello, M.; Casarini, D.; Giorgio, E.; Rosini, C. *Tetrahedron* **2004**, *60*, 4975; Superchi, S.; Nardiello, M.; Donnoli, M. I.; Scafato, P.; Menicagli, R.; Rosini, C. *C. R. Chim.* **2005**, *8*, 867



Equation III-9: Michael – double bond – transposition reaction on α,β-enones under PTC conditions with X = electron-donating group and R = bulky subsituent)

III-2.6.d Other reactions

Enantioselective variants of the aza-Henry (or nitro-Mannich) reaction have also been developed under PTC in the presence of non racemic ammonium salts. Palomo, Bernardi and coworkers have shown independently that the reaction proceeds nicely in the presence of catalysts of type **37**; additions of nitromethane onto enolisable α-amido sulfones being slightly more efficient than those of non-enolisable derivatives (Equation III-10, ee up to 98%).[70]



Equation III-10: Nitro-Mannich reaction onto α-amido sulfones in PTC conditions

Nitroalkanes were also used as nucleophiles in combination with alkylidenemalonates; catalyst **38f** favoring the formation of the *anti* diastereomer with sometimes high selectivity (de up to 90%, ee up to 99%, Scheme III-1, pathway a).[71] With cyclic α,β-unsaturated ketones as electrophiles, catalyst **38e** was more effective in favor of the *syn* diastereomers (de up to 96%, ee up to 92%, Scheme III-1, pathway b).[72]

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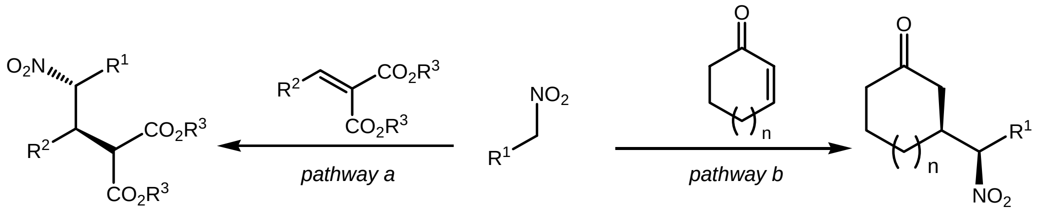
[69] Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3397

[70] Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975; Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622

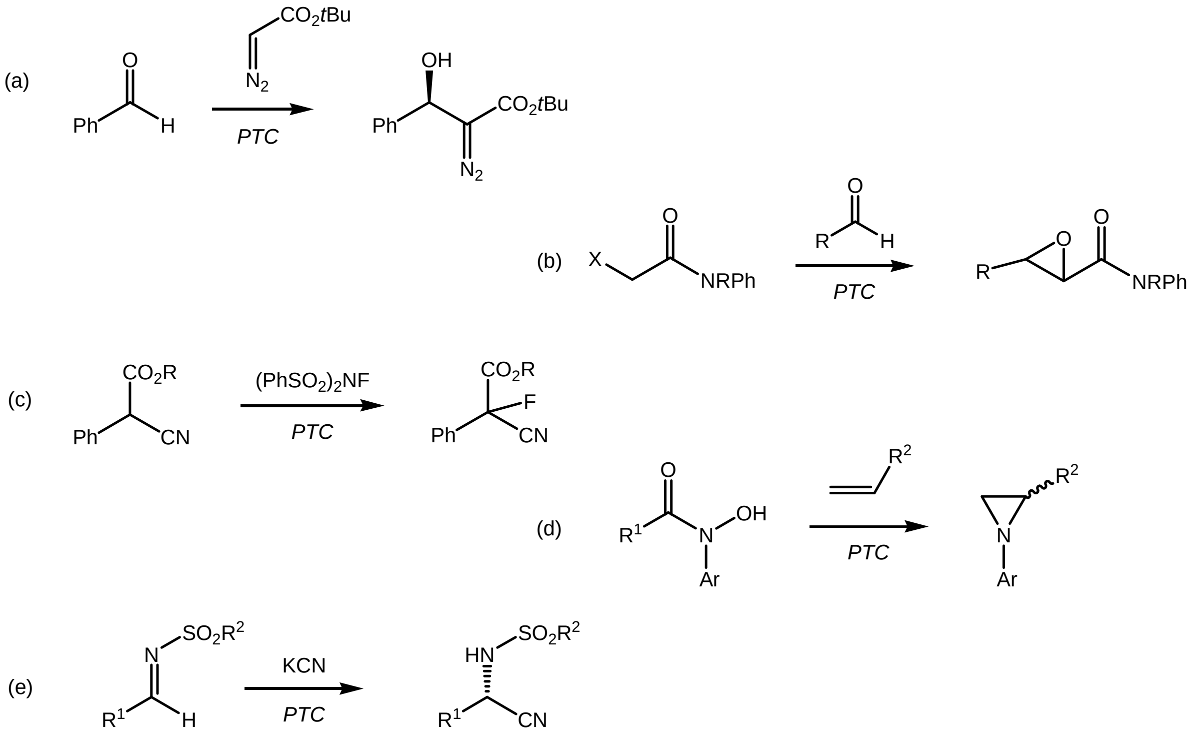
[71] Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790

[72] Ooi, T.; Takada, S.; Fujioka, S.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5143



Scheme III-1: Michael addition of nitroalkanes onto acylic (pathway a) or cyclic (pathway b) enones

Promising results were also obtained in the addition of *tert*-butyl diazoacetate to aromatic aldehydes for the one-pot synthesis of α-diazo-β-hydroxyesters; catalyst of type **37** being studied in the context of this reaction (Scheme III-2, reaction (a), ee up to 79%).[73] Darzens reaction of α-chloro amides in the presence of catalyst **62** gave glycidic acid derivatives (Scheme III-2, reaction (b), ee up to 70%).



Scheme III-2: Various reactions using PTC conditions reported in the literature

In another report, the fluorination of α-cyano esters in the presence of *N*-fluorobenzenesulfonimide and substoichiometric amounts of **42b** was studied (Scheme III-2,

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[73] Arai, S.; Hasegawa, K.; Nishida, A. *Tetrahedron Lett.* **2004**, *45*, 1023

reaction (c), ee up to 76%). Two unprecedented reactions were also successfully performed under enantioselective PTC that are:

(i) an aziridination reaction in the presence of catalyst **44**, and (ii) a Strecker reaction in the presence of ammonium **55**; both reactions proceeding with high levels of stereoinduction (Scheme III-2, reaction (d), ee up to 95% and reaction (e), up to 98%).

III-3 Synthesis and resolution of “naked” bis-ammonium salts for PTC

As mentioned above, despite the fact that compounds of type **38** have proven to be very efficient ammonium catalysts for asymmetric phase transfer reactions, their long and laborious synthesis can be a major obstacle for their application in industrial scales. We thought that by simplifying considerably the structure of these catalysts, we could readily access, in a few step synthesis and starting from cheap and achiral substrates, novel interesting compounds that could be applied for PTC processes. Taking into account that the dicationic catalysts of Jew, Park and Najera were particularly efficient catalysts, we decided to combine both approaches by incorporating in the design of the new ammoniums structures:

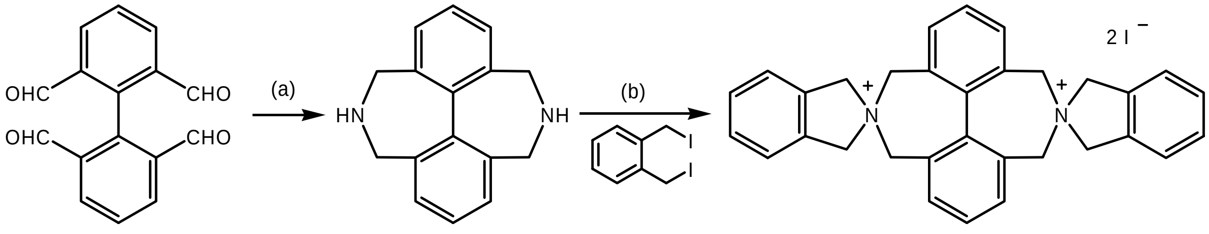
(i) axially chiral stereogenic elements

(ii) more than one positively charged ammonium centers

III-3.1 Bis-ammonium 67 as simple and straightforward catalyst

III-3.1.a Synthesis

With theses considerations, the structure of the DBBA moiety seemed to be an ideal core framework for the PTC study. As a first approach, compound **67**, which is a C_2-symmetric bis-spiro bis-ammonium salt combining two external five-membered rings with two internal seven-membered rings was synthesized. This compound is chiral due to the non-coplanarity of the central biphenyl moiety and exists as two enantiomers with *R*a and *S*a configurations. In view of the results obtained in chapter I on neutral DBBA derivatives, a relatively high barrier to interconversion was expected between the atropiosmers. In terms of synthesis, **67** was easily prepared in three steps from pyrene (Figure III-10). As showed in chapter I, ozonolysis of pyrene afforded biphenyl-2,2’,6,6’-tetracarboxaldehyde, which was directly transformed in compound **68** by reductive amination in presence of an excess of ammonium acetate (20 eq.) and sodium cyanoborohydride (2.8 eq.) with a good yield (88%, step (a)). Bis-alkylation of the latter compound in presence of bis(iodomethyl)benzene and potassium carbonate as a base afforded the racemic [**67**][I]$_2$ salt with a very good yield (96%, step (b)).



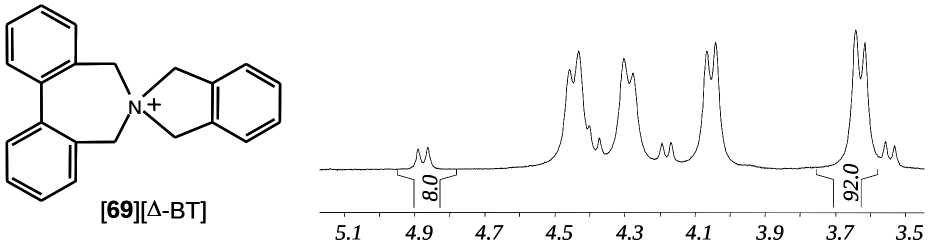
68

[67][I]$_2$

Figure III-10: Synthesis of ammonium salt [**67**][I]$_2$ from tetraldehyde **67**

III-3.1.b Resolution

In order to use compound **67** in asymmetric phase transfer catalysis we needed to resolve the racemic [**67**][I]$_2$ ammonium salt. As mentioned in the introduction TRISPHAT anion has proven to be a valuable NMR-solvating, resolving and asymmetry inducing agent in particular for cationic metallo-organic and organometallic substrates.[74] However C_2-symmetric BINPHAT (BT) is usually best suited for purely organic molecules as this anion display, in general, superior chiral solvating properties when associated with chiral ammoniums. Moreover better asymmetric inductions were observed onto structurally related *tropos* derivatives, and a de up to 84% in CD_2Cl_2 has been observed on the analogous monocationic salt [**69**][Δ-BT] (Figure III-11).



[69][Δ-BT]
d.e= 84% with Δ-BINPHAT
In CD_2Cl_2 at 233 K

Figure III-11: Asymmetric induction of BINPHAT anion onto configurationally labile ammonium

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[74] Lacour, J.; Frantz, R. *Org. Biomol. Chem.* **2005**, *3*, 15

This led us to envisage the use of BINPHAT anion for the resolution of bis-cation **67**. An ion exchange metathesis was thus performed by mixing a solution of [**67**][I]$_2$ in a 1:1 mixture of DCM/MeOH of this latter salt with a solution of [Me$_2$NH$_2$][Δ-BT] in acetone (Figure III-12). The desired salt was recovered after chromatography on basic alumina with 80% yield as the 1:1 mixture of two diastereomers; [(*S*a)-**67**][Δ-BT]$_2$ and [(*R*a)-**67**][Δ-BT]$_2$ eluted rapidly on the polar chromatographic phase, BINPHAT anion conferring to its salts an added lipophilicity.[75]

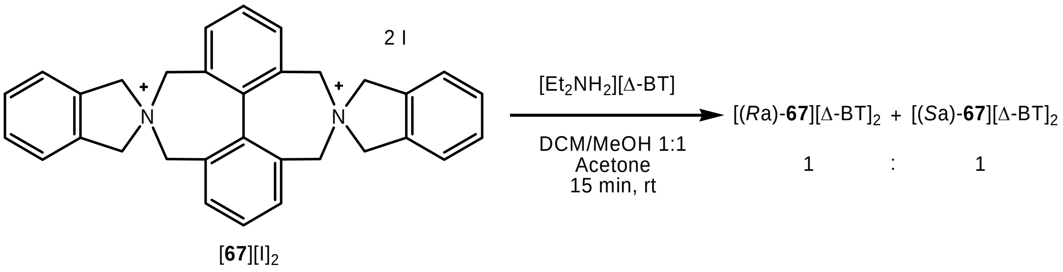

Figure III-12: Ion exchange metathesis of [**67**][I]$_2$ with [Me$_2$NH$_2$][Δ-BT]

Although these two diastereomers have different chromatographic properties ($r_f = 0.8$ and 0.6, basic alumina, DCM/MeOH 9:1), a clean separation appeared to be difficult. Another strategy was to consider their different solvatation properties: a solution of the 1:1 diastereomeric salts in a mixture of THF/Benzene was freezed to -20 °C for few hours and allowed to warm up to room temperature. The resulting solid at the bottom obtained was filtered and the mother liquors concentrated, both fractions were analyzed by ^{1}H NMR in a combination of solvents allowing a good separation of the signals of each diastereomer ($CDCl_3$ / 25% CD_3CN). As shown on Figure III-13, a diastereomerically pure salt was obtained in the "precipitate" in 48% yield; the other diastereomer being present with a 96% de in the other fraction (47% yield).

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[75] Lacour, J.; Torche-Haldimann, S.; Jodry, J. J. *Chem. Comm.* **1998**, 1733; Lacour, J.; Barchechath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567

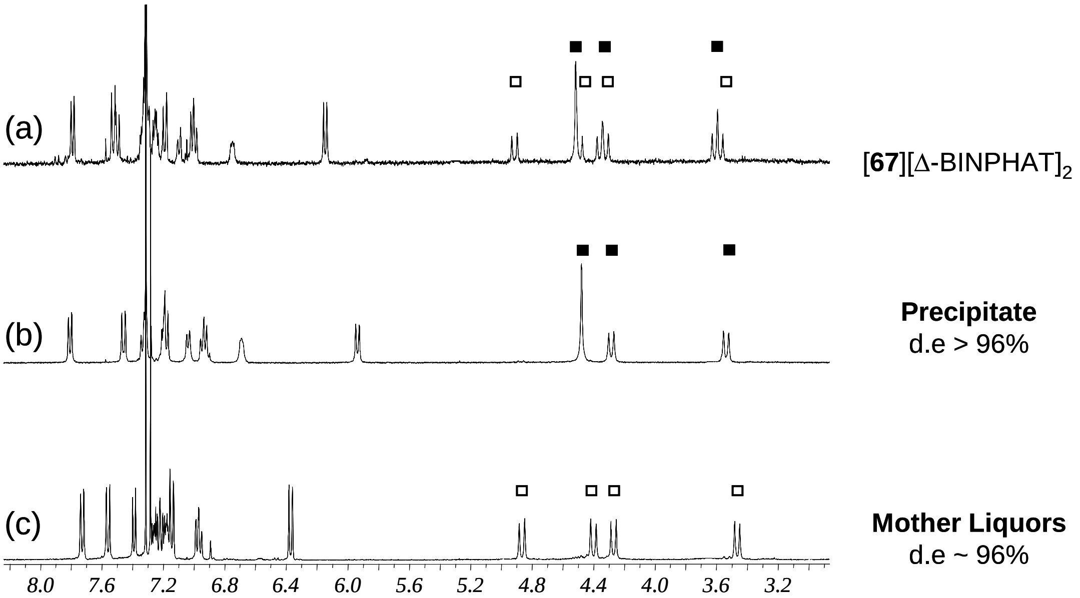

Figure III-13: NMR (400 MHz, $CDCl_3$ / 25% CD_3CN) of [**67**][Δ-BT]$_2$ with (a): 1:1 mixture of the two diastereomers; (b): precipitate (■), de> 96%; (c): mother liquors (□), d.e ~ 96%

In order to (i) complete the resolution and (ii) be able to determine the absolute configuration of the resolved ammonium, the chiral anions was exchanged by CD silent anions such as PF_6. Indeed, when BINPHAT are present, there is a strong overlap in the Circular Dichroism spectrum between the Cotton effect of the cation and those of the anions at 240-260 nm which renders any extrapolation impossible. This ion exchange can be easily achieved for BINPHAT anion due to its high sensitivity for Brönsted acids. By addition of an excess of an aqueous solution of HPF_6 to a solution of [**67**][Δ-BT]$_2$ in dichloromethane, the desired [**67**][PF_6]$_2$ salts precipitated exclusively after addition of Et_2O, and this, with no loss of enantiopurity of the cation.[76] Dextrorotatory and levorotatory samples were obtained from the precipitate and mother liquor respectively. CD analysis of the enantiomers was then performed. As shown in Figure III-14, a positive Cotton effect at around 250 nm was obtained for the (+)- enantiomer coming from the precipitate which corresponds, according to Mislow and Sandstrom, to a M (or *R*a) configuration for the biphenyl moeity.[77] On the other hand a negative cotton effect is observed for its (–)-enantiomer coming from the mother liquor to which a *P* (or *S*a) configuration can be attributed. Thus, a "heterochiral" association between

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[76] Determined by ^1H NMR after addition of [nBu_4N][Δ-BT] on the isolated (+)-[**67**][PF_6]$_2$ and (–)-[**67**][PF_6]$_2$

[77] Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc* **1962**, *84*, 1455; Sandstrom, J. *Chirality* **2000**, *12*, 162; Mislow, K.; Simon, E.; Glass, M. A. W.; Wahl, G. H.; Hopps, H. B. *J. Am. Chem. Soc* **1964**, *86*, 1710; Loncar-Tomascovic, L.; Sarac-Arneri, R.; Hergold-Brundic, A.; Nagl, A.; Mintas, M.; Sandstrom, J. *Helv. Chim. Acta* **2000**, *83*, 479

anions and cation is present in the precipitate, [*M*-**67**][Δ-BT]$_2$, whereas a “homochiral” association is present in the mother liquor, [*P*-**67**][Δ-BT]$_2$.

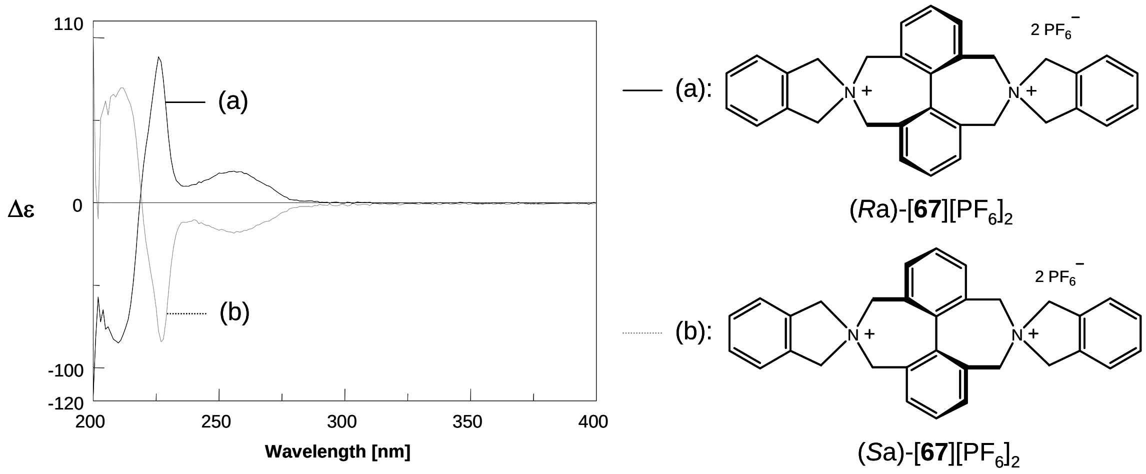
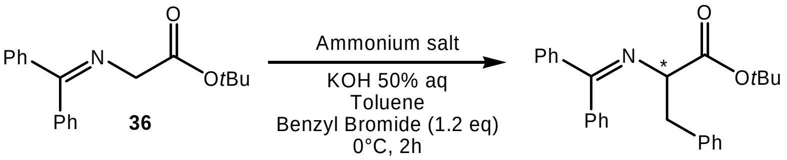


Figure III-14: CD spectrum ($c \sim 1.10^{-5}$M, MeOH) of (a) [(*R*a)-**67**][PF$_6$]$_2$ and (b) [(*S*a)-**67**][PF$_6$]$_2$

III-3.1.c Configurational stability

With the separated enantiomers in our hands, a determination of the configurational stability of bis-ammonium **67** was attempted. Racemization kinetics were performed experimentally by heating a solution of salt (+)-[**67**][PF$_6$]$_2$ at elevated temperatures (80, 90, 100, 110 °C) and taking aliquots samples at given times. The Δε values at 227 nm in the ECD spectra provided a measurement of the optical purity. By plotting the ee in function of time, kinetic constants were calculated at the four different temperatures allowing then a full determination of the activation parameters. A free Gibbs energy $\Delta G^{\neq}$ value of 28,5 kcal.mol^{-1} was obtained for **67** which corresponds to a half life of more than 6 years at 20 °C, thus demonstrating a very high configurational stability for the bis-ammonium DBBA ($\Delta H^{\neq} = 23.3$ kcal.mol^{-1} and $\Delta S^{\neq} = -17.7$ cal/(mol.K)).

III-3.1.d Test of ammonium **67** as a phase transfer catalyst



Equation III-11: Maruoka's conditions for the alkylation of glycine Schiff base ester **36**

As mentioned in this chapter, most reported studies have used the alkylation of glycine Schiff Base ester **36** as an "acid test" to measure and compare the efficiency of their catalyst systems. The alkylation of **36** with benzyl bromide as the electrophile was tested in presence of [(*R*a)-**67**][Δ-BT]$_2$ and [(*R*a)-**67**][PF$_6$]$_2$ under reported conditions: 5 mol% of catalyst in a toluene / 50% aqueous KOH mixture as biphasic solvent medium at 0 °C; the reaction was quenched after two hours and analyzed by HPLC (Equation III-11); the results are shown in Table III-1.

Catalyst	loading	Conv. %[b]	ee %[b]	Benzophenone %[c]
[(*R*a)-**67**][Δ-BT]$_2$	5 mol%	100	<5	12
[(*R*a)-**67**][PF$_6$]$_2$	5 mol%	100	<5	18

[a] Conditions : 5 mol % catalyst, 1.2 eq Benzyl bromide, Toluene/50% aq. KOH (3:2), 0 °C, 2 hours. Average of at least two runs. [b] Determined by CSP-HPLC (Chiralcel OD-H). [c] Benzophenone can be generated from decomposition of the starting material in presence of air in the medium.

Table III-1: Phase transfer alkylation of **36** with catalysts [(*R*a)-**67**][Δ-BT]$_2$ and [(*R*a)-**67**][PF$_6$]$_2$

In both cases, complete conversions were obtained within 2 hours (yet with a slight degradation of **36** into benzophenone), but, despite the fact that enantiopure catalysts were used, the reaction afforded racemic benzylated products. Ammonium salts of **67** were also tested on other phase transfer reactions described previously such as the fluorination of β-keto esters (Equation III-6) and the epoxidation of *trans*-chalcone (Equation III-8), all leading to good conversions but racemic materials. These rather disappointing results were rationalized by regarding the results of the "naked" ammonium **38a** (73% yield and 79% ee in 6h at 0 °C) to that of catalyst **38b** which possess the same structure with *β*-naphthyl substituents at 3,3' positions of the binaphthyl core (95% yield and ee = 96% in 30 min at 0 °C). To possibly make this project get off the ground of 0% ee, it was decided to modify the structural framework of the bis-ammonium structure by the introduction of functional groups at various positions that could then be replaced by bulky substituants.

III-3.2 Synthesis and study of seven membered rings spiro bis-ammonium 71

In the meantime, we were also interested in another C_2-symmetric bis-spiro bis-ammonium salt, this time combining four seven-membered rings linked by the two nitrogens; This compound being an extended version of a well-studied compound in the group which is the Spirobi[dibenzazepinium] cation **70** (Figure III-15).[78]

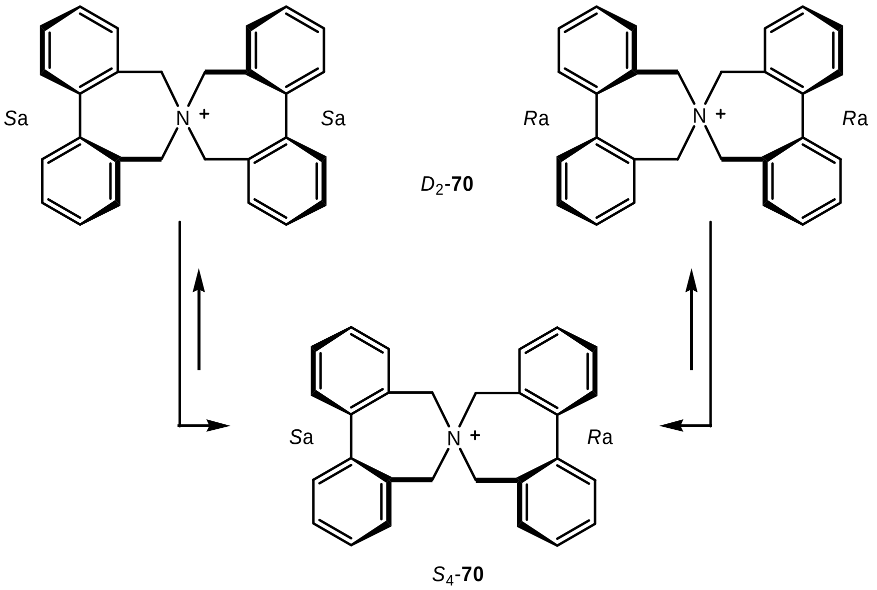


Figure III-15: Equilibrium between the D_2 and S_4 symmetries of cation **70**

Conformational analyses on **70** have revealed that the unique conformer present at 233 K in solution (CD_2Cl_2) is the chiral D_2-symmetric ammonium and the barrier of interconversion is only ~12.9 kcal.mol^{-1}. Upon association with BINPHAT anion, this ammonium have been used for an intramolecular asymmetric [1,2]-Stevens rearrangement with supramolecular transfer of chirality from the anion to the tertiary amine product (ee up to 11%).[79]

The synthesis of the dicationic **71** was thus attempted. Bis-alkylation of racemic **68** in presence of 2,2'-bis-bromomethyl-biphenyl and potassium carbonate as a base afforded the racemic [**71**][Br]$_2$ salt with excellent yield (98%, (a), Figure III-16).

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[78] Martínez-Viviente, E.; Pregosin, P. S.; Vial, L.; Herse, C.; Lacour, J. *Chem. Eur. J.* **2004**, *10*, 2912

[79] Vial, L.; Goncalves, M.-H.; Morgantini, P.-Y.; Weber, J.; Bernardinelli, G.; Lacour, J. *Synlett* **2004**, 1565

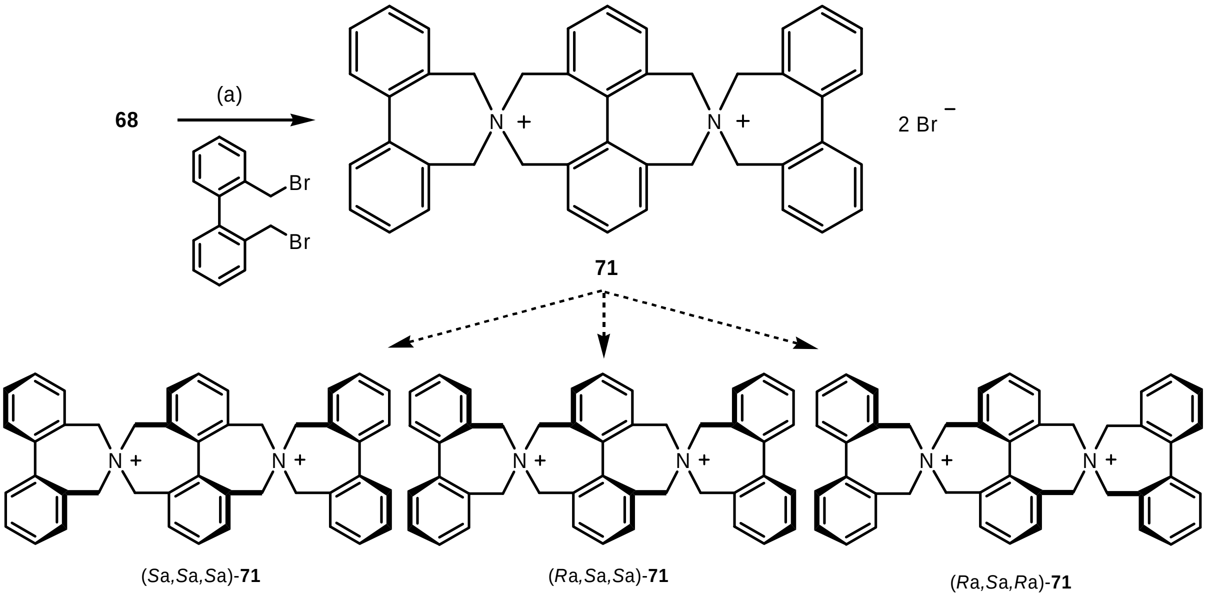

Figure III-16: Synthesis of ammonium [**71**][Br]$_2$ which can exist as three different diastereomers (their respective enantiomers are not shown here)

Formally, compound **71** can exist as three observable pairs of enantiomers, (six stereoisomeres) and would present a maximum of three diastereomers observable in ^{1}H NMR. Three of them are arbitrary drawn in Figure III-16, the other three isomers are their respective enantiomers. Interestingly, only one spot is observed in TLC ($r_f \sim 0.29$ in DCM/MeOH 9:1) indicating that, *a priori*, a single compound or a mixture of rapidly equilibrating derivatives are formed, the second hypothesis being in any case likely due to the probably low barrier of interconversion of the external seven-membered rings (*vide supra*).

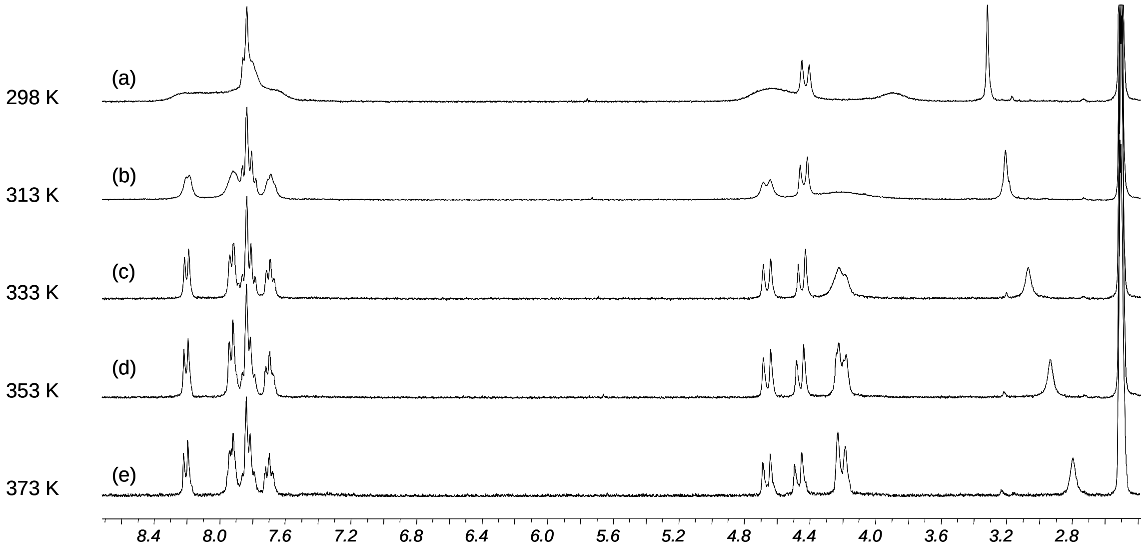

Figure III-17: ^{1}H VT NMR (400 MHz, DMSO-d_6) of [**71**][Br]$_2$ (298 – 373 K)

Room temperature ^{1}H NMR in DMSO-d_6 of [**71**][Br]$_2$ exhibited a broad resonnances for almost all the signals ((a), Figure III-17). At that stage, at least two hypotheses could be suggested: either the presence of stereodynamics with kinetics around the NMR time scale or a complex behavior of the cation in DMSO solution. To have a better insight, a VT NMR in DMSO-d_6 was first performed ((b-e), Figure III-17). Gradual heating of this compound up to 373 K led to only one well resolved set of signals which tends to favor the first hypothesis and prove that, at this temperature, kinetics of exchange are fast and an average spectrum is measured. In view of this analysis, the sharp doublet in spectrum (a) corresponds probably to the benzylic protons of the rigid core and the broaden signals to the protons of the *tropos* external rings. It was therefore interesting to perform low temperature VT-NMR experiments. As the melting point of DMSO is quite high (16 °C), CD_2Cl_2 was used as deuterated solvent. Unfortunatly, [**71**][Br]$_2$ was not enough soluble and an ion exchange metathesis with [Et_2NH_2][*rac*-TT] was thus performed to generate [**71**][*rac*-TT]$_2$ (26% yield); this salt was studied in ^{1}H VT NMR (Figure III-18).

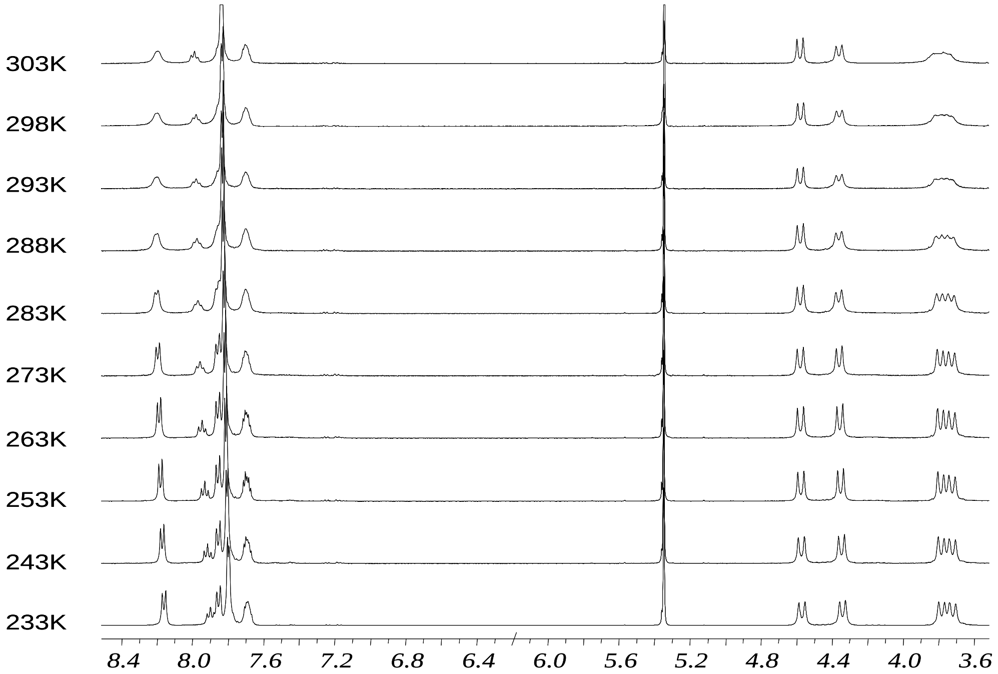

Figure III-18: ^{1}H VT NMR (400 MHz,CD_2Cl_2) of [**71**][*rac*-TT]$_2$ (233 – 303 K)

First, in CD_2Cl_2, broad resonances were again observed for some of the protons which may correspond to those of the external parts of the molecule. By cooling down the compound, better line shapes were observed for the overall spectrum, again with only one set of signal demonstrating that, *a priori*, only one diastereomeric pair is present at low temperature. Performing the same experiment in THF-d_8 as solvent led to a different behavior of the cation. Indeed, by lowering the temperature, at least two sets of signals appeared in the benzylic region (□, Figure III-19). The peak broadening from 253 K to 273 K and sharpening to two sets of four benzylic signals at lower temperatures (nearly a 10:1 ratio between signals marked with ■ and with □, Figure III-19) clearly indicates that there are different diastereomeric conformation for **71** in rapid equilibrium at elevated temperatures and "slow motion" on the NMR time scale at temperature inferior to 253 K. Furthermore, the different behavior between the DCM and THF experiments indicate that the conformational population is dependant upon the medium polarity and nature. In conclusion, at room temperature, compounds **71** exists as a mixture of rapidly exchanging conformers in solution; the population and the nature of them being impossible to determine. Obviously, the stereodynamics involves the two external seven-membered rings rather than the central rigid core.

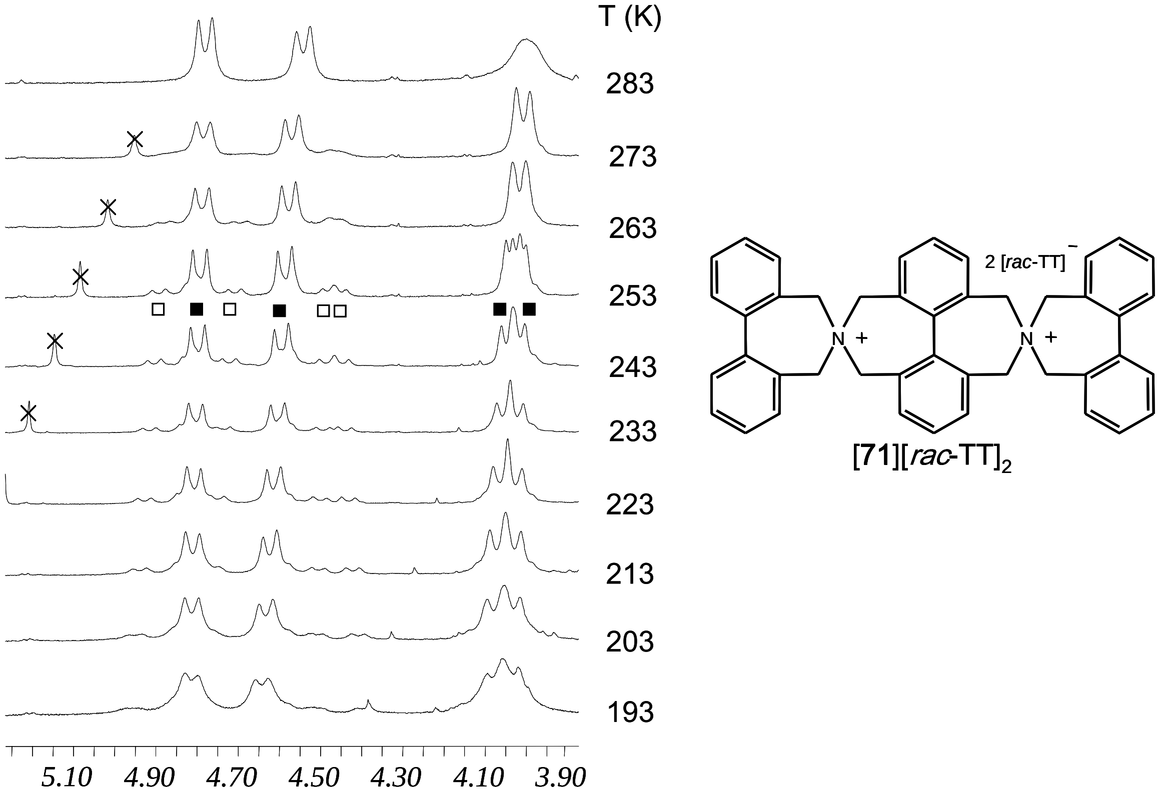

Figure III-19: ^{1}H VT NMR (298 – 193 K) of [**71**][*rac*-TT]$_2$ (left, 400 MHz,THF [d_8]) and [(*R*)-**59c**][Br] (right, 400 MHz, CD_2Cl_2)

Unfortunately it has also been impossible to resolve this ammonium **71** using chiral hexacoordinated TRISPHAT and BINPHAT anions, neither by chromatography (one spot is observed) nor by selective precipitation. This might be due to the presence of the interconverting diastereomeric species that disfavor the chiral recognition. Consequently, we have not been able to explore the asymmetric efficiency of this dication in the phase transfer benzylation described previously.

III-4 Design and synthesis of bulkier ammonium catalysts

As mentioned above, introduction of sterically hindered substituents on the bis-ammonium catalyst framework seemed to be crucial to attain decent levels of selectivities and in view of literature precedents, functionalizing the 3,3' positions of the biphenyl moieties seemed more logical. To do so, two possible strategies were conceivable when starting from the bis-ammonium **71** skeleton (Figure III-20):

(i) Introduction of aromatic groups in 3,3' positions of the two external biphenyl moieties or

(ii) Introduction of aromatic groups in 3,3' and 5,5' positions of the internal doubly bridged biphenyl moiety.

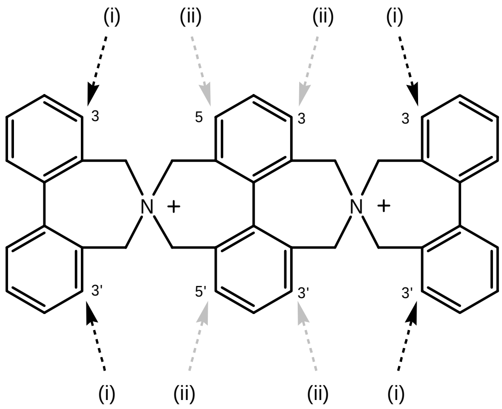

Figure III-20: Two possible strategies for the functionalisation around structural framework of **71**

III-4.1 Functionalization of 3,3' positions of the external biphenyl moieties

III-4.1.a Synthesis of the precursor

Concerning the introduction of aromatic groups in 3,3' positions of the external biphenyl moieties we thought about mimicking the structural framework of Lygo's ammonium catalyst **58**. In this compound, two 3,5-bis(trifluoromethyl)-phenyl groups are present in 3,3' positions of the biphenyl moiety, the chirality being brought by a chiral exocyclic appendage. The synthesis of the 2,2'-bis(bromomethyl)biphenyl **77**, precursor of the desired ammoniums, was succinctly reported in a first communications; the authors kindly provided further synthetic details allowing a clean and rapid synthesis of **77** in five steps from commercially available sources (Figure III-21).

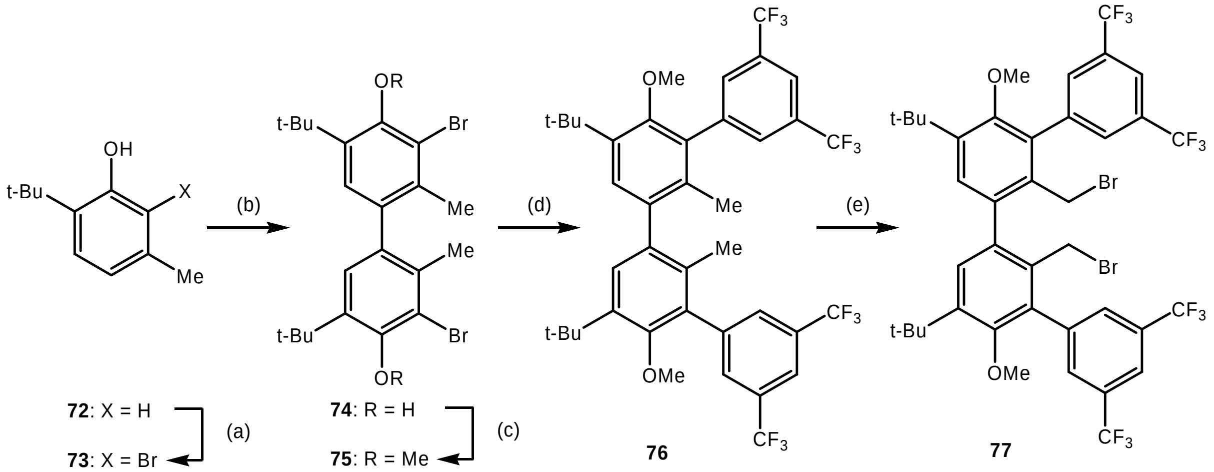

Figure III-21: Synthesis in four steps of compound **77** starting from 6-*tert*-butyl-*m*-cresol (**72**)

Selective mono-bromination in ortho position of the phenol of the 6-*tert*-butyl-*m*-cresol (**72**) was realized by slow addition of **72** on a solution of *tert*-butylamine and bromine at low temperature, which yielded bromophenol **73** in moderate yield (47%, (a), Figure III-21).[80] Oxidative coupling of the latter compound using Cu (I) chloride and TMEDA as catalyst (10 mol%) in open air for 3 days afforded biphenol **74** in 57% yield after purification by flash chromatography ((b), Figure III-21).[81] Bis-methylation of the latter compound was performed in DMF with iodomethane and potassium carbonate as a base, which gave compound **75** in 94% yield ((c), Figure III-21). A Suzuki cross-coupling between bis-arylbromide **75** and 3,5-

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[80] Jung, K.-y.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 5667

[81] Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-i. *J. Org. Chem.* **1999**, *64*, 2264

bis(trifluoromethyl)-phenyl boronic acid in presence of aqueous potassium carbonate (2M) and palladium tetrakis triphenylphosphine as catalyst (10 mol%) was performed at reflux of THF overnight to afford the desired product **76** in 74% yield after recrystallisation ((d), Figure III-21). Finally, bis-bromination of the methylene groups of **76** was performed in CCl_4 using NBS and a catalytic amount of AIBN (5 mol%) under light bulb irradiation which gave quantitatively the desired compound **77**.

III-4.1.b Study of sterically hindered *tropos* ammoniums

Before synthesizing the desired bis-ammonium catalysts, we wanted to study the influence of these two aromatic groups in the 3,3’ positions on the configurational stability of simple mono-cationic ammonium salts. Previous studies in the group have shown that the configurational stabilities of spiro-ammoniums of type **70** are slightly influenced by the skeleton (Figure III-22).[82]

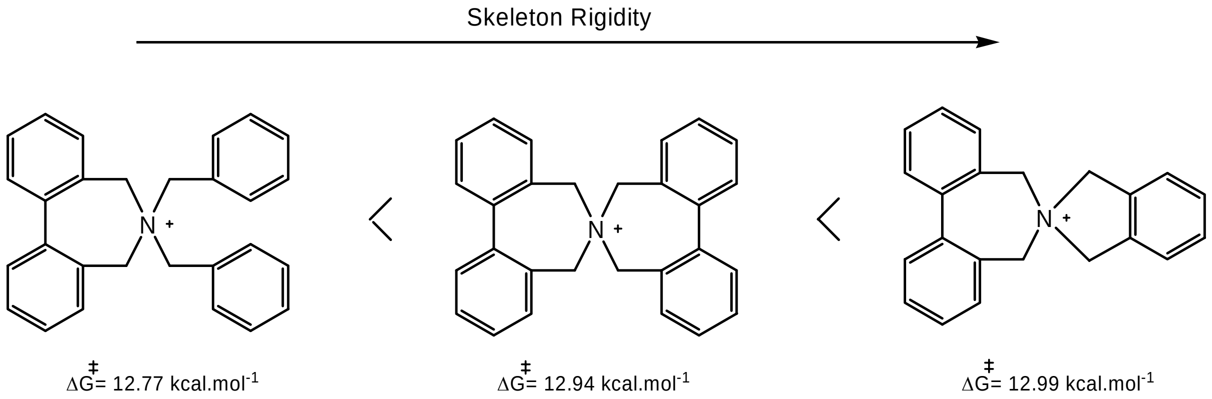

Figure III-22: Increasing or the configurational stability of some spiro ammonium with smaller ring sizes

Ammoniums **78**, **79** and **80** combining the dibromo derivative **77** with dibenzylamine, 6,7-Dihydro-5H-dibenz[c,e]azepine **1**, and isoindoline respectively were then prepared (Figure III-23). Reaction were performed in reflux of acetonitrile, overnight, in presence of potassium carbonate as a base, affording the desired ammoniums **78**, **79** and **80** as their bromides salts with 33%, 87% and 73% yield respectively.

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[82] Vial, L. (Group of Prof. J. Lacour) Thèse de l’Université de Genève n°3463, **2003**

Room temperature ^{1}H NMR spectroscopy revealed the existence of stereodynamics for the ammonium salt of **78** whereas for ammoniums **79** and **80**, the presence of diastereomeric signals indicated a slow rotation around the biphenyl core on the NMR time scale at 298 K (Figure III-24). ^{19}F NMR showed similar behavior as only one CF_3 group was apparent for **78** at 298 K whereas two well separated signals were observed for **79** and **80**, showing the magnetic non-equivalency of the two CF_3 groups present on the aromatic substituents in 3,3' positions of the biphenyl moiety. These observations are consistent with the fact that the rotation around the central C-C bond of **78** was faster than that of *spiro* analogous **79** and **80** due to the lack of the second ring acting as a steric constrains.

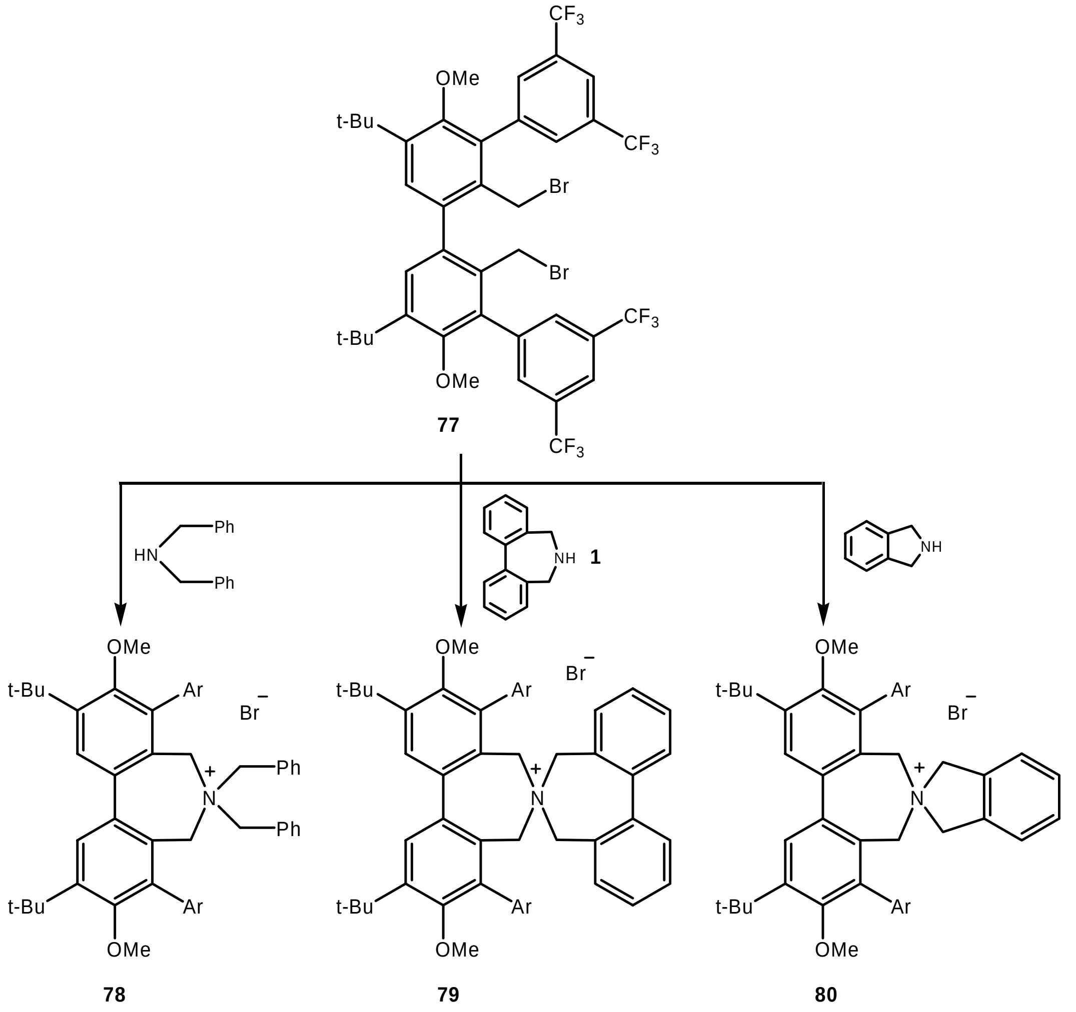


Figure III-23: Preparation of ammonium [**78**][Br]**,** [**79**][Br]and [**80**][Br] from **77** and the corresponding amine

Two motions for ammoniums **78**, **79** and **80** can be envisioned: (i) a rotation around the central bridged biphenyl axis ((a), Figure III-25), and (ii) a rotation of the bis-

(trifluoromethyl)-phenyl group around the C(sp^2) – C(sp^2) σ-bond ((b), Figure III-25). ^{1}H NMR spectra reveals that both motions are fast on the NMR time scale for **78** whereas they are both slow for **79** and **80**.

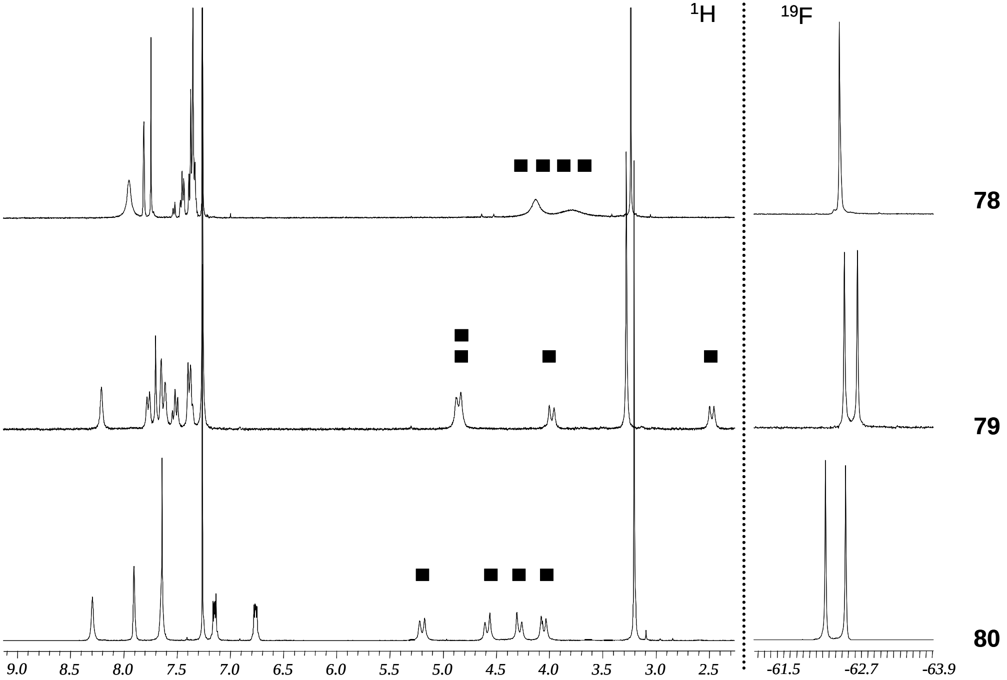


Figure III-24: ^{1}H and ^{19}F NMR of [**78**][Br]**,** [**79**][Br]and [**80**][Br] ($CDCl_3$, 298K, 500MHz) with ■ : benzylic CH_2 protons

Concerning **79**, the presence of a second bridged biphenyl group could lead to the formation of 4 diastereomers (*RR*, *SS*, *RS*, *SR*) existing as two pairs of enantiomers. Similarly to spirobi[dibenzazepinium] cation **70** at 233 K (Figure III-15) it seems that a unique conformer is present in solution for **79** at 298 K, as only one set of signals is observed. VT-NMR experiments, with both ^{1}H and ^{19}F probes were undergone. The separated CF_3 groups were particularly easy to monitor in ^{19}F NMR as well as the diastereotopic benzylic CH_2 protons in ^{1}H NMR. Compounds **78** was dissolved in CD_2Cl_2 and analyzed at low temperatures whereas **79** and **80** were dissolved in DMSO-d_6 and analyzed at elevated temperatures. Stereodynamics were detected when heating compound **79** and **80** as broadening of analogous NMR signals occurred. Activation parameters of the rotation barriers were determined by line-shape analysis (WinDNMR) of the broadened exchange signals that gave rate constants *k* at different temperatures. The experimental and calculated line shape is depicted in Figure

III-26, the activation parameters ($\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$) being calculated using the Arrhenius and Eyring equations. Concerning **78**, the $\Delta G^{\neq}$ value had been estimated using the relationship $\Delta G^{\neq} = RTc(22.96 + \ln(Tc/(\Delta\nu^2+J^2)^{1/2})$ with Tc ~ 273 K. The results are reported in Table III-2.

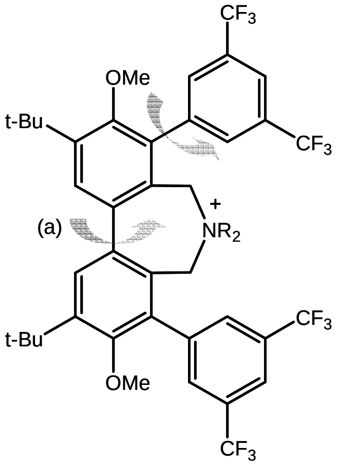


Figure III-25: Conformations of catalyst **78**, **79** and **80** as a combination of atropisomeric (a) and rotameric (b) geometries

A confirmation of the increasing rigidity of the ammonium skeleton when moving from **78** to **79** and –less significantly– from **79** to **80** can be noticed. Interestingly, quite similar values are obtained for both the rotameric appendage and the central atropoisomeric motions for each ammonium. Although it would seem that the motions are synchronous, meaning that the rotameric motion is somehow facilitated by the atropoisomeric movement. In practice, the large entropy of activation for some of the process renders this possibility unlikely. Therefore, it should be interesting to see whether the rotameric motion occurs on a configurationally rigid molecule, and if yes, if the energy barrier is higher than those reported for the configurationally labile ammoniums. This experiment will be detailed later in the manuscript.

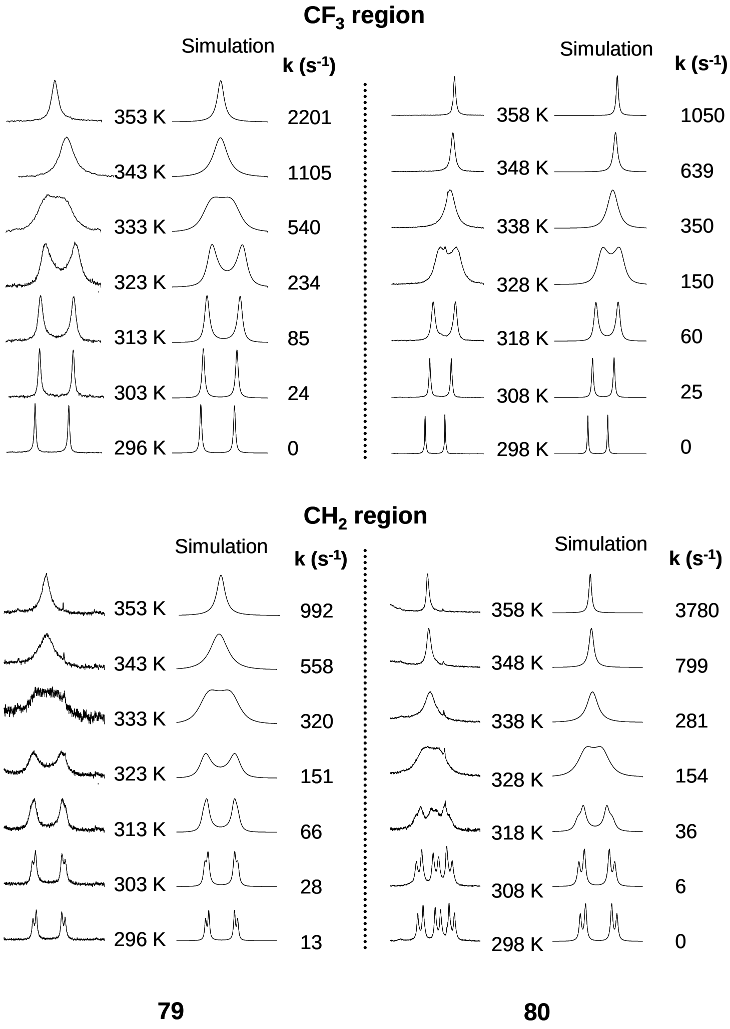


Figure III-26: Experimental (DMSO-d_6, 500 MHz, 296-358 K) and best-fit calculated ^{1}H NMR spectra of **79** (left) and **80** (right), (CF$_3$ region (up, – 60.5 - – 62.0 ppm) CH$_2$ region (down, 5.5 - 4.5 ppm))

Entry	Ammonium	Probe	$\Delta G^{\neq\,a}$	$\Delta S^{\neq\,a}$	$\Delta H^{\neq\,b}$
1	**78**	CF$_3$	13.6	[e]	[e]
2		CH$_2$	12.8	[e]	[e]
3	**79**	CF$_3$	15.9	12.3	19.6
4		CH$_2$	15.8	-2.1	15.2
5	**80**	CF$_3$	16.1	-1.0	15.8
6		CH$_2$	17.0	24.2	24.2

[a] In kJ.mol^{-1}. [b] In J.mol^{-1}.K^{-1}. [c] Activation parameters calculated by using line-shape analysis (WinDNMR) and $\Delta G^{\neq}$ reported for a 25 °C temperature. [d] $\Delta G^{\neq}$ estimated by using the relationship $\Delta G^{\neq} = RTc(22.96 + \ln(Tc/(\Delta\mu^2+J^2)^{1/2})$ with $Tc \sim 273$ K. [e] Not determined

Table III-2: Relevant data for the stereodynamics among ammonium **78**, **79** and **80**

III-4.1.c Study of a sterically hindered *atropos* ammonium

As mentioned above, DBBA **68** confers to the molecule a quite larger configurational stability than that of single bridged species. To evaluate the influence of aromatic groups in 3,3' positions of the two external biphenyl moieties on (i) the configurational stability of the DBBA derivative and (ii) in a case of successful resolution on the subsequent enantioselective PTC reaction, the synthesis of bis-ammonium **82** was envisioned. All attempts to make **68** react with dibromo **77** failed to produce the desired salt [**82**][Br]$_2$. For the preparation of this highly crowded molecule a more reactive bis-alkyl halide électrophile was needed. As iodide is a better nucleofuge than bromide, a Finkelstein reaction was performed on **77** with an excess of sodium iodide at reflux of acetone to afford **81** in good yield (81%). Reaction between this latter compound with half an equivalent of bisamine **68** at reflux of acetonitrile proceeded, in this case, smoothly to afford bisiodide salt [**82**][I]$_2$ with good yield (83%, Figure III-27).

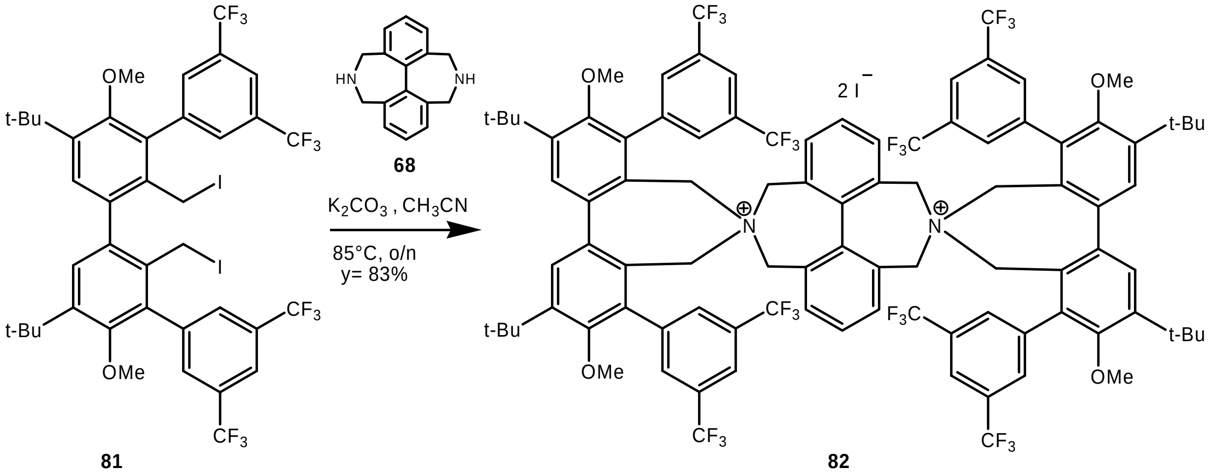


Figure III-27: Synthesis of [**82**][I]$_2$ from **81** and **68**

We were surprised to see that **82** presented the same behavior in ^{1}H NMR as **71** with broaden resonnances for the aromatic protons as well as for some of the benzylic hydrogens. As performed for **71**, high temperatures VT-NMR was performed for **82**, but in this case, as bis-trifluoromethyl-phenyl substituents were presents in the molecule, the stereodynamic could be followed in both ^{1}H and ^{19}F NMR. The results are shown in Figure III-28.

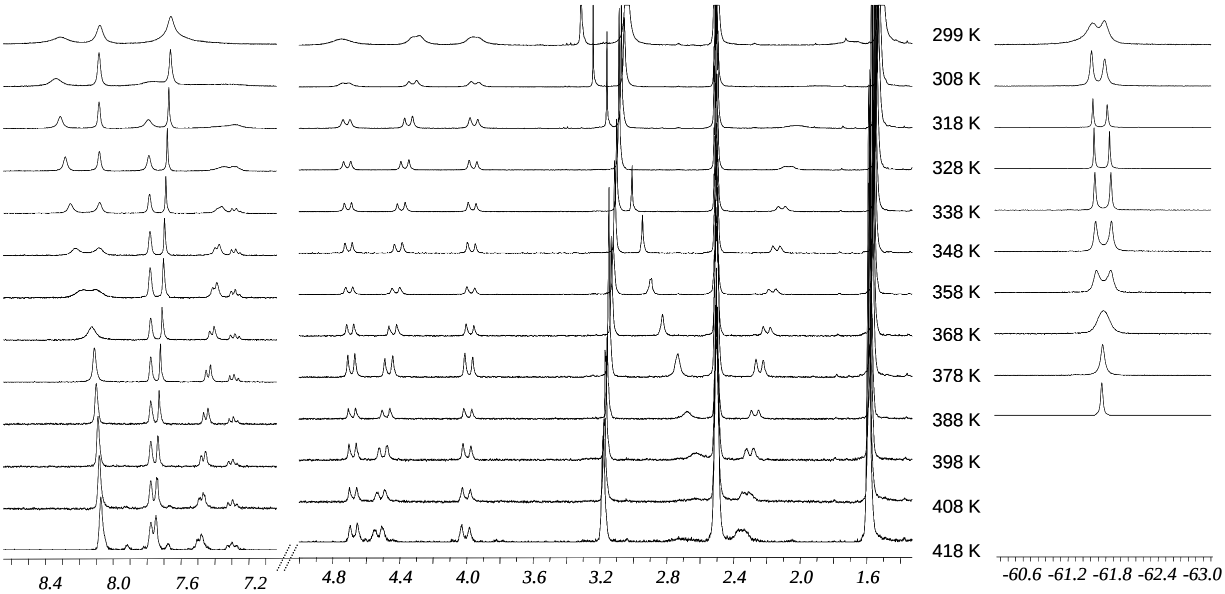


Figure III-28: VT ^{1}H (left) and ^{19}F (right) NMR (400 MHz, DMSO [d$_6$]) of [**82**][I]$_2$ (299 – 418 K)

Similarly to **71**, heating [**82**][I]$_2$ from 299-418 K led to only one well resolved set of signals for the benzylic diastereotopic protons in ^{1}H NMR. This tends to prove that the external rings are configurationally labile at elevated temperatures and an average spectrum is observed. Interestingly, three of the four doublets (two pairs of pseudo-axial protons and two pairs of pseudo-equatorial protons) are gathered in the same region of 4.0 – 5.0 ppm whereas the fourth doublet his abnormally shifted at low frequencies. Each doublet corresponds to four protons and these protons are then probably in the cone of anisotropy of the bis-trifluoromethyl-phenyl substituent. Moreover these protons seem highly affected by the temperature as heating the compound leads to a downfield shift. This can be rationalized by looking to the ^{19}F NMR spectra; a coalescence of the two peaks belonging to each CF$_3$ group is observed above 368 K. This means that rotation of the bis-trifluoromethyl-phenyl substituent is then faster than the NMR time scale, and, as such, the benzylic protons localized in the anisotropy cone are presumably less affected at higher temperatures. This motion can also be observed in the aromatic region (8.4 - 8.0 ppm), as the two non-magnetically equivalent ortho and ortho' protons of the bis-trifluoromethyl-phenyl substituents also coalesce above 368 K. For that motion, the rotational barrier can be estimated as previously by line-shape analysis (WinDNMR), similar values being obtained either by taking ^{19}F NMR spectrum or ^{1}H NMR spectrum in the aromatic region (Figure III-29). The data for activation parameters are reported in Table III-3.

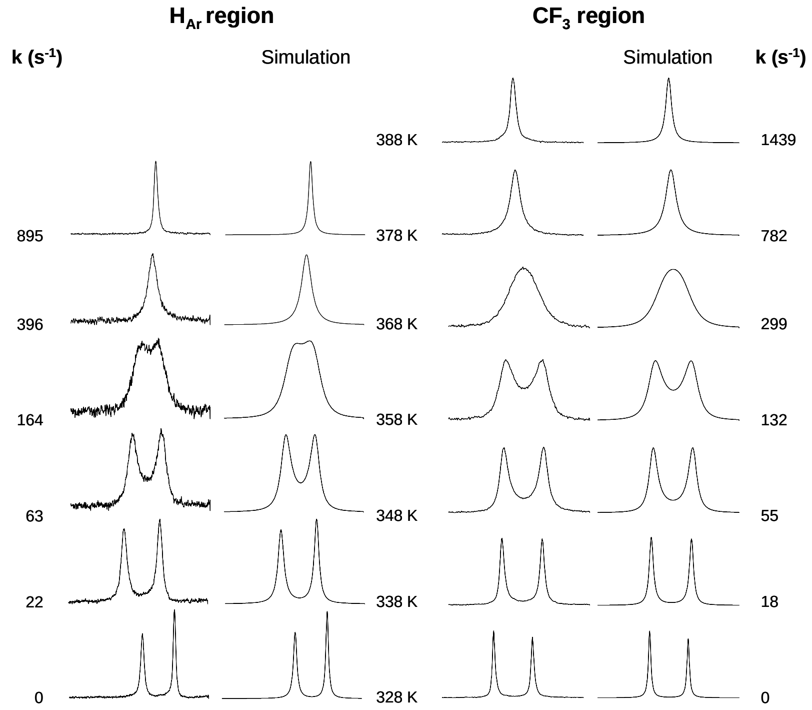


Figure III-29: Experimental (DMSO-d_6, 400 MHz, 328-388 K) and best-fit calculated ^{1}H NMR spectrum (left, 8.4 – 8.0 ppm) and ^{19}F NMR (right, – 61.2 - – 62.0 ppm) of [**82**][I]$_2$

Interestingly, the rotation barrier of the bis-trifluoromethyl-phenyl substituent in this configurationally rigid ammonium is 2.6 kcal.mol^{-1} higher than for the configurationally labile homologous ammoniums **79**. This suggests that the rotameric motion of the bis-trifluoromethyl-phenyl substituent is to some extent facilitated by the atropoisomeric motion of the external bridged biphenyl moiety.

Entry	Ammonium	Probe	$\Delta G^{\neq a}$	$\Delta S^{\neq a}$	$\Delta H^{\neq b}$
1	**82**	CF$_3$	18.5	12.9	22.3
2		H	18.5	15.2	23.0

[a] In kJ.mol^{-1}. [b] In J.mol^{-1}.K^{-1}. [c] Activation parameters calculated by using line-shape analysis (WinDNMR) and $\Delta G^{\neq}$ reported for a 25 °C temperature.

Table III-3: Relevant data for the stereodynamics among ammonium **82**

Unfortunately, as for ammonium **71**, it has been impossible also in this case to resolve this cation using chiral hexacoordinated TRISPHAT and BINPHAT anions, neither by chromatography (one spot is observed) nor by selective precipitation. This was particularly frustrating regarding the number of steps to achieve this catalyst.

III-4.2 Introduction of aromatic groups in 3,3’ and 5,5’ positions of the internal doubly bridged biphenyl moiety

III-4.2.a Preparation of the ammoniums

In chapter I was described the synthesis of 2,2’,6,6’-tetrakis(bromomethyl)biphenyl compound **9**. This molecule possesses the required aromatic substituents in 3,3’ and 5,5’ positions as well as the four bromomethyl moieties in 2,2’ and 6,6’ positions that could be easily functionalized by alkylation with secondary amines to form the desired quaternary ammoniums. Although it has been shown that simple phenyl groups were not the best discriminating groups on C_2-symmetric spiro ammoniums, it was interesting to test the efficiency of these newly synthesized ammoniums and to see whether the presence of these phenyl groups could bring some enantioselectivity in the PTC reactions. As these compounds require less synthetic steps than the Binaphthyl base ammonium of type **3** described by Maruoka, these catalysts, if efficient, could be potentially a good alternative. For that purpose, three different ammoniums, **83**, **83** and **85** were synthesized starting from the same precursor **9** (Figure III-30). Ammonium [**83**][Br]$_2$, product of bis-alkylation on **9** by two isoindoline molecules was obtained as a racemic mixture in moderate to good yield (56-77%). The reaction, using potassium carbonate as a base, could be either done at reflux of acetonitrile overnight, or using micro-wave apparatus at 160 °C for 30 min with similar yields. Concerning the synthesis of [**84**][Br]$_2$, the same procedure but with using 6,7-Dihydro-5H-dibenz[c,e]azepine **1** as the secondary amine led to similar yields. In the present case, an impurity generated during the synthesis was isolated and based on ^{1}H NMR and Mass spectroscopy, it seems that the impurity has a single ammonium function and twenty benzylic protons. The structure **86** fitting the spectra characterization best (Figure III-31).

Contrary to ammoniums **71** and **82**, only one set of sharp signals was observed in ^{1}H NMR for ammonium salt [**84**][Br]$_2$. In view of the results on mono-ammonium **79**, it probably indicates that the rotation around the C-C bound of simple biphenyl is fast on the NMR time scale.

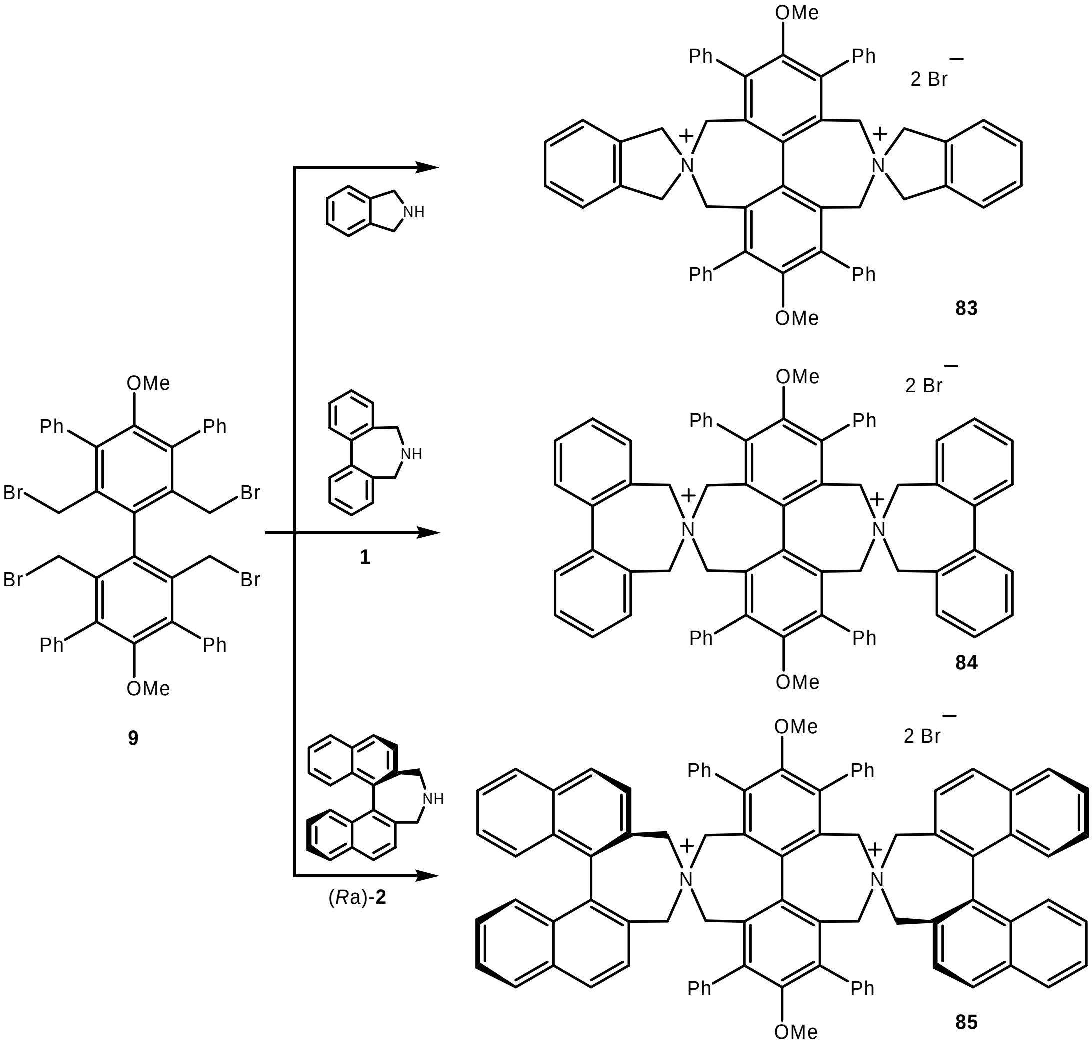


Figure III-30: Preparation of chiral ammoniums [**83**][Br]$_2$, [**84**][Br]$_2$ and [**85**][Br]$_2$ made from alkylation of **9** by isoindoline, amine **1** and amine (*R*a)-**2** respectively

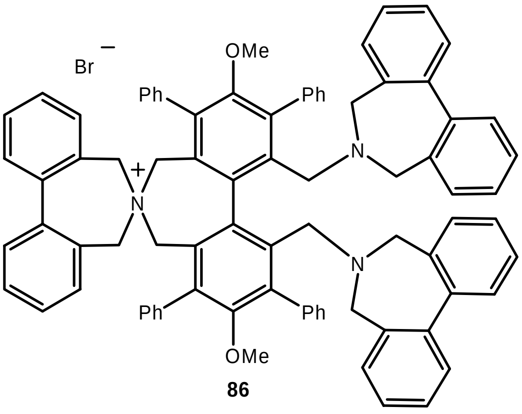


Figure III-31: Presumed impurity **86** generated during the synthesis of [**84**][Br]$_2$

However, to be useful for subsequent application, ammoniums **83** and **84** need to be resolved at the next stage, which means that at least, one half of the catalyst is “lost” at the final step. A parallel strategy was therefore looked for and the introduction of an enantiopure axially chiral *atropos* secondary amine was envisioned to generate, in the same manner as **84**, one diastereomer exclusively, but in this case directly as a single enantiomer. To do so, (*R*a)-4,5-dihydro-3H-naphtho[1,2,1,2-cde]azepine **2** was prepared from enantiopure and commercially available (*R*a)-BINOL, in five steps with 32% overall yield following reported procedures. Bis-alkylation of **9** with a slight excess (2.5 eq.) of (*R*a)-**2** was found to be more difficult as longer reaction times were needed and lower yields (31-43%) were obtained after purification. As expected, only one set of signal in ^{1}H NMR was obtained for compound [**85**][Br]$_2$ meaning that, *a priori* and similarly to compounds of type **71**, only one diastereomer was exclusively formed. In order to confirm this hypothesis, and demonstrate also that this unique diastereomer is enantiopure, ^{1}H NMR titration experiments using enantiopure [*n*Bu$_4$N][Δ-TT] were performed. Indeed, if a racemization of **2** had occurred during the reaction, then the two enantiomers of the diastereomerically pure ammonium **85** ought to be present and their respective ^{1}H HMR signals would be split in presence of Δ-TRISPHAT anion, indicating the final enantiomeric ratio. As it could be expected, no enantiodifferentiation appeared in ^{1}H HMR during this experiment, meaning that, only one enantiomer of **84** is formed. Further configurational analysis has to be performed in order to determine the exact nature of this optically pure stereoisomer.

III-4.2.b Resolution of ammoniums **83** and **84** with BINPHAT anion

Considering that Δ-BINPHAT had been an effective an effective resolving agent for **67**, racemic dications **83** and **84** were associated with it. Ion exchange metathesis were thus performed by adding a solution of [**83**][Br]$_2$ or [**84**][Br]$_2$ in MeOH onto solutions of [Me$_2$NH$_2$][Δ-BT] in MeOH. Due to their highly lipophilic nature, the desired salts instantaneously precipitated during the association and were recovered by filtration as a 1:1 mixture of two diastereomers: [(*S*a)-**83**][Δ-BT]$_2$ and [(*R*a)-**83**][Δ-BT]$_2$ in 66% yield for ammonium **83** ((a), Figure III-32) and [(*S*a)-**84**][Δ-BT]$_2$ and [(*R*a)-**84**][Δ-BT]$_2$ in 75% yield for ammonium **84** ((a), Figure III-33).

As mentioned previously, BINPHAT anion confers to its salts a poor affinity for low polar chromatographic phases and elute rapidly over silica gel/alumina.[75] Separation of the two diastereomers [(*S*a)-**83**][Δ-BT]$_2$ and [(*R*a)-**83**][Δ-BT]$_2$ appeared to be quite easy as very different eluting properties of these two diastereomers were observed on TLC plates of basic alumina. While the first eluted diastereomer was recovered with DCM as an eluent (r_f ~ 0.8 in DCM), (b), Figure III-32), the second one was still at the top of the column (r_f ~ 0.2 in DCM) and was further recovered with a 95:5 mixture of DCM/MeOH as eluent ((c), Figure III-32).

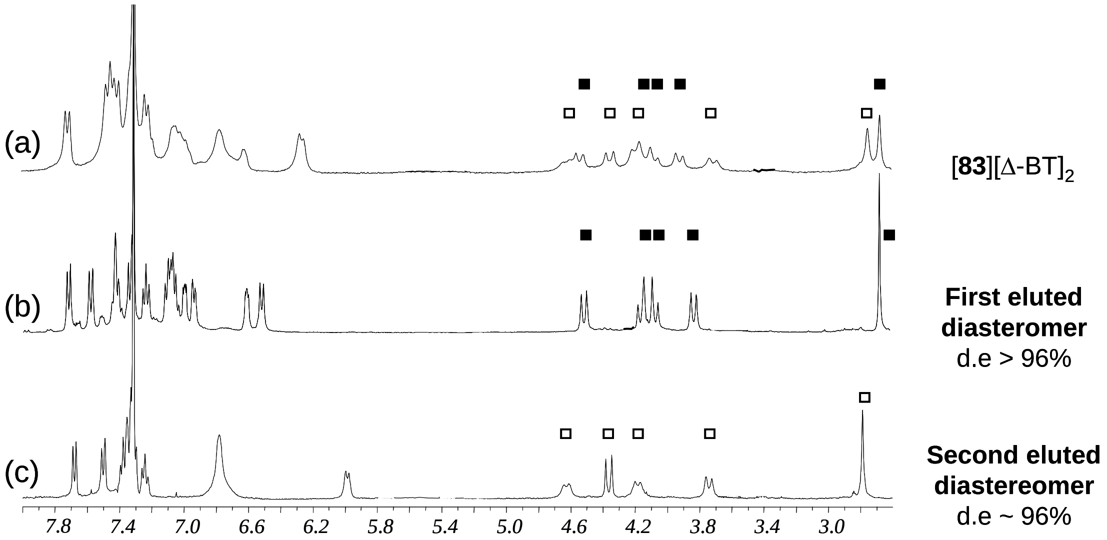


Figure III-32: NMR (400 MHz, CDCl$_3$/ 15% CD$_3$CN) of [**83**][Δ-BT]$_2$ with (a): 1:1 mixture of the two diastereomers; (b): first eluted diastereomer (■), d.e > 96%; (c): second eluted diastereomer (□),d.e ~ 96%

As shown on Figure III-32, the stereochemical purity of the salts was simply effected by ^{1}H NMR using the methoxy signals as probe (~ 2.8 ppm) as for the benzylic CH$_2$ protons, overlapping of the signals were observed.

Concerning the separation of the 1:1 mixture of the two diastereomers [(*S*a)-**84**][Δ-BT]$_2$ and [(*R*a)-**84**][Δ-BT]$_2$, the above protocol failed unfortunately (almost identical r_f on TLC). However, while performing a ^{1}H NMR analysis of the equimolar mixture of diastereomers in CDCl$_3$ / 15% CD$_3$CN, a precipitate appeared in the NMR tube. Further analysis showed that this precipitate was a single enantiopure diastereomeric ion pair ((b), Figure III-33), while the mother liquor contained the other diastereomer in a 92:8 diastereomeric ratio ((c), Figure III-33).

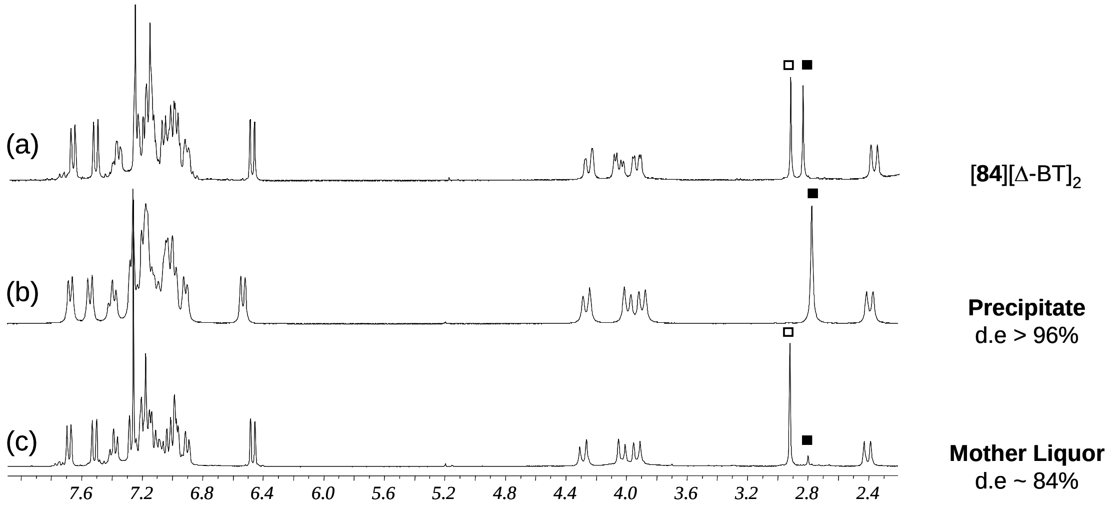


Figure III-33: NMR (400 MHz, $CDCl_3$ / 33% CD_3CN) of [**84**][Δ-BT]$_2$ with (a): 1:1 mixture of the two diastereomers; (b): first eluted diastereomer (■), d.e > 96%; (c): second eluted diastereomer (□),d.e ~ 84%

As usual and as shown on Figure III-33, the diastereomeric purity of the ammonium salts could be checked by ^{1}H NMR, the methoxy signals around 2.8 ppm serving again as probes.

III-4.2.c Configurational analysis

To determine the absolute configuration of the ammonium ion resolved, the chiral anions were removed and replaced by CD-silent PF_6. To do this, the method described for **67** was applied and afforded [**83**][PF_6]$_2$ and [**84**][PF_6]$_2$ almost quantitatively from the diastereomerically enriched fractions. Optical rotations were then performed and indicates for **83** that the PF_6 salts from first eluted (less polar) and second eluted (more polar) diastereomers are of (+) and (−) nature respectively, while for **84**, a levorotatory and dextrorotatory nature was determined for the sample from the precipitate and the mother liquor respectively.

CD spectra were then measured and intense Cotton effects were again observed for all the fractions. Salts (−)-[**83**][PF_6]$_2$ and (−)-[**84**][PF_6]$_2$ displayed negative Cotton effects around 250 nm; an opposite situation being of course observed for the dextrorotatory enantiomers (Figure III-34).

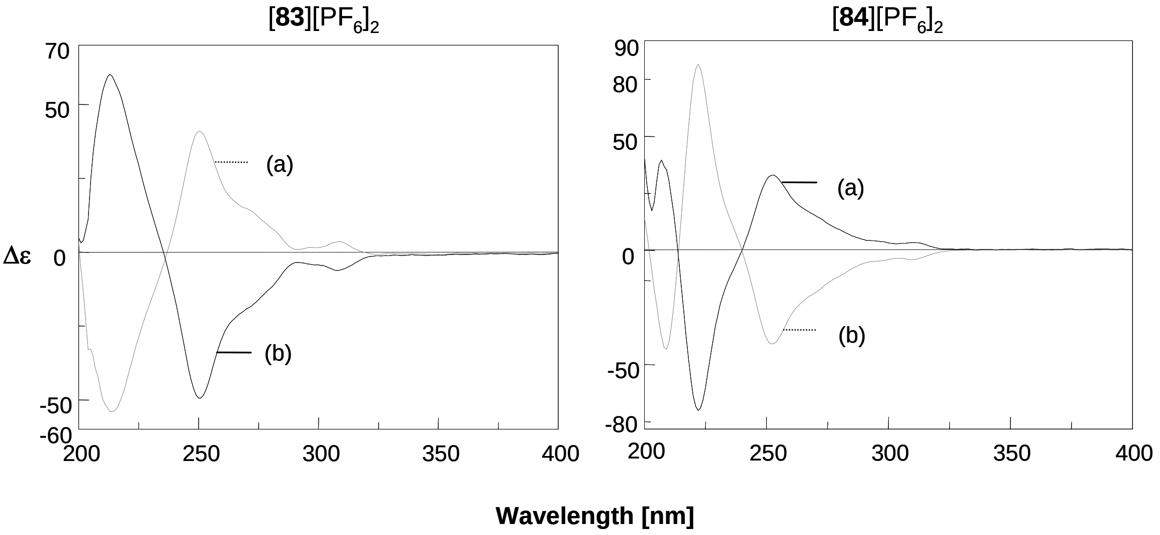


Figure III-34: CD spectrum ($c \sim 1.10^{-5}$ M, MeOH) with on the left:

(a) (+)-[(*R*a)-**83**][PF$_6$]$_2$ coming from the first eluted diastereomer of [**83**][Δ-BT]$_2$ (dashed)

(b) (−)-[(*S*a)-**83**][PF$_6$]$_2$ coming from the second eluted diastereomer of [**83**][Δ-BT]$_2$ (plain)

And CD spectrum ($c \sim 1.10^{-5}$ M, MeOH) with on the right:

(a) (+)-[(*R*a)-**84**][PF$_6$]$_2$ coming from the diastereomer in the mother liquors of [**84**][Δ-BT]$_2$ (dashed)

(b) (−)-[(*S*a)-**84**][PF$_6$]$_2$ coming from the precipitated diastereomer of [**84**][Δ-BT]$_2$ (plain)

By assuming that, again, a negative cotton effect at ~ 250 nm corresponds to a *P* helicity or a *S*a configuration for the doubly bridged biphenyl moiety (and the other way round) the following configuration of the salt are obtained: (+)-[(*R*a)-**83**][PF$_6$]$_2$, (−)-[(*S*a)-**83**][PF$_6$]$_2$ and (+)-[(*R*a)-**84**][PF$_6$]$_2$, (−)-[(*S*a)-**84**][PF$_6$]$_2$

As mentioned previously, in the case of ammonium [**85**][Br]$_2$ the two enantiopure (*R*a)-binaphthylazepines present in the molecule control during the synthesis the final configuration of the central doubly bridged biphenyl moiety in a complete stereoselective manner. Based on the chemistry of **70** favoring the D_2-symmetry conformers, one would assume that **85** would prefer a all-(*R*) or a all-(*S*) configuration. There is however no proof of it and caution has to be taken as Maruoka and coworkers have previously characterized astonishing reversal of conformational preference at low or high temperatures. The CD spectrum of [**85**][Br]$_2$ was measured (Figure III-35) but unfortunately, in view of the result, it is impossible to confirm or reject that hypothesis as a succession of positive and negative Cotton effect (or exciton coupling) is present between 200 and 350 nm. Attempts to determine the configuration by X-ray structural analysis are currently performed.

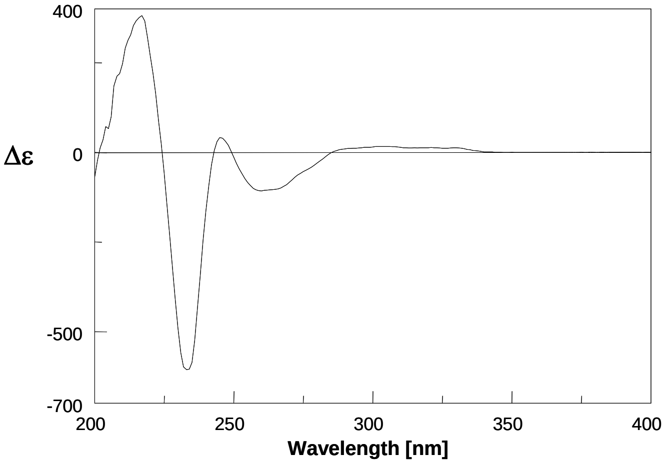
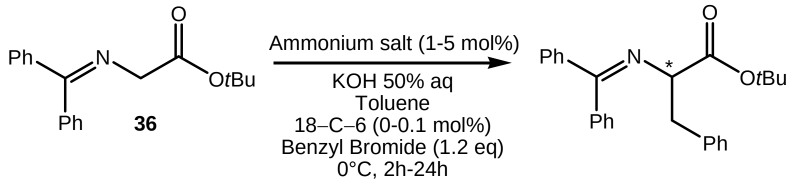


Figure III-35: CD spectrum (*c*~ 1.10^{-5} M, MeOH) of [**85**][Br]$_2$

III-4.2.d PTC with ammoniums salts of **83**, **84** and **85**

As done previously for ammonium catalyst **67**, the alkylation of glycine Schiff Base ester **36** (Equation III-11) was performed as an "acid test" to measure and compare the efficiency of catalysts **83**, **84** and **85**. Due to the high molecular weight of these ammoniums salts (above 1000 with PF_6 and above 2400 with BINPHAT as counter ions) we thought about using the conditions that would allow a rate enhancement of the reaction with only 1 mol% catalyst loading or even less. This consisted in adding a catalytic amount (≤ 1 mol%) of an achiral co-catalyst, 18-crown-6, which helps extract the inorganic base (in this case KOH) to the interfacial layer or the organic layer, the completion of the reaction being reached after 2-3 hours. To follow the reaction, an aliquot was taken after two hours of reaction (and analyzed by CSP-HPLC) and then after 24 hours. As previously, both Δ-BINPHAT and PF_6 salts of ammoniums **83** were tested to see if there is a counter ion effect could occur on the reaction. In the case of [**85**][Br]$_2$, no further ion exchange were performed and was thus tested as such; the results are shown in Table III-4.



entry	Catalyst	Catalyst (mol%)	18-C-6 (mol%)	After 2 h		After 24 h		
				Conv. %[b]	ee %[b]	Conv. %[b]	ee %[b]	Conf.[b]
1	none	-	1	10	-	90	-	-
2	(+)-[(*R*a)-**83**][Δ-BT]$_2$	1	1	52	27	nd	nd	(–)-*S*
3	(+)-[(*R*a)-**83**][Δ-BT]$_2$	1	0.1	15	27	98	14	(–)-*S*
4	(+)-[(*R*a)-**83**][PF$_6$]$_2$	1	0.1	nd	nd	95	14	(–)-*S*
5	(+)-[(*R*a)-**83**][PF$_6$]$_2$	1	none	1	-[c]	2	-[c]	-[c]
6	(+)-[(*R*a)-**83**][PF$_6$]$_2$	5	none	nd	nd	82	12	(–)-*S*
7	(+)-[(*R*a)-**84**][PF$_6$]$_2$	1	0.1	4	30	32	25	(–)-*S*
8	(–)-[**85**][Br]$_2$	1	0.1	14	48	100	40	(–)-*S*
9	(–)-[**85**][Br]$_2$	5	none	7	51	90	39	(–)-*S*

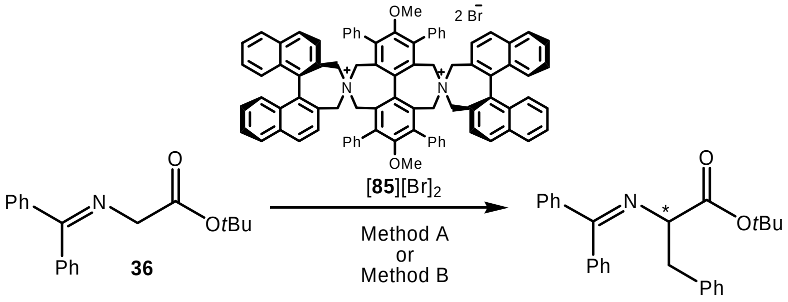
[a] Conditions 1.2 eq. Benzyl bromide, Toluene/50% aq. KOH (3:2), 0 °C, 2 to 24 hours. [b] Determined by CSP-HPLC (Chiralcel OD-H). [c] Conversion too low to allow a precise determination of the enantiomeric excess and the absolute configuration.

Table III-4: Phase transfer alkylation of **36** with catalysts [(*R*a)-**83**][Δ-BT]$_2$, [(*R*a)-**83**][PF$_6$]$_2$, [(*R*a)-**84**][PF$_6$]$_2$ and [**85**][Br]$_2$

A first test showed that 1 mol% of 18-C-6 allowed the reaction to proceed without the presence of any ammonium catalysts with good yields after 24 h (90%, entry 1, Table III-4). It was therefore interesting to see if the ammoniums would catalyze the reaction faster than 18-C-6. Data indicates that it is the case as, after 2h, a better conversion (52 %) and a moderate but definite 27% ee was obtained using catalysts [(*R*a)-**83**][Δ-BT]$_2$ (entry 2, Table III-4). However, to minimize this possible competition between the chiral catalyst and the achiral co-catalyst (which would result in a decrease in the enantioselectivity), the loading of 18-C-6 was decreased to 0.1 mol% as Maruoka and coworkers report it. Using these conditions and the same catalyst, the reaction appeared to be slower as after two hours, only 15% conversion was observed with the same enantiomeric excess (27%, entry 3, Table III-4). An almost complete conversion was obtained after one day but with a decrease of the enantioselectivity (14%, entry 3, Table III-4). No counter ion effect was observed as similar conversions (95%) and enantioselectivities (14%) were obtained with catalyst [(*R*a)-**83**][PF$_6$]$_2$ (entry 4, Table III-4). These results can be rationalized if we consider a degradation of the catalyst in these basic conditions (50% KOH *aq.*) *via* a an intramolecular [1,2]-Stevens rearrangement which has been observed on similar compounds in presence of a strong base (P_4-tBu). To avoid any competition with the achiral cocatalyst, further test without 18-C-6 were performed. If 1 mol% ammonium catalyst loading was not sufficient (2% conversion in 24 h, entry 5, Table III-4) a loading of 5 mol% led to good conversions (82%) but with similar enantioselectivity as before (12%, entry 6, Table III-4). Hence, it seems that it's not a competition with the achiral cocatalyst that is responsible of the decreased enantioselectivity but the product of degradation of the catalyst, which is, if we consider an intramolecular [1,2]-Stevens rearrangement on one side of the molecule, still an ammonium. However, it has not been possible to prove that hypothesis.

Concerning catalyst [(*R*a)-**84**][PF_6]$_2$ (1 mol% loading) a slight increase in the enantioselectivity using 0.1 mol% of 18-C-6 (30% after 2h, entry 7, Table III-4). However, slower reaction rate led to lower conversion and, again, a slight decrease in the enantioselectivity after 24 h reaction (25% after 20h, entry 7, Table III-4). In these conditions, ammonium salt [**85**][Br]$_2$ exhibited better activity (100% conversion after 24h) and a higher enantioselectivity (40% after 24h, entry 8, Table III-4). With this latter ammonium salt, almost similar results were obtained without achiral cocatalyst and with 5 mol% catalyst loading (entry 9, Table III-4). Interestingly, the same (−)-(*S*) configuration for the benzylated product were obtained for the three ammonium catalyst (*R*a)-**83**, (*R*a)-**84** and **85** of undetermined central configuration of the central doubly bridged biphenyl axis. This result would tend to prove that, as supposed before, the two external (*R*a) configured binaphthyl moieties impose a homochiral (*R*a) configuration of the central doubly bridged biphenyl axis of **85**.

At that stage, it was debatable whether the latter conditions used were the best suited for our catalysts as low conversions were obtained after a few hours of reaction (where usually Maruoka sees complete conversions with catalysts of type **38** after 3h); the decrease of enantioselectivity with time being also detrimental due to probable catalyst degradation. As a low solubility in toluene was observed for the previous ammonium tested, we thought about using DCM as solvent or co-solvent where our ammonium salts are totally soluble. Thus, two other sets of reaction conditions were tested with ammonium salt [**85**][Br]$_2$ which appeared to be, so far, the best catalyst synthesized in the group.



Catalyst	Method	Yield. %[c]	ee %[d]	Conf.[d]
[**85**][Br]$_2$	A[a]	54	41	(–)-*S*
[**85**][Br]$_2$	B[b]	70	7	(–)-*S*

[a] Conditions : 5 mol % catalyst, 5 eq. Benzyl bromide, 10 eq. $CsOH.H_2O$, Toluene / DCM (7:3),-70 °C, 24 hours. [b] Conditions : 5 mol % catalyst, 5 eq. Benzyl bromide, 10 eq. $CsOH.H_2O$, DCM,-78 °C, 24 hours.[c] Isolated Yield after column chromatography. [d] Determined by CSP-HPLC (Chiralpack IB).

Table III-5: Phase transfer alkylation of **36** with catalyst [**85**][Br]$_2$ using Shibasaki's (method A) and Corey's (method B) procedures

The first protocol (method A, Table III-5) uses a 7:3 ratio of toluene / DCM with a large excess of base ($CsOH.H_2O$, 10 eq.) and an excess of benzylbromide (5 eq.), the reaction being performed at -70 °C during 24h.[83] The second method (method B, Table III-5) uses exclusively DCM as solvent and was performed at -78 °C with the same quantities of reagents and reaction time as the first method.[84] In these two cases, the solid – liquid phase transfer catalysis was described with 10 mol% of the catalyst. As **85** is a dication, we thus reduced the catalyst loading at 5 mol%. The results are listed in Table III-5, in this case, isolated yield are reported. Using method A, a moderate yield and enantioselectivity was obtained (54% yield and 41% ee), the rest being essentially starting material. With method B, the yield was better but a serious drop in enantioselectivity was observed (70% yield with 7% ee). The better yield can be explained by the fact that, with method B, the catalyst [**85**][Br]$_2$ is fully dissolved in the reaction mixture (as only DCM was used as solvent) which is not completely the case with the 7:3 toluene/ DCM mixture of method A. However, in the more polar medium of method B (pure DCM), a looser ion pairing situation between the enolate of **36** and the ammonium catalysts could explain the lower enantioselectivity obtained. Hence, better enantioselectivities could probably be obtained by reducing the quantity of DCM, but longer

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[83] See supporting information of : Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206

[84] See supporting information of : Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414

reaction times are expected and the gain in enantioselectivity should not be so important. At that stage, it seems preferable to bring structural modifications to our ammonium catalyst rather than improving reaction conditions.

III-5 Conclusion and Outlook

In this chapter we have seen that Phase Transfer Catalysis (PTC) is a valuable methodology to have access to a wide range of useful synthetic compounds in high enantiomeric purity. However, the best ammonium catalysts described so far in the literature are either derived from the chiral pool or purely synthetic species. The first category appears to be not easily tunable and therefore restricted to some particular reactions and the second category often requires a long and tricky preparation. In this context we thought about simple ammonium structures such as **67** and **71** available from cheap and achiral starting material in a few step syntheses. In the case where it was possible to resolve the racemic dication with BINPHAT anion (for instance ammonium **67**), the catalyst appeared however to be inefficient for the asymmetric phase transfer benzylation of Schiff base ester **36**. Structural modification were brought on the biphenyl core of the molecule with phenyl substituents in 3,3' and 5,5' positions and two enantiopure binaphthyl subunits at the periphery of the molecule leading to ammonium **85**. In this case, no resolution was needed and ee up to 41% was obtained for the benzylation of **36**. As these results are far from the one obtained with catalysts **38c** bearing bis(3,4,5-F_3-Ph) substituents in 3,3' positions (essentially enantiopure natural and unnatural α-amino acids can be afforded with PTC alkylation on **36**), further structural modifications to our catalysts have to be brought. Moreover, other details can also be improved such as:

(i) decreasing the number of synthetic steps for the preparation of the catalysts
(ii) having the opportunity in the synthetic pathway to introduce various aryl substituents in the latest possible stage of the synthesis
(iii) removing the methoxy substituent on the biphenyl core of the molecule whose influence is unknown

This is actually an undergoing project in the group with the following synthetic sequence which consists in ten steps with a maximum of five in a row ((a) to (e) Figure III-36).

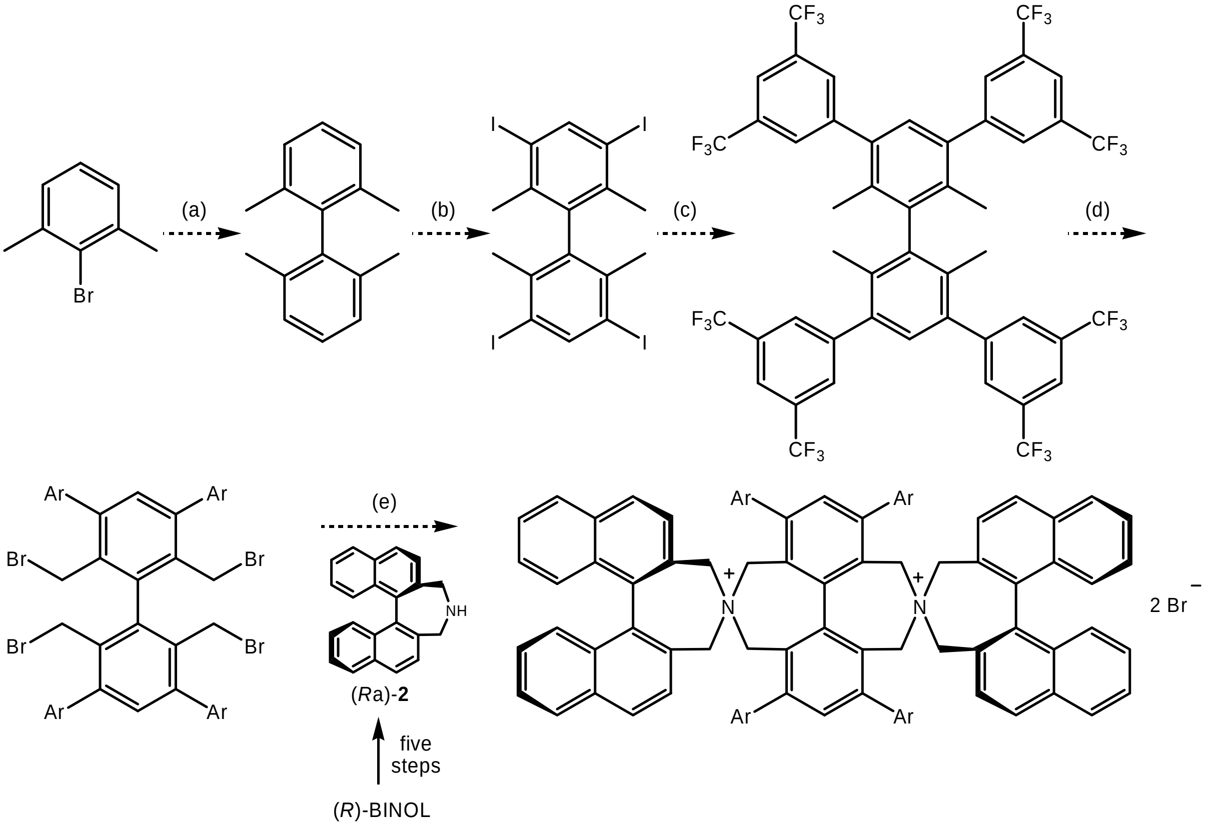


Figure III-36: New synthetic sequence to prepare more efficient phase transfer ammonium catalysts

Currently desymmetrizing the catalyst structure by putting non symmetrical secondary amine on both sides of the molecule is also envisioned. This could be achieved by making react indoline to the tetrabromide derivatives as shown on Figure III-37. This would of course require resolution of the ammonium with BINPHAT anion, something that remains to be seen.

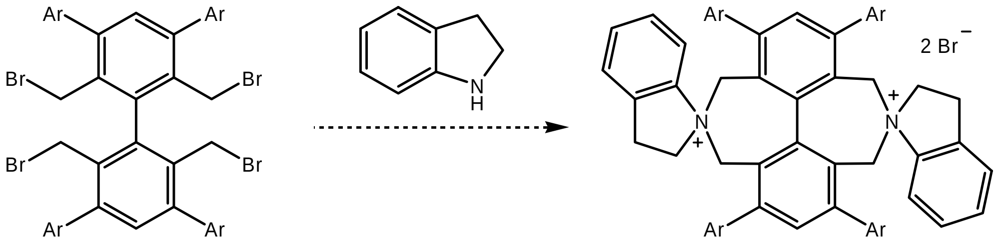


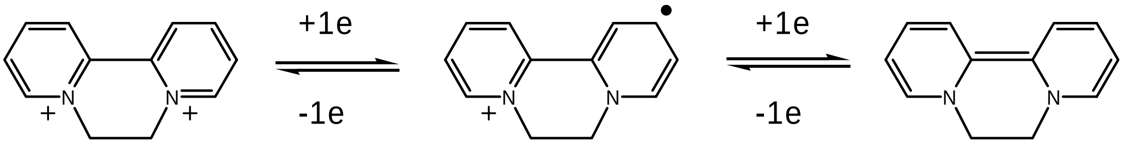
Figure III-37: Desymmetrization of the bisammonium compound with indoline

Chapter IV

SYNTHESIS AND RESOLUTION OF THE FIRST NON-RACEMIC DIQUATS

IV-1 Introduction and previous studies

Tricyclic diquats, which are bridged pyridiniums rings linked by a carbocyclic chain, are an important class of compounds which has been extensively used for more than fifty years. Since the 1950s, their herbicidal activity was known and is related to their ability to reversibly accept one electron to form a radical cation which can interfere during the electron-transfer step of the photosynthesis.[1] Many groups have been interested in this class of compounds for that purpose, the first reduction potential being quite low and the radical monocation formed being relatively stable (Scheme IV-1).[2,3]



Scheme IV-1: Radical cation and fully reduced species formed from diquat after one-electron reduction and two-electron reduction respectively

Diquats can be further used:

(i) as structural templates for efficient supramolecular synthesis.[4]

(ii) as electron acceptors in light harvesting chromophore-quencher systems.[5]

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[1] Brian, R. C.; Driver, G. W.; Homer, R. F.; Jones, R. L., 1048070, 1958; Boon, W. R.; Homer, R. F., 1129016, 1962; Boon, W. R. *Chem. Ind. (London)* **1965**, 782; Summers, L. A. *The Bipyridinium Herbicides* Academic; New York, 1980; Homer, R. F.; Mees, G. C.; Tomlinson, T. E. *J. Sci. Food Agric.* **1960**, *11*, 309

[2] Homer, R. F.; Tomlinson, T. E. *Nature (London)* **1959**, *184*, 2012; Tsukahara, K.; Wilkins, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 2632; Kuzuya, M.; Kondo, S.; Murase, K. *J. Phys. Chem.* **1993**, *97*, 7800

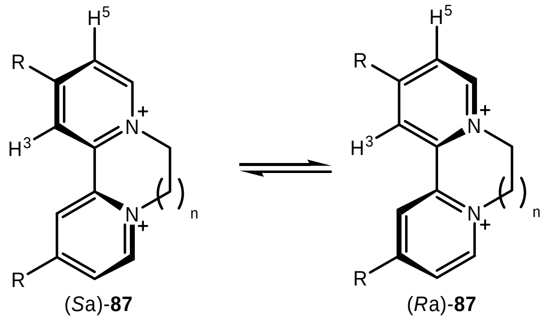
[3] Homer, R. F.; Tomlinson, T. E. *J. Chem. Soc.* **1960**, 2498; Thummel, R. P.; Lefoulon, F.; Chirayil, S.; Goulle, V. *J. Org. Chem.* **1988**, *53*, 4745; Brienne, S. H. R.; Boyd, P. D. W.; Schwerdtfeger, P.; Bowmaker, G. A.; Cooney, R. P. *J. Mol. Struct.* **1995**, *356*, 81; Coe, B. J.; Curati, N. R. M.; Fitzgerald, E. C. *Synthesis* **2006**, *1*, 146

[4] Allwood, B. L.; Kohnke, F. H.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 311

(iii) as ion-pair charge-transfer complexes.[6]

(iv) in non linear optics.[7]

Diquat derivatives are also noteworthy for their axial chirality. Due to the non coplanarity of the two linked pyridinium rings, these compounds exhibit atropoisomeric conformations ((*R*a) and (*S*a)) and the dihedral angle depends on the size of the non aromatic ring (Equation IV-1). Departure from coplanarity can be estimated by several spectroscopic methods. Early work by Homer *et al.* showed that the more planar the molecule is, the more shifted to longer wavelength is the UV absorption maximum due to gain of conjugation between the two aromatic rings.[8] This phenomenon can also be observed by NMR spectroscopy by looking at the multiplicity and the coupling constant of the proton of the non aromatic ring,[9] as well as regarding the difference in chemical shift of the H^3 and H^5 proton (Equation IV-1).[10] Indeed, the more planar the molecule is, the less shielded is the H_3 proton which beneficiate from the anisotropy of the vicinal pyridinium ring.



Equation IV-1: H^3 and H^5 protons of configurationally labile diquat **87**

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[5] Klumpp, T.; Linsenmann, M.; Larson, S. L.; Limoges, B. R.; Bürssner, D.; Krissinel, E. B.; Elliott, C. M.; Steiner, U. E. *J. Am. Chem. Soc.* **1999**, *121*, 1076; Vitale, M.; Castagnola, N. B.; Ortins, N. J.; Brooke, J. A.; Vaidyalingam, A.; Dutta, P. K. *J. Phys. Chem. B* **1999**, *103*, 2408; Kim, Y.; Lee, H.; Dutta, P. K.; Das, A. *Inorg. Chem.* **2003**, *42*, 4215; Kim, Y.-H.; Das, A.; Zhang, H.-Y.; Dutta, P. K. *J. Phys. Chem. B* **2005**, *109*, 6929

[6] Nunn, I.; Eisen, B.; Benedix, R.; Kisch, H. *Inorg. Chem.* **1994**, *33*, 5079; Unamuno, I.; Gutiérrez-Zorrilla, J. M.; Luque, A.; Román, P.; Lezama, L.; Calvo, R.; Rojo, T. *Inorg. Chem.* **1998**, *37*, 6452; Vitoria, P.; Beitia, J. I.; Gutiérrez-Zorrilla, J. M.; Sáiz, E. R.; Luque, A.; Insausti, M.; Blanco, J. J. *Inorg. Chem.* **2002**, *41*, 4396

[7] Coe, B. J.; Jones, L. A.; Harris, J. A.; Asselberghs, I.; Wostyn, K.; Clays, K. J.; Persoons, A. P.; Brunschwig, B. S.; Garin, J.; Orduna, J. *Proceedings of SPIE-The International Society for Optical Engineering* **2003**, *5212*, 122; Coe, B. J.; Harris, J. A.; Brunschwig, B. S.; Garin, J.; Orduna, J. *J. Am. Chem. Soc.* **2005**, *127*, 3284

[8] Homer, R. F.; Tomlinson, T. E. *J. Chem. Soc.* **1960**, 2498

[9] Thummel, R. P.; Lefoulon, F.; Mahadevan, R. *J. Org. Chem.* **1985**, *50*, 3824

[10] Calder, I. C.; Spotswood, T. M.; Tanzer, C. I. *Aust. J. Chem.* **1967**, *20*, 1195; Voegtle, F.; Bombach, D. *Chem. Ber.* **1975**, *108*, 1682; Campa, C.; Camps, J.; Font, J.; De March, P. *J. Org. Chem.* **1987**, *52*, 521

Despite the huge number of publications dealing with diquat compounds, none of them reports their isolation in an enantioenriched form. To the best of our knowledge, diquats have only been reported as configurationally labile molecules or – for the structures that could have been stable – as racemic mixtures. As already mentioned, BINPHAT and TRISPHAT have been used successfully for the resolution of dicationic organic substrates. A successful application of the anions in the context of novel *atropos* diquats would then afford a short and direct access to new non-racemic dicationic derivatives that could be tested as catalysts in enantioselective PTC and other asymmetric chemistry.

The group of Professor Lacour reported a few years ago the supramolecular stereocontrol of the configuration of *tropos* diquats of type **87** through an asymmetric ion pairing with BINPHAT and TRISPHAT anions.[11] A diastereomeric excess of 36% was obtained using diquat **87** (R = ^{t}Bu, n = 2) with BINPHAT counterions at 22 °C. Racemization barrier measurements showed that compounds of type **87** (n= 1, 2) were configurationally labile at room temperature (with $\Delta G^{\neq}$ values < 19 kcal.mol^{-1}). Isolation of such molecules in enantioenriched or enantiopure form was thus not feasible. Alternative more rigid structures were thus looked for as the compound would possibly present an *atropos* character this time. By analyzing the behavior of ortho-ortho'-bridged biphenyls derivatives which are the carbocyclic analogs of diquats, a general trend was noticed that added ring constrain in the bridging group increases indeed the configurational stability (Figure IV-1).

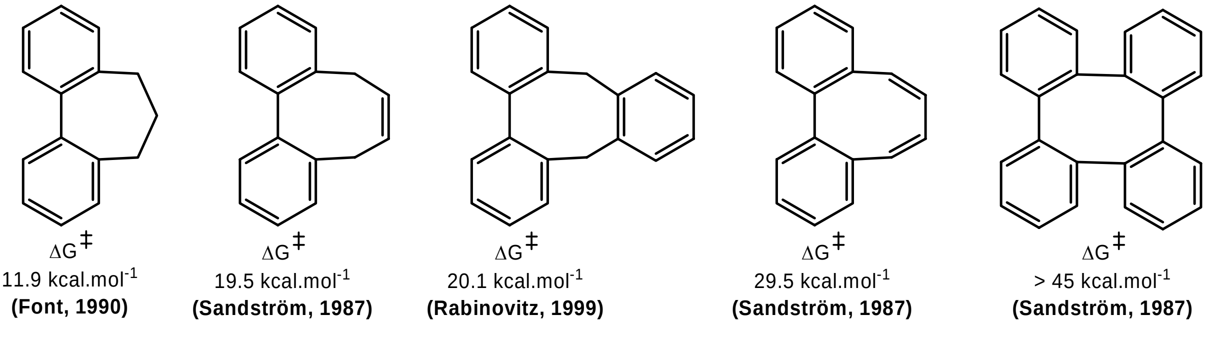

Figure IV-1: Racemization barriers of several carbocyclic analogs of diquats

For instance, incorporation of double bonds in the eight-membered ring increases the racemization barrier of several kcal.mol^{-1}. In the same way, if an aromatic group is present

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[11] Pasquini, C.; Desvergnes-Breuil, V.; Jodry, J. J.; Dalla Cort, A.; Lacour, J. *Tetrahedron Lett.* **2002**, *43*, 423

instead of a double bond, the ring constrain is increased and so is the racemization barrier.[12] Due to the electrostatic repulsion of the charged nitrogen atoms, diquat derivatives present greater dihedral angles between the two aromatic rings, and larger racemization barriers are expected from increased repulsion in the transition state. This is the case if we compare diquat **87** (R = H, n =2, $\Delta G^{\neq} = 16.9$ kcal.mol^{-1}) with its biphenyl analogue ($\Delta G^{\neq} = 11.9$ kcal.mol^{-1}). An increase of 5 kcal.mol^{-1} is observed. As mentioned in Chapter I, as an arbitrary definition, it is recognized that atropisomers are defined as physically separable species when, at a given temperature, they have a half-life of at least 1000 s (16.7 min) which correspond to aproximativelly a $\Delta G^{\neq}$ of 22 kcal.mol^{-1}.[13] Assuming that the introduction of two positive nitrogen atoms on the various skeletons detailed in Figure IV-1 would lead also to an increase of the racemization barriers of 5 kcal.mol^{-1}, then eight-membered ring diquat of type **88** (Equation IV-2) would present a barrier in the range of 25 kcal.mol^{-1} and would then be considered as configurationally stable. Salt [**88a**]$[I]_2$ (R= H) was reported more than thirty years ago by Vögtle and coworkers. Its stereodynamics were studied by VT-NMR in D_2O on a 60 MHz machine.[14] An effective magnetic non-equivalency was observed for the diastereotopic hydrogen atoms ($\Delta\nu = 0.36$ ppm, $J_{AB} = 21.4$ Hz) that did not change upon temperature increase (up to 100 K). This indicated a rather high barrier ($\Delta G^{\neq} > 23$ kcal.mol^{-1} using the formula $\Delta G^{\neq} = RTc(22.96 + \mathrm{n}(Tc/(\Delta\nu^2+J^2)^{1/2})$ with $Tc > 100$ K) that could however not be calculated precisely. With these information in our hands about a probable *atropos* nature of **88a**, the synthesis and the resolution of the derivatives was started.

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[12] Rashidi-Ranjbar, P.; Sandstrom, J. *Tetrahedron Lett.* **1987**, *28*, 1537; Jaime, C.; Font, J. *J. Org. Chem.* **1990**, *55*, 2637; Eshdat, L.; Shabtai, E.; Saleh, S. A.; Sternfeld, T.; Saito, M.; Okamoto, Y.; Rabinovitz, M. *J. Org. Chem.* **1999**, *64*, 3532

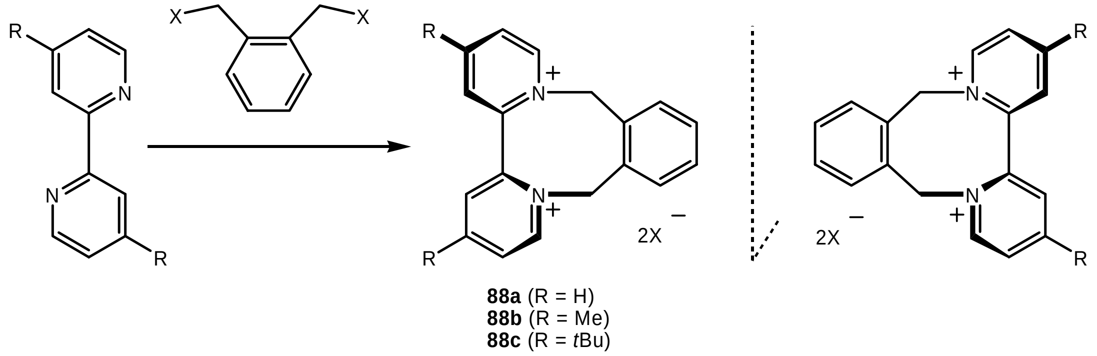
[13] Bringmann, G.; Anne J. Price Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384 – 5427

[14] Voegtle, F.; Bombach, D. *Chem. Ber.* **1975**, *108*, 1682

IV-2 Synthesis and study of eight-membered ring diquats

IV-2.1 Synthesis of diquats of type 88

As mentioned, the eight-membered ring diquat **88a** and its preparation have already been described in the literature.[15] Its synthesis consisted in mixing 2,2'-bipyridine with α,α'-dibrom-*o*-xylene in refluxing acetronitrile for several hours.



Equation IV-2: Synthesis of diquats [**88a-c**][X]$_2$ from 2,2'-dipyridyl and α,α'-dihalo-*o*-xylene

Application of this method worked nicely for compound **88b** (R= Me, Table IV-1, entry 2) but failed for the synthesis of compound **88c** (R= t-Bu, Table IV-1, entries 3 and 4). For the latest compound harsher conditions were necessary that required two equivalents of α,α'-diiodo-*o*-xylene in 1,2-dichlorobenzene, at 120 to 160 °C during four hours. This afforded compound **88c** as a precipitate in a reasonable 66% yield (Table IV-1, entry 5).

entry	R	X	Solvent	T°C	Time	Product	Yield
1	H	Br	Acetonitrile	90 °C	14h	**88a**	85%
2	Me	Br	Acetonitrile	90 °C	14h	**88b**	88%
3	*t*Bu	Br	Acetonitrile	90 °C	14h	**88c**	0%
4	*t*Bu	I	Acetonitrile	90 °C	14h	**88c**	0%
5	*t*Bu	I	1,2-Dichlorobenzene	120-160 °C	4h	**88c**	66%

Table IV-1: Conditions (solvent, temperature, time) for the preparation of diquats **88a**, **88b** and **88c**

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[15] Popp, F. D.; Chesney, D. K. *J. Heterocycl. Chem.* **1972**, *9*, 1165; Voegtle, F.; Foerster, H. *Chemiker-Zeitung* **1973**, *97*, 386; Voegtle, F.; Bombach, D. *Chem. Ber.* **1975**, *108*, 1682

To confirm the results observed by Vögtle, care was taken in the studies to select the NMR machine with the lowest frequency available (300 Mhz) for the high temperature measurement. VT-NMR experiment on [**88c**][I]$_2$ was performed and the result is shown on Figure IV-2. Fluctuations were not observed for the diastereotopic benzylic protons proving the rather high conformational stability of these compounds at elevated temperatures. The resolution of diquats **88a-c** was then started using chiral anions.

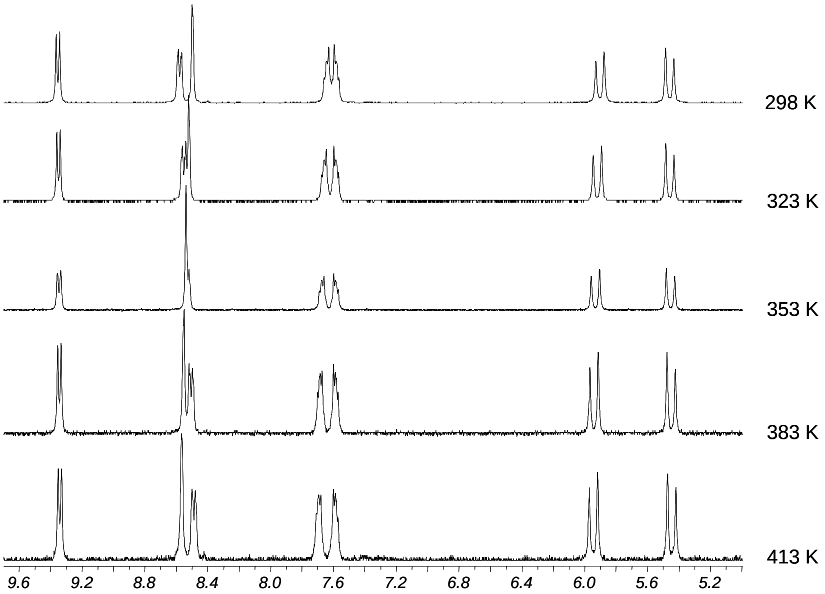

Figure IV-2: ^{1}H VT NMR experiment on [**88c**][I]$_2$ (300 MHz, DMSO-*d6*, 298 – 413 K)

IV-2.2 Resolution of diquats 88a-88c

Ion exchange metathesis with enantiopure TRISPHAT and BINPHAT salts of halide salts of diquats **88a-c** afforded the desired epimeric mixture of compounds, namely salts [**88a-c**][Δ-TT]$_2$ and [**88a-c**][Δ-BT]$_2$ in good yields. As a general trend, TRISPHAT salts were isolated by column chromatography (basic Al_2O_3, eluant: acetronitrile) whereas BINPHAT salts usually precipitated during the ion exchange metathesis in methanol; ^{1}H NMR analysis of the isolated salts indicating the 1:1 mixture of the diastereomers.

As already mentioned in chapter III, hexacoordinated anions TRISPHAT and BINPHAT confer to their salts a poor affinity for polar chromatographic phases and consequently elute rapidly over silica gel/alumina.[16] A separation of the diastereomers from the ion triple

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[16] Lacour, J.; Torche-Haldimann, S.; Jodry, J. J. *Chem. Comm.* **1998**, 1733; Lacour, J.; Barchechath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567

diastereomeric mixture by column chromatography was envisioned. Unfortunately, in all the common solvent tested, only one spot on TLC was observed for all the salts. But, to our surprise, by triturating the epimeric salts [**88a**][Δ-BT]$_2$ and [**88b**][Δ-BT]$_2$ in a given volume of acetronitrile, a partial dissolution occured, and after filtration, high levels of diastereoselectivity were observed for the precipitates (96% d.e., Table IV-2, entries 1 and 2).

entry	Salts	d.e [a] (precipitate)	d.e [a] (mother liquor)
1	[**88a**][Δ-BT]$_2$	96%	40%
2	[**88b**][Δ-BT]$_2$	96%	92%
3	[**88c**][Δ-BT]$_2$	88%	40%
4	[**88c**][Δ-TT]$_2$	> 96%[b]	95%[b]

[a] d.r measured by ^{1}H NMR (400MHz, 14% DMSO[d$_6$] in CDCl$_3$) otherwise stated. [b] d.r measured by ^{1}H NMR (400MHz, 3% CD$_3$CN in CDCl$_3$).

Table IV-2: Diastereoselectivities obtained with TRISPHAT and BINPHAT anions during the separation of the two diastereomers of each phosphate salts of **88a-c**

The more soluble mixture of [**88c**][Δ-BT]$_2$ was dissolved in CH$_3$CN and cooling a saturated solution to ~ 4 °C for few hours resulted in the appearance of a precipitate which was filtered; ^{1}H NMR analysis indicating the occurrence of 88% de value (Table IV-2, entry 3). Several attempts to apply this method on salts [**88a**][Δ-TT]$_2$ and [**88b**][Δ-TT]$_2$ failed. However, by cooling a saturated solution of [**88c**][Δ-TT]$_2$ ((b), Figure IV-3) in acetonitrile at -20 °C, a diastereomerically pure (and enantiopure) salt precipitated (*pre*-[**88c**][Δ-**2**]$_2$) which was filtered ((c), Figure IV-3 and Table IV-2, entry 4). In the mother liquor, only small traces of this diastereomer remained as the ^{1}H NMR spectra displayed quasi exclusively the signals of the other diastereomer ((d), Figure IV-3: *ML*-[**88c**][Δ-**2**]$_2$). The resolution procedure was then continued by exchanging the anionic resolving agent for PF$_6$ anions. As usual, the isolated BINPHAT salts were treated with an excess of an aqueous solution of HPF$_6$ in DCM, the desired [**88a-c**][PF$_6$]$_2$ being isolated as solids after the addition of Et$_2$O, with no loss of enantiomeric purity.[17] All the salts [**88a-c**][PF_6]$_2$ derived from the precipitates were of levorotatory nature; the compounds form the mother liquor being of course dextrorotatory.

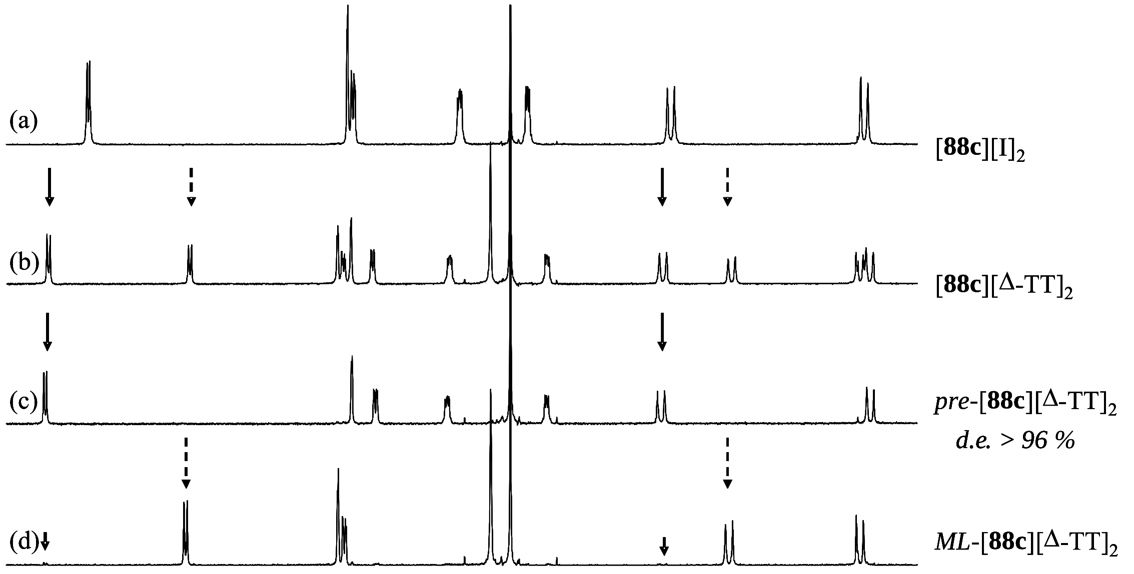

Figure IV-3: 1H NMR (400 MHz, 3% CD_3CN in $CDCl_3$) of (a) [**88c**][I]$_2$, (b) ~ 1:1 mixture of the two diastereomers of [**88c**][Δ-TT]$_2$, (c) *pre*-[**88c**][Δ-TT]$_2$ and (d) *ML*-[**88c**][Δ-TT]$_2$

IV-2.3 Configurational analysis

To remove the TRISPHAT anion which, contrary to BINPHAT anion, does not decompose in presence of Brönsted acids, the use of stronger Lewis acids was required. An excess of anhydrous $FeCl_3$ was added to a solution of [**88c**][Δ-TT]$_2$ in dichloromethane at 0 °C. An extraction with a saturated aqueous solution of KPF_6 was then performed. After filtration on Celite® of the precipitate suspended in the organic phase, the desired (−)-[**88c**][PF_6]$_2$ salt was precipitated with Et_2O. Unfortunately, during this procedure, a slight epimerization of the cation was observed (Figure IV-4). Having the salts with a CD silent anion, CD experiments were performed on (−)-[**88a-c**][PF_6]$_2$ (Figure IV-8). Interstingly, essentially superposable spectra were obtained for the three salts with negative Cotton effects from 230 to 270 nm. All three salts thus the same absolute configurations.

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[17] Checked by ^{1}H NMR by adding a chiral shift agent ([nBu_4N][Δ-BT])

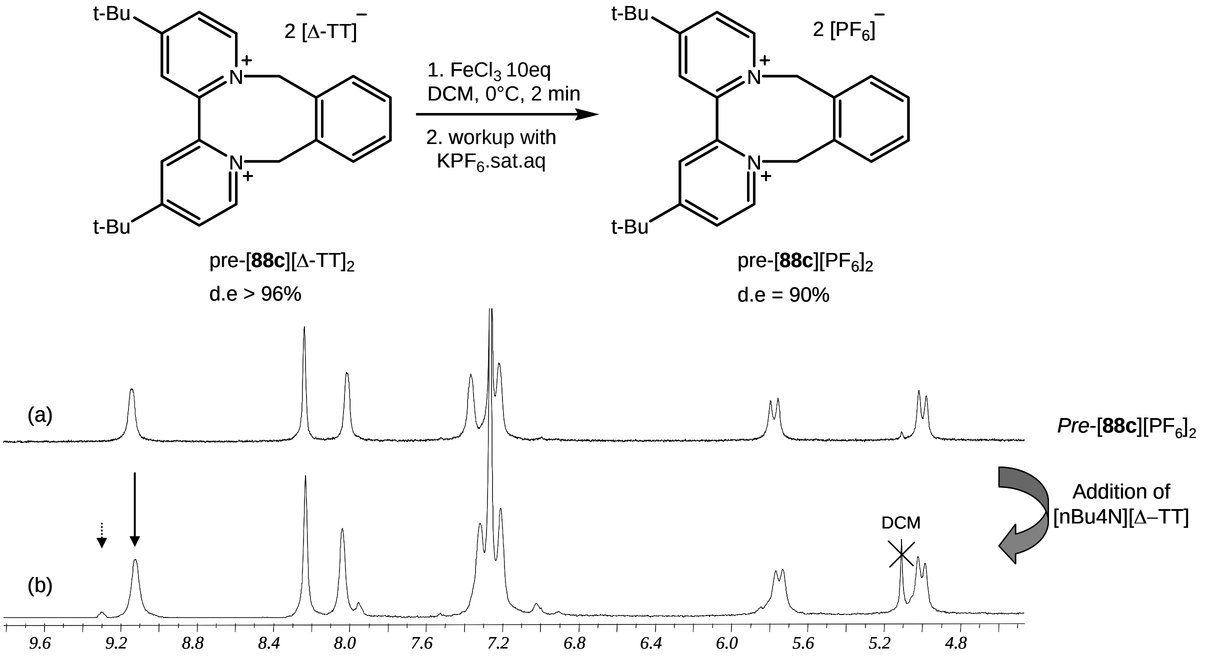

Figure IV-4: Ion metathesis from enantiopure *pre*-[**88c**][Δ-TT]$_2$ to *pre*-[**88c**][PF$_6$]$_2$ using FeCl$_3$ and KPF$_6$ with 1H NMR (400 MHz, 14% DMSO-d_6 in CDCl$_3$) of (a) *pre*-[**88c**][PF$_6$]$_2$ and (b) *pre*-[**88c**][PF$_6$]$_2$ after addition of [nBu$_4$N][Δ-TT] in the NMR tube

As mentioned in chapter I, Mislow and Sandström showed that ortho,ortho'-bridged biphenyl derivatives that exhibit a negative cotton effect in the specific region around 250 nm have a *P* (or *S*a) configuration for the biphenyl.[18] If this rule is also true for diquats, then all measured fractions would be of *P* configurations. However, the structural analogy between the "simple" biphenyl and diquats was deemed to be not so trivial, and care was taken to assign the absolute configurations by another method.

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[18] Sandstrom, J. *Chirality* **2000**, *12*, 162

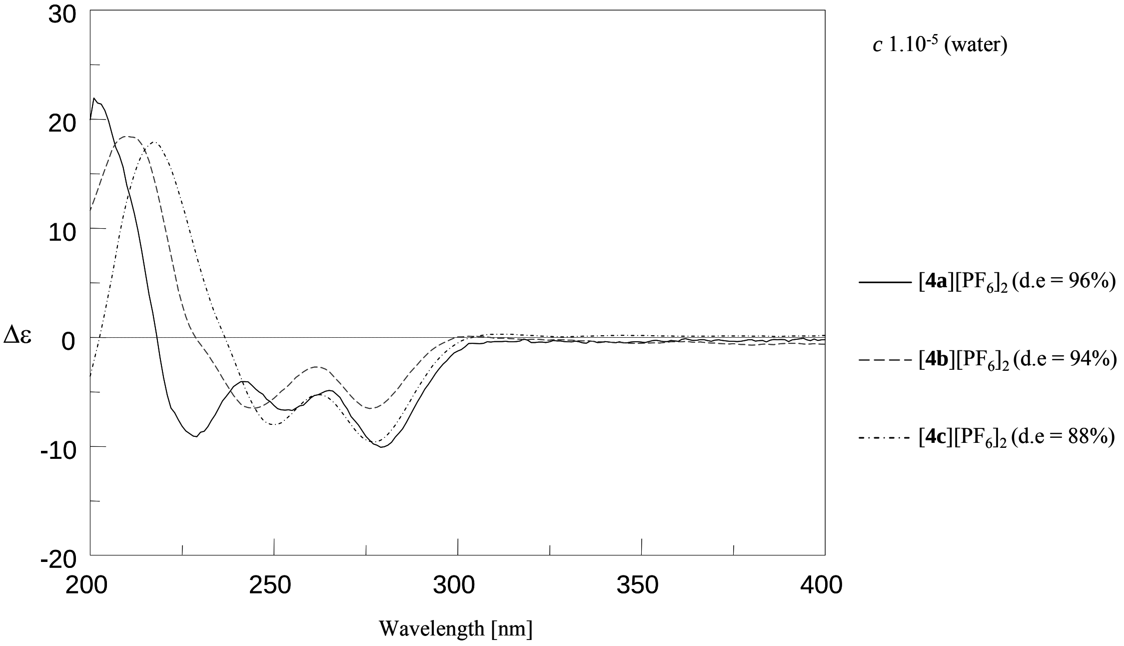


Figure IV-5: CD spectra of (a) (–)-[88a][PF$_6$]$_2$, (b) (–)-[88b][PF$_6$]$_2$ and (c) (–)-[88c][PF$_6$]$_2$ in water (c 1.10^{-5}M)

A X-ray structural analysis was performed on a monocrystal of *pre*-[**88c**][Δ-TT]$_2$, precursor to (–)-[**88c**][PF$_6$]$_2$, confirming the existence of a single diastereomeric species (Figure IV-6). A Flack parameter analysis confirmed the Δ configuration for the TRISPHAT anion and a (*S*a) configuration could be thus determined for **88c** using this internal reference.

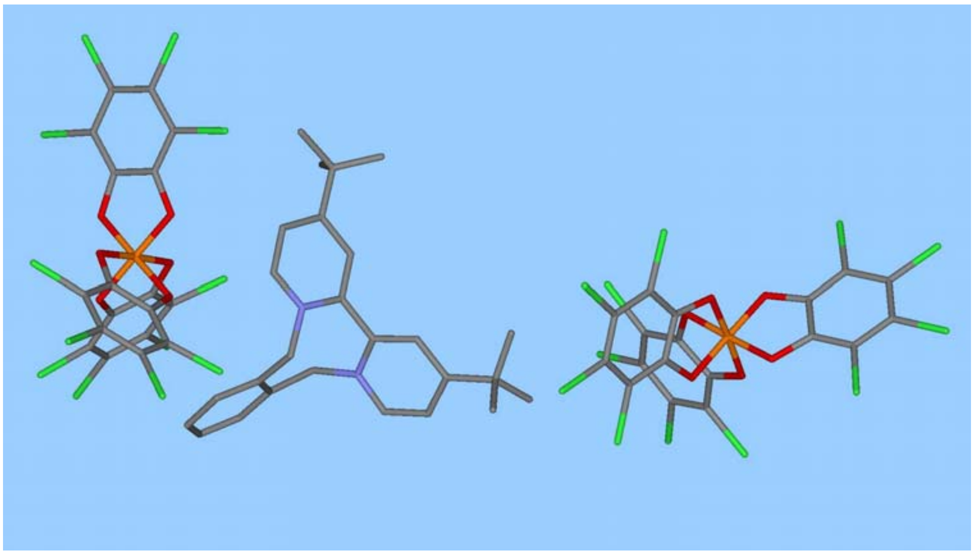


Figure IV-6: X-Ray diffraction analysis of *pre*-[**88c**][Δ-TT]$_2$ which corresponds to [(*S*a)-**88c**][Δ-TT]$_2$

Assuming that the configuration of the cation does not change upon removal, then (−)-[**88c**][PF_6]$_2$ and all the other levorotatory salts are of (*S*a) configuration. As both enantiomers of TRISPHAT and BINPHAT anions are available, it is possible, following the resolution procedure, to obtain both enantiomers of diquats **88a-c** with similar enantiopurities.

IV-2.4 Configurational stabilities of diquats 88a-88c

With these samples in hands, it was possible to determine the free energy of activation of the racemization barriers, for all the resolved diquats. CD time course measurements were performed in water, at one given wavelength (276 nm) and four different temperatures (50, 60, 70 and 80 °C) for the PF_6 salts of **88a**, **88b** and **88c**. In this case, it was easier to use dextrorotatory samples.

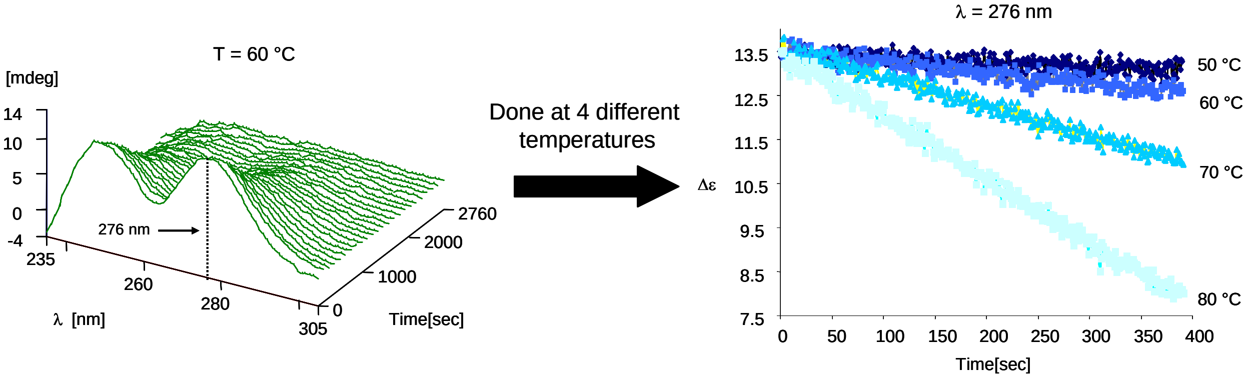


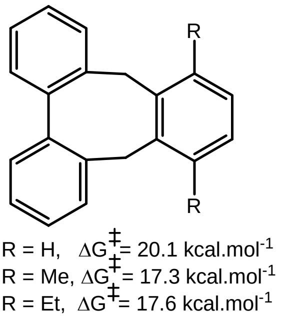
Figure IV-7: : Racemization studies (H_2O, *c* 1•10-5) performed on (+)-[(*R*a)-**88c**][PF_6]$_2$

A typical experiment is shown on Figure IV-7. After heating (+)-[(*R*a)-**88c**][PF_6]$_2$ for few minutes at 60 °C, the Cotton effect at 276 nm decreases and assures after some time a zero value, meaning that a complete racemization occurs. The same experiment was performed on (+)-[(*R*a)-**88a**][PF_6]$_2$ and (+)-[(*R*a)-**88b**][PF_6]$_2$ and the results are summarized in Table IV-3. As expected the $\Delta G^{\neq}$ values are higher than 23 kcal.mol^{-1}, the smallest of the three being for [**88c**][PF_6]$_2$ (Table IV-3, entry 3). Entropy values are rather low which is expected for an intramolecular process. Interestingly, there exists a 1.5 kcal.mol^{-1} difference between the lowest and the highest $\Delta G^{\neq}$ value irrespective of the size of the alkyl chain.

Entry	diquat	$\Delta H^{\neq}$ (kcal.mol^{-1})	$\Delta S^{\neq}$ (cal.mol^{-1}.k$^{-1)}$	$\Delta G^{\neq}$ (kcal.mol^{-1})	$t_{1/2}$ (half life)
1	[**88a**][PF_6]$_2$	23.9	-5.2	25.4	12 days
2	[**88b**][PF_6]$_2$	26.5	0.0	26.5	71.3 days
3	[**88c**][PF_6]$_2$	22.8	-8.0	25.1	7.25 days

Table IV-3: Relevant data for the stereodynamics among ammonium **88a**, **88b** and **88c**

Similarly, Rabinovitz *et al.* observed variations of racemization barriers for substituted ortho-ortho'-bridged biphenyls derivatives, with alkyl substituants on the third aromatic ring (Figure IV-8).[19] The lower values observed were explained by raised ground state energy on derivatives with bulky substituants, closer to the energy of the transition state. They also mention a noticeable influence of the solvent in which the experiment is done, a phenomenon that we have observed to a higher degree with our highly polarized diquats. Unfortunatly, no linearity between the $\Delta G^{\neq}$ values and classical parameters accounting for solvents (ε, μ, Reichardt coefficient $E^N{}_T$) could be found. (*e.g* [**88c**][PF_6]$_2$, $\Delta G^{\neq}$= 24.9 kcal.mol^{-1} in 1,2-dichloroethane, $\Delta G^{\neq}$= 24.8 kcal.mol^{-1} in THF, $\Delta G^{\neq}$= 23.4 kcal.mol^{-1} in dioxane).



R = H, $\Delta G^{\ddagger}$= 20.1 kcal.mol^{-1}
R = Me, $\Delta G^{\ddagger}$= 17.3 kcal.mol^{-1}
R = Et, $\Delta G^{\ddagger}$= 17.6 kcal.mol^{-1}

Figure IV-8: Influence of the R substituents onto configurational stability of carbocyclic analog of diquats

IV-2.5 Application of diquats in PTC

The enantioenriched PF_6 salts were then tested as PTC catalysts. In a first set of experiments the benzylation of Schiff base ester **36** (see chapter III) was tested in the presence of (−)-[(*S*a)-**88c**][PF_6]$_2$. If good conversions were usually observed (~ 70%), only racemic materials were obtained. Further modification of the initial structure of the bipyridine was then

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[19] Eshdat, L.; Shabtai, E.; Saleh, S. A.; Sternfeld, T.; Saito, M.; Okamoto, Y.; Rabinovitz, M. *J. Org. Chem.* **1999**, *64*, 3532

attempted by introducing phenyl groups in 6,6' positions as these substituents seemed crucial to obtain decent level of selectivity (see Chapter III). Following a reported procedure, a Chichibabin-type reaction on 2,2'-bipyridine with phenyl lithium gave **89** in low but definite 18% yield.[20]

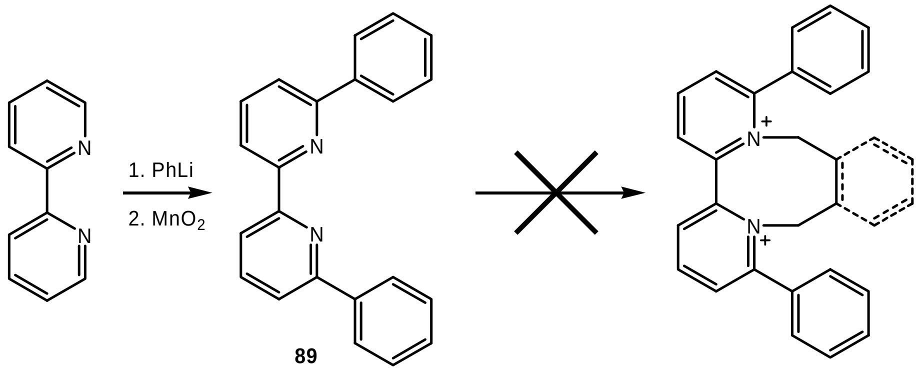

Figure IV-9: Failure in ring closing dipyridyl **89** to form sterically indered diquats

However, any attempts to form a cyclic diquat from **89** by reaction with various dialkyl halides failed, the starting material being untouched during the reaction. The hindered diquats were never made and their possible efficiency as PT catalysts remains to be seen.

IV-2.6 Conclusion and outlook

In conclusion, the resolution of configurationally stable diquats **88a**, **88b** and **88c** bearing different substituants in 4,4' positions (H, Me and *t*Bu) have been performed using chiral hexacoordinated TRISPHAT and BINPHAT phosphate anions. Compounds could be obtained with high diastereo and enantiomeric purity (>96% ee in some cases). X-ray diffraction analysis, coupled with chiral anion removal and CD measurement, allowed the determination of the absolute and relative configurations of the salts. The barriers to racemization of these compounds were calculated using CD time-course measurements affording $\Delta G^{\neq}$ values above 25 $kcal.mol^{-1}$, thus proving a high configurational stability. If, at the moment, these diquats were found to be ineffective catalysts for asymmetric phase transfer processes, further structural modifications can be envisioned to improve their efficiency. However, in any case, these three derivatives are the first eight-membered ring with only three ring constrains to be ever resolved.

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[20] Dietrick-Buchecker, C. O.; Marnot, P. A.; Sauvage, J. P. *Tetrahedron Lett.* **1982**, *23*, 5291

- GENERAL CONCLUSION -

The purpose of this thesis was to synthesize efficient non racemic nitrogen-based cations for applications in asymmetric chemistry. To distinguish this approach from what has been reported before, we wanted to prove that, by a careful combination of achiral and chiral entities, in very few steps, new synthetically useful cations could be obtained and then be used to induce decent level of stereoselectivity.

In the first chapter we have presented an already known C_2-symmetric amine, namely the “Doubly Bridged Biphenyl Azepine” (DBBA). Interestingly, this skeleton framework which is the central core of most of the compounds presented in this manuscript, has been rarely used and studied. Trying to find a good balance between decent configurational stability at room temperature and concomitant stereocontrol at elevated temperature of the central biphenyl axis by exocyclic stereogenic elements, doubly bridged biphenyl azepines (DBBA) of type **4** were shown to be interesting compounds for that purpose. However, it appeared to be quite difficult to separate both diastereomers in good yields for simple derivatives, and the diastereoselectivity obtained, either during the synthesis (kinetic diastereoselectivity) or after complete epimerization at high temperatures of these compounds (thermodynamic diastereoselectivity) is quite low (d.r up to 4.3:1). On the whole, these problems have been solved by introducing phenyl substituent in 3,3’ and 5,5’ positions of the central biphenyl core. Indeed, these newly synthesized hindered doubly bridged biphenyl azepines (HDBBA) appeared easier to purify and isolate in a diastereomerically pure form in the cases were another diastereomer is formed. Epimerization of these amines was feasible though much higher temperature and reaction times were required. In the following chapters we will see that these compounds could be easily derivatized in order to form new organocatalysts for asymmetric reactions.

In the second chapter, we have proved that starting from the biphenyl azepines described previously, together with the association of TRISPHAT anion, it was possible to synthesize in one step, quite efficient iminium catalysts for the asymmetric epoxidation of some prochiral olefins. While singly bridged biphenyl azepinium of type **23** led to enantioselectivities up to 80% ([**23f**][*rac*-TT]), slightly better results were obtained by using doubly bridged biphenyl azepinium catalysts of type **30** (ee up to 86% with [**30e**][Δ-TT]) or binaphthyl azepinium of type **24** (ee up to 87% with [(*R*a,*R*)-**24f**][*rac*-TT]). In addition to that, we could show that tertiary amines precursors of the iminium salt catalysts could be effective catalysts for the asymmetric epoxidation of the same prochiral olefins; their efficiency being almost similar in terms of activity and enantioselectivity. The 95% ee obtained by Page and coworkers with iminium catalyst **24g** could not be exceeded but iminium catalyst **25f** and amine catalyst **35f** showed promising results. However, many issues are still unsolved concerning the mechanism with these tertiary amines catalysts. Many clues tend to prove that, these compounds do not behave like ammonium catalysts described by Aggarwal and Yang which are derived from pyrrolidine. Some experiments have to be pursued to determine the exact nature of the active species that catalyze the epoxidation reaction.

In the third chapter, we have again used the DBBA core to prepare several bis-ammonium catalysts for phase transfer processes. Initially, “naked” ammonium structures such as **67** and **71** available from cheap and achiral starting materials in a few step syntheses were prepared. In one instance, it was possible to resolve the racemic cation with BINPHAT anion (ammonium **67**), but the catalyst appeared to be inefficient for the asymmetric phase transfer benzylation of Schiff base ester **36**. Structural modifications were brought on the biphenyl core of the molecule with phenyl substituents in 3,3’ and 5,5’ positions and two enantiopure binaphthyl subunits at the periphery of the molecule leading to dicationic bis-ammonium **85**. In this case, no resolution was needed and ee up to 41% was obtained for the benzylation of **36**. As these results are far from the one obtained with catalysts **38c** bearing bis(3,4,5-F_3-Ph) substituents in 3,3’ positions (essentially enantiopure natural and unnatural α-amino acids can be afforded with PTC alkylation on **36**), further structural modifications to our catalysts are required.

In the fourth chapter, the resolution of configurationally stable diquats **88a**, **88b** and **88c** bearing different substituants in 4,4’ positions (H, Me and *t*Bu) have been performed using chiral hexacoordinated TRISPHAT and BINPHAT phosphate anions. Compounds could be obtained with high diastereo and enantiomeric purity (>96% ee in some cases). X-ray diffraction analysis, coupled with chiral anion removal and CD measurement, allowed the determination of the absolute and relative configurations of the salts. The barriers to racemization of these compounds were calculated using CD time-course measurements affording $\Delta G^{\neq}$ values above 25 kcal.mol^{-1}, thus proving a high configurational stability. If, at the moment, these diquats were found to be ineffective catalysts for asymmetric phase transfer processes, further structural modifications can be envisioned to improve their efficiency. However, in any case, these three derivatives are the first eight-membered ring with only three ring constrains to be ever resolved, further structural modifications can be envisioned to improve its efficiency. Moreover, as Diquats are used in various domains of chemistry, some previous applications can now be revisited with enantioenriched materials and, as such other purposes can be found.

EXPERIMENTAL PART

GENERAL REMARKS

All reactions were carried out under dry N_2 or Ar by means of an inert gas/vacuum double manifold line with magnetic stirring, unless otherwise stated. Solvents were dried and distilled prior to use: toluene was freshly distilled from sodium; dichloromethane and hexane were freshly distilled from Calcium hydride, diethylether and tetrahydrofuran from sodium-benzophenone. $CHCl_3$, CH_2Cl_2, $CDCl_3$ and CD_2Cl_2 (SDS) were filtered on basic alumina. Analytical thin-layer chromatography (TLC) was performed with Merck SIL G/UV_{254} plates or Flucka 0.25 mm basic alumina (pH = 9.9) plates. Visualization of the developed chromatogram was performed by UV/VIS detection. Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Unless otherwise noted, column chromatography (silicagel 60, 40 μm or Fluka basic alumina type 5016A) was performed in air and under pressure (0.1-0.3 bar).

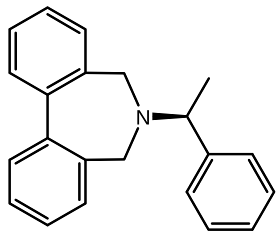
NMR spectra were recorded on Bruker AMX-400 at room temperature unless otherwise stated. ^{1}H-NMR: chemical shifts are given in ppm relative to Me_4Si with the solvent resonance used as the internal standard. ^{31}P-NMR (162 MHz): chemical shifts were reported in ppm relative to H_3PO_4. ^{13}C-NMR (100 MHz): chemical shifts were given in ppm relative to Me_4Si, with the solvent resonance used as the internal standard ($CDCl_3$ δ 77.0 ppm; DMSO-d_6 δ 39.5 ppm; CD_2Cl_2 δ 53.8 ppm; $(CD_3)_2CO$ δ 206.3, 29.8 ppm; CD_3CN δ 118.3, 1.3 ppm; CD_3OD δ 49.0 ppm). Assignments may have been achieved using COSY, HSQC and HMBC experiments. IR spectra were recorded with a Perkin-Elmer 1650 FT-IR spectrometer using a diamond ATR Golden Gate sampling. Melting points (M.p.) were measured in open capillary tubes on a Stuart Scientific SMP3 melting point apparatus and were uncorrected. Electrospray mass spectra (ES-MS) were obtained on a Finnigan SSQ 7000 spectrometer and EI-MS spectra were obtained on a *Varian CH4* or *SM1* spectrometer; ionizing voltage 70eV; *m*/z (intensity in %) by the Department of Mass Spectroscopy of the University of Geneva. UV spectra were recorded on a CARY-

1E spectrometer in a 1.0 cm quartz cell; λ_{max} are given in nm and molar adsorption coefficient ε in $cm^{-1}\cdot dm^{3}\cdot mol^{-1}$. Circular dichroism spectra were recorded on a JASCO J-715 polarimeter in a 1.0 cm quartz cell; λ are given in nm and molar circular dichroic absorptions (Δε in $cm^{2}\cdot mmol^{-1}$). Optical rotations were measured on a JASCO P-1030 polarimeter in a thermostated (20 °C) 10.0 cm long microcell with high pressure lamps of sodium or mercury and are reported as follows: $[\alpha]_{\lambda}^{20}$ (c (g/100 ml), solvent). HPLC analyses were performed on an Agilent 1100 apparatus (binary pump, autosampler, column thermostat and diode array detector using Chiralcel OD-H (0.46 x 25 cm) and Chiralpack IB (0.46 x 25 cm) columns. Chiral stationary phase (CSP) chromatography was performed on a *Hewlett Packard 6890* GC chromatograph using a Hydrodex -β column (25m x 0.25 m, H_2, 40 Psi). Retention times (t_R) are given in minutes (min). X-ray diffraction structures were solved at the “Laboratoire de Cristallographie aux rayons X, Service de Resolution Structurale par Diffraction des Rayons X” by Dr. G. Bernardinelli.

CHAPTER I – DOUBLY BRIDGED BIPHENYL AZEPINES

General procedure for the synthesis of azepines 1a to 1e: To a solution of biphenyl-2,2'-dicarboxaldehyde (1.0 eq.) in CH_3CN (6 mL per 0.1g of dicarboxaldehyde) was added the corresponding enantiopure amine **a** to **h** (2.0 eq.). After 15 min of stirring, $NaBH_3CN$ (2.0 eq.) was added and the reaction was stirred for 20h before the addition of AcOH (~5 eq.). After 1h, the reaction mixture was diluted with 2% $MeOH/CH_2Cl_2$ (30 mL), washed with 1M NaOH (until pH>10), dried over Na_2SO_4 and concentrated under reduce pressure. The compound was obtained after purification over silica gel or basic alumina.

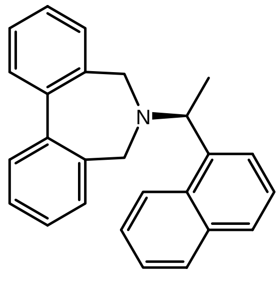
6-N-(*S*-1-Phenylethyl)-5H-dibenz[c,e]azepine or 1a



Starting from 425 mg of biphenyl-2,2'-dicarboxaldehyde, compound **1a** was obtained as a yellow oil (488 mg, 97%) after chromatography over silica gel DCM/MeOH 95:5 as eluent.

R R_f = 0.51 (SiO_2, DCM/MeOH 95:5); **$[\alpha]_D^{20}$** – 45.0 (*c* 1.3, MeOH); **IR** (neat) 3024, 2926, 2792, 1450, 1082, 921, 747 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (m, 13H), 3.63 (q, 1H, *J* = 6.5 Hz), 3.55 (d, 2H, *J* = 12.5 Hz), 3.32 (d, 2H, *J* = 12.5 Hz), 1.48 (d, 3H, *J* = 6.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.9 (C^{IV}), 141.2 (C^{IV}), 135.0 (C^{IV}), 129.7 (CH), 128.6 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 126.9 (CH), 62.4 (CH), 53.0 (CH_2), 22.6 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 299.7 (100, M), 194.3 (100, M-C_8H_{10}), 179.1 (95).

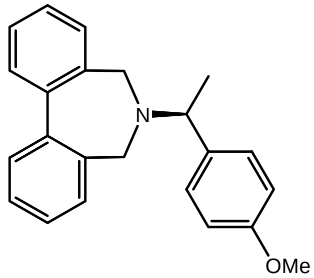
6-N-((*S*)-1-(2-Naphthyl)ethyl)-5H-dibenz[c,e]azepine or 1b



Starting from 500 mg of biphenyl-2,2'-dicarboxaldehyde, compound **1b** was obtained as a pale yellow solid (650 mg, 77%) after chromatography over basic alumina using *c*-Hex then *c*-Hex/EtOAc 9:1 as eluent.

R_f = 0.6 (SiO_2, *c*-Hex /EtOAc 9:1); **M.p.** 80-85 °C; **$[\alpha]^{20}_D$** – 72.0 (*c* 0.1, CH_2Cl_2); **IR** (neat) 3056, 2971, 2795, 1600, 1506, 1480, 1450, 1366, 1301, 1266, 1218, 1192, 1175, 1144, 1122, 1090, 1069, 1018, 1008, 942, 922, 894, 857, 821, 779, 746 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09-8.04 (m, 4H), 7.92-7.90 (m, 1H), 7.71-7.60 (m, 6H), 7.58-7.51 (m, 4H), 4.00 (q, *J* = 6.6 Hz, CHN, 1H), 3.80 (d, *J* = 12.4 Hz, 2H), 3.58 (d, *J* = 12.6 Hz, 2H), 1.75 (d, *J* = 6.6 Hz, CH_3, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.9 (C^{IV}), 141.5 (C^{IV}), 135.4 (C^{IV}), 133.9 (C^{IV}), 133.1 (C^{IV}), 130.01(CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 126.1 (CH), 125.8 (CH), 62.8 (CH), 53.4 (CH_2), 22.9 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 350.3 (100), 197.5 (62), 139.7 (70); **HRMS**: Calcd. for $C_{26}H_{24}N^+$ ($[M+H]^+$) : 350.1903, found 350.1904.

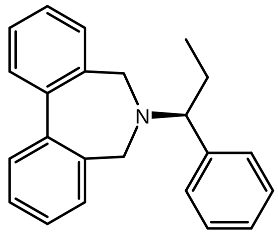
6-N-(*S*-1-(4-Methoxy-Phenyl)ethyl)-5H-dibenz[c,e]azepine or 1d



Starting from 100 mg of biphenyl-2,2'-dicarboxaldehyde, compound **1b** was obtained as a pale yellow solid (125 mg, 81%) after chromatography over basic alumina using *c*-Hex/EtOAc 75:25 as eluent.

***R*$_f$** = 0.30 (SiO_2, *c*-Hex/EtOAc 75:25); **M.p.** 103-105 °C; **$[\alpha]_D^{20}$** – 45.0 (*c* 1.3, MeOH); **IR** (neat) 3006, 2931, 1584, 1509, 1247, 1140, 1001, 831, 746, cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (m, 10H), 6.96 (d, 2H, *J* = 8.4 Hz), 3.87 (s, 3H), 3.61 (q, 1H, *J* = 6.5 Hz), 3.58 (d, 2H, *J* = 12.6 Hz), 3.34 (d, 2H, *J* = 12.6 Hz), 1.50 (d, 3H, *J* = 6.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.6 (C^{IV}), 141.3 (C^{IV}), 138.2 (C^{IV}), 135.3 (C^{IV}), 129.8 (CH), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 113.9 (CH), 61.8 (CH), 55.3 (OCH_3), 51.3 (CH_2), 22.8 (CH_3); **MS-EI** *m/z* (rel intensity) 329 (13, M), 314 (100, M-CH_3); **HRMS**: Calcd. for $C_{23}H_{23}NO$: 329.17796, found 329.17681.

6-N-(*S*-1- Phenylpropyl)-5H-dibenz[c,e]azepine or 1e

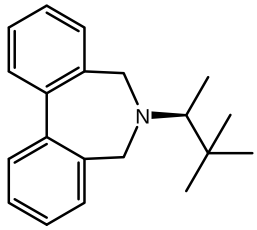


Starting from 250 mg of biphenyl-2,2'-dicarboxaldehyde, compound **1e** was obtained as a colorless oil (260 mg, 70%) after chromatography over silica gel using *c*-Hex /EtOAc 9:1 as eluent.

***R*$_f$** = 0.4 (SiO_2, *c*-Hex /EtOAc 4:1); **$[\alpha]_D^{20}$** – 49.0 (*c* 0.1, MeOH); **IR** (neat) 3061, 3023, 2969, 2791, 1451, 1023, 748, 701 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53-7.29 (m, 13H), 3.58 (2H, *J* = 12.4 Hz, Ar-CH_2-N), 3.29

(2H, *J* =12.4 Hz, Ar-CH_2-N), 3.42 (dd, 1H, *J* = 9.6 and 3.8 Hz, CH-N), 2.14-2.07 (m, 1H, CH), 1.81-1.73 (m, 1H, CH_2), 0.69 (t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.4 (C^{IV}), 141.3 (C^{IV}), 135.3 (C^{IV}), 129.9 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 127.0 (CH), 69.0 (CH-N), 53.2 (NCH_2), 27.3 (CH_2), 10.4 (CH_2); **MS-ES**(+) *m/z* (rel intensity) 179.1 (100), 196.3 (86, M+1-$C_{10}H_{14}$), 314.3 (69, M+1); **HRMS**: Calcd. for $C_{23}H_{24}N^+$ ($[M+H]^+$) : 314.1903, found 314.1887.

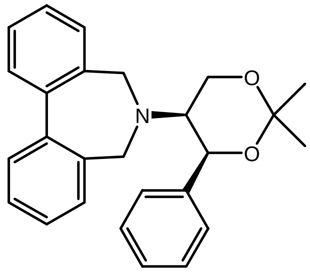
6-N-((*S*)-1,2,2-Trimethylpropyl)-5H-dibenz[c,e]azepine or 1f



Starting from 250 mg of biphenyl-2,2'-dicarboxaldehyde, compound **1f** was obtained as a colorless oil (266 mg, 80 %) after chromatography over basic alumina using *c*-Hex as eluent.

***R*$_f$** = 0.6 (Al_2O_3 basic, *c*-Hex); **$[\alpha]_D^{20}$** + 38.7 (*c* 0.1, MeOH); **IR** (neat) 3064, 3017, 2950, 2866, 1481, 1450, 1356, 1096, 751, 609 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.5-7.4 (m, 8H), 3.60 (CH_2N, 2H), 2.67 (q, CHN, *J* = 7.1 Hz,1H), 1.15 (d, CH_3, *J* = 7.1 Hz, 3H), 1.03 (s, tBu, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.0 (C^{IV}), 137.1 (C^{IV}), 129.8 (CH), 127.8 (CH), 127.4 (CH), 127.4 (CH), 68.7 (CHN), 54.7 (CH_2N), 36.8 (C^{IV}), 27.1 (CH_3), 11.6 (CH_3); **MS-EI** *m/z* (rel intensity) 222 (100%), 279 (1%); **HRMS**: Calcd. for $C_{20}H_{26}N^+$ ($[M+H]^+$) : 280.2060, found 280.2043.

6-N-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-5H-dibenz[c,e]azepine or 1g

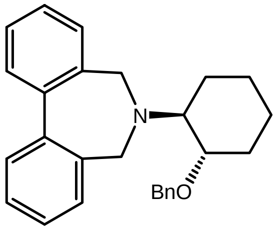


Starting from 1.0 g of biphenyl-2,2'-dicarboxaldehyde, compound **1g** was obtained as a white solid (714 mg, 77%) after chromatography over silica gel *c*-Hex/EtOAc 4:1 as eluent.

***R*$_f$** = 0.3 (SiO_2, *c*-Hex /EtOAc 4:1); **M.p.** 115-120 °C; **$[\alpha]_D^{20}$** + 95.5 (*c* 0.6, EtOH); **IR** (neat) 2856, 1450, 1257, 1073, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (m, 13H), 5.25 (d, 1H, *J* = 3.3 Hz), 4.29 (d, 2H, *J* = 2.8 Hz), 3.72 (d, 2H, *J* = 12.5 Hz), 3.54 (d, 2H, *J* = 12.5 Hz), 3.00 (s, 1H), 1.63 (s, 3H), 1.62 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.0 (C^{IV}), 140.2 (C^{IV}), 136.7 (C^{IV}), 129.4 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 126.8 (CH), 126.3 (CH), 99.1 (C^{IV}), 74.8

(CH), 62.2 (CH_2), 60.9 (CH), 54.0 (CH_2), 29.5 (CH_3), 30.0 (CH_2), 19. (CH_3); **MS-EI** *m/z* (rel intensity) 385 (1 %); 179 (100 %); **HRMS**: Calcd. for $C_{26}H_{27}NO_2$: 385.20418 (100 %); found 385.20040.

6-N-((*S*)-*trans*-2-Phenylmethoxycyclohexyl)-5H-Dibenz[c,e]azepine or 1h

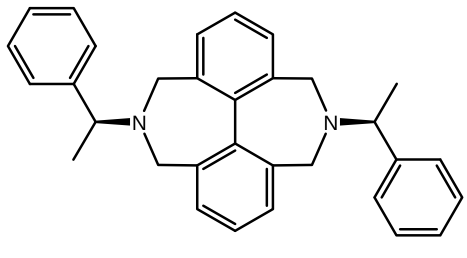


Starting from 250 mg of biphenyl-2,2'-dicarboxaldehyde, compound **1h** was obtained as a colorless oil (377 mg, 83%) after chromatography over basic alumina using *c*-Hex then *c*-Hex/AcOEt (90/10) as eluent.

R_f = 0.4 (Al_2O_3 basic, *c*-Hex /EtOAc 9:1); **$[\alpha]_D^{20}$** + 43.3 (*c* 0.1, MeOH); **IR** (neat) 3062, 3027, 2928, 2856, 1450, 1084, 748, 697 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$) δ 7.6-7.3 (m, 8H), 4.69 (CHO, 1H), 3.75 (2 x CH_2N and CH-O, 5H), 2.91 (m, CHN, 1H), 2.29 (m, CH, 1H), 2.02 (m, CH, 1H), 1.82 (m, CH_2, 2H), 1.67-1.32 (m, 2 x CH_2, 4H), ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.2 (C^{IV}), 139.3 (C^{IV}), 136.7 (C^{IV}), 129.9 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 78.2 (CH), 71.0 (CH_2), 67.4 (CH), 52.7 (CH_2), 30.9 (CH_2), 28.1 (CH_2), 24.7 (CH_2), 24.1 (CH_2); **MS-ES** (+) *m/z* (rel intensity) 382.3 (100 %); 284.2 (24 %); **HRMS**: Calcd. for $C_{27}H_{30}NO^+$ ($[M+H]^+$) : 384.2322, found 384.2311.

General procedure for the synthesis of azepines 4a, 4b, 4d, 4e, 4f and 4g:

To a solution of biphenyl-2,2',6,6'-tetracarboxaldehyde (1.0 eq.) in CH_3CN (6 mL per 0.1 g of aldehyde) was added the corresponding enantiopure amine **a** to **e** (2.2 eq.). After 15 min of stirring, $NaBH_3CN$ (4 eq.) was added and the reaction was stirred for 20h before the addition of AcOH (~10 eq.). After 1h, the reaction mixture was diluted with 2% MeOH/CH_2Cl_2 (40 mL), washed with 1M NaOH (until pH>10), dried over Na_2SO_4 and concentrated under reduce pressure. Unless otherwise stated, the compounds were obtained after purification over silica gel.



Starting from 150 mg of biphenyl-2,2',6,6'-tetracarboxaldehyde, compound **4a** was obtained as a mixture of 2 diastereomers (63:37 ratio, 165 mg, 65%). Diastereomers were separated by chromatography on silica gel using benzene/ether 2:1 as eluent.

(–)-5,11-Bis((*S*)-1-phenylethyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*S*a)-4a

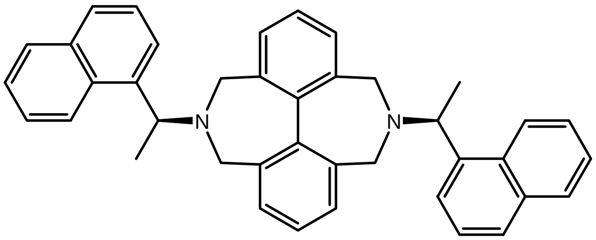
(*S*a)-**4a** was obtained as a white solid (76 mg, 30%)

$\boldsymbol{R_f}$ = 0.19 (benzene/ether 2/1); **M.p.** 60-65 °C; $\mathbf{[\alpha]_D^{20}}$ – 336 (*c* 0.2, MeOH); **IR** (neat) 2960, 2921, 2800, 1601, 1491, 1451, 1370, 1340, 1282, 1224, 1111, 1060, 919 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.53 (d, 4H, J = 7.0 Hz), 7.36 (m, 12H), 3.78 (d, 4H, J_{AB} = 12.5 Hz), 3.10 (d, 4H, J_{AB} = 12.5 Hz), 3.64 (q, 2H, J = 6.5 Hz), 1.41 (d, 6H, J = 6.5 Hz); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 146.6, 140.7, 135.0, 129.6, 129.1, 128.0, 127.9, 127.4, 63.2, 53.4, 23.0; **MS-EI** *m/z* (rel intensity) 444 (20%), 429 (100%). **HRMS**: Calcd. for $C_{32}H_{32}N_2$: 444.25655, found 444.25820.

(+)-5,11-Bis((*S*)-1-phenylethyl)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene (*R*a)-4a

(*R*a)-**4a** was obtained as a white solid (33 mg, 13%)

$\boldsymbol{R_f}$ = 0.05 (benzene/ether 2/1); **M.p.** 128-132 °C; $\mathbf{[\alpha]_D^{20}}$ + 69.5 (*c* 0.2, MeOH); **IR** (neat) 2968, 2795, 1634, 1599, 1491, 1451, 1264, 1083, 921 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.38 (m, 16H), 3.77 (d, 4H, J_{AB} = 17.0 Hz), 3.15 (d, 4H, J_{AB} = 17.0 Hz), 3.58 (q, 2H, J = 8.5 Hz), 1.67 (d, 6H, J = 8.5 Hz); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 145.9, 140.6, 134.9, 129.3, 128.9, 128.7, 128.0, 27.9, 127.4, 62.8, 53.2, 22.9; **MS-EI** *m/z* (rel intensity) 444 (35%), 429 (100%).



Starting from 506 mg of biphenyl-2,2',6,6'-tetracarboxaldehyde, compound **4b** was obtained as a mixture of 2 diastereomers (58:42 ratio, 600 mg, 58%) as a white solid.

(–)-5,11-Bis((*S*)-1-(2-Naphthyl)ethyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*S*a)-4b

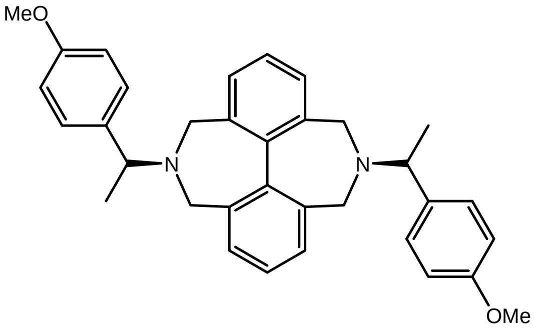
This first eluted diastereomer (*S*a)-**4b** was isolated by chromatography on basic alumina using toluene as eluent and obtained as a white solid (163 mg, 16%).

M.p. 101 °C; **$[\alpha]_D^{20}$** – 11.2 (*c* 0.20, DCM); **IR** (neat) 2971, 2791, 1594, 1509, 1450, 1372, 1225, 1112, 1068 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (s, 2H), 7.6-7.8 (m, 6H), 7.3-7.45 (m, 6H), 7.0-7.25 (m, 6H), 4.29 (d, 2H, *J* = 6.3 Hz), 3.69 (d, 4H, *J* = 12.4 Hz), 3.06 (d, 4H, *J* = 12.1 Hz), 1.37 (d, 6H, *J* = 6,6 Hz), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.2, 140.5, 140.2, 138.0, 135.0, 134.4, 134.2, 131,3, 129.3, 129.2, 129.0, 128.9, 128.3, 127.8, 127.6, 127.4, 126.0, 125.8, 125.4, 124.1, 59.5, 53.5, 21.9; **MS-ES** (+) *m/z* (rel intensity) 545.3 (100, M+1), 391.3 (40, [M-$C_{12}H_{12}$]+1), 357.3 (20), 277.5 (25), 237.5 (20, [M-2x$C_{12}H_{12}$]+1).

(+)-5,11-Bis((*S*)-1-(2-Naphthyl)ethyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-4b

This second eluted diastereomer (*R*a)-**4b** was isolated by chromatography on basic alumina using ether as eluent and obtained as white solid (41 mg, 4%).

M.p. 118.0 °C; **$[\alpha]_D^{20}$** + 3.4 (*c* 0.23, DCM); **IR** (neat) 2975, 2793, 1595, 1507, 1452, 1372, 1224, 1111, 1068 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (s, 2H), 8.0-7.0 (m, 18H), 4.27 (s, 2H), 3.74 (d, 4H, *J* = 12.4 Hz), 3.10 (d, 4H, *J* = 12.4 Hz), 1.75 (d, 6H, *J* = 6,1 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.3, 133.9, 133.2, 133.0, 130.5, 127.9, 127.7, 126.8, 126.7, 126.6, 126.4, 125.0, 124.8, 125.6, 124.4, 124.0, 123.1, 58.3, 52.0, 20.5; **MS-ES** (+) *m/z* (rel intensity) 545.3 (100, M+1), 391.3 (70, [M-$C_{12}H_{12}$]+1), 237.5 (30, [M-2x$C_{12}H_{12}$]+1).



Starting from 208 mg of biphenyl-2,2',6,6'-tetracarboxaldehyde, compound **4d** was obtained as a mixture of 2 diastereomers (52:48 ratio, 275 mg, 70%).

(–)-5,11-Bis((*S*)- 1-(4-methoxyphenyl)ethanamine)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*S*a)-4d

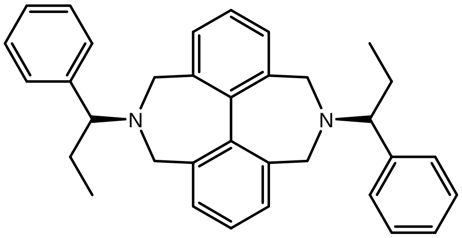
This first eluted diastereomer (*S*a)-**4d** was isolated by chromatography on silica gel using benzene/ether 2:1 as eluent and obtained as white solid (86 mg, 22%).

***R*f** = 0.18 (benzene/ether 1:1); **M.p.** 84-85 °C; $[\alpha]_D^{20}$ – 263.5 (*c* 0.26, $CHCl_3$); **IR** (neat) 2967, 2792, 1610, 1509, 1454, 1240, 1171, 1101, 1035, 918, 832 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.42 (m, 10H), 7.0 (d, 4H, *J* = 8.5 Hz), 3.90 (s, 6H), 3.82 (d, 4H, J_{AB} = 12.5 Hz), 3.12 (d, 4H, J_{AB} = 12.5 Hz), 3.63 (q, 2H, *J* = 6.5 Hz), 1.43 (d, 6H, *J* = 6.5 Hz); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 158.6, 140.3, 138.5, 134.8, 129.1, 128.6, 128.4, 127.4, 114.0, 62.1, 55.3, 53.0, 22.7; **MS-EI** *m/z* (rel intensity) 504 (3, M), 135 (100); **HR-MS**: Calcd for $C_{34}H_{36}N_2O_2$: 504.27768; found: 504.28246

(+)-5,11-Bis((*S*)- 1-(4-methoxyphenyl)ethanamine)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-4d

This second eluted diastereomer (*R*a)-**4d** was isolated using a semi-preparative HPLC column (hexane/isopropanol 95:5) and obtained as a white solid.

***R*f** = 0.10 (DCM); $[\alpha]_D^{20}$ + 62.1 (*c* 0.26, $CHCl_3$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.31(m, 10H), 6.90 (d, 4H, *J* = 8.8 Hz), 3.89 (s, 6H), 3.74 (d, 4H, J_{AB} = 12.9 Hz), 3.53 (q, 2H, *J* = 6.3 Hz) 3.11 (d, 4H, J_{AB} = 12.9 Hz), 1.63 (d, 6H, *J* = 6.5 Hz); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 158.6, 140.3, 137.5, 134.8, 128.8, 128.5, 127.5, 113.8, 61.6, 55.3, 52.9, 22.5; **MS-ES** (+) *m/z* (rel intensity) 505.3 (95, M+1), 371.5 (100, $[M-C_9H_{12}O]+1$), 237.3 (95, $[M-2xC_9H_{12}O]+1$).



Starting from 197 mg of biphenyl-2,2',6,6'-tetracarboxaldehyde, compound **4e** was obtained as a mixture of 2 diastereomers (52:48 ratio, 310 mg, 88%) as a white foam.

(–)-5,11-Bis((*S*)-1- Phenylpropyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*S*a)-4e

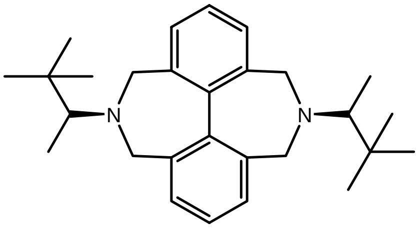
This first eluted diastereomer (*S*a)-**4e** was obtained by selective precipitation in MeOH. The crude mixture containing the two diastereomers (310 mg) was dissolved in methanol (~4 mL)and after few seconds, a white precipitate appears. This precipitate was filtered, washed with cold methanol to give the desired diasteromer as a white powder (99 mg, 28%).

***R*f** = 0.21 (DCM); **M.p.** 100 °C; **[α]$_D^{20}$** – 298.2 (*c* 0.39, MeOH); **IR** (neat) 2961, 2797, 1730, 1492, 1453, 1353, 1261, 1083, 1024, 961 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.23 (m, 16H), 3.76 (d, 4H, J_{AB} = 12.3 Hz), 3.36 (dd, 2H, *J* = 9.4 Hz and 3.8 Hz), 3.06 (d, 4H, J_{AB} = 12.4 Hz), 1.96 (m, 2H), 1.68 (m, 2H), 0.61 (t, 6H, *J* = 7.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 128.9, 128.7, 128.2, 127.6, 127.1, 69.1, 52.9, 27.5, 10.6; **MS-ES** (+) *m/z* (rel intensity) 473.3 (100, M+1), 355.1 (70, [M-C_9H_{12}]+1), 277.3 (40), 237.1 (30, [M-2xC_9H_{12}]+1).

(+)-5,11-Bis((*S*)-1- Phenylpropyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-4e

This second eluted diastereomer (*R*a)-**4e** was isolated using a semi-preparative HPLC column (hexane /isopropanol 95:5).

***R*f** = 0.37 (benzene/ether 2:1); **M.p.** 89 °C; **[α]$_D^{20}$** + 51.0 (*c* 0.39, MeOH); **IR** (neat) 2965, 2789, 1631, 1598, 1451, 1356, 1220, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52-7.31 (m, 16H), 3.81 (d, 4H, J_{AB} = 12.4 Hz), 3.44 (dd, 2H, *J* = 9.6 Hz and 3.5 Hz), 3.06 (d, 4H, J_{AB} = 12.4 Hz), 2.04 (m, 2H), 1.74 (m, 2H), 0.69 (t, 6H, *J* = 7.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.5, 140.3, 134.7, 129.0, 128.7, 128.3, 127.3, 126.9, 69.1, 53.0, 27.1, 10.3; **MS-ES** (+) *m/z* (rel intensity) 473.3 (100, M), 355.1 (100, [M-C_9H_{12}]+1), 237.3 (80, [M-2xC_9H_{12}]+1).



Starting from 250 mg of biphenyl-2,2',6,6'-tetracarboxaldehyde, compound **4f** was obtained as a mixture of 2 diastereomers (58:42 ratio, 380 mg, 100%).

(+)-5,11-Bis((*S*)-1,2,2-Trimethylpropyl)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-4f

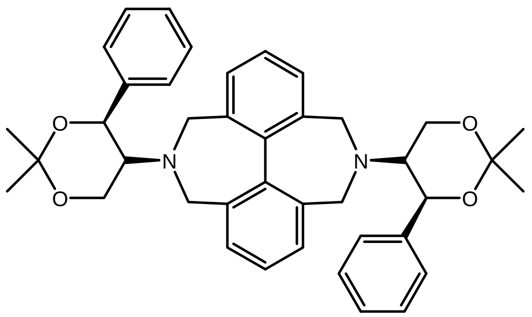
This first eluted diastereomer (*R*a)-**4f** was isolated by chromatography on silica gel using benzene as eluent and obtained as white solid (76 mg, 20%).

***R*f** = 0.91 (benzene/ether 1:1); **M.p.** 171-172 °C; $[\alpha]_D^{20}$ + 256.0 (*c* 0.41, $CHCl_3$); **IR** (neat) 2967, 2863, 1459, 1356, 1154, 1116 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.35 (m, 6H), 3.65 (d, 4H, J_{AB} = 12.5 Hz), 3.48 (d, 4H, J_{AB} = 12.5 Hz), 2.53 (q, 2H, *J* = 7.0 Hz), 1.19 (d, 6H, *J* = 7.0 Hz), 0.99 (s, 18H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 139.6, 136.4, 128.9, 128.0, 68.2, 54.1, 27.0, 11.6; **MS-ES** (+) *m/z* (rel intensity) 405.7 (100, M+1).

(–)-5,11-Bis((*S*)-1,2,2-Trimethylpropyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*S*a)-4f

This second eluted diastereomer **(*S*a)-4f** was isolated by a preparative chromatography on basic alumina using pentane/*c*-hexane/ethyl acetate (50:50:1.2) as eluent and obtained as a pale yellow viscous oil (22.8 mg, 6%).

***R*f** = 0.18 (*c*-hexane); $[\alpha]_D^{20}$ –100.0 (*c* 0.41, $CHCl_3$); **IR** (neat) 2949, 2902, 2865, 1637, 1480, 1548, 1355, 1154, 1114, 1074, 927 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.35 (m, 6H), 3.56 (dd, 8H, J_{AB} = 12.0 Hz), 2.84 (q, 2H, *J* = 7.1 Hz), 1.19 (d, 6H, *J* = 7.0 Hz), 1.02 (s, 18H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 139.6, 136.4, 128.1, 127.8, 69.8, 55.4, 27.4, 11.6; **MS-ES** (+) *m/z* (rel intensity) 405.5 (100, M+1), 321.5 (80, [M-C_6H_{14}]+1), 237.1 (20, [M-2xC_6H_{14}]+1).



Starting from 300 mg of biphenyl-2,2',6,6'-tetracarboxaldehyde, compound 4g was obtained as a mixture of 2 diastereomers (65:35 ratio, 590 mg, 85%).

(+)-5,11-Bis((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-4g

This first eluted diastereomer (*R*a)-**4g** was isolated by chromatography on silica gel using benzene/ether 2:1 as eluent and obtained as white solid (177 mg, 26%).

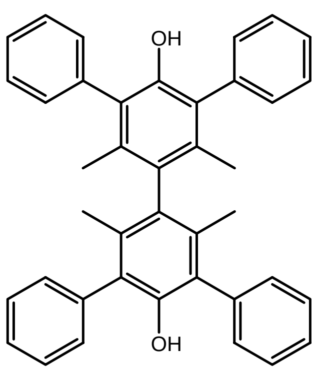
R_f = 0.66 (benzene/ether 2:1); **M.p.** 174-176 °C; **$[\alpha]_D^{20}$** + 235.5 (*c* 0.2, MeOH); **IR** (neat) 2989, 2862, 1635, 1449, 1380, 1200, 1153, 1076 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (m, 16H), 5.19 (d, 2H, J = 3.0 Hz), 4.27 (d, 4H, J_{AB} = 11.0 Hz), 3.80 (d, 4H, J_{AB} = 12.5 Hz), 3.27 (d, 4H, J_{AB} = 12.5 Hz), 2.73 (d, 2H, J = 2.5 Hz), 1.70 (s, 6H), 1.70 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.3, 139.6, 135.6, 128.4, 128.3, 128.0, 127.6, 126.8, 126.5, 99.2, 75.0, 61.5, 59.9, 53.1, 29.7, 19.1; **MS-ES** (+) *m/z* (rel intensity) 615.9 (100, M+1).

5,11-Bis((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*S*a)-4g

This second eluted diastereomer (*S*a)-**4g** was isolated by a preparative chromatography on basic alumina using pentane/ethyl acetate (85/15) and obtained as a white solid (68.3 mg, 10%).

R_f = 0.30 (pentane/ethyl acetate 9:1); **M.p.** 118 °C; **$[\alpha]_D^{20}$** 0.0 (*c* 0.2, MeOH); **IR** (neat) 29889, 2852, 1449, 1378, 1264, 1196, 1139, 1075, 1023, 950, 852 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (m, 16H), 5.23 (d, 2H, J = 3.6 Hz), 4.21 (m, 4H), 3.62 (d, 4H, J_{AB} = 12.8 Hz), 3.49 (d, 4H, J_{AB} = 12.8 Hz), 3.15 (d, 2H, J = 2.3 Hz), 1.54 (s, 6H), 1.49 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.1, 139.6, 136.1, 128.1, 127.8, 126.8, 126.1, 98.9, 74.5, 62.6, 61.8, 54.5, 29.2 ,19.2; **MS-ES** (+) *m/z* (rel intensity) 615.9 (100, M+1).

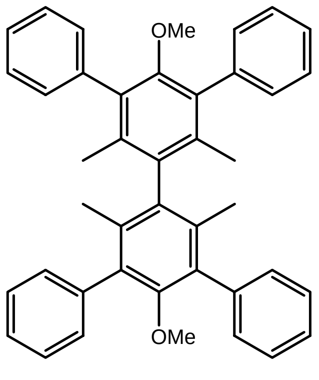
2,2’,6,6’-Tetramethyl-3,3’,5,5’-tetraphenyl-4,4’-dihydroxybiphenyl or 7



To a solution 2,6-diphenyl-3,5-dimethylphenol (4.59 g, 16.730 mmol) in glacial acetic acid (140 mL) was added manganese III acetate diydrate (13.46 g, 50.189 mmol). After 2h of stirring at room temperature (till the disappearance of the starting material, checked by TLC), the mixture solvent was evaporated under vaccum. DCM was added (100 mL) and the solid was filtrated on celite. After several washings with DCM, the mother liquors were evaporated. The solid obtained was then filtrated on SiO_2 (eluent DCM / Pentane 1:2) to yield 4,0 g of a yellow solid containing 2,6-dimethyl-3,5-diphenylcyclohexa-2,5-diene-1,4-dione (63%) and the desired product (37%). After recrystallisation (Ether / Hexane) the desired biphenol was obtained as a pale yellow solid (1.53 g, 33%).

***R*$_f$** = 0.50 (pentane/DCM 2:1); **M.p**. 286 °C; **IR** (neat) 3545, 3522, 3052, 2918, 1602, 1562, 1492, 1438, 1399, 1282, 1232, 1164, 1048 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (t, 8H, *J* = 7.5 Hz), 7.38 (m, 12H), 4.68 (s, 2H), 1.79 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.7 (C^{IV}), 137.4 (C^{IV}), 134.5 (C^{IV}), 133.6 (C^{IV}), 130.7 (CH), 129.0 (CH), 127.6 (CH), 126.6 (C^{IV}), 18.2 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 547.3 (90, M+1), 279.1 (70), 184.3 (100).

2,2’,6,6’-Tetramethyl-3,3’,5,5’-tetraphenyl-4,4’-dimethoxybiphenyl or 8

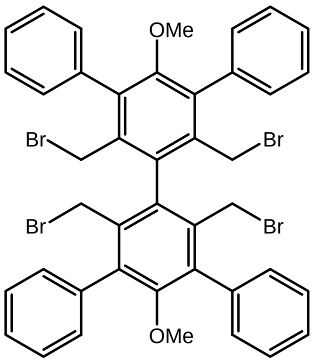


In a dried 100 mL round bottom flask containing sodium hydride (washed with hexane and the dried under vaccum, 360 mg, 8.231 mmol), under argon atmosphere was added a suspension of 2,2’,6,6’-tetramethyl-3,3’-5-5’-tetraphenyl-4,4’-dihydroxy biphenyl (1.50 g, 2.744 mmol) in dry DMF (40 mL). The mixture was stirred for about 3h and then iodomethane (0.85 mL, 13.72 mmol) was introduced. After 5h of stirring at room temperature (till the disappearance of the starting material, checked by TLC) the reaction was quenched by addition of water and ice. The precipitate obtained was filtered and washed with water. The recovered solid was solubilised in DCM and dried (Na_2SO_4).

After concentration on reduced pressure, the desired compound was obtained without purification as a pale yellow solid (1.46g, 93%).

***R*$_f$** = 0.66 (pentane/DCM 2:1); **M.p**. 259 °C; **IR** (neat) 3055, 2921, 2854, 1601, 1495, 1455, 1440, 1389, 1275, 1066, cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.42 (m, 8H), 7.34 (m, 12H), 3.01 (s, 6H), 1.78 (s, 12H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 154.1 (C^{IV}), 138.7 (C^{IV}), 137.3 (C^{IV}), 134.5 (C^{IV}), 134.0 (C^{IV}), 130.5 (CH), 128.1 (CH), 126.8 (CH), 60.6 (OCH$_3$), 18.2 (CH$_3$); **MS-ES** (–) *m/z* (rel intensity) 559.3 (20, [M-CH$_3$]$^-$), 339.4 (100).

2,2’,6,6’-Tetrakis(bromomethyl)-3,3’,5,5’-tetraphenyl-4,4’-dimethoxybiphenyl or 9

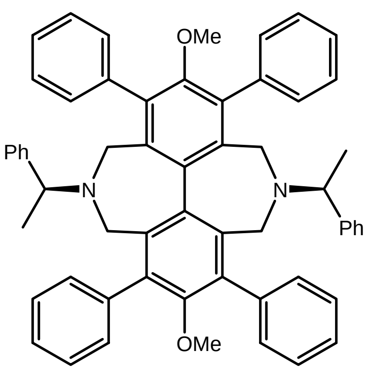


In a 100 mL round bottom flask containing 2,2’,6,6’-tetramethyl-3,3’,5,5’-tetraphenyl-4,4’-dimethoxybiphenyl (1.46 g, 2.538 mmol), N-bromosuccinimide (1.853 g, 10.407 mmol) and AIBN (12.5 mg, 0.076 mmol) was added CCl$_4$ (60 mL). The resulting suspension was stirred at reflux (by light bulb irradiation) under argon for 6 h. The crude suspension was filtered through silica, washed with DCM (300 mL) and concentrated to yellow foam (2.29g, 100%).

***R*$_f$** = 0.95 (cyclohexane/DCM 1:1); **M.p**. 161 °C (decomposition); **IR** (neat) 2934, 2859, 1602, 1494, 1443, 1390, 1280, 1210, 1124, 1064 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.50-7.41 (m, 20H), 4.31 (s, 8H), 3.08 (s, 6H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 156.9 (C^{IV}), 139.2 (C^{IV}), 135.6 (C^{IV}), 135.1 (C^{IV}), 133.8 (C^{IV}), 130.1 (CH), 128.4 (CH), 128.0 (CH), 61.1 (OCH$_3$), 32.7 (CH$_2$); **MS-ES** (–) *m/z* (rel intensity) 395.3 (30), 339.1 (100), 254.4 (30).

General procedure for the synthesis of azepines 10a, 10b, 10f and 10g:

To a suspension of **9** (1.0 eq) in CH$_3$CN (3 mL per 0.1 g of **9**), was added the corresponding enantiopure amine **a, b f or g** (5.0 eq.) and K$_2$CO$_3$ (5.0 eq) in a microwave sealed tube. The mixture was heated at 160 °C for 30 min with the microwave apparatus. After evaporation to dryness, the product was filtered on basic alumina with ethyl acetate as eluent.



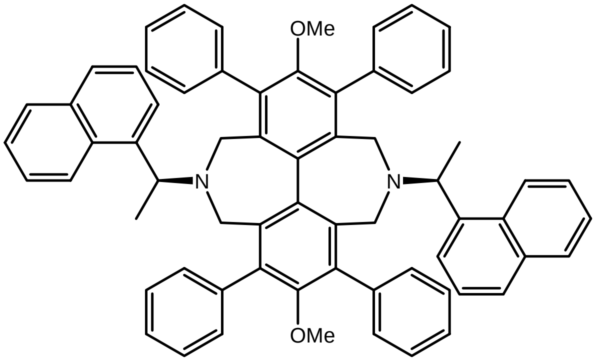
Starting from 107 mg of **9**, compound 10a was obtained as a mixture of 2 diastereomers (15:85 ratio, 98 mg, 100%). Diastereomers were purified and separated by chromatography on silica gel using DCM as eluent for the first eluted diastereomer and ethyl acetate for the second eluted diastereomer.

(–)-5,11-Bis((*S*)-1-phenylethyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*S*a)-10a

This first eluted diastereomer (*S*a)-**10a** was obtained as an orange solid (14,0 mg, 14%). ***R*$_f$** = 0.77 (DCM); **M.p.** 101 °C; **[α]$_D$^{20}** – 27.8 (*c* 0.1, MeOH); **IR** (neat) 2921, 2850, 1728, 1451, 1359, 1276, 1129, 1064, 1027, 699 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.92 (d, 4H, *J* = 7.4 Hz), 7.58 (t, 4H, *J* = 7.4 Hz), 7.40 (m, 4H), 7.32-7.26 (m, 10H), 7.11 (dd, 4H, *J* = 3.1 Hz), 6.83 (m, 4H), 3.87 (d, 4H, J_{AB} = 12.1 Hz), 3.47 (q, 2H, *J* = 6.6 Hz), 3.16 (d, 4H, J_{AB} = 12.1 Hz), 2.92 (s, 6H), 0.92 (d, 6H, *J* = 6.8 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 154.7 (C^{IV}), 147.4 (C^{IV}), 137.0 (C^{IV}), 135.0 (C^{IV}), 133.7 (C^{IV}), 131.8 (CH), 130.7 (CH), 128.6 (CH), 128.4 (C^{IV}), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.7 (CH), 125.8 (CH), 60.6 (CH), 59.7 (CH$_3$), 48.4 (CH$_2$), 22.8 (CH$_3$); **MS-ES** (+) *m/z* (rel intensity) 809.8 (100, M+1), 705.7 (10, M-C$_8$H$_8$).

(+)-5,11-Bis((*S*)-1-phenylethyl)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-10a

This least eluted diastereomer (*R*a)-**10a** was obtained as an orange solid (70,0 mg, 72%). ***R*$_f$** = 0.17 (DCM); **M.p.** 197.4 °C; **[α]$_D$^{20}** + 17.5 (*c* 0.1, MeOH); **IR** (neat) 2928, 1451, 1386, 1275, 1048, 757, 698 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.64 (d, 4H, *J* = 6.4 Hz), 7.48 (m, 4H), 7.37-7.26 (m, 12H), 6.98-6.91 (m, 6H), 6.87 (d, 4H, *J* = 6.5 Hz), 3.71 (d, 4H, J_{AB} = 12.6 Hz), 3.14 (q, 2H, *J* = 6.1 Hz), 2.97 (s, 6H), 2.90 (d, 4H, J_{AB} = 12.4 Hz), 0.44 (d, 6H, *J* = 6.1 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 154.5 (C^{IV}), 145.1 (C^{IV}), 137.7 (C^{IV}), 137.3 (C^{IV}), 135.3 (C^{IV}), 133.8 (C^{IV}), 131.5 (CH), 130.6 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.4 (CH), 127.1 (CH), 126.4 (CH), 62.0 (CH), 60.4 (CH$_3$), 49.1 (CH_2), 22.3 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 809.8 (100, M+1), 705.7 (20, M-C_8H_8), 601.5 (15, M-$C_{16}H_{16}$).



Starting from 200 mg of **9**, compound **10b** was obtained as a mixture of 2 diastereomers. Diastereomers were separated by chromatography on silica gel using DCM as eluent for the first eluted diastereomer and DCM/Ethyl acetate 1:1 for the second eluted diastereomer

(–)-5,11-Bis((*S*)-1-(2-Naphthyl)ethyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene (*S*a)-10b

This first eluted diastereomer (*S*a)-**10b** was obtained as an orange solid (30,0 mg, 15%).

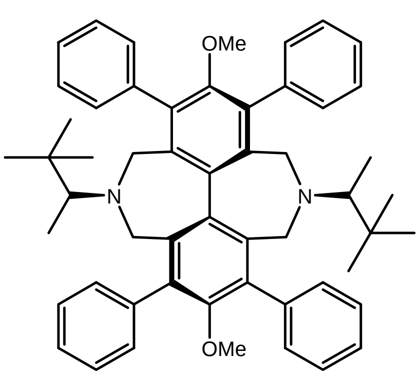
M.p. 130 °C; **[α]$_D$^{20}** – 80.0 (*c* 0.10, MeOH); **IR** (neat) 2929, 1723, 1676, 1598, 1451, 1386, 1275, 1114, 1059 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.80 (m, 2H), 7.67 (d, 4H, *J* = 7.1 Hz), 7.57 (d, 2H, *J* = 8.1 Hz), 7.47-7.30 (m, 6H), 7.22 (m, 6H), 7.12 (t, 4H, *J* = 7.3 Hz), 6.98 (q, 8H, *J* = 6.8 Hz), 4.20 (q, 2H, *J* = 6.6 Hz), 4.04 (d, 4H, *J* = 12.1 Hz), 3.32 (d, 4H, *J* = 12.4 Hz), 2.86 (s, 6H), 1.14 (d, 6H, *J* = 6,6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.8 (C^{IV}), 141.4 (C^{IV}), 137.9 (C^{IV}), 136.6 (C^{IV}), 135.3 (C^{IV}), 134.3 (C^{IV}), 133.9 (C^{IV}), 131.4 (C^{IV}), 131.4 (C^{IV}), 131.3 (CH), 130.5 (CH), 128.8 (CH), 127.9 (CH), 127.2 (CH), 126.7 (CH), 126.7 (CH), 125.3 (CH), 125.0 (CH), 125.0 (CH), 60.0 (CH_3), 48.8 (CH_2), 21.1 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 909.5 (100, M+1), 755.7 (33, M-$C_{12}H_{10}$).

(+)-5,11-Bis((*S*)-1-(2-Naphthyl)ethyl)-(*S*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene (*R*a)-10b

This second eluted diastereomer (*R*a)-10b was obtained as an orange solid (132,0 mg, 65%).

M.p. 179 °C; **[α]$_D$^{20}** + 77.0 (*c* 0.10, MeOH); **IR** (neat) 2930, 1722, 1677, 1599, 1494, 1441, 1385, 1273, 1056 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* = 7.8 Hz), 7.72 (m, 6H), 7.54-7.25 (m, 22H), 6.96 (m, 4H), 4.07 (m, 2H), 3.91 (d, 4H, *J* = 12.4 Hz), 3.03 (s, 6H), 3.00 (d, 4H, *J* = 12.6 Hz), 0.56 (d, 6H, *J* = 6,3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.5 (C^{IV}), 140.3 (C^{IV}), 137.5 (C^{IV}), 137.2 (C^{IV}), 135.1 (C^{IV}), 133.7 (C^{IV}), 133.6 (C^{IV}), 131.1 (CH), 131.0 (C^{IV}), 130.5 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.0 (CH), 126.2 (CH), 125.7 (CH), 125.2 (CH), 124.8 (CH), 124.6 (CH), 60.3 (CH_3), 48.3 (CH_2), 21.0 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 909.5 (100, M+1), 755.7 (40, M-$C_{12}H_{10}$), 601, 3 (15, M-$C_{24}H_{20}$).

(+)-5,11-Bis((*S*)-1,2,2-Trimethylpropyl)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-10f



Starting from 570 mg of **9**, compound **10f** was obtained as a single diastereomer. The product was purified on basic alumina using DCM/EtOAc 9:1 as eluent to yield the desired compound as a pale yellow solid (320 mg, 43%).

***R*f** = 0.77 (DCM/ethyl acetate 9:1); **M.p.** 180 °C; **$[\alpha]_D^{20}$** – 81.5 (*c* 0.1, MeOH); **IR** (neat) 2950, 1602, 1450, 1387, 1279, 1054 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70-7.20 (b, 20H), 3.90-3.10 (b, 8H), 3.03 (s, 6H), 1.88 (q, 2H, *J* = 6.7 Hz), 0.70 (d, 6H, *J* = 7.1 Hz), 0.48 (s, 18H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 155.9 (C^{IV}), 132.1 (b, CH), 131.4 (b, CH), 128.8 (b, CH), 128.5 (CH), 127.9 (CH), 67.8 (CH), 60.5 (b, CH_2), 37.0 (C^{IV}), 27.0 (CH_3), 12.1 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 769.7 (100, M+1), 685.7 (5, M-C_6H_{12}).[i]

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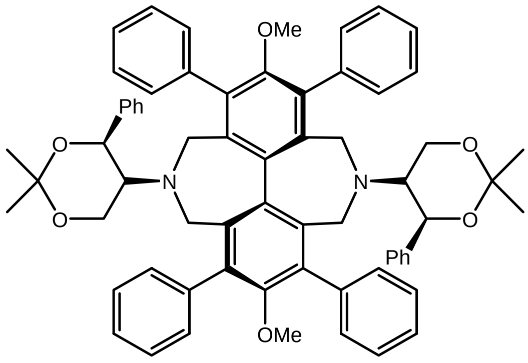
[i] Some C^{IV} in ^{13}C NMR could not be seen due to broad signals and low resolution of the spectra

(+)-5,11-Bis((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-(*R*)-5,6,11,12-tetrahydro-4*H*,10*H*-5,11-diazadibenzo [*ef,kl*]heptalene or (*R*a)-10g

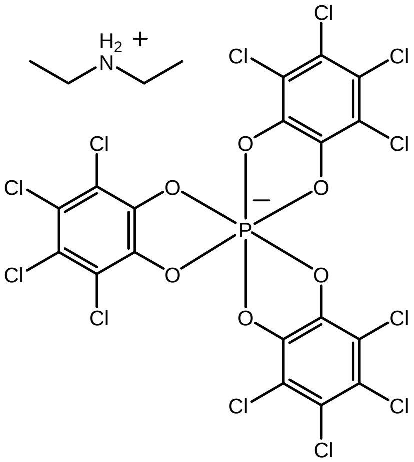


Starting from 155 mg of **9**, compound **10g** was obtained as a single diastereomer. The product was purified on basic alumina using DCM/EtOAc 9:1 as eluent to yield the desired compound as a pale yellow solid (115 mg, 67%).

R_f = 0.71 (DCM/EtOAc 9:1); **M.p.** 157 °C; **$[\alpha]_D^{20}$** – 59.4 (*c* 0.1, MeOH); **IR** (neat) 2989, 1601, 1495, 1450, 1381, 1276, 1197, 1073 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.53-7.42 (b, 20H), 7.17 (m, 6H), 6.70 (d, 4H, *J* = 7.4 Hz), 4.49 (s, 2H), 3.85 (d, 2H, *J* = 11.0 Hz), 3.65 (d, 2H, *J* = 13.1 Hz), 3.20-2.60 (b, 14H), 2.24 (b, 2H), 1.25 (s, 6Hz), 0.89 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 154.8 (C^{IV}), 140.3 (C^{IV}), 137.0 (b, C^{IV}), 134.2 (b, C^{IV}), 131.3 (CH), 130.8 (CH), 128.5 (b, CH), 127.6 (CH), 127.4 (b, CH), 126.7 (CH), 126.6 (CH), 98.3 (C^{IV}), 74.4 (CH), 67.5 (CH$_2$), 61.0 (CH$_2$), 58.3 (CH$_3$), 29.5 (CH$_3$), 25.6 (CH$_2$), 19.5 (CH$_3$); **MS-ES** (+) *m/z* (rel intensity) 982.0 (100, M+1).

CHAPTER II – IMINIUM CATALYSTS IN BIPHASIC ENANTIOSELECTIVE OLEFIN EPOXIDATION

Racemic diethylammonium TRISPHAT salt or [H_2NEt_2][*rac*-TT].



Under a nitrogen atmosphere, in a flame-dried 250 mL two-necked round-bottomed flask, equipped with a magnetic stirring bar, an addition funnel for solid and a reflux condenser (topped with a gas outlet connected to a conc. NaOH trap), 6.0 g of tetrachlorocatechol (crystallized and sublimed) (24.2 mmol, 3 eq.) was added portion wise as a solid, over a 30 min period, to a 50 °C solution of 1.68 g of PCl_5 (8.1 mmol, 1 eq.) in toluene (20 mL) (HCl_g evolution). Dry toluene (20 mL) was further added to wash the glassware. After 14 hours of stirring at 70 °C, the reaction was cooled to room temperature (precipitation) and concentrated *in vacuo*. The resulting gray powder was suspended in CH_2Cl_2 (43 mL). A solution of diethylamine (8.1 mmol, 1 eq.) in CH_2Cl_2 (17 mL) was then slowly added leading to the precipitation of a white solid. After 12 hours of stirring at 25 °C to insure maximum precipitation, reaction was filtered over a Büchner funnel. The solid was washed with CH_2Cl_2 and dried under reduced pressure to afford the desired ammonium TRISPHAT salt (5.72 g, 86 %).

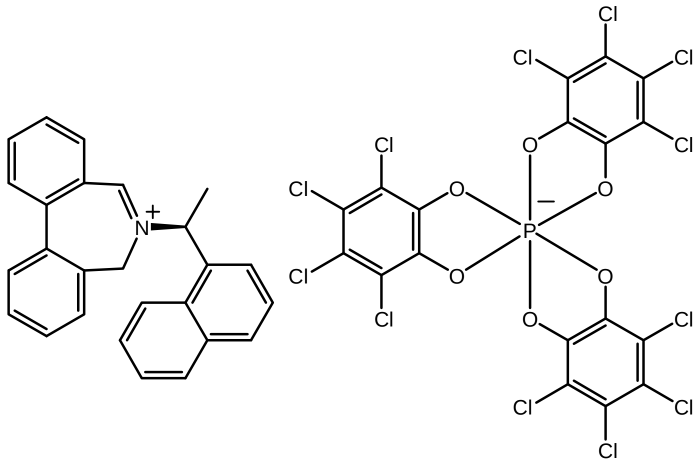
M.p. 220 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.16 (br, NH_2, 2H), 2.92 (q, NCH_2, J = 7.1 Hz, 4H), 1.16 (t, J = 7.1 Hz, Me, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 141.6 (C^{IV}, J_{CP} = 6.6 Hz), 122.6 (C^{IV}), 113.6 (C^{IV}, J_{CP} = 19.8 Hz), 41.8 (CH_2), 11.5 (CH_3); **^{31}P NMR** (162 MHz, DMSO-d_6) δ –80.83; **MS-ES** (–) *m/z* 768.5. Anal. Calcd for $C_{22}H_{12}Cl_{12}NO_6P{\cdot}0.1C_5H_{12}$: C, 31.79: H, 1.57. Found: C, 31.82; H, 1.70.

Biphasic asymmetric epoxidation procedure: In a 10 ml flask equipped with a magnetic stirring bar, $NaHCO_3$ (67.0 mg, 0.80 mmol, 4.0 eq.) was added to 800 μL of water. Oxone® (132.0 mg, 0.21 mmol, 1.0 eq.) was then added and the solution was stirred for 2 minutes until effervescence subsided. 400 μL of a 0.5 mol/L solution of the alkene (0.20 mmol, 1.0 eq.) and naphthalene/dodecane (0.20 mmol, 1.0 eq., internal reference) in CH_2Cl_2 was added. The iminium catalyst (10.0 μmol, 5 mol%) in CH_2Cl_2 (600 μL) was added, followed by a solution of 18-crown-6 (1.0 mg, 5.0 μmol, 2.5 mol%) in CH_2Cl_2 (200 μL). The reaction mixture was then stirred at room temperature for 2h.

General procedure for the synthesis of the iminium TRISPHAT salts [23b][*rac*-TT], [23e][*rac*-TT], [23f][*rac*-TT], [23g][*rac*-TT] and [23h][*rac*-TT].

To a solution of azepines **11b**, **11e**, **11f**, **11g** and **11h** (1 eq.) in CCl_4 (3 mL per 1 mmol of substrate) was added NBS (1.3 eq.) and AIBN (0.05 eq.). The flask was protected with an aluminum foil. The mixture was stirred overnight. The reaction was diluted with water (15 mL per 1 mmol of substrate) and extracted with CH_2Cl_2 (2 x 10 mL). The organic phase was dried ($MgSO_4$) and filtered. A solution of salt $[Et_2NH_2]$[*rac*-TT] (1.2 eq.) in acetone was added and the crude evaporated under reduced pressure. The desired iminium salts were then isolated by chromatography on basic alumina (otherwise stated).

(–)-[6-N-((*S*)-1-(2-Naphthyl)ethyl)-5H-dibenz[c,e]azepinium][*rac*-TT] or [23b][*rac*-TT]



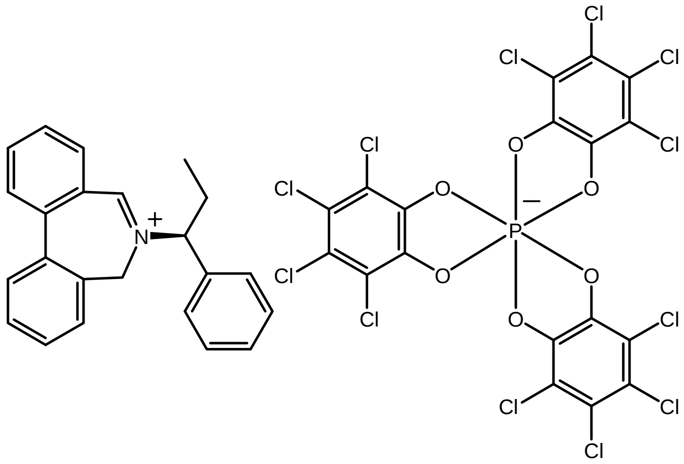
Starting from 627 mg of **11b**, salt [**23b**][*rac*-TT] was obtained as a pale yellow solid (1.31 g, 66%) after chromatography (eluent: DCM).

R

$\boldsymbol{R_f}$ = 0.9 (Al_2O_3 basic, CH_2Cl_2); **M.p.** 220 °C (decomposition); $[\alpha]^{20}_{D}$ – 28.2 (*c* 0.1, CH_2Cl_2); **IR** (neat) 1641, 1597, 1556, 1444, 1389, 1301, 1236, 1008, 989, 819, 718, 668 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, 298K) δ 2.27 (b, Me, 3H), 4.38 (b, N-CH, 1H), 4.88 (b, CHN, 1H), 6.13 (b, CHN, 1H), 6.55 (b, 1H), 7.08 (b, 1H), 7.25-7.95 (m, 11H), 8.26 (s, 1H), 9.95 (b, N=CH, 1H); **^{31}P NMR** (162 MHz, $CDCl_3$) –80.97, –81.01; **MS-ES** (–) *m/z* 768.5 (100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 348.3 (55), 194.5 (100), 155.6 (100); **CD** (CH_2Cl_2, 10^{-5} M) λ

(Δε) 235 (–9); **UV** (CH_2Cl_2, 10^{-5} M) λ (log ε) 229 (5.08), 301 (4.36). Anal. Calcd for $C_{44}H_{22}Cl_{12}NO_6P$: C, 47.31: H, 1.99. Found: C, 47.51; H, 2.21.[ii]

(–)-[6-N-((*S*)-1-Phenylpropyl)-5H-dibenz[c,e]azepinium][*rac*-TT] or [23e][*rac*-TT]

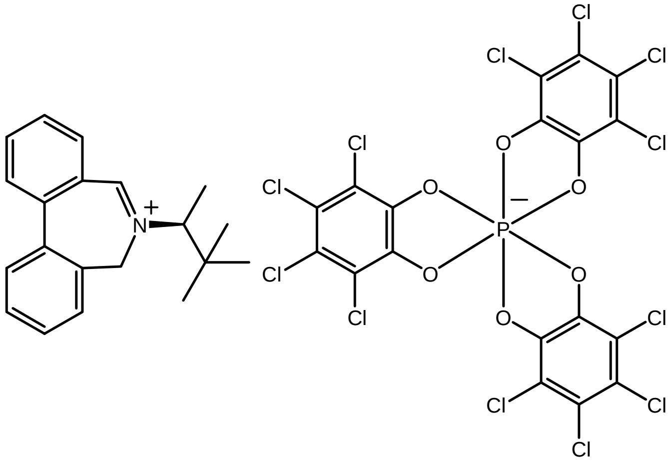


Starting from 250 mg of **11e**, salt [**23e**][*rac*-TT] was obtained as a pale yellow solid (552 mg, 64%) after chromatography (eluent: DCM).

***R*$_f$** = 0.9 (Al_2O_3 basic, CH_2Cl_2); **M.p.** 195 °C (decomposition); **[α]$^{20}_D$** – 31.7 (*c* 0.1, CH_2Cl_2); **IR** (neat) 1640, 1598, 1556, 1445, 1389, 1301, 1236, 990, 819, 758, 718, 700, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.86 (b, CHN, 1H), 7.85-7.06 (m, 13H), 5.61 (m, NCH, 1H), 4.75 (m, CHN, 1H), 4.19 (m, NCH, 1H), 2.38 (m, CH_2, 2H), 1.13-0.69 (b, CH_3, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ –80.97, –81.01; **MS-ES** (–) *m/z* (rel intensity) 768.5 (100, TRISPHAT) ; **MS-ES** (+) *m/z* (rel intensity) 194.5 (70, M-C_9H_{11}), 312.3 (100, M) ; **CD** (CH_2Cl_2, 10^{-5} M) λ (Δε) 237 (–3); **UV** (CH_2Cl_2, 10^{-5} M) λ (log ε) 227 (4.795), 240 (4.74), 301 (4.34), 363 (3.50). Anal. Calcd for $C_{41}H_{22}Cl_{12}NO_6P$: C, 45.55: H, 2.05. Found: C, 45.38; H, 2.25.[ii]

[ii] Assignment in ^{13}C NMR spectroscopy could not be performed due to the low resolution of the spectra resulting from the slow interconversion of the biphenyl moiety on NMR time scale leading to a broadening of the NMR signals

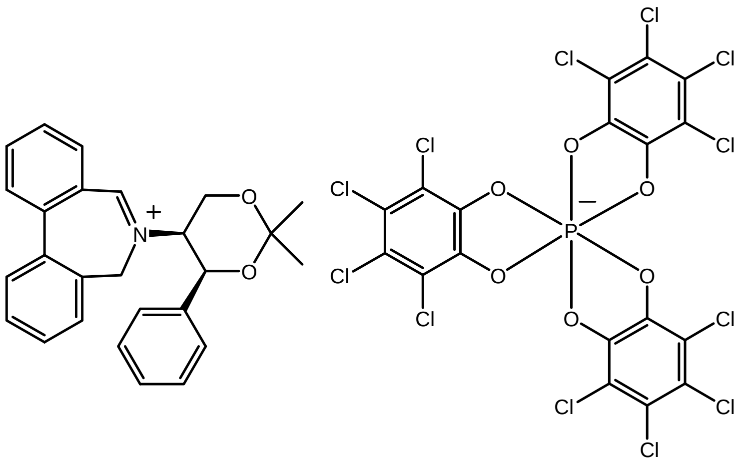
(–)-[6-N-((*S*)-1,2,2-Trimethylpropyl)-5H-dibenz[c,e]azepinium][*rac*-TT] or [23f][*rac*-TT]



Starting from 250 mg of **11f**, salt [**23f**][*rac*-TT] was obtained as a pale yellow solid (544 mg, 58%) after chromatography (eluent: DCM).

***R*$_f$** = 0.9 (Al_2O_3 basic, CH_2Cl_2); **M.p.** 160 °C (decomposition); **$[\alpha]^{20}_D$** – 31.2 (*c* 0.1, CH_2Cl_2); **IR** (neat) 2923, 1636, 1597, 1556, 1445, 1389, 1302, 1236, 1091, 1046, 1008, 989, 818, 760, 718, 668 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.49 and 9.20 (2s, CH=N, 1H), 8.1-7.0 (m, 8H), 4.82-4.33 (m, CH_2-N and CHN, 3H), 1.75 (m, CH_3, 3H), 1.19 (s, *t*Bu, 9H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ –80.92, –81.00; **MS-ES** (–) m/z = 768.5 (100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 194.5 (100, M-C_6H_{13}), 278.5 (25, M); **CD** (CH_2Cl_2, 10^{-5} M) λ (Δε) 252 (–6), 277 (–2), 296 (–3), 351 (2); **UV** (CH_2Cl_2, 10^{-5} M) λ (log ε) 227 (4.75), 239 (4.70), 301 (4.27), 356 (3.49). Anal. Calcd for $C_{38}H_{24}Cl_{12}NO_6P$: C, 43.59: H, 2.31. Found: C, 43.47; H, 2.51.[ii]

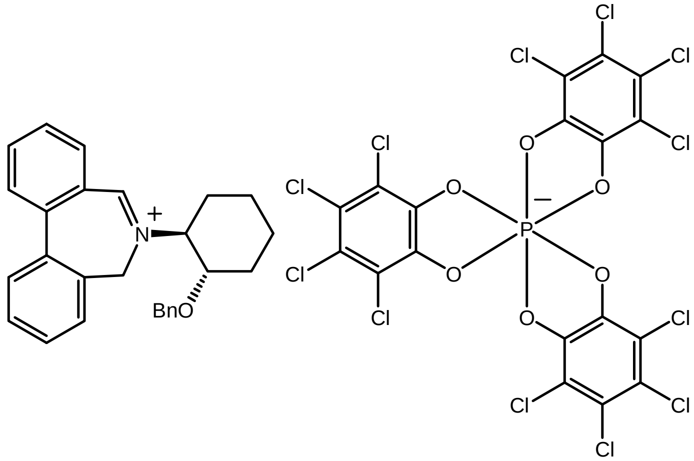
(+)-[6-N-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-5H-dibenz[c,e]azepinium] [*rac*-TT] or [23g][*rac*-TT]



Starting from 250 mg of **11g**, salt [**23g**][*rac*-TT] was obtained as a pale yellow solid (456 mg, 61%) after chromatography over silica gel (eluent: DCM).

***R*$_f$** = 0.3 (SiO_2, CH_2Cl_2); **M.p.** 200 °C (decomposition); **$[\alpha]^{20}_D$** + 28.0 (*c* 0.1, CH_2Cl_2); **IR** (neat) 1625, 1581, 1537 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.34–8.83 (b, CH=N, 2H), 7.87-7.17 (m, 13H), 5.87 (s, CH-Ar, 1H), 5.34-4.00 (m, CH_2-N and CHN and CH_2-O, 5H), 1.86 (s, CH_3, 3H), 1.77 (s, CH_3, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ –80.9, –80.80; **MS-ES** (-) *m/z* 769.0 (44, TRISPHAT); 113.7 (100); **MS-ES** (+) *m/z* (rel intensity) 152.7 (100), 384.4 (16, M); **CD** (CH_2Cl_2, 10^{-5} M) λ (Δε) 244 (8.6), 265 (-1.5), 320 (0.8); **UV** (CH_2Cl_2, 10^{-5} M) λ (log ε) 237 (4.82), 300 (4.41), 356 (3.95). Anal. Calcd for $C_{44}H_{26}Cl_{12}NO_8P{\cdot}H_2O$: C, 45.13: H, 2.41. Found: C, 44.75; H, 2.47.

(–)-[6-N-((*S*)-*trans*-2-Phenylmethoxycyclohexyl)-5H-dibenz[c,e]azepinium][*rac*-TT] or [23h][*rac*-TT]



Starting from 350 mg of **11h**, salt [**23h**][*rac*-TT] was obtained as a pale yellow solid (526 mg, 50%) after chromatography (eluent: DCM).

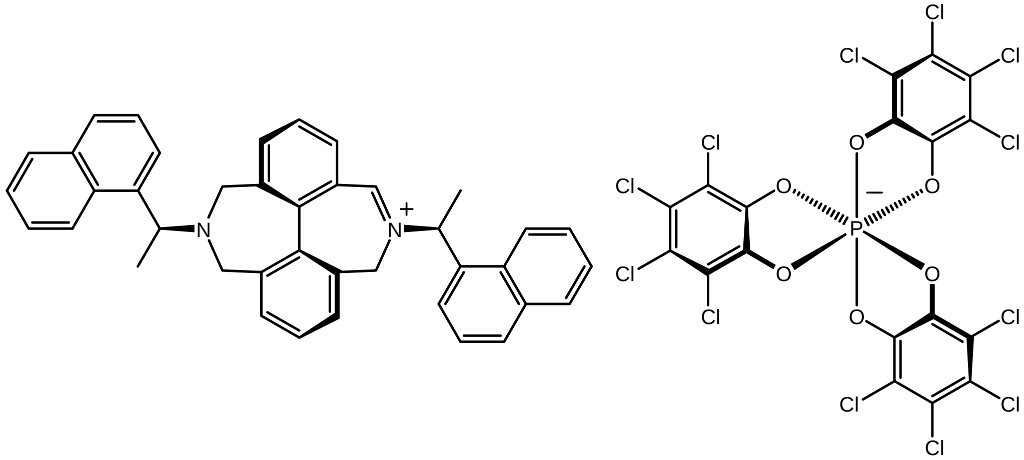
***R*f** = 0.9 (Al_2O_3 basic, CH_2Cl_2); **M.p.** 185 °C (decomposition); **$[\alpha]^{20}_D$** – 8.0(*c* 0.1, CH_2Cl_2); **IR** (neat) 2935, 1707, 1641, 1597, 1556, 1446, 1389, 1302, 1236, 1074, 990, 819, 759, 718, 668 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.95 (s, CH=N, 1H), 7.97-7.45 (m, 8H), 7.19-6.89 (m, 5H), 4.44-3.67 (m, 6H), 2.49 (b, 1H), 2.12 (b, 1H), 1.93 (b, 3H), 1.39 (b, 3H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ –80.83, –80.87; **MS-ES** (–) *m/z* 768.5 (100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 382.4 (100, M); **CD** (CH_2Cl_2, 10^{-5} M) λ (Δε) 252 (–11), 282 (–2), 300 (–3), 357 (4); **UV** (CH_2Cl_2, 10^{-5} M) λ (log ε) 227 (4.79), 240 (4.75), 300 (4.35), 351 (3.55). Anal. Calcd for $C_{45}H_{28}Cl_{12}NO_6P$: C, 46.95: H, 2.45. Found:C,47.22;H,2.73.

General procedure for the oxidation and for the association of the iminium salt with [Cinchonidinium][Δ-TT]

In a 50 ml round-bottomed flask equipped with a magnetic stirring bar, diazepine **4b**, **4e**, **4f** or **4g** (0.25 mmol, 1.0 eq.) was dissolved in 5 ml of $CHCl_3$ and N-bromosuccinimide

(0.32 mmol, 1.3 eq.) was added to the solution. The mixture was stirred at room temperature for few seconds then a solution of [Cinchonidinium][Δ-TT] (0.275 mmol, 1.1 eq.) in a minimum amount of acetone was added. After 5 minutes of stirring at room temperature the solvents were removed under reduced pressure. The desired iminium Δ-TRISPHAT salts were recovered after column chromatography (Silica gel 60; CH_2Cl_2).

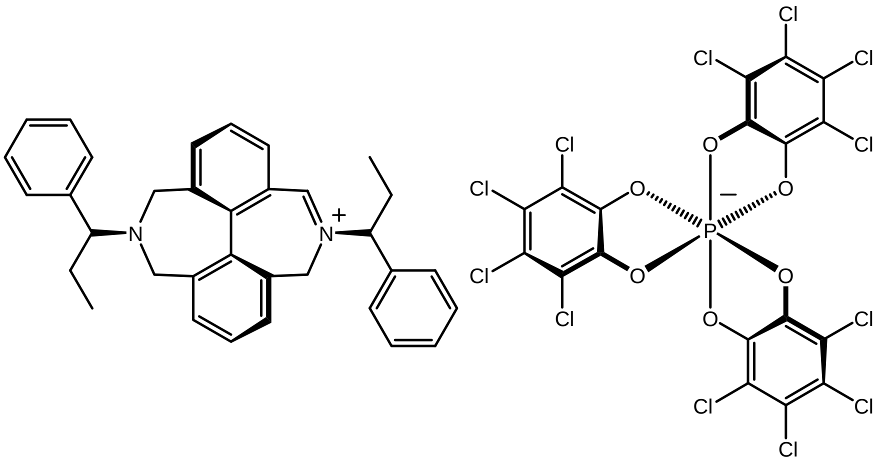
(–)-[(*S*a)-30b][Δ-TT]



Starting from (*S*a)-**4b** (30 mg, 0.055 mmol), the desired compound was obtained as a yellow solid (65 mg, 90%).

M.p. 210.1 °C; **$[\alpha]_D^{20}$** – 1587.4 (*c* 0.10, MeOH); **IR** (neat) 2928, 1692, 1640, 1594, 1448, 1390, 1302, 1236, 991, 823, 670 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.5 (s, 1H), 8.4 (s, 1H), 8.3-6.5 (m, 20H), 5.45 (d, 1H, *J* = 7.6 Hz), 4.7 (d, 1H, *J* = 12.8 Hz), 4.3 (d, 1H, *J* = 6.2 Hz), 4.1 (d, 1H, *J* = 13.0 Hz), 3.8 (d, 1H, *J* = 12.2), 3.65 (d, 1H, *J* = 12.6 Hz), 3.0 (q, 2H, *J* = 12.2 Hz), 2.34 (d, 3H, *J* = 6.6 Hz), 1.45 (d, 3H, *J* = 6.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0 (CH), 141.5 (C^{IV}, d, *J* = 6.4 Hz), 140.9 (C^{IV}), 137.9 (C^{IV}), 137.5 (CH), 136.4 (C^{IV}), 136.0 (C^{IV}), 134.4 (C^{IV}), 133.6 (C^{IV}), 133.0 (CH), 131.9 (CH), 131.8 (C^{IV}), 131.6 (CH), 130.9 (C^{IV}), 129.7 (CH), 129.1 (CH), 128.9 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 126.6 (C^{IV}), 126.5 (CH), 126.2 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 124.7 (CH), 123.1 (C^{IV}), 121.4 (CH), 114.2 (C^{IV}, d, *J* = 20.0 Hz), 68.1 (CH), 53.6 (CH_2), 53.1 (CH_2), 51.1 (CH_2), 29.7 (CH_2), 21.7 (CH), 18.6 (CH_3), 14.2 (CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$): -80.99; **MS-ES** (+) *m/z* (rel intensity) 575.3 (30), 543.7 (100, M^+), 389.3 (60, M-$C_{12}H_{12}$), 235.3 (10, M-2x $C_{12}H_{12}$); **MS-ES** (–) *m/z* (rel intensity) 769.0 (100, TRISPHAT).

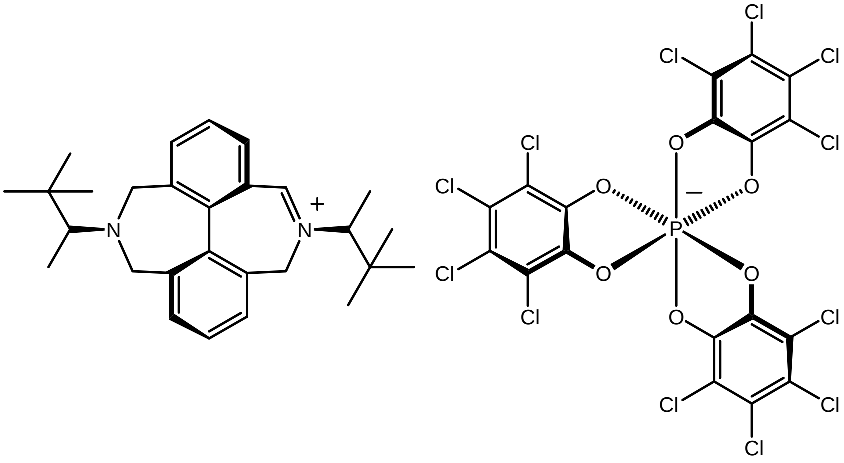
(+)-[(*S*a)-30e][Δ-TT]



Starting from (*S*a)-**4e** (45 mg, 0.095 mmol),, the desired compound was obtained as a yellow solid (100 mg, 85%).

***R*f** = 0.72 (DCM/MeOH 95:5, SiO_2); **M.p.** 200 °C (decomposition); **$[\alpha]_D^{20}$** – 3551.6 (*c* 0.12, MeOH); **IR** (neat) 2934, 1640, 1593, 1562, 1445, 1389, 1301, 1235, 990, 819, 718, 669 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.81-7.1 (m, 13H), 6.3 (d, 1H, *J* = 7.5 Hz), 5.9 (t, 1H, *J* = 7.2), 4.7 (d, 1H, *J* = 13.0 Hz), 4.3 (d, 1H, *J* = 13.2 Hz), 3.7 (dd, 2H, *J* = 25.0 Hz, *J* = 37.9 Hz), 3.05 (t, 3H, *J* = 11.7 Hz), 2.55 (m, 3H), 2 (m, 1H), 1.65 (m, 2H), 1.15 (t, 3H, *J* = 7.2 Hz), 0.9 (m, 1H), 0.65 (t, 3H, *J* = 7.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): -80.97**; ^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2 (CH), 142.7 (C^{IV}), 141.9 (C^{IV}), 141.5 (C^{IV}, d, *J* = 6.4 Hz), 138.4 (C^{IV}), 137.6 (CH), 136.5 (C^{IV}), 136.0 (C^{IV}), 133.4 (CH), 133.1 (C^{IV}), 132.8 (C^{IV}), 132.0 (CH), 130.4 (CH), 130.3 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 127.0 (CH), 126.1 (C^{IV}), 123.0 (C^{IV}), 114.0 (C^{IV}, d, *J* = 20.0 Hz), 68.7 (CH), 53.2 (CH_2), 53.0 (CH_2), 51.6 (CH_2), 27.2 (CH_2), 25.2 (CH), 23.9 (CH_2), 11.0 (CH_3), 10.1 (CH_3); **MS-ES** (–) *m/z* (rel intensity) 768.5 (100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 471.5 (100, M^+), 197.4 (20).

(+)-[(*R*a)-30f][Δ-TT]

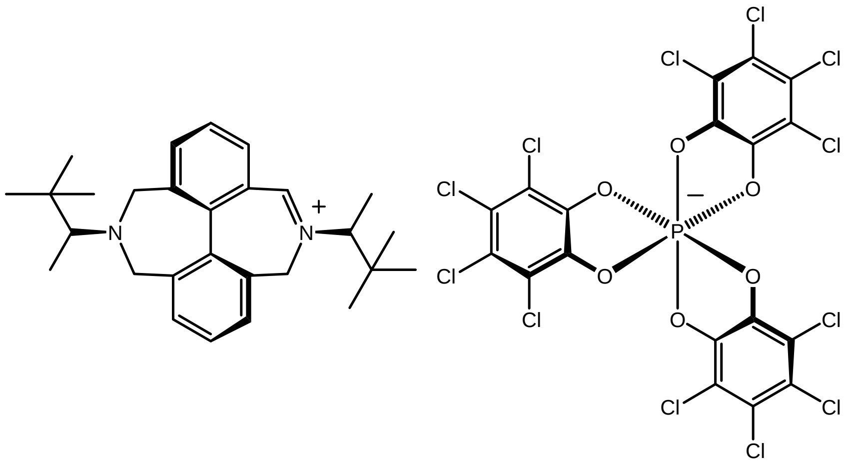


Starting from (*R*a)-**4f** (20.0 mg, 0.050 mmol), the desired compound was obtained as an orange solid (46 mg, 79%).

***R*$_f$** = 0.67 (DCM/MeOH 9:1); ***R*$_f$** = 0.42 (DCM, Al_2O_3 basic); **M.p.** 241.3 °C; **$[\alpha]_D^{20}$** −329.6 (*c* 0.1, MeOH); **IR** (neat) 2959, 1634, 1591, 1559, 1446, 1388, 1302, 1235, 990, 819, 718, 669 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.82 (d, 1H, *J*= 7.8 Hz), 7.67-7.44 (m, 4H), 4.90 (d, 1H, *J* = 13.4 Hz), 4.12 (q, 1H, *J* = 6.8 Hz), 3.83 (d, 1H, *J*= 10.4 Hz), 3.79 (d, 1H, *J*= 9.0 Hz), 3.64 (d, 1H, *J*= 12.5 Hz), 3.51 (d, 1H, *J*= 11.9 Hz), 3.25 (d, 1H, *J*= 13.1 Hz), 2.63 (q, 1H, *J*= 7.0 Hz), 1.75 (d, 3H, *J*= 7.1 Hz), 1.22 (d, 3H, *J*= 7.0 Hz), 1.12 (s, 9H), 1.01 (s, 9H); **^{31}P NMR** (162 MHz, $CDCl_3$): -80.99; **MS-ES** (−) *m/z* (rel intensity) 768.7(100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 403.5 (100, M$^+$), 197.5 (12).[iii]

[iii] Assignment in ^{13}C NMR spectroscopy could not be performed due to epimerization of the compound during the acquisition

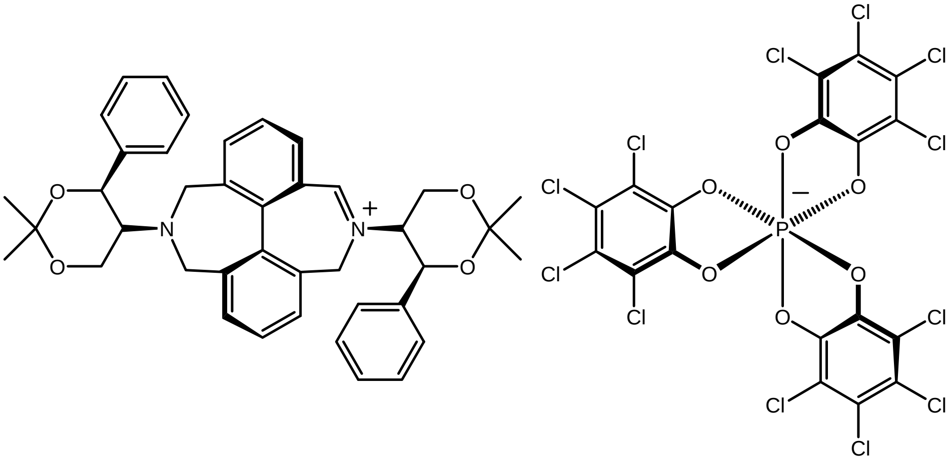
(–)-[(*S*a)-30f][Δ-TT]



Starting from (*S*a)-**4f** (13 mg, 0.032 mmol), the desired compound was obtained as a yellow solid (16.5 mg, 92%).

***R*$_f$** = 0.65 (DCM/MeOH 9:1); **M.p.** 237.8 °C; **$[\alpha]_D^{20}$** – 134.0 (*c* 0.1, MeOH); **IR** (neat) 2963, 1633, 1591, 1559, 1447, 1389, 1302, 1260, 1235, 1096, 990, 819 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.91 (m, 1H), 7.78 (d, 1H, *J*= 7.5 Hz), 7.63 (m, 2H), 7.49 (d, 1H, *J*= 7.2 Hz), 7.31 (m, 1H), 4.83 (d, 1H, *J* = 13.3 Hz), 4.48 (d, 1H, *J* = 13.3 Hz) 4.21 (q, 1H, *J* = 7.0 Hz), 3.62 (m, 3H), 3.40 (d, 1H, *J*= 11.6 Hz), 2.91 (q, 1H, *J*= 7.1 Hz), 1.66 (d, 3H, *J*= 7.0 Hz), 1.21 (s, 9H), 1.04 (m, 12 H); **^{31}P NMR** (162 MHz, $CDCl_3$): -80.81; **MS-ES** (+) *m/z* (rel intensity) 319.3 (50, M-C_6H_{14}), 403.3 (100, M); **MS-ES** (–) *m/z* (rel intensity) 768.8 (100, TRISPHAT).

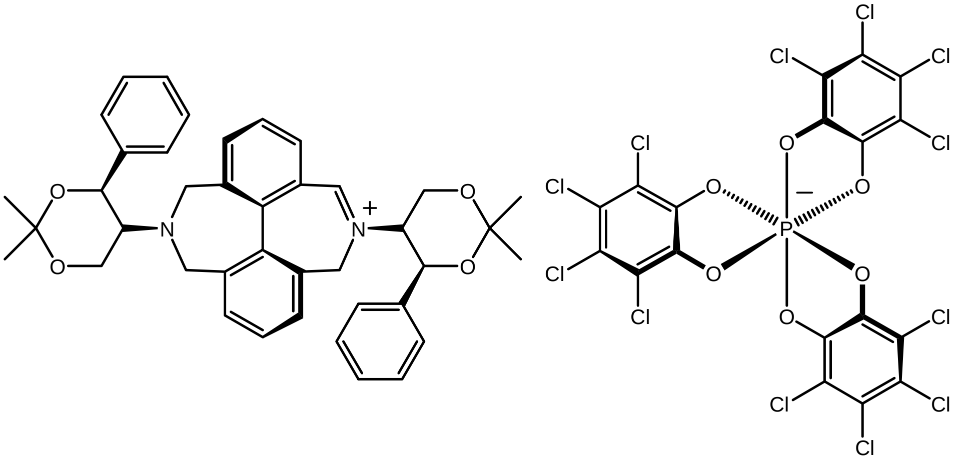
(+)-[(*R*a)-30g][Δ-TT]



Starting from (*R*a)-**4g** (50 mg, 0.081 mmol),, the desired compound was obtained as a yellow solid (70 mg, 62%).

M.p. 223 °C (decomposition); **$[\alpha]_D^{20}$** + 14.3 (*c* 0.1, MeOH); **IR** (neat) 2992, 1705, 1633, 1591, 1558, 1447, 1386, 1302, 1236, 1200, 1081, 990, 819 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.42 (s, 1H); 7.49-7.22 (m, 10H); 7.03 (m, 3H); 5.82 (s, 1H); 5.35 (m, 1H) 5.26 (s, 1H); 4.81 (m, 2H); 4.49 (d, 1H, *J* = 13.4 Hz); 4.30 (dd, 1H, *J* = 12.6, 3.1 Hz); 4.11 (d, 1H, *J*= 12.9 Hz); 3.98 (d, 1H, *J* = 13.6 Hz); 3.88 (d, 1H, *J* = 11.9 Hz); 3.54 (d, 1H, *J*= 12.9 Hz); 3.33 (d, 1H, *J* = 11.9 Hz); 3.16 (m, 2H); 1.87 (s, 3H); 1.77 (s, 3H); 1.51 (s, 3H); 1.31 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9, 141.8, 141.7, 141.2, 140.1, 139.4, 138.2, 135.3, 135.2, 132.7, 132.5, 132.1, 131.7, 129.3, 129.0, 128.7, 127.8, 127.7, 127.0, 126.0, 125.2, 124.7, 122.9, 114.0, 113.7, 101.1, 99.5, 74.8, 71.8, 67.5, 61.6, 61.2, 59.6, 56.8, 30.0, 29.7, 18.8, 18.71; **MS-ES** (+) *m/z* (rel intensity) 279.5 (70), 615.3 (100, M), 645.1 (90); **MS-ES** (–) *m/z* (rel intensity) 769.0 (100, TRISPHAT).

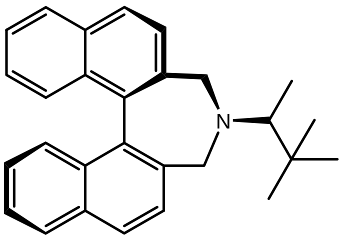
(−)-[(*S*a)-30g][Δ-TT]



Starting from (*S*a)-**4g** (37 mg, 0.060 mmol), the desired compound was obtained as a yellow solid (45 mg, 54%).

M.p. 206 °C; **$[\alpha]_D^{20}$** – 215.1 (*c* 0.1, MeOH); **IR** (neat) 3057, 2923, 2852, 1691, 1593, 1448, 1436, 1328, 1241 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.66 (s, 1H); 7.70 (d, 1H, *J*= 6.8 Hz); 7.57-7.21 (m, 15H); 5.83 (d, 1H, *J* = 2.8 Hz); 5.69 (d, 1H, *J* = 13.2 Hz) 5.26 (d, 1H, *J* = 3.0 Hz); 4.72 (m, 1H); 4.56 (s, 1H); 4.34 (m, 2H); 4.07 (m, 4H); 3.27 (d, 1H, *J* = 12.1 Hz); 3.03 (d, 1H, *J* = 12.4 Hz); 2.80 (s, 1H); 1.81 (s, 3H); 1.75 (s, 3H); 1.72 (s, 3H); 1.68 (s, 6H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 172.0, 141.7, 141.6, 141.2, 139.7, 139.5, 138.4, 137.9, 135.3, 134.3, 132.9, 131.5, 129.3, 129.2, 128.9, 128.2, 128.1, 128.0, 127.8, 127.1, 128.9, 124.8, 123.1, 114.2, 113.9, 101.2, 99.1, 74.1, 71.4, 68.0, 62.7, 61.3, 31.0, 29.8, 29.7, 29.3, 19.0, 18.6; **MS-ES** (+) *m/z* (rel intensity) 279.4 (20), 615.5 (100, M), 645.2 (30). **MS-ES** (–) *m/z* (rel intensity) 769.1 (100, TRISPHAT)

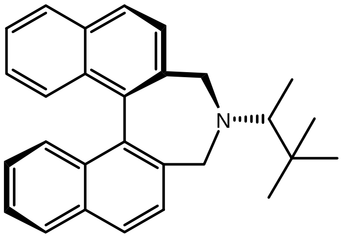
(−)-(*R*$_a$)-4,5-dihydro-3H-4-[(*S*)-3,3-dimethylbutan-2-yl]dinaphth[2,1-c;1',2'-e] azepine or (*R*a,*S*)-35f



In a 25 mL round bottom flask containing a solution of (*S*)-1,2,2-trimethyl-propylamine (82.2 mg, 0.8124 mmol) in acetonitrile (10 mL) was added (*R*a)-2-(bromomethyl)-1-(2-(bromomethyl)naphthalen-1-yl)naphthalene (298.0 mg, 0.6770 mmol) and potassium carbonate (374.3 mg, 2.708 mmol). The mixture was heat at reflux (80 °C) for approximatively 3 hours (till the complete consumption of the starting material, checked by TLC on SiO_2, eluent DCM) and was then evaporated to dryness. The solid was directly chromatographied on SiO_2, (eluent DCM) to yield the desired compound as a yellow solid (185 mg, 72%).

M.p. 174°C; **[α]$_D^{20}$** – 272.4 (*c* 0.10, MeOH); **IR** (neat) 3054, 2968, 2858, 2795, 1689, 1595, 1507, 1459, 1268, 1143, 1114 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (2d, 4H, *J* = 8.1 Hz), 7.58 (d, 2H, *J* = 8.3 Hz), 7.46-7.41 (m, 4H), 7.26-7.22 (m, 2H), 3.73 (d, 2H, *J* = 12.4 Hz), 3.53 (d, 2H, *J* = 12.4 Hz), 2.51 (q, 1H, *J* = 7.1 Hz), 1.13 (d, 3H, *J* = 7.1 Hz), 0.97 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.3 (C^{IV}), 134.9 (C^{IV}), 133.0 (C^{IV}), 131.5 (C^{IV}), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 125.7 (CH), 125.4 (CH), 68.1 (CH), 54.3 (CH_2), 36.9 (C^{IV}), 27.3 (CH_3), 12.3 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 479.5 (50), 412.5 (60), 396.3 (80), 379.3 (100, M), 294.1 (95, M-C_6H_{14}), 279.1 (100), 266.1 (97), 252.3 (75).

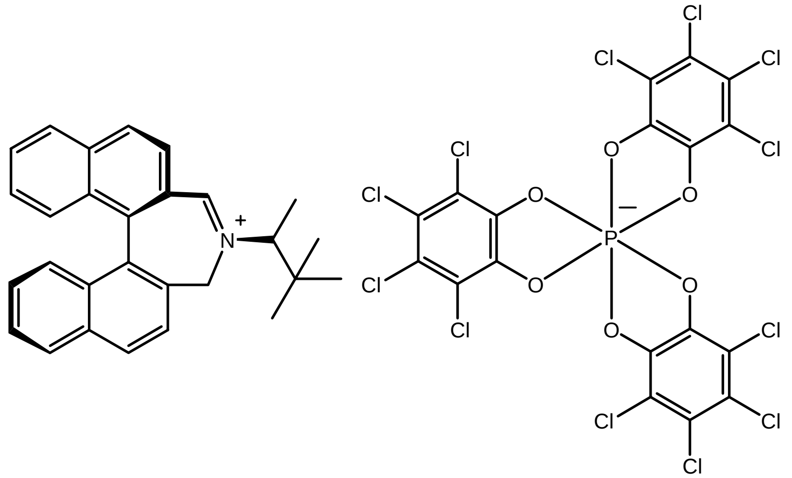
(–)-(*R*$_a$)-4,5-dihydro-3H-4-[(*R*)-3,3-dimethylbutan-2-yl]dinaphth[2,1-c;1',2'-e] azepine or (*R*a,*R*)-35f



Similar procedure but with instead (*R*)-1,2,2-trimethyl-propylamine led to the desired compound obtained as a yellow solid with 76% yield.

M.p. 193 °C; **[α]$_D^{20}$** – 255.8 (*c* 0.10, MeOH); **IR** (neat) 3052, 2957, 2866, 1592, 1457, 1377, 1357, 1109 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, 4H, *J* = 8.1 Hz), 7.55 (d, 2H, *J* = 8.4 Hz), 7.49 (d, 2H, *J* = 8.6 Hz), 7.45 (d, 2H, *J* = 7.0 Hz), 7.26 (m, 2H), 3.58 (d, 2H, *J* = 12.1 Hz), 3.52 (d, 2H, *J* = 12.4 Hz), 2.81 (q, 1H, *J* = 7.1 Hz), 0.97 (s, 9H), 0.84 (d, 3H, *J* = 7.1 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.0 (C^{IV}), 134.6 (C^{IV}), 133.0 (C^{IV}), 131.3 (C^{IV}), 128.6 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.6 (CH), 125.2 (CH), 69.7 (CH), 53.4 (CH_2), 37.1 (C^{IV}), 27.3 (CH_3), 11.7 (CH_3); **MS-ES** (+) *m/z* (rel intensity) 394.3 (75), 379.3 (97, M), 294.3 (100, M-C_6H_{14}), 267.3 (95), 252.3 (20).

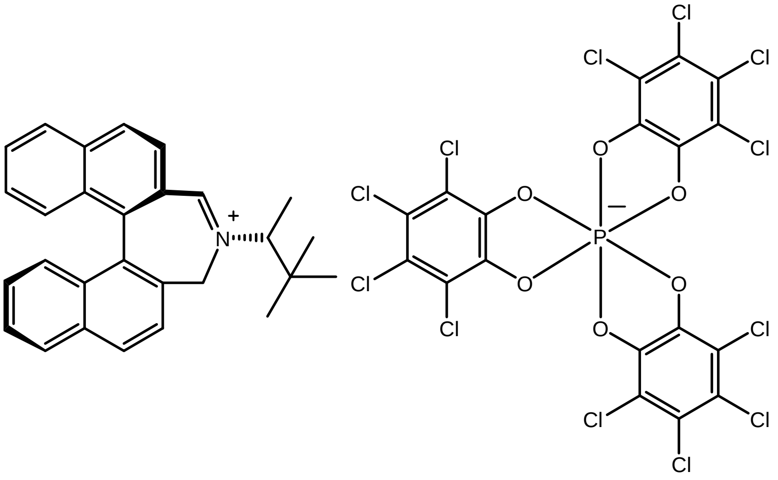
(–)-[(R_a)-[(*S*)-3,3-dimethylbutan-2-yl]-3H-4-azapinium-cyclohepta[2,1-a;3,4-a']dinaphthalene][*rac*-TT] or [(*R*a,*S*)-24f][*rac*-TT]



To a solution of (*R*a,*S*)-**35f** (115 mg, 0.3030 mmol) in $CHCl_3$ (2 mL) was added NBS (59.3 mg, 0.3333 mmol). After 20 minutes stirring at room temperature (till the complete consumption of the starting material, checked by TLC on SiO_2, eluent DCM), was added a solution of [Et_2NH_2][*rac*-TT] (296.0 mg, 0.3636 mmol) in acetone (2 mL). After two minutes stirring, the mixture was evaporated to dryness. The desired salt was recovered after column chromatography (SiO_2, eluent DCM) as a intense yellow solid (300 mg, 86%)

***R*~f~** = 0.70 (DCM/EtOAc 9:1); **M.p.** 251 °C; **$[\alpha]_D^{20}$** – 207.4 (*c* 0.10, MeOH); **IR** (neat) 2959, 1611, 1590, 1548, 1445, 1388, 1302, 1235, 970, 818 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.13 (d, 1H, *J* = 8.3 Hz), 8.01 (d, 1H, *J* = 8.3 Hz), 7.95 (m, 3H), 7.74 (t, 1H, *J* = 8.1 Hz), 7.59 (d, 1H, *J* = 8.3 Hz), 7.56 (t, 1H, *J* = 7.8 Hz), 7.50 (d, 1H, *J* = 8.6 Hz), 7.40 (t, 1H, *J* = 8.3 Hz), 7.29 (d, 1H, *J* = 8.6 Hz), 7.07 (d, 1H, *J* = 8.8 Hz), 5.02 (d, 1H, *J* = 13.1 Hz), 4.56 (d, 1H, *J* = 12.6 Hz), 4.15 (q, 1H, *J* = 6.8 Hz), 1.71 (d, 3H, *J* = 6.6 Hz), 1.09 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.8 (N=CH), 142.7 (C^{IV}), 142.2 (C^{IV}, TT, *J*= 6.4 Hz), 142.1 (C^{IV}, TT, *J*= 5.5 Hz), 135.9 (C^{IV}), 134.2 (C^{IV}), 134.1 (C^{IV}), 132.3 (CH), 132.1 (C^{IV}), 132.0 (C^{IV}), 131.7 (C^{IV}), 130.1 (CH), 129.7 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 126.0 (CH), 125.6 (C^{IV}), 125.3 (CH), 122.9 (C^{IV}, TT), 122.8 (C^{IV}, TT), 114.2 (C^{IV}, TT, *J*= 7.4 Hz), 114.0 (C^{IV}, TT, *J*= 7.4 Hz), 79.7 (CH), 36.4 (C^{IV}), 29.9 (CH_2), 27.3 (CH_3), 14.2 (CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -80.70, -80.75; **MS-ES** (+) *m/z* (rel intensity) 378.3 (100, M^+), 294.3 (70, M-C_6H_{13}), 267.5 (80). **MS-ES** (–) *m/z* (rel intensity) 768.3 (100, TRISPHAT).

(–)-[(R_a)-[(R)-3,3-dimethylbutan-2-yl]-3H-4-azapinium-cyclohepta[2,1-a;3,4-a']dinaphthalene][*rac*-TT] or [(*R*a,*R*)-24f][*rac*-TT]

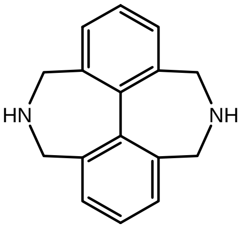


Similar procedure but with instead (*R*a,*R*)-**35f** led to the desired salt obtained as an intense yellow solid with 88% yield.

***R*f** = 0.76 (DCM); **M.p.** 220 °C; **[α]$_D$^{20}** – 264.3 (*c* 0.10, MeOH); **IR** (neat) 3052, 2957, 2866, 1592, 1457, 1377, 1357, 1109 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.14 (d, 1H, *J* = 8.3 Hz), 8.00 (d, 1H, *J* = 8.1 Hz), 7.75-7.64 (m, 4H), 7.57 (t, 1H, *J* = 7.1 Hz), 7.44-7.36 (m, 2H), 7.31 (d, 1H, *J* = 8.6 Hz), 7.10 (d, 1H, *J* = 8.8 Hz), 4.97 (d, 1H, *J* = 13.6 Hz), 4.66 (d, 1H, *J* = 13.4 Hz), 4.36 (q, 1H, *J* = 6.6 Hz), 1.65 (d, 3H, *J* = 6.3 Hz), 1.08 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 68.6 (N=CH), 142.6 (C^{IV}), 142.1 (C^{IV}, TT, *J*= 6.4 Hz), 135.8 (C^{IV}), 134.1 (C^{IV}), 134.0 (C^{IV}), 132.2 (C^{IV}), 132.0 (CH), 131.7 (C^{IV}), 131.3 (CH), 129.6 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 126.1 (C^{IV}), 125.7 (CH), 123.1 (C^{IV}, TT), 123.0 (C^{IV}, TT), 114.2 (C^{IV}, TT, *J*= 7.4 Hz), 114.0 (C^{IV}, TT, *J*= 7.4 Hz), 77.3 (CH), 36.4 (C^{IV}), 29.9 (CH_2), 27.2 (CH_3), 14.4 (CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -80.77, -80.81; **MS-ES** (+) *m/z* (rel intensity) 393.3 (33), 378.1 (100, M^+), 294.3 (90, M-C_6H_{13}), 267.3 (85), 252.3 (20). **MS-ES** (–) *m/z* (rel intensity) 768.3 (100, TRISPHAT).

CHAPTER III – PHASE TRANSFER CATALYSIS USING CHIRAL AMMONIUM SALTS

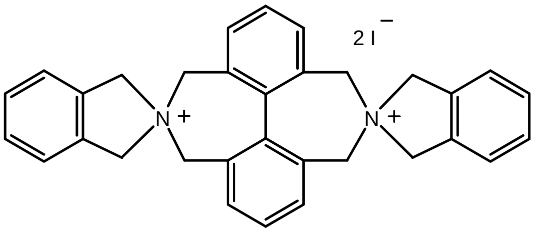
4,5,6,10,11,12-hexahydro-5,11-diaza-dibenzo[ef,kl]heptalene or 68



To a suspension of biphenyl-2,2',6,6'-tetracarboxaldehyde (1.14 g, 4.282 mmol) in MeOH (30 mL) were added ammonium acetate (6.61 g, 85.755 mmol) and then sodium cyanoborohydride (755 mg, 12.015 mmol). After 24h of reaction at room temperature, HCl (~36% *aq.*) was added dropwise till pH ~ 1-2. The solvents were evaporated and the wet residue was dissolved in water. The aqueous phase was washed with Et_2O (3x50 mL) and basicified with KOH pellets until pH>7. The basic aqueous phase was saturated with NaCl and extracted with DCM (3x100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to yield the desired product as a white foam (890 mg, 88%).

IR (neat): 2575, 1447, 1425, 1024 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.32 (m, 6H, CH_{Ar}), 3.72 (d, 4H, *J* = 12.4 Hz, CH_2), 3.47 (d, 4H, *J* = 12.4 Hz ,CH_2), 2.44 (s, 2H, NH); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 139.8 (C^{IV}), 136.2 (C^{IV}), 128.54 (CH), 127.9 (CH), 48.42 (CH_2); **MS-ES** (+) *m/z* (rel intensity) 237.3 (100, M+1), 225.3 (50, [M-CH_3]+1).

4,5,6,10,11,12-hexahydro-5,11-diisoindoline-dibenzo[ef,kl]heptalenium diiodie or [67][I]$_2$

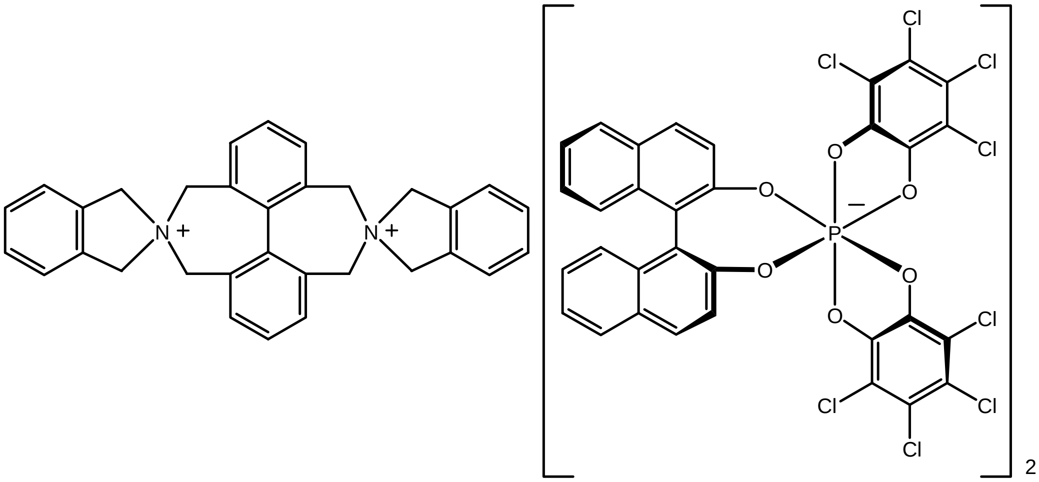


To a suspension of **68** (78.7 mg, 0.333 mmol) in dry MeOH (3 mL) were added 1,2-bis(iodomethyl)benzene (262.6 mg, 0.733 mmol) and potassium carbonate (202.5 mg, 1.465 mmol). The mixture was heated at reflux (70 °C) for 15h. After evaporation of the solvent, the solid residue was retaken in DCM/MeOH 1:1 and the inorganic salts were filtrated. The mother liquors were evaporated to dryness. The solid was dissolved in a minimum amount of DCM/MeOH

1:1 and the product precipitated upon addition of Et_2O to yield, after filtration, the desired salt as a pale brown solid (222 mg, 96%).

M.p. 363 °C (decomposition); **IR** (neat): 3466, 2995, 1668, 1436, 1299, 1181, 1057, 890 cm^{-1}; **^{1}H-NMR** (400 MHz, DMSO-d_6, 298 K) δ 8.06 (d, 4H, J = 7.6 Hz), 7.83 (t, 2H, J = 7.6 Hz), 7.51 (m, 8H), 5.33 (d, 4H, J = 14.4 Hz), 4.98 (d, 4H, J = 14.6 Hz), 4.81 (d, 4H, J = 13.4 Hz), 4.17 (d, 4H, J = 13.4 Hz); **^{13}C-NMR** (100 MHz, DMSO-d_6, 298 K) δ 140.2 (C^{IV}), 134.5 (CH), 132.8 (C^{IV}), 130.1 (CH), 129.5 (C^{IV}), 128.9 (CH), 123.7 (CH), 67.4 (CH_2), 62.0 (CH_2); **MS-ES** (+) *m/z* (rel intensity) 569.1 (20, $[M+I]^+$), 473.1 (25), 457.5 (25), 337.3 (100), 221.3 (100, $[M^{2+}/2]$).

Ion Metathesis with anion Δ-BINPHAT



To a solution of [**67**]$[I]_2$ (200 mg, 0.287 mmol) in a minimum amount of DCM/MeOH 1:1 (20 mL) was added a solution of $[Me_2NH_2]$[Δ-BT] in a minimum amount of acetone (30 mL). After 30 min, the $[Me_2NH_2][I]_2$ precipitate was filtered and after evaporation of the mother liquors, the desired salt was obtained as a pale pink solid (470 mg, 80%) as a 1:1 mixture of two diastereomeric salts.

Separation of the two diastereomers: [(*R*a)-**67**][Δ-BT]$_2$ and [(*S*a)-**67**][Δ-BT]$_2$

In a round bottom flask, [**67**][Δ-BT]$_2$ (150 mg) was dissolved in THF/Benzene 5:1 (the compound was first dissolved in THF then benzene was introduced) and the flask was put overnight at -20 °C. The precipitate was filtered and washed several times with pentane to afford the [(*R*a)-**67**][Δ-BT]$_2$ diastereomer as a white solid (72 mg, ~ 48%, d.e > 96%). The mother liquors were evaporated to yield the [(*S*a)-**67**][Δ-BT]$_2$ diastereomer as a brown solid (71 mg, ~ 47%, d.e ~ 90%).

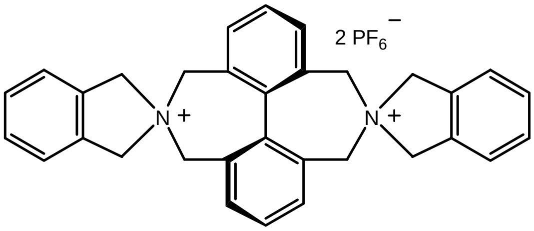
(–)-(*R*a)-[4,5,6,10,11,12-hexahydro-5,11-diisoindoline-dibenzo[ef,kl]heptalenium][Δ-BT]$_2$ or [(*R*a)-67][Δ-BT]$_2$

M.p. 277 °C (decomposition); **$[\alpha]_D^{20}$** – 716.0 (*c* 0.04, MeOH); **IR** (neat): 3053, 1592, 1451, 1388, 1235, 991, 952, 818 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3/CD_3CN$ 25%, 298 K) δ 7.80 (d, 4H, *J* = 8.1 Hz, BT), 7.46 (d, 4H, *J* = 8.8 Hz, BT), 7.33 (d, 4H, *J* = 7.8 Hz, BT), 7.19 (m, 8H, BT+cation), 7.03 (d, 4H, *J* = 7.3 Hz, cation), 6.94 (m, 6H, BT+cation), 6.69 (b, 4H, cation), 5.93 (d, 4H, *J* = 8.6 Hz, BT), 4.48 (s, 8H, CH_2), 4.28 (d, 4H, *J* = 13.4 Hz, CH_2), 3.53 (d, 4H, *J* = 13.9 Hz, CH_2); **^{13}C-NMR** (100 MHz, CD_3CN, 298 K) δ 154.3 (C^{IV}), 143.4 (C^{IV}), 141.2 (C^{IV}), 135.3 (C^{IV}), 134.8 (CH), 133.4 (C^{IV}), 131.6 (CH), 131.4 (C^{IV}, d, *J* = 1.8 Hz), 131.1 (CH), 130.5 (CH), 130.2 (C^{IV}, d, *J* = 2.9 Hz), 129.3 (C^{IV}), 129.2 (CH), 127.7 (CH), 127.6 (C^{IV}), 126.8 (C^{IV}), 125.4 (C^{IV}), 125.2 (CH), 124.9 (CH), 124.2 (CH), 124.0 (C^{IV}, d, *J* = 3.7 Hz), 123.3 (C^{IV}, d, *J* = 4.6 Hz), 119.4 (CH), 114.6 (C^{IV}), 68.7 (CH_2), 63.4 (CH_2); **^{31}P NMR** (162 MHz, $CDCl_3/CD_3CN$ 25%, 298 K) δ -83.30; **MS-ES** (-) *m/z* (rel intensity) 806.6 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 221.4 (100, $M^{2+}/2$), 160.8 (12), 103.0 (36).

(–)-(*S*a)-[4,5,6,10,11,12-hexahydro-5,11-diisoindoline-dibenzo[ef,kl]heptalenium][Δ-BT]$_2$ or [(*S*a)-67][Δ-BT]$_2$

M.p. 276 °C (decomposition); **$[\alpha]_D^{20}$** – 14.8 (*c* 0.1, MeOH); **IR** (neat): 2922, 2853, 1592, 1450, 1388, 1334, 1235, 992, 952, 818 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3/CD_3CN$ 25%, 298 K) δ 7.73 (d, 4H, *J* = 8.1 Hz, BT), 7.56 (d, 4H, *J* = 8.8 Hz, BT), 7.39 (d, 4H, *J* = 7.6 Hz, BT), 7.27-7.13 (m, 18H, BT+cation), 6.97 (t, 4H, *J* = 7.5 Hz, BT), 6.37 (d, 4H, *J* = 8.8 Hz, BT), 4.46 (d, 4H, *J* = 14.1 Hz, CH_2), 4.40 (d, 4H, *J* = 14.4 Hz, CH_2), 4.27 (d, 4H, *J* = 13.4 Hz, CH_2), 3.46 (d, 4H, *J* = 13.4 Hz, CH_2); **^{13}C-NMR** (100 MHz, CD_3CN, 298 K) δ 154.2 (C^{IV}), 143.3 (C^{IV}), 141.1 (C^{IV}), 135.2 (C^{IV}), 134.7 (CH), 133.3 (C^{IV}), 131.5 (CH), 131.0 (CH), 131.0 (CH), 130.4 (CH), 130.1 (C^{IV}, d, *J* = 5.5 Hz), 129.1 (C^{IV}), 129.0 (CH), 127.5 (CH), 126.6 (C^{IV}), 125.2 (C^{IV}), 125.0 (CH), 124.8 (CH), 124.1 (CH), 123.9 (C^{IV}, d, *J* = 3.7 Hz), 123.1 (C^{IV}, d, *J* = 1.9 Hz), 120.5 (C^{IV}), 119.2 (CH), 114.5 (C^{IV}), 68.7 (CH_2), 63.4 (CH_2); **^{31}P NMR** (162 MHz, $CDCl_3/CD_3CN$ 25%, 298 K) δ -83.69; **MS-ES** (-) *m/z* (rel intensity) 806.6 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 221.4 (100, $M^{2+}/2$), 160.8 (12), 103.0 (36).

(+)-(*R*a)-[4,5,6,10,11,12-hexahydro-5,11-diisoindoline-dibenzo[ef,kl]heptalenium] [PF_6]$_2$ or [(*R*a)-67][PF_6]$_2$



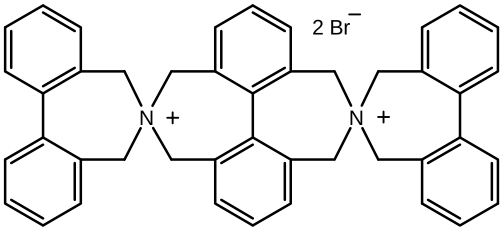
To a suspension of [(*R*a)-**69**][Δ-BT]$_2$ (25.0 mg, 0.0121 mmol) in DCM (3 mL) was added HPF_6.aq. (~ 7.9 M, 0.030 mL, 0.2432 mmol). After two minutes stirring, Et_2O was added to precipitate the desired salt which was washed thoroughly with Et_2O and pentane to yield the desired compound as white solid (8.7 mg, 98%).

M.p. 384 °C (decomposition); **$[\alpha]_D^{20}$** + 60.6 (*c* 0.05, MeOH); **IR** (neat): 1646, 1460, 1446, 1061, 829, 716 cm^{-1}; **^{1}H-NMR** (400 MHz, CD_3CN, 298 K) δ 7.92 (d, 4H, *J* = 7.6 Hz), 7.81 (t, 2H, *J* = 7.6 Hz), 7.52 (m, 8H), 5.16 (d, 4H, *J* = 14.6 Hz), 4.81 (d, 4H, *J* = 14.6 Hz), 4.60 (d, 4H, *J* = 13.4 Hz), 4.09 (d, 4H, *J* = 13.4 Hz); **^{13}C-NMR** (100 MHz, DMSO-*d*$_6$, 298 K) δ 141.3 (C^{IV}), 134.9 (CH), 133.4 (C^{IV}), 131.8 (CH), 130.6 (CH), 130.4 (C^{IV}), 125.0 (CH), 68.9 (CH_2), 63.5 (CH_2); **^{31}P NMR** (162 MHz, $CDCl_3/CD_3CN$ 25%, 298 K) δ -144.6 (sept, *J* = 706 Hz); **MS-ES** (+) *m/z* (rel intensity) 587.7 (80, $[M+PF_6]^+$), 337.3 (85), 220.9 (100, $[M^{2+}/2]$).

(–)-(*S*a)-[4,5,6,10,11,12-hexahydro-5,11-diisoindoline-dibenzo[ef,kl]heptalenium] [PF_6]$_2$ or [(*S*a)-67][PF_6]$_2$

$[\alpha]_D^{20}$ – 58.9 (*c* 0.05, MeOH);

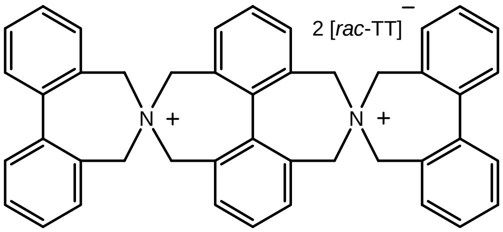
4,5,6,10,11,12-hexahydro-5,11-di-[6,7-Dihydro-5H-dibenz[c,e]azepine]-dibenzo[ef,kl]heptalenium bromide or [71][Br]$_2$



To a suspension of **68** (35.9 mg, 0.1480 mmol) in dry MeOH (3 mL) were added 2,2'-bis-bromomethyl-biphenyl (141.8 mg, 0.3270 mmol) and potassium carbonate (90.4 mg, 0.6540 mmol). The mixture was heated at reflux (70 °C) for 15h. After evaporation of the solvent, the solid residue was retaken in DCM/MeOH 2:1 and the inorganic salts were filtrated. The mother liquors were concentrated and the resulting solid was dissolved in a minimum amount of DCM/MeOH 2:1 and the product precipitated upon addition of Et_2O to yield, after filtration, the desired salt as a white powder (124 mg, 98%).

M.p. 391 °C (decomposition); **IR** (neat): 3412, 2995, 1645, 1442, 1302, 1184, 1077, 892, 825 cm^{-1}; **^{1}H-NMR** (400 MHz, DMSO-d_6, 353 K) δ 8.20 (b, 4H), 7.93-7.68 (b, 18H), 4.63 (d, 4H, J = 13.2 Hz), 4.45 (d, 4H, J = 13.2 Hz), 4.22 (d, 8H, J = 10.5 Hz); **^{13}C-NMR** (100 MHz, DMSO-d_6, 353 K) δ 141.5 (C^{IV}), 141.1 (C^{IV}), 135.0 (CH), 132.8 (CH), 131.9 (CH), 131.1 (CH), 129.7 (CH), 129.4 (C^{IV}), 129.3 (CH), 127.8 (C^{IV}), 62.0 (CH$_2$), 61.2 (CH$_2$); **MS-ES** (+) *m/z* (rel intensity) 297.2 (100, M^{2+}/2).

[4,5,6,10,11,12-hexahydro-5,11-di-[6,7-Dihydro-5H-dibenz[c,e]azepine]-dibenzo[ef,kl]heptalenium][*rac*-TT]$_2$ or [71][*rac*-TT]$_2$

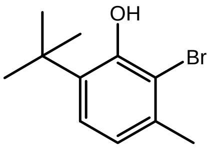


To a solution of [**71**][Br]$_2$ (23.2 mg, 0.0273 mmol) in H$_2$O/Acetone 9:1 (10 mL) was added a solution of [Et$_2$NH$_2$][rac-TT] (46.0 mg, 0.0546 mmol) in DCM/MeOH 9:1 (20 mL). After two hours of vigorous stirring, the organic phase was recovered. The aqueous phase was extracted with DCM and the combined organic phases were washed with water (2 x 10mL). After drying (Na$_2$SO$_4$), filtration and evaporation to dryness, a brown solid was recovered. Purification on column chromatography (Al$_2$O$_3$

basic, eluent DCM/MeOH 95:5) affored the desired [**71**][*rac*-TT]$_2$ salt as a white solid (15 mg, 26%).

M.p. 314 °C (decomposition); **IR** (neat): 1595, 1446, 1389, 1301, 1260, 1235, 1093, 989, 817, 755, 718, 668 cm^{-1}; **^{1}H-NMR** (400 MHz, CD_2Cl_2, 298 K) δ 8.18 (b, 4H), 7.97 (t, 2H, *J* = 7.9 Hz), 7.84 (m, 12H), 7.70 (b, 4H), 4.58 (d, 4H, *J* = 13.4 Hz), 4.36 (d, 4H, *J* = 12.4 Hz), 3.78 (b, 8H); **^{13}C-NMR** (100 MHz, CD_2Cl_2, 298 K) δ 141.9 (d, C^{IV}, *J* = 7.1 Hz), 140.8 (C^{IV}), 139.5 (C^{IV}), 135.4 (C^{IV}), 132.7 (CH), 132.5 (CH), 131.9 (CH), 131.2 (CH), 130.2 (CH), 129.8 (CH), 128.0 (C^{IV}), 125.1 (C^{IV}), 122.5 (C^{IV}), 113.9 (d, C^{IV}, *J* = 20.0 Hz), 61.4-61.0 (b, 2 CH_2); **^{31}P NMR** (162 MHz, CD_2Cl_2, 298K) δ -80.85; **MS-ES** (-) *m/z* (rel intensity) 768.5 (100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 297.2 (100, $M^{2+}/2$).

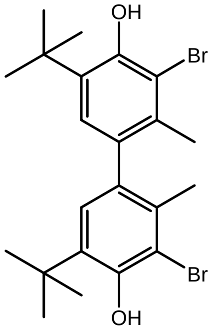
2-Bromo-6-*tert*-butyl-3-methyl-phenol or 73



To a solution of *tert*-butylamine (16.56 g, 0.2264 mol) in freshly distilled toluene (200 mL), at -30 °C, under Argon atmosphere was added dropwise bromine (18.09 g, 0.1132 mol). The mixture was cooled down to -78 °C and a solution of 6-*tert*-butyl-*m*-cresol (37.20 g, 0.2264 mol) in dry DCM (80 mL) was added dropwise. The reaction was left to warm up to room temperature overnight. After dilution with DCM (200 mL), the organic phase was washed with water (4x200 mL) and dried (Na_2SO_4). The solution was then concentrated to yield a yellow oil (~51.4 g) containing a 1:1 ratio of the starting material and the desired product. Purification by column chromatography (SiO_2, 25 cm x 6 cm, cyclohexane) afforded XX as a colorless oil (25.6 g, 47%).

***R*$_f$** = 0.50 (petroleum ether); **IR** (neat): 3497, 3076, 2997, 2957, 2919, 2870, 1602, 1488 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.09 (d, 1H, *J* = 8.0 Hz, CH), 6.72 (d, 1H, *J* = 8.0 Hz, CH), 5.90 (s, 1H, OH), 2.34 (s, 3H, CH_3), 1.38 (s, 9H, ^{t}Bu); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 150.4 (C^{IV}), 136.0 (C^{IV}), 134.7 (C^{IV}), 125.5 (CH), 121.6 (CH), 115.4 (C^{IV}), 35.1 (C^{IV}), 29.5 (CH_3), 23.1 (CH_3); **MS-EI** *m/z* (rel intensity) 244 (M^+, ^{81}Br, 51%), 242 (M^+, ^{79}Br, 51%), 229 (100%), 227 (100%).

3,3’-Dibromo-5, 5’-di-*tert*-butyl-2,2’-dimethylbiphenyl-4,4’-diol or 74

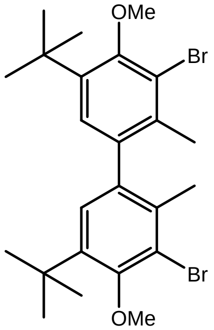


To TMEDA (1.70 mL, 0.0113 mol) in MeOH (260 mL) was added copper (I) chloride (1.05 g, 0.0106 mol) and the resulting solution stirred for 20 min. Compound **73** (25.60 g, 0.1053 mol) was then added and the mixture stirred under open air for further 3 days. The solution was then concentrated, dissolved in ether and filtered through silica and washed with ether. Concentration yielded a tacky orange solid which was purified by column chromatography (SiO_2, petroleum ether) to afford a white solid (14.60 g, 57%).

R

$\boldsymbol{R}_\mathbf{f}$ = 0.40 (9:1 petroleum ether/ethyl acetate); **IR** (neat): 3494, 2978, 2957, 2935, 2891, 1596 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 6.95 (s, 2H, CH), 5.96 (s, 2H, OH), 2.09 (s, 6H, CH_3), 1.40 (s, 18H, ^{t}Bu); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 149.5 (C^{IV}), 134.2 (C^{IV}), 134.1 (C^{IV}), 134.0 (C^{IV}), 127.6 (CH), 116.0 (C^{IV}), 35.2 (C^{IV}), 29.6 (CH_3), 20.9 (CH_3); **MS-EI** *m/z* (rel intensity) 486 (M^+, $^{81}Br_2$, 56%), 485 ($M+H^+$, $^{79}Br^{81}Br$, 41%), 484 (M^+, $^{79}Br^{81}Br$, 65%), 483 ($M+H^+$, $^{79}Br_2$, 25%), 482 (M^+, $^{79}Br_2$, 57%), 471 (55%), 470 (39%), 469 (64%), 468 (21%), 467 (57%).

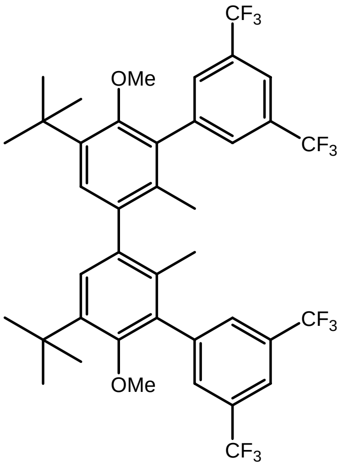
3,3’-Dibromo-5, 5’-di-*tert*-butyl-4,4’-dimethoxy-2,2’-dimethylbiphenyl or 75



To a solution of **74** (14.60 g, 30.15 mmol) in DMF (300 mL) was added potassium carbonate (12.50 g, 90.45 mmol), methyl iodide (4.70 mL, 75.38 mmol) and the resulting solution stirred at room temperature for 19h. Water (350 mL) was added and the resulting solution extracted with ether (2 x 350 mL). The combined organics were washed with brine (2 x 200 mL), dried ($MgSO_4$) and concentrated to an orange foam (15.60 g). The product was dissolved in ether and filtrated through silica to yield yellow foam (14.5 g, 94%).

$\boldsymbol{R}_\mathbf{f}$ = 0.60 (9:1 petroleum ether/ethyl acetate); **M.p.** 105-107 °C. **IR** (neat): 3048, 2960, 2868, 2841, 1529 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.00 (s, 2H, CH), 3.96 (s, 6H, OMe), 1.39 (s, 18H, ^{t}Bu); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 155.9, 141.7, 137.8, 135.8, 127.6, 122.1, 61.5, 35.3, 31.1, 21.0; **MS-EI** *m/z* (rel intensity) 515 (M+H$^+$, ^{81}Br$_2$, 23%), 514 (M$^+$, ^{81}Br$_2$, 65%), 513 (M+H$^+$, ^{79}Br^{81}Br, 26%), 512 (M$^+$, ^{79}Br^{81}Br, 100%), 510 (M$^+$, ^{79}Br$_2$, 67%), 499 (50%), 497 (89%), 495 (45%).

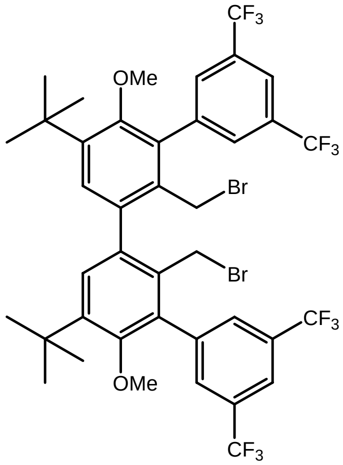
5',5''-Di-tert-butyl-4',4''-dimethoxy-2',2''-dimethyl-3,5,3''',5'''-tetrakis-trifluoro methyl -[1,3';1',1'';3'',1''']quaterphenyl or 76



To a solution of **75** (1.34 g, 2.613 mmol) in THF (70mL, degassed with argon) was added 3,5 bis(trifluoromethyl)phenyl boronic acid (2.02 g, 7.839 mmol) followed by aqueous potassium carbonate (2M, 5 mL degassed with argon), palladium tetrakis triphenylphosphine (302 mg, 0.261 mmol) and the resulting solution refluxed at 80°C. After 24h the reaction mixture was acidified with 2M HCl and extracted with ether (2 x 50mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated to a brown oil. The crude product was recrystallised form ether/methanol to afford the product as an offwhite solid (800 mg, 74%).

M.p. 168 °C; **IR** (neat): 2955, 1355, 1275, 1131 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.90 (4H, s, CH), 7.86 (2H, s, CH), 7.18 (2H, s, CH), 3.16 (6H, s), 1.77 (4H, s, CH_2), 1.42 (18H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 156.3 (C^{IV}), 141.0 (C^{IV}), 140.4 (C^{IV}), 137.5 (C^{IV}), 133.2 (C^{IV}), 133.0 (C^{IV}), 131.7 (C^{IV}), 131.4 (C^{IV}), 131.0 (b, CH), 129.1 (CH), 124.8 (C^{IV}), 122.0 (C^{IV}), 120.8 (m, CH), 60.6 (CH_3), 35.0 (C^{IV}), 31.0 (CH_3), 18.1 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ - 62.57, - 62.60; **MS-ES (+)** *m/z* (rel intensity) 279.3 (100), 227.3 (33).

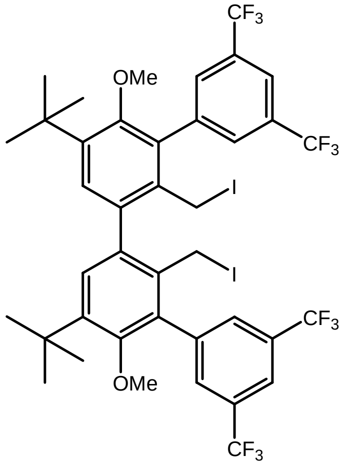
2',2''-Bis-bromomethyl-5',5''-di-tert-butyl-4',4''-dimethoxy-3,5,3''',5'''-tetrakis-trifluoro methyl-[1,3';1',1'';3'',1''']quaterphenyl or 77



To a solution of **76** (955 mg, 1.226 mmol) in CCl_4 (15mL) was added N-bromosuccinimide (458 mg, 2.575 mmol) and AIBN (3.0 mg, 0.0154 mmol) and the resulting suspension stirred at reflux (by light bulb irradiation) under argon for 20 min. The crude suspension was filtered through silica, washed with CCl_4 (15mL) and concentrated to a white foam (1.15 g, 100%).

M.p. 205 °C; **IR** (neat): 2967, 1359, 1276, 1128 cm^{-1}: ^{1}**H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.15 (2H, s, CH), 7.97 (4H, d, J = 6.6 Hz, CH), 7.40 (2H, s, CH), 3.95 (2H, d, J_{AB} = 10.1 Hz, CH_2), 3.89 (2H, d, J_{AB} = 10.1 Hz, CH_2), 3.22 (6H, s, CH_3), 1.44 (18H, s, CH_3); ^{13}**C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 157.4 (C^{IV}), 143.9 (C^{IV}), 138.9 (C^{IV}), 135.8 (C^{IV}), 134.1 (C^{IV}), 132.8 (C^{IV}), 131.6 (qd, J_1 = 9.1 Hz, J_2 = 33.2 Hz, C^{IV}), 130.9 (d, J = 25.6 Hz, CH), 130.3 (CH), 124.7 (d, J = 3.3 Hz, C^{IV}), 121.9 (d, J = 4.1 Hz, C^{IV}), 121.6 (m, CH), 61.0 (CH_3), 35.4 (C^{IV}), 30.8 (CH_3), 30.3 (CH_2); ^{19}**F NMR** (282 MHz, $CDCl_3$) δ - 62.61, - 62.71; **MS-ES (+)** *m/z* (rel intensity) 383.3 (90), 279.3 (100), 227.3 (50).

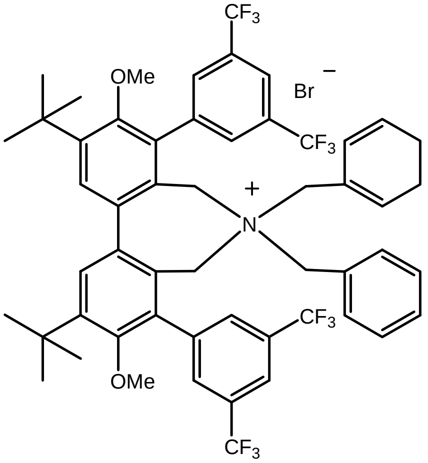
2',2''-Bis-iodomethyl-5',5''-di-tert-butyl-4',4''-dimethoxy-3,5,3''',5'''-tetrakis-trifluoro methyl-[1,3';1',1'';3'',1''']quaterphenyl or 81



To a solution of **76** (100.0 mg, 0.1068 mmol) in acetone (3 mL) was added sodium iodide (128.0 mg, 0.8542 mmol). The mixture was heat at reflux for 1h and cooled down to room temperature. After filtration, the solution was evaporated to dryness and solubilized in Et_2O. After washing with $Na_2S_2O_3$.aq 10% and with water, drying (Na_2SO_4) and concentration, the desired product was obtained pure without purification as a yellow solid (100.0 mg, 91%)

M.p. 199 °C (decomposition); **IR** (neat): 2966, 1464, 1358, 1275, 1126 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.17 (2H, s, CH), 8.02 (4H, s), 7.40 (2H, s, CH), 3.98 (2H, d, J_{AB} = 9.6 Hz, CH_2), 3.84 (2H, d, J_{AB} = 9.6 Hz, CH_2), 3.28 (6H, s, CH_3), 1.50 (18H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 157.7 (C^{IV}), 143.5 (C^{IV}), 139.1 (C^{IV}), 135.5 (C^{IV}), 133.9 (C^{IV}), 133.0 (C^{IV}), 131.7 (qd, J_1 = 4.6 Hz, J_2 = 33.1 Hz, C^{IV}), 130.7 (dd, J_1 = 3.7 Hz, J_2 = 27.6 Hz, CH), 129.7 (CH), 124.7 (d, J = 3.7 Hz, C^{IV}), 122.0 (d, J = 3.7 Hz, C^{IV}), 121.7 (m, CH), 61.0 (CH_3), 35.5 (CH_3), 30.8 (C^{IV}), 3.9 (CH_2); **^{19}F NMR** (282 MHz, $CDCl_3$) δ - 62.61, - 62.69; **MS-EI** *m/z* (rel intensity) 779 (100, M-2I+1), 720 (60), 508 (100).

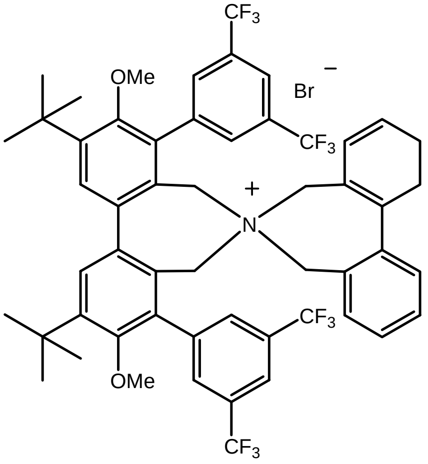
[78][Br]



To a suspension of **77** (198.4 mg, 0.1925 mmol) and potassium carbonate (79.8 mg, 0.5775 mmol) in acetonitrile (6 mL) was added dibenzylamine (76.0 mg, 0.3851 mmol). The mixture was heat at reflux (85 °C) for 17 h and let cool down. After adding water, the compound was extracted with DCM (2x10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vaccum. The compound was purified by column chromatography (SiO_2, DCM then DCM/MeOH 1%) to yield the desired compound as a pale brown solid (70 mg, 33%).

M.p. 173 °C; **IR** (neat): 2960, 1458, 1361, 1275, 1184, 1132 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.00 (4H, b), 7.86 (2H, b), 7.80 (2H, b), 7.50 (2H, m), 7.40 (8H, m), 4.40-3.60 (8H, b, CH_2), 3.29 (6H, s, CH_3), 1.60 (18H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 158.4 (C^{IV}), 148.0 (C^{IV}), 138.7 (C^{IV}), 137.7 (C^{IV}), 134.9 (C^{IV}), 132.6 (C^{IV}), 132.3 (CH), 131.6 (CH), 131.5 (CH), 130.8 (CH), 130.5 (CH), 129.8 (CH), 129.3 (CH), 125.8 (C^{IV}), 124.3 (C^{IV}), 123.5 (CH), 122.0 (C^{IV}), 121.6 (CH), 61.6 (CH_3), 61.3 (CH_2), 59.5 (CH_2), 36.0 (C^{IV}), 31.0 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ - 62.56; **MS-ES (+)** *m/z* (rel intensity) 972.5 (M^+, 100%), 197.6 (10%).

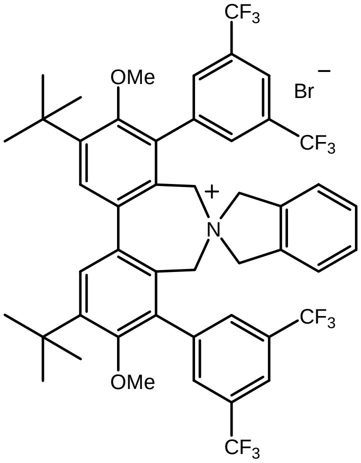
[79][Br]



To a suspension of **77** (103.0 mg, 0.1000 mmol) and potassium carbonate (41.5 mg, 0.3000 mmol) in acetonitrile (3 mL) was added 6,7-Dihydro-5H-dibenz[c,e]azepine (21.5 mg, 0.1100 mmol). The mixture was heat at 75 °C for 17 h and let cool down. After adding water, the compound was extracted with DCM (2x10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vaccum. The compound was purified by column chromatography (SiO_2, DCM then DCM/MeOH 1%) to yield the desired compound as a pale yellow solid (95 mg, 87%).

M.p. 330 °C (decomposition); **IR** (neat): 2956, 1469, 1393, 1362, 1278, 1182, 1131 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.24 (2H, s), 7.75 (8H, m), 7.58 (2H, s), 7.45 (4H, m), 4.76 (4H, m), 4.11 (2H, d, J_{AB} = 13.9 Hz, CH_2), 3.30 (6H, s, CH_3), 2.50 (2H, d, J_{AB} = 12.8 Hz, CH_2), 1.59 (18H, s, CH_3); **^{13}C-NMR** (100 MHz, MeOD, 298 K) δ 159.4 (C^{IV}), 148.4 (C^{IV}), 141.8 (C^{IV}), 139.9 (C^{IV}), 139.0 (C^{IV}), 136.0 (C^{IV}), 133.6 (CH), 133.3 (d, J = 11.6 Hz, C^{IV}), 132.9 (d, J = 11.6 Hz, C^{IV}), 132.7 (CH), 132.5 (CH), 131.6 (CH), 130.3 (CH), 130.2 (CH), 129.4 (CH), 128.3 (C^{IV}), 127.6 (C^{IV}), 125.8 (C^{IV}), 125.6 (C^{IV}), 122.9 (C^{IV}), 122.7 (CH), 64.1 (CH_2), 61.9 (CH_3), 59.8 (CH_2), 36.6 (C^{IV}), 31.1 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ - 62.64, - 62.84; **MS-ES (+)** *m/z* (rel intensity) 970.5 (M^+, 100%), 197.6 (75%).

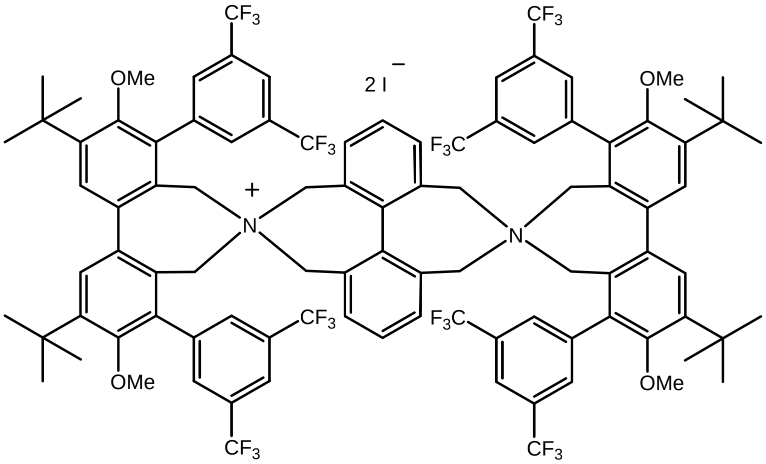
[80][Br]



To a suspension of **77** (209.0 mg, 0.2028 mmol) and potassium carbonate (112.1 mg, 0.8112 mmol) in acetonitrile (6 mL) was added isoindoline (48.0 mg, 0.4033 mmol). The mixture was heat at reflux (85 °C) for 17 h and let cool down. After adding water, the compound was extracted with DCM (2x10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vaccum. The compound was purified by column chromatography (SiO_2, DCM then DCM/MeOH 1%) to yield the desired compound as a pale brown solid (151 mg, 73%).

M.p. 197 °C (decomposition); **IR** (neat): 2955, 1468, 1393, 1366, 1244, 1173, 1129 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.33 (2H, s), 7.88 (2H, s), 7.62 (4H, s), 7.13 (2H, m), 6.76 (2H, m), 5.26 (2H, d, J_{AB} = 13.6 Hz, CH_2), 4.50 (2H, d, J_{AB} = 13.4 Hz, CH_2), 4.30 (2H, d, J_{AB} = 13.6 Hz, CH_2), 4.05 (2H, d, J_{AB} = 13.6 Hz, CH_2), 3.202 (6H, s, CH_3), 1.51 (18H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 158.4 (C^{IV}), 147.9 (C^{IV}), 138.0 (C^{IV}), 137.4 (C^{IV}), 134.9 (C^{IV}), 132.6 (q, J = 34.0 Hz, C^{IV}), 131.9 (CH), 131.4 (C^{IV}), 131.3 (CH), 129.6 (CH), 129.5 (CH), 128.1 (CH), 126.0 (CH), 124.7 (C^{IV}), 124.5 (C^{IV}), 124.2 (C^{IV}), 123.2 (CH), 122.5 (CH), 122.0 (C^{IV}), 121.4 (C^{IV}), 67.1 (CH_2), 61.5 (CH_3), 58.6 (CH_2), 35.9 (C^{IV}), 30.8 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ - 62.35, - 62.66; **MS-ES (+)** *m/z* (rel intensity) 894.5 (M^+, 100%).

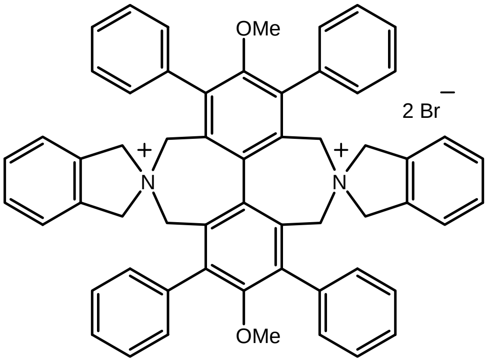
[82][I]$_2$



To a suspension of **77** (258.0 mg, 0.2504 mmol) and potassium carbonate (86.5 mg, 0.6260 mmol) in acetonitrile (6 mL) was added **68** (42.6 mg, 0.1377 mmol). The mixture was heat at 75 °C for 18 h and let cool down. After adding water, the compound was extracted with DCM (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vaccum. The compound was purified by precipitation in DCM / ether to yield the desired compound as a yellow solid (225 mg, 88%).

***R*$_\mathbf{f}$** = 0.55 (1:1 DCM/Acetonitrile); **M.p.** 285 °C (decomposition); **IR** (neat): 2956, 1467, 1393, 1361, 1276, 1174, 1130 cm^{-1}; **^{1}H-NMR** (500 MHz, DMSO-*d*$_6$, 353 K) δ 8.26 (4H, bs), 8.08 (4H, bs), 7.77 (4H, bs), 7.67 (4H, bs), 7.37 (3H, bs), 7.26 (3H, bs), 4.71 (4H, d, *J* = 12.9 Hz, CH_2), 4.38 (4H, d, *J* = 14.2 Hz, CH_2), 3.95 (4H, d, *J* = 12.9 Hz, CH_2), 3.05 (12H, s, OCH_3), 2.06 (4H, b, CH_2), 1.53 (36H, s, CH_3); **^{13}C-NMR** (125 MHz, DMSO-*d*$_6$, 353 K) δ 157.9 (C^{IV}), 146.7 (C^{IV}), 139.2 (C^{IV}), 138.3 (C^{IV}), 137.6 (C^{IV}), 134.7 (C^{IV}), 133.1 (b, CH), 132.3 (b, CH), 131.0 (m, CF_3), 129.9 (b, CH), 129.5 (CH), 128.0 (C^{IV}), 124.4 (C^{IV}), 123.3 (q, *J*= 273.1 Hz, C^{IV}-CF_3), 121.5 (b, CH), 61.5 (CH_2), 61.2 (OCH_3), 59.1 (CH_2), 35.8 (C^{IV}), 31.2 (CH_3); **^{19}F NMR** (126 MHz, DMSO-*d*$_6$, 353 K) δ - 61.14, - 61.34; **MS-ES (+)** *m/z* (rel intensity) 893.5 ($M^{2+}/2$, 100%), 1914.2 ($[M][I]^+$, 5%).

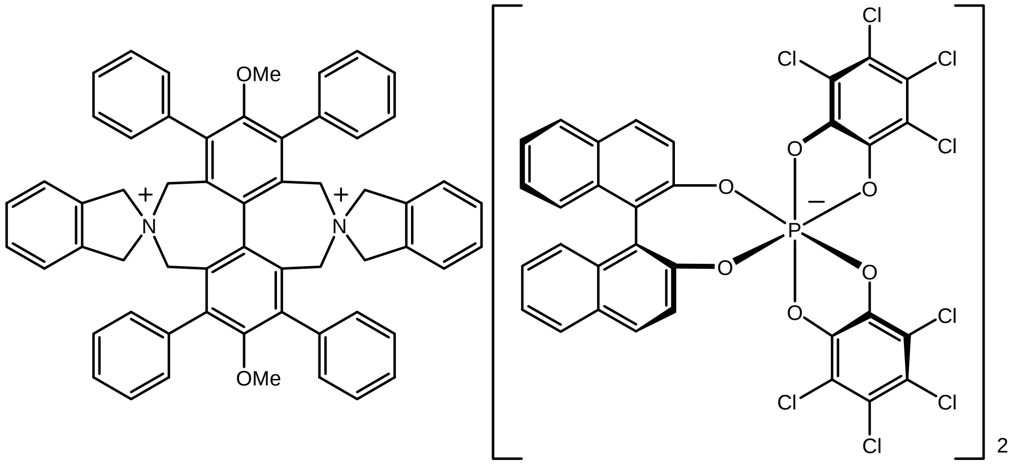
[83][Br]$_2$



To a suspension of **9** (69.9 mg, 0.0785 mmol) and K_2CO_3 (54.3 mg, 0.3926 mmol) was added a solution of isoindoline (46.7 mg, 0.3926 mmol) in dry CH_3CN (3 mL). The mixture was heated at 80 °C for 24h (or at 160 °C for 30 min with the microwave apparatus). After evaporation of the solvent, the solid residue was retaken in DCM/MeOH 1:1 and the inorganic salts were filtrated. The mother liquors were evaporated to dryness. The solid was dissolved in a minimum amount of DCM and the product precipitated upon addition of Et_2O to yield, after filtration, the desired salt as a pale gray solid (58 mg, 77%).

M.p. 220 °C (decomposition) **IR** (neat): 3385, 2941, 2828, 1696, 1556, 1440, 1384, 1288, 1083 cm^{-1}; ^{1}**H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.65(d, 4H, *J* = 7.6 Hz), 7.52 (m, 8H), 7.35-7.14 (m, 12H), 6.82 (m, 4H), 4.98 (d, 4H, *J* = 13.4 Hz), 4.62 (d, 4H, *J* = 13.4 Hz), 4.57 (d, 4H, *J* = 14.4 Hz), 4.20 (d, 4H, *J* = 14.4 Hz), 3.23 (s, 6H). ^{13}**C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 157.1 (C^{IV}), 139.8 (C^{IV}), 137.2 (C^{IV}), 134.7 (C^{IV}), 134.0 (C^{IV}), 131.4 (C^{IV}), 131.0 (CH), 130.3 (CH), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.1 (C^{IV}), 123.5 (CH), 122.9 (CH), 66.9 (CH_2), 61.7 (CH_3, 58.6 (CH_2), 50.1 (CH_2); **MS-ES** (+) *m/z* (rel intensity) 403.8 (100, $M^{2+}/2$), 951.5 (40).

Ion Metathesis with anion Δ-BINPHAT



To a solution of [**83**][Br]$_2$ (43.9 mg, 0.045 mmol) in a minimum amount of MeOH (1 mL) was added a solution of [Me$_2$NH$_2$][Δ−BT] (81.3 mg, 0.095 mmol) in a minimum amount of methanol (2 mL). After 5 min stirring, the desired salt [**83**][Δ−BT]$_2$ that precipitated was filtered, washed thoroughly with Et$_2$O and pentane and obtained as an off white solid (73 mg, 66%) as a 1:1 mixture of two diastereomers.

Separation of the two diastereomers: [(*S*a)-**83**][Δ−BT]$_2$ and [(*R*a)-**83**][Δ−BT]$_2$

The 1:1 mixture of diastereomers was separated by column chromatography on basic alumina starting from 73 mg of material. The first eluted diastereomer, [(*R*a)-**83**][Δ−BT]$_2$ was recovered as a white solid using DCM as eluent (24 mg, 33%, d.e > 96%). The second eluted diastereomer [(*S*a)-**83**][Δ−BT]$_2$ was recovered as a white solid using DCM/CH$_3$CN 99:1 as eluent (22 mg, 29%, d.e ~ 96%).

(−)-[(Ra)-83][Δ−BT]$_2$

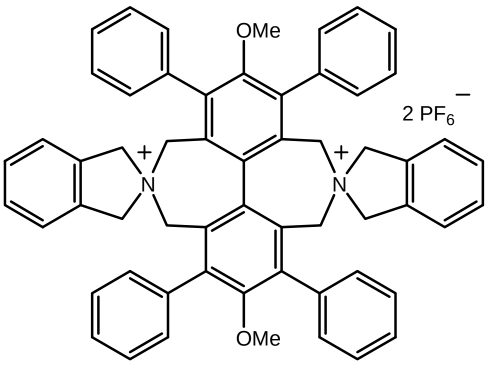
***R*$_f$** = 0.80 (DCM, Al$_2$O$_3$ basic); **M.p.** 248 °C (decomposition); **[α]$_D^{20}$** − 1.9 (*c* 0.15, MeOH); **IR** (neat): 2923, 2853, 1721, 1593, 1454, 1386, 1233, 992, 954 cm^{-1}; **^{1}H-NMR** (400 MHz, CDCl$_3$/CD$_3$CN 25%, 298 K) δ 7.62 (d, 4H, *J* = 7.8 Hz, BT), 7.45 (d, 4H, *J* = 8.1 Hz, BT), 7.34-7.24 (m, 24H, BT+cation), 7.19 (t, 4H, *J* = 7.6 Hz, BT), 6.73 (b, 12H), 5.93 (d, 4H, *J* = 8.1 Hz, BT), 4.47 (d, 4H, *J* = 11.1 Hz), 4.31 (d, 4H, *J* = 14.4 Hz), 4.12

(d, 4H, *J* = 13.6 Hz), 3.69 (d, 4H, *J* = 14.2 Hz), 2.73 (s, 6H); ^{31}**P NMR** (162 MHz, $CDCl_3$, 298 K) δ – 83.2; **MS-ES** (-) *m/z* (rel intensity) 807.0 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 403.8 (100, $M^{2+}/2$), 950.5 (60).[iv]

(–)-[(*S*a)-83][Δ–BT]$_2$

***R*$_f$** = 0.20 (DCM, Al_2O_3 basic); **M.p.** 202 °C (decomposition); **$[\alpha]_D^{20}$** – 66.3 (*c* 0.15, MeOH); **IR** (neat): 2923, 2853, 1712, 1593, 1452, 1386, 1231, 992, 953 cm^{-1}; ^{1}**H-NMR** (400 MHz, $CDCl_3/CD_3CN$ 25%, 298 K) δ 7.66 (d, 4H, *J* = 8.1 Hz, BT), 7.52 (d, 4H, *J* = 8.8 Hz, BT), 7.38-7.27 (m, 12H, BT+cation), 7.18 (t, 4H, *J* = 7.1 Hz, BT), 7.06-7.00 (m, 12H, BT+cation), 6.95 (d, 4H, *J* = 7.1 Hz, cation), 6.95 (m, 4H, cation), 6.88 (d, 4H, *J* = 8.8 Hz, BT), 6.55 (m, 4H, cation), 6.46 (d, 4H, *J* = 7.8 Hz, BT), 4.45 (d, 4H, *J* = 13.7 Hz), 4.10 (d, 4H, *J* = 14.4 Hz), 4.01 (d, 4H, *J* = 14.2 Hz), 3.77 (d, 4H, *J* = 13.4 Hz), 2.62 (s, 6H); ^{31}**P NMR** (162 MHz, $CDCl_3$, 298 K) δ – 82.9; **MS-ES** (-) *m/z* (rel intensity) 807.0 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 403.8 (100, $M^{2+}/2$), 950.5 (30).

[83][PF$_6$]$_2$



To a solution of [**83**][Δ–BT]$_2$ (40.0 mg, 0.0165 mmol) in DCM (3 mL) was added HPF_6.aq. (~ 7.9 M, 0.042 mL, 0.3304 mmol). After two minutes stirring, pentane was added to precipitate the desired salt which was washed thoroughly with Et_2O and pentane to yield the desired compound as an off white solid (18 mg, 99%).

M.p. 214 °C (decomposition); **IR** (neat): 2926, 1713, 1444, 1384, 1274, 1083, 835, 751, 705 cm^{-1}; ^{1}**H-NMR** (400 MHz, $CDCl_3/CD_3CN$ 14%, 298 K) δ 7.57 (m, 10H), 7.36 (m, 10H), 7.13 (b, 4H), 6.82 (b, 4H), 4.60 (d, 4H, *J* = 11.8 Hz), 4.37 (d, 4H, *J* = 13.7 Hz), 4.21 (d, 4H, *J* = 11.8 Hz), 4.11 (d, 4H, *J* = 13.7 Hz),

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[iv] Assignment in ^{13}C NMR spectroscopy could not be performed due to degradation of BINPHAT anion during the experiment though filtration of $CDCl_3$ on basic alumina

3.16 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3/CD_3CN$ 14%, 298 K) δ 157.3 (C^{IV}), 140.2 (C^{IV}), 136.8 (C^{IV}), 134.5 (CIV), 131.3 (C^{IV}), 131.4 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 127.7 (C^{IV}), 123.5 (CH), 66.5 (CH_2), 61.4 (CH_3) 57.4 (CH_2); **^{31}P NMR** (162 MHz, , $CDCl_3/CD_3CN$ 14%, 298 K) δ – 144.4 (sept, *J* = 713.7 Hz); **MS-ES** (+) *m/z* (rel intensity) 403.0 (100, $M^{2+}/2$), 952.0 (50, $[M+PF_6]^+$).

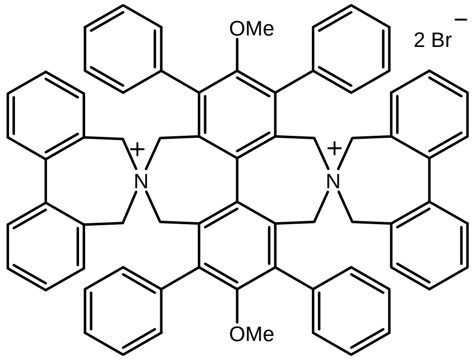
(+)-[(*R*a)-83][PF$_6$]$_2$

$[\alpha]_D^{20}$ + 31.2 (*c* 0.1, MeOH)

(−)-[(*S*a)-83][PF$_6$]$_2$

$[\alpha]_D^{20}$ – 29.2 (*c* 0.1, MeOH)

[84][Br]$_2$



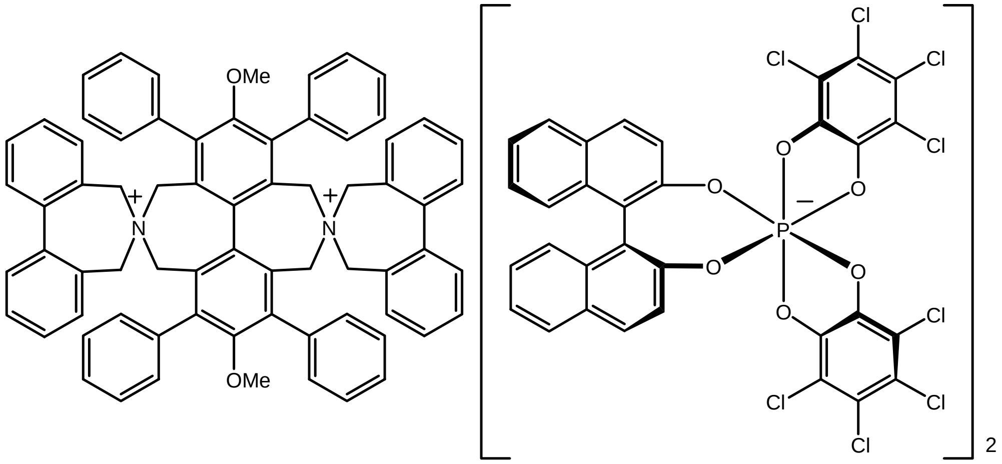
To a suspension of **9** (51.0 mg, 0.057 mmol) and K_2CO_3 (39.6 mg, 0.286 mmol) was added a solution of 6,7-Dihydro-5H-dibenz[c,e]azepine (53.1 mg, 0.229 mmol) in CH_3CN (3 mL). The mixture was heated at 80 °C for 24h (or at 160 °C for 30 min with the microwave apparatus). After evaporation of the solvent, the solid residue was retaken in DCM/MeOH 1:1 and the inorganic salts were filtrated. The mother liquors were evaporated to dryness. The solid was dissolved in a minimum amount of DCM and the product precipitated upon addition of Et_2O to yield, after filtration, the desired salt as a brown solid (43 mg, 67%). However, during this reaction, an impurity may be generated (from 5 to 50%) and can be get rid off by adding methanol to the solid. The desired salt is poorly soluble in this solvent and can be filtered off as a yellow solid.

M.p. 290 °C (decomposition); **IR** (neat): 2957, 1619, 1467, 1393, 1361, 1276, 1174, 1130, 1083 cm^{-1}; **^{1}H-NMR** (400 MHz,$CDCl_3$, 298 K) δ 7.75 (d, 4H, *J* = 6.8 Hz), 7.60 (d, 4H, *J* = 7.1 Hz), 7.52 (t, 4H, *J* = 6.8 Hz), 7.44-7.10 (m, 24H), 5.22 (d, 4H, *J* = 13.0 Hz), 4.56 (d, 4H, *J* = 12.9 Hz), 4.36 (d, 4H, *J* = 12.7 Hz), 3.26 (s, 6H), 2.58 (d, 4H, *J* = 12.6

Hz); ^{13}**C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 156.9 (C^{IV}), 140.5 (C^{IV}), 139.7 (C^{IV}), 137.8 (C^{IV}), 134.7 (C^{IV}), 131.4 (CH), 131.3 (CH), 130.6 (CH), 130.3 (CH), 129.2 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (C^{IV}), 126.7 (C^{IV}), 63.5 (CH_2), 61.8 (CH_3), 59.5 (CH_2); **MS-ES** (+) *m/z* (rel intensity) 479.8 (100, $M^{2+}/2$), 1104.4 (50).

Ion Metathesis with anion Δ-BINPHAT

To a solution of [**84**][Br]$_2$ (43 mg, 0.038 mmol) in a minimum amount of DCM/MeOH 1:9 (1 mL) was added a solution of [Me_2NH_2][Δ−BT] (72 mg, 0.085 mmol) in a minimum amount of methanol (2 mL). After 5 min stirring, the desired salt [**84**][Δ−BT]$_2$ that precipitated was filtered, washed thoroughly with Et_2O and pentane and obtained as an pale brown solid (75 mg, 76%) as a 1:1 mixture of two diastereomers.



Separation of the two diastereomers: [(*S*a)-**84**][Δ−BT]$_2$ and [(*R*a)-**84**][Δ−BT]$_2$

In a round bottom flask, the 1:1 mixture of diastereomers [(*S*a)-**XX**][Δ−BT]$_2$ and [(*R*a)-**84**][Δ−BT]$_2$ (100 mg) was dissolved in $CHCl_3/CH_3CN$ 6:1. The precipitate was filtered and washed several times with pentane to afford the [(*S*a)-**84**][Δ−BT]$_2$ diastereomer as a white solid (46 mg, 46%, d.e > 96%). The mother liquors were evaporated to yield the [(*R*a)-**84**][Δ−BT]$_2$ diastereomer as a brown solid (51 mg, ~ 51%, d.e ~ 84%).

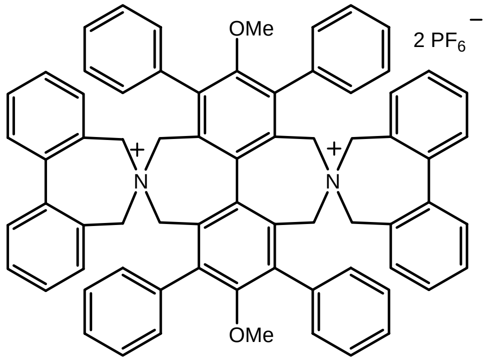
(−)-[(*S*a)-84][Δ−BT]$_2$

***R*$_f$** = 0.10 (DCM, Al_2O_3 basic); **M.p.** 283 °C (decomposition); **$[\alpha]_D^{20}$** − 101.8 (*c* 0.05, MeOH); **IR** (neat): 3093, 2941, 2823, 1686, 1593, 1556, 1451, 1387, 1232, 1075, 993, 953 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3/CD_3CN$ 33%, 298 K) δ 7.67 (d, 4H, *J* = 7.9 Hz, BT), 7.54 (d, 4H, *J* = 8.9 Hz, BT), 7.40 (t, 4H, *J* = 7.5 Hz, BT), 7.28-6.98 (m, 36H, BT+cation), 6.91 (d, 4H, *J* = 7.0 Hz, BT), 6.53 (d, 4H, *J* = 8.6 Hz, BT), 4.26 (d, 4H, *J* = 13.0 Hz), 4.00 (d, 4H, *J* = 13.0 Hz), 3.90 (d, 4H, *J* = 12.7 Hz), 2.78 (s, 6H), 2.39 (d, 4H, *J* = 12.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3/CD_3CN$ 33%, 298 K) δ – 77.51; **MS-ES** (-) *m/z* (rel intensity) 807.0 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 479.8 (100, $M^{2+}/2$), 944.8 (30), 1103.8 (80).

(−)-[(*R*a)-84][Δ−BT]$_2$

***R*$_f$** = 0.10 (DCM, Al_2O_3 basic); **M.p.** 280 °C (decomposition); **$[\alpha]_D^{20}$** + 78.2 (*c* 0.05, MeOH); **IR** (neat): 3056, 1696, 1593, 1452, 1388, 1304, 1232, 1074, 993, 953 cm^{-}1; **1H-NMR** (400 MHz, $CDCl_3/CD_3CN$ 33%, 298 K) δ 7.68 (d, 4H, *J* = 7.9 Hz, BT), 7.52 (d, 4H, *J* = 8.8 Hz, BT), 7.39 (t, 4H, *J* = 7.3 Hz, BT), 7.28-6.96 (m, 36H, BT+cation), 6.90 (d, 4H, *J* = 7.3 Hz, BT), 6.46 (d, 4H, *J* = 9.3 Hz, BT), 4.28 (d, 4H, *J* = 13.1 Hz), 4.03 (d, 4H, *J* = 13.3 Hz), 3.93 (d, 4H, *J* = 13.3 Hz), 2.92 (s, 6H), 2.40 (d, 4H, *J* = 12.9 Hz); **^{31}P NMR** (162 MHz, $CDCl_3/CD_3CN$ 33%, 298 K) δ – 77.58; **MS-ES** (-) *m/z* (rel intensity) 806.6 (100, BINPHAT), **MS-ES** (+) *m/z* (rel intensity) 479.5 (100, $M^{2+}/2$), 777.5 (25), 1765.3 (37, M^{2+}+BINPHAT).

[84][PF$_6$]$_2$



To a solution of [**84**][Δ–BT]$_2$ (44.0 mg, 0.0171 mmol) in DCM (1 mL) was added HPF$_6$.aq. (~ 7.9 M, 0.043 mL, 0.3420 mmol). After two minutes stirring, pentane was added to precipitate the desired salt which was washed thoroughly with Et$_2$O and pentane to yield the desired compound as an pale brown solid (21 mg, 98%).

M.p. 333 °C (decomposition); **IR** (neat): 1454, 1384, 1354, 1246, 1026, 886, 843, 756, 708 cm^{-1}; **^{1}H-NMR** (400 MHz, CDCl$_3$, 298 K) δ 7.55 (m, 10H), 7.45 (m, 12H), 7.27 (m, 6H), 7.13 (m, 8H), 4.63 (d, 4H, *J* = 13.1 Hz), 4.50 (d, 4H, *J* = 13.1 Hz), 4.01 (d, 4H, *J* = 12.6 Hz), 3.20 (s, 6H), 2.55 (d, 4H, *J* = 12.6 Hz); **^{13}C-NMR** (100 MHz, CD$_3$OD, 298 K) δ 158.1 (C^{IV}), 141.9 (C^{IV}), 141.4 (C^{IV}), 138.7 (C^{IV}), 135.8 (C^{IV}), 132.6 (CH), 132.0 (CH), 131.8 (CH), 131.1 (CH), 130.1 (CH), 129.6 (CH), 129.5 (CH), 129.5 (C^{IV}), 129.4 (CH), 129.0 (C^{IV}), 127.9 (C^{IV}), 118.1 (C^{IV}), 64.8 (CH$_2$), 61.9 (CH$_3$), 59.5 (CH$_2$); **^{31}P NMR** (162 MHz, CDCl$_3$/CD$_3$CN 14%, 298 K) δ −144.4 (sept, *J* = 712.9 Hz); **MS-ES** (+) *m/z* (rel intensity) 479.0 (100, M^{2+}/2), 1103.9 (70, [M+PF$_6$]$^+$).

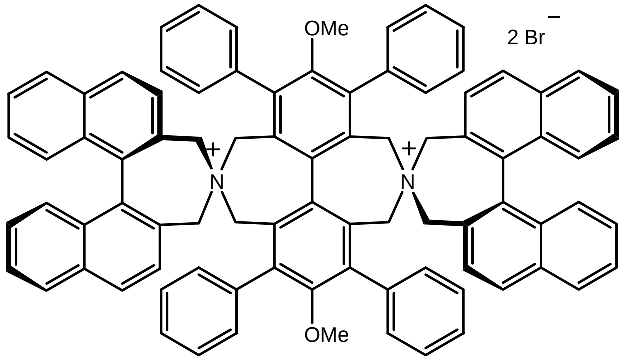
(−)-(*S*a)-[84][PF$_6$]$_2$

[α]$_D^{20}$ − 97.7 (*c* 0.1, MeOH)

(+)-(*R*a)-[84][PF$_6$]$_2$

[α]$_D^{20}$ + 89.3 (*c* 0.1, MeOH)

(–)-[85][Br]$_2$

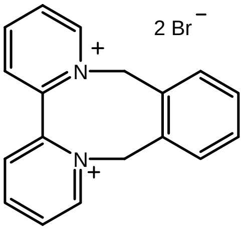


To a suspension of **9** (107.6 mg, 0.1208 mmol) and K_2CO_3 (83.5 mg, 0.6040 mmol) was added a solution of dinaphthylazepine (*R*a)-**2** (100.0 mg, 0.3021 mmol) in CH_3CN (10 mL). The mixture was heated at 80 °C for 48h (or at 160 °C for 160 min with the microwave apparatus). After evaporation of the solvent, the solid residue was retaken in DCM/MeOH 1:1 and the inorganic salts were filtrated. The mother liquors were evaporated to dryness. The solid was dissolved in a minimum amount of DCM and the product precipitated upon addition of Et_2O to yield, after filtration, the desired salt as a pale gray solid (100 mg, 62%). If needed, this compound could be further purified by column chromatography on basic alumina using DCM as eluent and then DCM/MeOH from 1 to 10%.

M.p. 291 °C (decomposition); **$[\alpha]_D^{20}$** – 187.2 (*c* 0.1, MeOH); **IR** (neat): 2937, 1666, 1596, 1454, 1389, 1245 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$, 298 K) δ 8.00 (dd, 4H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 7.83 (d, 4H, *J* = 8.3 Hz), 7.59 (t, 4H, *J* = 7.3 Hz), 7.44 (t, 4H, *J* = 7.6 Hz), 7.34-7.26 (m, 12H), 7.01 (t, 4H, *J* = 7.3 Hz), 6.88 (t, 4H, *J* = 7.3 Hz), 6.64 (t, 4H, *J* = 7.6 Hz), 5.21 (d, 4H, *J* = 13.4 Hz), 4.41 (d, 4H, *J* = 12.6 Hz), 4.34 (d, 4H, *J* = 13.1 Hz), 3.22 (s, 6H), 2.64 (d, 4H, *J* = 12.9 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$, 298 K) δ 156.4 (C^{IV}), 139.2 (C^{IV}), 137.9 (C^{IV}), 136.3 (C^{IV}), 134.6 (C^{IV}), 134.3 (C^{IV}), 130.7 (C^{IV}), 130.4 (CH), 130.0 (CH), 129.9 (CH), 128.6 (CH), 128.2 (CH), 128.1 (C^{IV}), 127.8 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.4 (C^{IV}), 64.1 (CH_2), 61.6 (CH_3), 59.1 (CH_2). **MS-ES** (+) *m/z* (rel intensity) 1240.7 (20, M^{2+}+Br), 579.3 (98, $M^{2+}/2$), 296.4 (100), 279.4 (64).

CHAPTER IV – SYNTHESIS AND RESOLUTION OF THE FIRST NON-RACEMIC DIQUATS

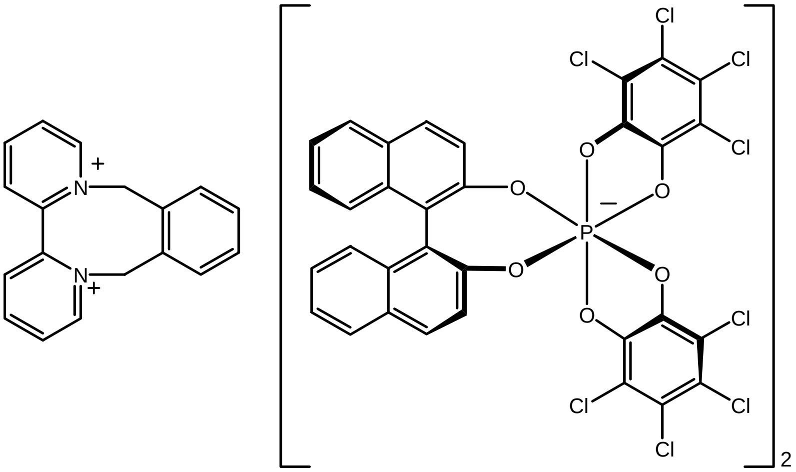
10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4]diazocindium dibromide or [88a][Br]$_2$



A sealed tube containing 2,2'-dipyridyl (107 mg, 0.685 mmol) and α,α'-dibromo-*o*-xylene (181 mg, 0.685 eq) in acetonitrile (2.5 mL) was heated at 90°C for 15 hours. After cooling, 5 mL of Et$_2$O were added and the resulting precipitate was filtered, washed with Et$_2$O to obtain the desired compound as a white solid (200 mg, 70%).

M.p. 298 °C; **IR** (neat) 3007, 2985, 1622, 1585, 1505, 1470, 1193, 1164 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d$_6$*) δ 9.53 (d, 2H, *J* = 5.6 Hz), 8.97 (td, 2H, *J* = 1.0 Hz and 7.8 Hz), 8.55 (td, 2H, *J* = 1.3 Hz and 7.3 Hz), 8.51 (dd, 2H, *J* = 1.0 Hz and 7.8 Hz), 7.69 (m, 2H), 7.58 (m, 2H), 6.00 (d, 2H, *J* = 15.8 Hz), 5.48 (d, 2H, *J* = 15.8 Hz); **^{13}C NMR** (100 MHz, DMSO-*d$_6$*) δ 148.3 (CH), 147.6 (CH), 144.7 (C^{IV}), 131.6 (CH and C^{IV}), 131.0 (CH), 130.5 (CH), 130.0 (CH), 60.2 (CH$_2$); **UV** (CH$_3$CN, 10^{-5} M) λ (ε) 201 (3.53 × 10^5), 278 (1.15 × 10^5); **MS-ES** (+) *m/z* (rel intensity) 180.1 (100, M-C$_8$H$_8$+1), 259.3 (50, M-1).

Ion Metathesis with Δ-BINPHAT



To a solution of [Me$_2$NH$_2$][Δ−BT] (223.6 mg, 0.262 mmol) in methanol (10 mL) was added a solution of [**88a**][Br]$_2$ (55.0 mg, 0.131 mmol) in methanol (3 mL). The mixture was stirred for about 5 min and the precipitate appeared is filtered and washed with Et_2O. The diastereomeric salt was obtained as a yellow solid (210 mg, 86%), containing 60% of [(*S*a)-**88a**][Δ-BT]$_2$ and 40% of [(*R*a)-**88a**][Δ-BT]$_2$.

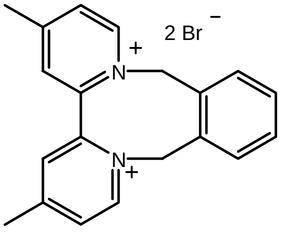
<u>**Separation of Diastereomers**</u> [(*S*a)-**88a**][Δ-BT]$_2$ and [(*R*a)-**88a**][Δ-BT]$_2$

In a round bottom flask containing [**88a**][Δ-BT]$_2$ (180 mg) was added acetonitrile (10 mL). The solid was triturated until a thin powder was obtained. The yellow precipitate was filtered to afford [(*S*a)-**88a**][Δ-BT]$_2$ (91 mg, ~ 50%, d.e = 96%) as a yellow solid. After evaporation to dryness of the mother liquor, [(*R*a)-**88a**][Δ-BT]$_2$ was obtained as a yellow solid (77 mg, ~ 43%, d.e ~ 40%).

(–)-(*S*a)-[10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4]diazocindium][Δ-BT]$_2$ or [(*S*a)-88a][Δ-BT]$_2$ (d.e.= 96%)

M.p. 235 °C; **$[\alpha]^{20}_D$** -43.4 (*c* 0.1, CH_3CN); **IR** (neat) 3077, 1614, 1592, 1450, 1235, 947, 819 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d$_6$*) δ 9.44 (s, 2H), 8.94 (s, 2H), 8.52 (b, 4H), 7.96 (d, 4H, *J* = 8.1 Hz, BT), 7.84 (d, 4H, *J* = 8.6 Hz, BT), 7.62 (s, 2H), 7.57 (s, 2H), 7.40 (m, 4H, BT), 7.27 (d, 4H, *J* = 3.3 Hz, BT), 6.57 (d, 8H, *J* = 8.8 Hz, BT), 5.90 (d, 2H, *J* = 13.4 Hz), 5.48 (d, 2H, *J* = 14.7 Hz); **^{13}C NMR** (100 MHz, DMSO-*d$_6$*) δ 151.8 (C^{IV}, d, *J* = 12.4 Hz, BT), 148.4 (CH), 147.6 (CH), 144.7 (C^{IV}), 142.6 (C^{IV}, d, *J* = 5.8 Hz, BT), 142.1 (C^{IV}, d, *J* = 9.1 Hz, BT), 131.8 (C^{IV}), 131.6 (CH), 131.5(C^{IV}, BT), 131.0 (CH), 130.5 (CH), 130.0 (CH cation and C^{IV}, BT), 129.1 (CH, BT), 128.3 (CH, BT), 126.3 (CH, BT), 125.7 (CH, BT), 124.1 (CH, BT), 122.6 (CH, d, *J* = 3.3 Hz, BT), 122.3 (C^{IV}, d, *J* = 3.3 Hz, BT), 121.4 (C^{IV}, BT), 119.9 (C^{IV}, BT), 112.9 (C^{IV}, d, *J* = 15.7 Hz, BT), 112.7 (C^{IV}, d, *J* = 14.1 Hz, BT), 60.2 (CH_2); **^{31}P NMR** (162 MHz, DMSO-*d$_6$*) δ -83.99; **UV** (CH_3CN, 10^{-5} M) λ (ε) 220 (2.81×10^5), 302 (2.9×10^4), 329 (1.5×10^4); **CD** (CH_3CN, 10^{-5} M) λ (Δε) 207 (-151.4), 231 (333.8), 244 (-120.7), 264 (38.7), 298 (-6.9), 328 (-2.5); **MS-ES** (-) *m/z* (rel intensity) 807.0 (100, BINPHAT), **MS-ES** (+) *m/z* (rel intensity) 184.4 (50), 259.4 (50, M-1), 371.5 (100).

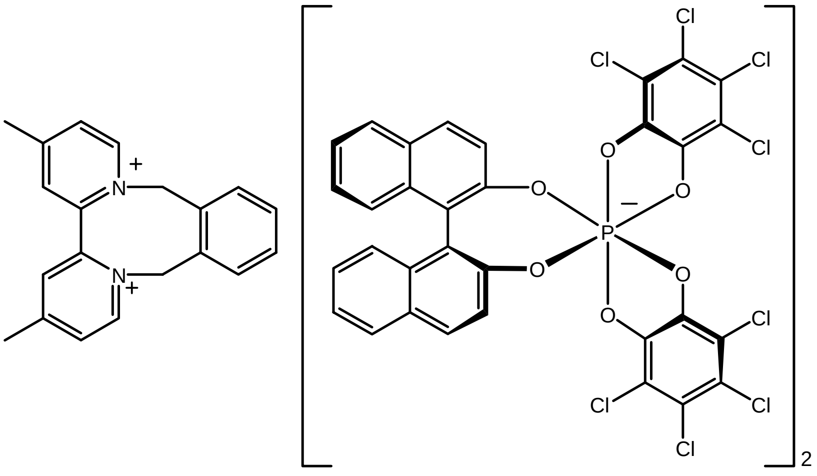
3,3’-Dimethyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2’,1’-c][1,4]diazocindium dibromide or [88b][Br]$_2$



A sealed tube containing 4,4’-dimethyl-2,2’-dipyridyl (117 mg, 0.636 mmol) and α,α’-dibromo-*o*-xylene (168 mg, 0.636 mmol) in acetonitrile (2.5 mL) was heated at 90°C for 15 hours. After cooling, 5 mL of Et$_2$O were added and the resulting precipitate was filtered, washed with Et$_2$O, to obtain the desired compound as a pale yellow solid (250 mg, 88%).

M.p. 293 °C; **IR** (neat) 3439, 2984, 2928, 1623, 1447, 1164, 845 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d$_6$*) δ 9.36 (d, 2H, *J* = 6.8 Hz), 8.37 (m, 4H), 7.66 (m, 2H), 7.56 (m, 2H), 5.92 (d, 2H, *J* = 15.9 Hz), 5.46 (d, 2H, *J* = 15.9 Hz), 2.74 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-*d$_6$*) δ 161.1 (C^{IV}), 147.1 (CH), 143.4 (C^{IV}), 131.6 (C^{IV}), 131.4 (CH), 130.9 (CH), 130.7 (CH), 129.9 (CH), 60.4 (CH$_2$), 21.8 (CH$_3$); UV (CH$_3$CN, 10^{-5} M) λ (log ε) 215 (1.51), 230 (1.16), 274 (0.82); **MS-ES** (+) *m/z* (rel intensity) 184.6 (95, M-C$_8$H$_8$+1), 287.6 (100, M-1)

Ion Metathesis with Δ-BINPHAT



To a solution of [Me$_2$NH$_2$][Δ-BT] (230.5 mg, 0.270 mmol) in methanol (10 mL) was added a solution of [**88b**][Br]$_2$ (55.0 mg, 0.135 mmol) in methanol (2 mL). The mixture was stirred for about 5 min and the precipitate appeared is filtered and washed with Et$_2$O. The diastereomeric salt was obtained as a yellow solid (216 mg, 84%), containing 56% of [(*S*a)-**88b**][Δ-BT]$_2$ and 44% of [(*R*a)-**88b**][Δ-BT]$_2$.

<u>Separation of Diastereomers</u> [(*S*a)-**88b**][Δ-BT]$_2$ and [(*R*a)-**88b**][Δ-BT]$_2$

In a round bottom flask containing [**88b**][Δ-BT]$_2$ (194 mg) was added acetonitrile (10 mL). The solid was triturated until a thin powder was obtained. The yellow precipitate was filtered to afford [(*S*a)-**88b**][Δ-BT]$_2$ (107 mg, ~ 55%, d.e = 96%) as a yellow solid. After evaporation to dryness of the mother liquor, [(*R*a)-**88b**][Δ-BT]$_2$ was obtained as a yellow solid (78 mg, ~ 40%, d.e ~ 92%).

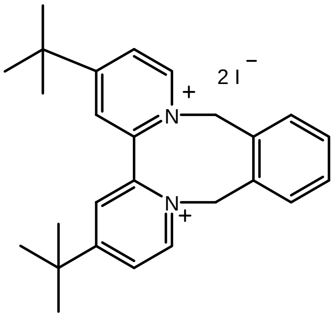
(−)-(*S*a)-[3,3'-Dimethyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4] diazocindium][Δ-BT]$_2$ or [(*S*a)-88b][Δ-BT]$_2$ (d.e.= 96%)

M.p. 255 °C; $[\alpha]^{20}_{D}$ -24.5 (*c* 0.04, CH$_3$CN); **IR** (neat) 2971, 1623, 1445, 1389, 1236, 989, 817 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 9.26 (d, 2H, *J* = 5.3 Hz), 8.32 (b, 4H), 7.96 (d, 4H, *J* = 8.1 Hz, BT), 7.84 (d, 4H, *J* = 8.8 Hz, BT), 7.57 (m, 4H), 7.40 (m, 4H, BT), 7.28 (m, 8H, BT), 6.59 (d, 4H, *J* = 8.8 Hz, BT), 5.80 (d, 2H, *J* = 16.1 Hz), 5.44 (d, 2H, *J* = 15.6 Hz), 2.71 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ 161.1 (C^{IV}), 151.8 (C^{IV}, d, *J* = 12.4 Hz, BT), 147.1 (CH), 143.8 (C^{IV}), 142.6 (C^{IV}, d, *J* = 5.0 Hz, BT), 142.1 (C^{IV}, d, *J* = 9.1 Hz, BT), 131.8 (C^{IV}), 131.5 (C^{IV}, BT), 131.4 (CH), 130.9 (CH), 130.6 (CH), 130.0 (C^{IV}, BT), 129.9 (CH), 129.1 (CH, BT), 128.3 (CH, BT), 126.3 (CH, BT), 125.7 (CH, BT), 124.1 (CH, BT), 122.6 (CH, d, *J* = 4.1 Hz, BT), 122.3 (C^{IV}, d, *J* = 3.3 Hz, BT), 121.4 (C^{IV}, BT), 119.9 (C^{IV}, BT), 112.9 (C^{IV}, d, *J* = 15.7 Hz, BT), 112.7 (C^{IV}, d, *J* = 15.0 Hz, BT), 60.5 (CH$_2$), 21.8 (CH$_3$); **^{31}P NMR** (162 MHz, DMSO-*d*$_6$) δ -83.83 **UV** (CH$_3$CN, 10^{-5} M) λ (ε) 220 (3.42 × 10^5), 274 (2.17 × 10^5), 323 (1.9 × 10^4); **CD** (CH$_3$CN, 10^{-5} M) λ (Δε) 207 (-178.3), 231 (396.8), 244 (-150.3), 264 (50.7), 298 (-10.7), 328 (-3.4); **MS-ES** (-) *m/z* (rel intensity) 807.0 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 184.1 (80, M-C$_8$H$_8$+1), 371.5 (100).

(+)-(*R*a)-[3,3'-Dimethyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4] diazocindium][Δ-BT]$_2$ or [(*R*a)-88b][Δ-BT]$_2$ (d.e= 92%)

M.p. 250 °C; **$[\alpha]^{20}_{D}$** 28.4 (*c* 0.1, CH$_3$CN); **IR** (neat) 3049, 2971, 1624, 1591, 1449, 1388, 1235, 991, 817 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 9.27 (b, 2H), 8.32 (b, 4H), 7.95 (d, 4H, *J* = 6.8 Hz, BT), 7.83 (d, 4H, *J* = 7.3 Hz, BT), 7.57 (d, 4H, *J* = 12.3 Hz), 7.40 (b, 4H, BT), 7.27 (b, 8H, BT), 6.57 (d, 4H, *J* = 8.1 Hz, BT), 5.83 (d, 2H, *J* = 15.9 Hz), 5.43 (d, 2H, *J* = 15.6 Hz), 2.71 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 161.6 (C^{IV}), 152.3 (C^{IV}, d, *J* = 12.2 Hz, BT), 147.6 (CH), 144.3 (C^{IV}), 143.0 (C^{IV}, d, *J* = 5.8 Hz, BT), 142.6 (C^{IV}, d, *J* = 9.0 Hz, BT), 132.3 (C^{IV}), 132.0 (C^{IV}, BT), 131.9 (CH), 131.4 (CH), 131.1 (CH), 130.5 (C^{IV}, BT), 130.4 (CH), 129.6 (CH, BT), 128.8 (CH, BT), 126.8 (C^{IV}), 126.3 (CH, BT), 126.1 (CH, BT), 124.9 (CH, BT), 123.0 (CH, d, *J* = 3.2 Hz, BT), 122.8 (C^{IV}, d, *J* = 3.2 Hz, BT), 121.8 (C^{IV}, BT), 120.4 (C^{IV}, BT), 113.4 (C^{IV}, d, *J* = 11.6 Hz, BT), 113.1 (C^{IV}, d, *J* = 10.3 Hz, BT), 60.9 (CH$_2$), 22.3 (CH$_3$); **^{31}P NMR** (162 MHz, DMSO-d_6) δ -84.01; **UV** (CH$_3$CN, 10^{-5} M) λ (ε) 222 (3.78 × 10^5), 301 (7.0 × 10^4), 329 (3.3 × 10^4); **CD** (CH$_3$CN, 10^{-5} M) λ (Δε) 245 (-88.5), 264 (29.2), 302 (-14.1), 330 (-8.5); **MS-ES** (-) *m/z* (rel intensity) 807.0 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 184.1 (80, M-C$_8$H$_8$+1), 371.5 (100).

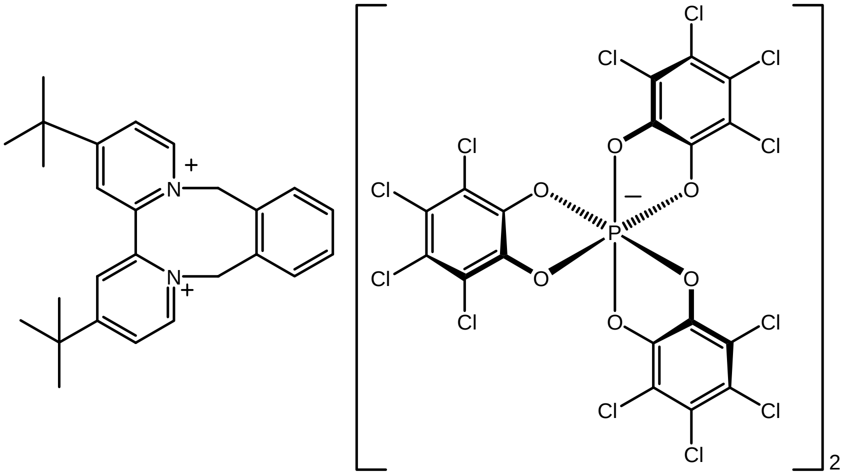
3,3’-Di-tert-buthyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2’,1’-c][1,4]diazocindium diiodide or [88c][I]$_2$



A sealed tube containing 4,4’-Di-*tert*-butyl-2,2’-dipyridyl (305.5 mg, 0.220 mmol), α,α’-diiodo-*o*-xylene (815 mg, 0.439 mmol) and 1,2 dichlorobenzene (freshly distilled on CaH$_2$) is heated from 120 °C to 160 °C in a 4 hour period. After cooling, the yellow precipitate is filtered, than washed with pentane thoroughly to afford [**88c**][I]$_2$ as a yellow powder (460 mg, 65%).

M.p. 258 °C; **IR** (neat) 3420, 3038, 2959, 1621, 1452, 1116, 847 cm^{-1}; **^{1}H NMR** (400 MHz, CD$_3$CN) δ 9.39 (d, 2H, *J* = 6.5 Hz), 8.63 (d, 2H, *J* = 2.0 Hz), 8.41 (dd, 2H, *J* = 2.3 Hz and 6.6 Hz), 7.81 (dd, 2H, *J* = 3.5 Hz and 5.3 Hz), 7.59 (dd, 2H, *J* = 3.4 Hz and 5.7 Hz), 6.10 (d, 2H, *J* = 16.2 Hz), 5.34 (d, 2H, *J* = 16.2 Hz), 1.52 (s, 18H); **^{13}C NMR** (100 MHz, CD$_3$CN) δ 173.6 (C^{IV}), 147.1 (CH), 144.4 (C^{IV}), 131.1 (CH), 130.4 (CH), 128.7 (CH), 128.6 (CH), 60.95 (CH$_2$), 37.3 (C^{IV}), 29.1 (CH$_3$); **UV** (CH$_3$CN, 10^{-5} M) λ (ε) 207 (7.3 × 10^4), 248 (6.3 × 10^4), 290 (4.2 × 10^4); **MS-ES** (+) *m/z* (rel intensity) 186.6 (1, M/2), 403.5 (100).

Ion Metathesis with Δ-TRISPHAT



To a solution of [cinchonidinium][Δ-TT] (303.2 mg, 0.285 mmol) in acetone (4 mL) was added a solution of [**88c**][I]$_2$ (85.0 mg, 0.136 mmol) in CH_2Cl_2/MeOH 4:1 (2 mL). The mixture was stirred for about 5 min and then evaporated to dryness. The diastereomeric salts were obtained, after chromatography over basic alumina with CH_3CN as eluent, with a 1.2 to 1 ratio (*i.e* 55% of [(*S*a)-**88c**][Δ-TT]$_2$ and 45% of [(*R*a)-**88c**][Δ-TT]$_2$) as a yellow solid.

Separation of Diastereomers [(*S*a)-**88c**][Δ-TT]$_2$ and [(*R*a)-**88c**][Δ-TT]$_2$

In a round bottom flask containing [**88c**][Δ-TT]$_2$ (210 mg) was added CH_3CN till complete solubilisation (~5 mL). The flask was cooled to –20 °C for a 30 min period. The yellow precipitate was filtered to afford [(*S*a)-**88c**][Δ-TT]$_2$ (110 mg, ~ 52%, d.e > 96%) as a yellow solid. After evaporation to dryness of the mother liquor, [(*R*a)-**88c**][Δ-TT]$_2$ was obtained as a yellow solid (90 mg, ~ 43%, d.e ~ 95%).

(–)-(*S*a)-[3,3'-Di-tert-buthyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4]diazocindium][Δ-TT]$_2$ or [(*S*a)-88c][Δ-TT]$_2$ (d.e.> 96%)

M.p. 300 °C; $[\alpha]^{20}_{D}$ -357.7 (*c* 0.1, CH_3CN); **IR** (neat) 2972, 1622, 1444, 1389, 1235, 989, 818 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3/CD_3CN$ 3%) δ 9.95 (d, 2H, *J* = 6.6 Hz), 8.22 (d, 2H, *J* = 2.3 Hz), 8.08 (dd, 2H, *J* = 2.0 Hz and 6.6 Hz), 7.67 (dd, 2H, *J* = 3.7 Hz and 5.3 Hz), 7.11 (dd, 2H, *J* = 3.7 Hz and 5.3 Hz), 6.46 (d, 2H, *J* = 16.0 Hz), 5.27 (d, 2H, *J* = 16.0 Hz), 1.51 (s, 18H); ^{13}**C NMR** (75 MHz, DMSO-*d*$_6$) δ 172.6 (C^{IV}), 147.5 (CH), 144.9 (C^{IV}), 141.6 (d, C^{IV}, *J* = 6.5 Hz), 132.0 (CH), 131.4 (C^{IV}), 130.4 (CH), 128.9 (CH), 127.8

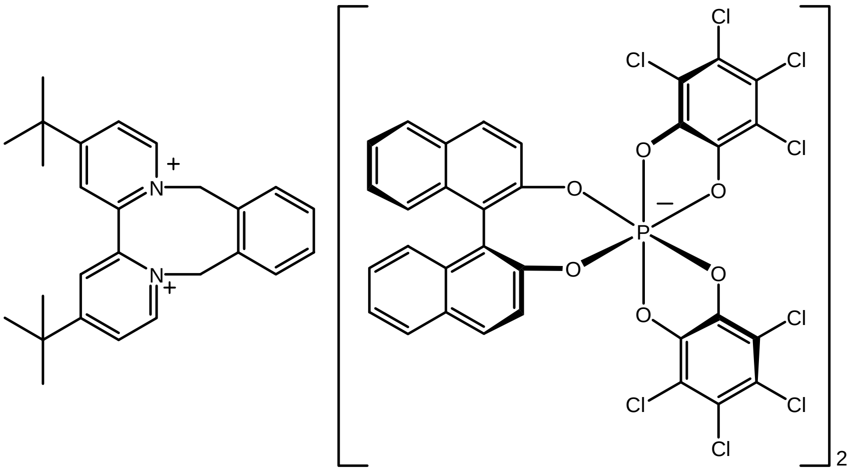
(CH), 122.6 (C^{IV}), 113.6 (d, C^{IV}, *J* = 20.0 Hz), 60.9 (CH_2), 37.4 (C^{IV}), 29.9 (CH_3); **^{31}P NMR** (162 MHz, DMSO-*d₆*) δ -81.25; **UV** (CH_3CN, 10^{-5} M) λ (ε) 216 (2.45×10^5), 300 (1.9×10^4), 399 (1×10^3); **CD** (CH_3CN, 10^{-5} M) λ (Δε) 212 (307.2), 223 (-298.7), 236 (-84.7), 243 (-95.7), 285 (-4.4), 300 (-6.1); **MS-ES** (-) *m/z* (rel intensity) 768.5 (100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 239.1 (90, M-C_8H_8 -2CH_3), 252.9 (100, M-C_8H_8-CH_3), 268.7 (86, M-C_8H_8+1), 186.6 (100, M/2)

(–)-(*R*a)-[3,3’-Di-tert-buthyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2’,1’-c][1,4]diazocindium][Δ-TT]₂ or [(*R*a)-88c][Δ-TT]₂ (d.e.= 95%)

M.p. 285 °C; **[α]$^{20}_{D}$** -335.6 (*c* 0.1, CH_3CN);**IR** (neat) 2974, 1624, 1445, 1389, 1235, 989, 818 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$/CD_3CN 3%) δ 9.15 (d, 2H, *J* = 6.5 Hz), 8.29 (d, 2H, *J* = 2.0 Hz), 8.26 (dd, 2H, *J* = 2.0 Hz and 6.3 Hz), 7.42 (s, 4H), 6.07 (d, 2H, *J* = 16.2 Hz), 5.32 (d, 2H, *J* = 16.2 Hz), 1.45 (s, 18H); **^{13}C NMR** (75 MHz, DMSO-*d₆*) δ 173.2 (C^{IV}), 147.5 (CH), 145.1 (C^{IV}), 143.9 (CH), 141.7 (d, C^{IV}, *J* = 6.5 Hz), 132.0 (CH), 131.5 (C^{IV}), 130.3 (CH), 128.8 (CH), 127.7 (CH), 122.3 (C^{IV}), 113.2 (d, C^{IV}, *J* = 20.0 Hz), 59.5 (CH_2), 35.5 (C^{IV}), 27.9 (CH_3); **^{31}P NMR** (162 MHz, DMSO-*d₆*) δ -81.05; **UV** (CH_3CN, 10^{-5} M) λ (ε) 213 (3.05×10^5), 300 (3.0×10^4), 398 (1×10^3); **CD** (CH_3CN, 10^{-5} M) λ (Δε) 208 (236.1), 225 (-251.4), 236 (-114.8), 243 (-128.8), 278 (-6.4), 300 (-8.4); **MS-ES** (-) *m/z* (rel intensity) 768.5 (100, TRISPHAT); **MS-ES** (+) *m/z* (rel intensity) 239.1 (97, M-C_8H_8 -2CH_3), 252.9 (100, M- C_8H_8-CH_3), 268.8 (87, M-C_8H_{8+1}), 186.3 (23, M/2)

Ion Metathesis with anion Δ-BINPHAT

To a solution of [**88c**][I]₂ (100 mg, 0.159 mmol) in a 5:1 mixture of DCM/MeOH (3 mL) was added a solution of [Me_2NH_2][Δ-BT] (340.5 mg, 0.399 mmol) in acetone (10 mL). After 5 min of stirring, the solution was evaporated to dryness. After filtration on basic alumina (eluant: acetonitrile), a orange solid was obtained containing an almost 1:1 mixture of the two diastereomers (290 mg, 91%).



Separation of Diastereomers [(*S*a)-**88c**][Δ-BT]$_2$ and [(*R*a)-**88c**][Δ-BT]$_2$

In a round bottom flask containing [**4c**][(Δ,*S*)-**3**]$_2$ (280 mg) was added acetonitrile (7 mL). The flask was placed a 4°C for 1h and the resulting precipitate was filtered and washed with Et$_2$O to afford [(*S*a)-**88c**][Δ-BT]$_2$ (105 mg, ~ 38%, d.e = 88%) as a yellow solid. After evaporation to dryness of the mother liquor, [(*R*a)-**88c**][Δ-BT]$_2$was obtained as a yellow solid (155 mg, ~ 55%, d.e ~ 40%).

(–)-(*S*a)-[3,3'-Di-tert-buthyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4]diazocindium][Δ-BT]$_2$ or [(*S*a)-88c][Δ-BT]$_2$ (d.e.= 88%)

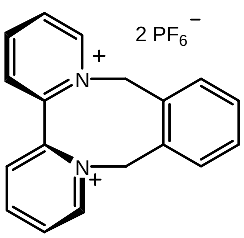
M.p. 245-250 °C; **$[\alpha]^{20}_D$** -65 (*c* 0.1, CH$_3$CN);**IR** (neat) 3054, 2970, 1622, 1450, 1234, 991, 816 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d$_6$*) δ 9.30 (d, 2H, *J* = 6.3 Hz), 8.53 (d, 2H, *J* = 6.3 Hz), 8.45 (d, 2H, *J* = 1.8), 7.96 (d, 4H, *J* = 8.0 Hz, BT), 7.84 (d, 4H, *J* = 8.8 Hz, BT), 7.54 (m, 4H), 7.40 (m. 4H, BT), 7.28 (d, 8H, *J* = 3.5 Hz, BT), 6.56 (d, 4H, *J* = 8.8 Hz, BT), 5.81 (d, 2H, *J* = 15.9 Hz), 5.44 (d, 2H, *J* = 15.6 Hz), 1.43 (s, 18H); **^{13}C NMR** (100 MHz, DMSO-*d$_6$*) δ 172.1 (C^{IV}), 151.8 (C^{IV}, d, *J* = 12.9 Hz, BT), 147.1 (CH), 144.4 (C^{IV}), 142.6 (C^{IV}, d, *J* = 5.5 Hz, BT), 142.1 (C^{IV}, d, *J* = 9.2 Hz, BT), 131.8 (C^{IV}), 131.5 (C^{IV}, BT), 130.0 (C^{IV}, BT), 129.9 (CH), 129.2 (CH, BT), 128.5 (CH), 128.3 (CH, BT), 127.3 (CH), 126.3 (CH, BT), 125.7 (CH, BT), 124.1 (CH, BT), 122.5 (C^{IV}), 122.3 (CH, d, *J* = 2.8 Hz, BT), 121.4 (C^{IV}, BT), 119.9 (C^{IV}, BT), 112.8 (C^{IV}, d, *J* = 14.7 Hz, BT), 112.7 (C^{IV}, d, *J* = 13.8 Hz, BT), 60.4 (CH$_2$), 37.0 (C^{IV}), 29.5 (CH$_3$); **^{31}P NMR** (162 MHz, DMSO-*d$_6$*) δ -83.41; **UV** (CH$_3$CN, 10^{-5} M) λ (ε) 230 (2.14 × 10^5), 275 (1.79 × 10^5), 329

(1.7 × 10^4); **CD** (CH_3CN, 10^{-5} M) λ (Δε) 233 (309.7), 245 (-174.4), 264 (54.4), 301 (-24.5), 322 (-8.4), 330 (-14.8); **MS-ES** (-) *m/z* (rel intensity) 807.0 (100, BINPHAT); **MS-ES** (+) *m/z* (rel intensity) 235.9 (100), 239.1 (67, M-C_8H_8 -2CH_3), 252.9 (73, M- C_8H_8-CH_3), 269 (53, M-C_8H_8+1), 186.1 (23, M/2)

General procedure for the ion exchange from BINPHAT to PF_6:

To a suspension of [**88a-88c**][Δ-BT]$_2$ in DCM (~1 mL per 0.01 mmol of substrate) was added HPF_6.aq. (~ 7.9 M, 10 eq.). After two minutes stirring, Et_2O was added to precipitate the desired [**88a-c**][PF_6]$_2$ salt which was washed thoroughly with Et_2O and pentane.

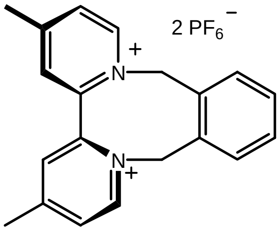
(–)-(*S*a)-[10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4]diazocindium][PF$_6$]$_2$ or [(*S*a)-88a][PF$_6$]$_2$ (e.e.= 96%) obtained as a white solid (94%)



M.p. 267 °C; **[α]^{20}$_D$** –207 (*c* 0.1, H_2O); **IR** (neat) 3090, 1622, 1585, 1501, 1469, 1311, 1197, 1164, 832 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d$_6$*) δ 9.47 (d, 2H, *J* = 5.6 Hz), 8.96 (t, 2H, *J* = 7.8 Hz), 8.54 (t, 2H, *J* = 6.7 Hz), 8.48 (d, 2H, *J* = 7.8 Hz), 7.65 (m, 2H), 7.59 (m, 2H), 5.92 (d, 2H, *J* = 15.8 Hz), 5.49 (d, 2H, *J* = 15.8 Hz); **^{13}C NMR** (100 MHz, DMSO-*d$_6$*) δ 148.4 (CH), 147.6 (CH), 144.7 (C^{IV}), 131.6 (CH), 131.5 (C^{IV}), 131.0 (CH), 130.4 (CH), 130.0 (CH), 61.4 (CH_2); **UV** (H_2O, 10^{-5} M) λ (ε) 200 (3.1 × 10^4), 239 (3 × 10^3), 278 (8 × 10^3); **CD** (H_2O, 10^{-5} M) λ (Δε) 203 (24.7), 229 (-9.9), 242 (-4.1), 253 (-7.1), 266 (-5.11), 279 (-10.97); **MS-ES** (+) *m/z* (rel intensity) 182.1 (100), 259.4 (50, M-1).

(+)-[(*R*a)-88a][PF$_6$]$_2$ (e.e.= 96%) obtained by resolution with Λ-BINPHAT
[α]^{20}$_D$ + 201 (*c* 0.1, H_2O)

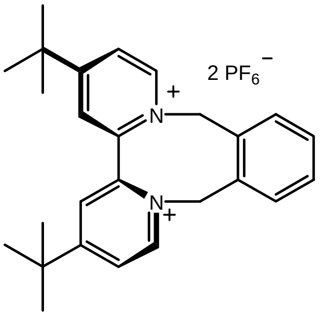
(–)-(*S*a)-[3,3'-dimethyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4] diazocindium][PF$_6$]$_2$ or [(Sa)-88b][PF$_6$]$_2$ (e.e.= 96%) obtained as a white solid (96%)



M.p. 270 °C; **[α]^{20}$_D$** –183 (*c* 0.1, H_2O); **IR** (neat) 3119, 1633, 1588, 1515, 1455, 1172, 824 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-*d$_6$*) δ 9.28 (d, 2H, *J* = 6.3 Hz), 8.35 (m, 4H), 7.62 (m, 2H), 7.57 (m, 2H), 5.82 (d, 2H, *J* = 15.9 Hz), 5.45 (d, 2H, *J* = 15.9 Hz), 2.74 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-*d$_6$*) δ 161.2 (C^{IV}), 147.1 (CH), 143.8 (C^{IV}), 131.6 (C^{IV}), 131.5 (CH), 130.9 (CH), 130.6 (CH), 129.9 (CH), 60.5 (CH_2), 21.8 (CH_3); **UV** (CH_3CN, 10^{-5} M) λ (ε) 206 (2.0 × 10^4), 231 (9 × 10^3), 274 (7 × 10^3); **MS-ES** (+) *m/z* (rel intensity) 184.6 (90, M-C_8H_8+1), 287.6 (100, M-1).

[(*R*a)-88b][PF$_6$]$_2$ (e.e.= 92%) obtained from mother liquors of the resolution with Δ-BT
[α]^{20}$_D$ (*c* 0.1, H_2O) +145

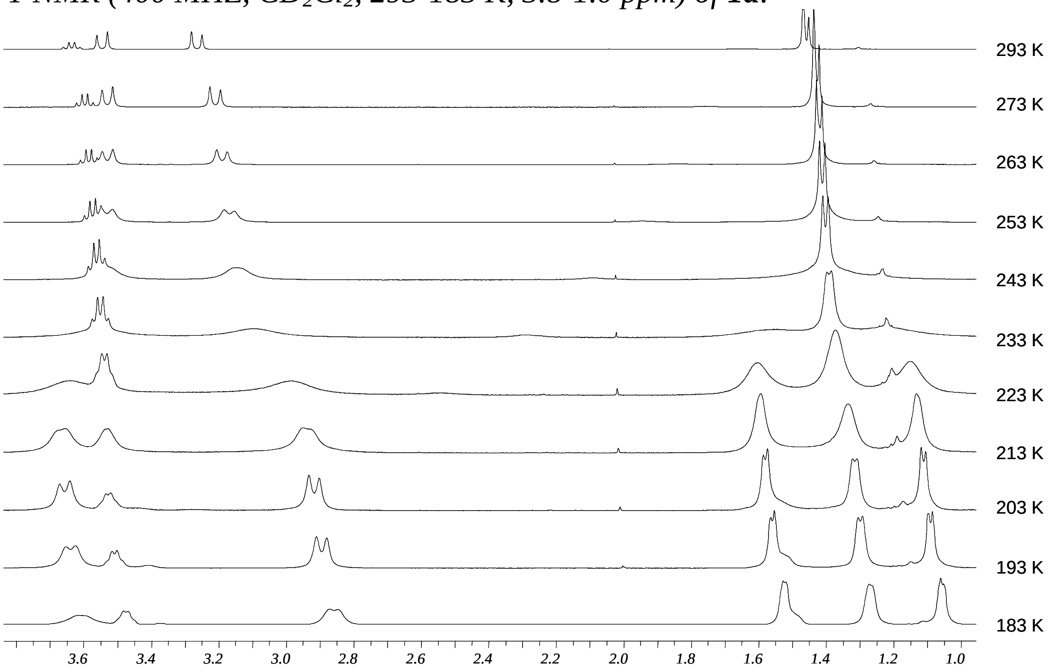
(–)-(*S*a)-[3,3'-di-tert-butyl-10,15-dihydrobenzo[*f*]dipyrido[1,2-a:2',1'-c][1,4] diazocindium][PF$_6$]$_2$ [(*S*a)-88c][PF$_6$]$_2$ (e.e = 88%) obtained as a white solid (96%)



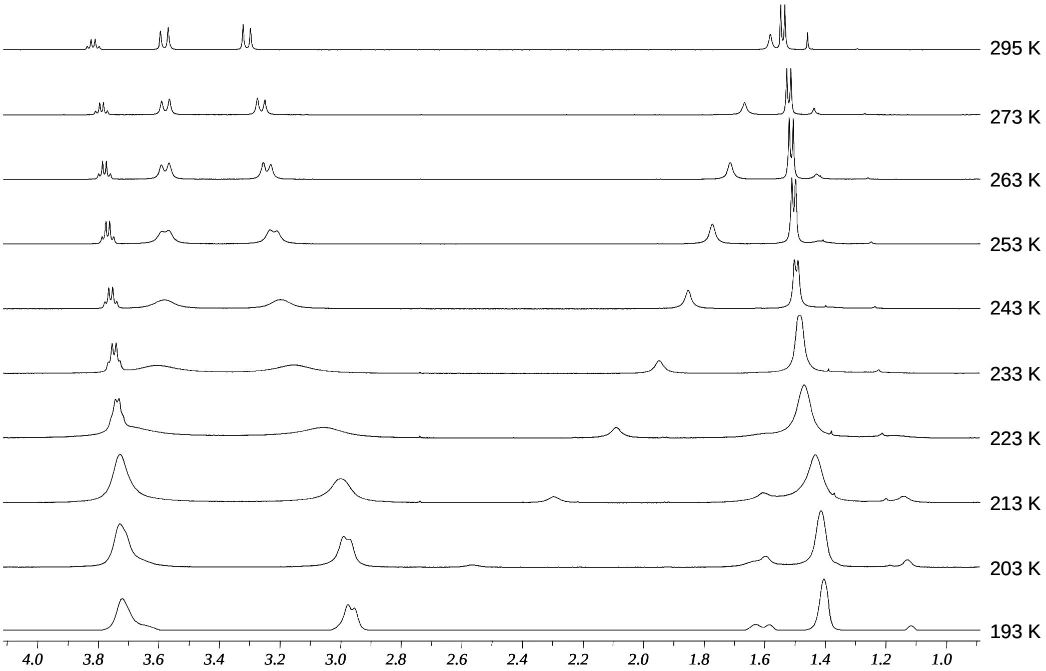
M.p. 220 °C; **[α]^{20}$_D$** –159 (*c* 0.1, H_2O); **IR** (neat) 2975, 1628, 1454, 1424, 1373, 827 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$/DMSO-*d$_6$* 14%) δ 9.14 (s, 2H), 8.24 (s, 2H), 8.01 (s, 2H), 7.36 (s, 2H), 7.22 (s, 2H), 5.77 (d, 2H, *J* = 15.1 Hz), 5.00 (d, 2H, *J* = 14.9 Hz), 1.26 (s, 18H); **^{13}C NMR** (100 MHz, DMSO-*d$_6$*) δ 172.1 (C^{IV}), 147.1 (CH), 144.4 (C^{IV}), 131.6 (C^{IV}), 130.9 (CH), 129.9 (CH), 128.5 (CH), 127.3 (CH), 60.4 (CH_2), 37.0 (C^{IV}), 29.5 (CH_3); **UV** (DCM, 10^{-5} M) λ (ε) 227 (3.8 × 10^4), 237 (2.9 × 10^4), 274 (2.1 × 10^4); **CD** (DCM, 10^{-5} M) λ (Δε) 219 (-19.0), 249 (8.3), 263 (3.6), 276 (9.8); **MS-ES** (+) *m/z* (rel intensity) 239.1 (90, M-C_8H_8 -2CH_3), 252.9 (100, M- C_8H_8-CH_3), 268.7 (86, M-C_8H_8+1), 186.6 (100, M/2).

[(*R*a)-88c][PF$_6$]$_2$ (e.e= 88%) obtained by resolution with Λ-BINPHAT
[α]^{20}$_D$ +161 (*c* 0.1, H_2O)

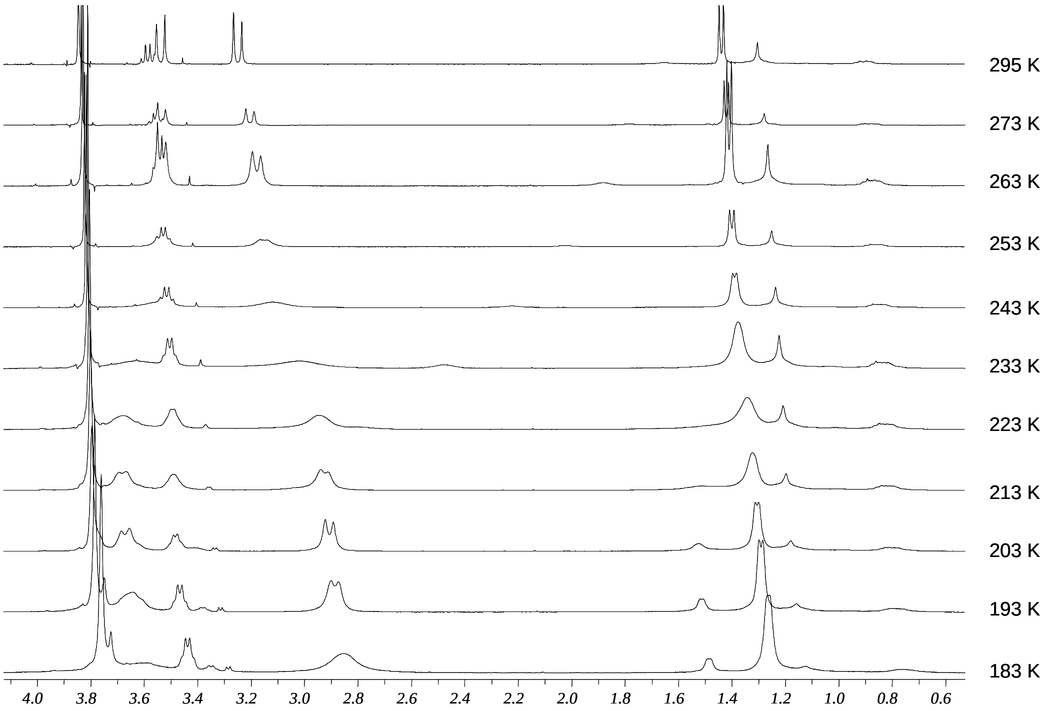
*^{1}H VT NMR (400 MHZ, CD_2Cl_2, 293-183 K, 3.8-1.0 ppm) of **1a**:*



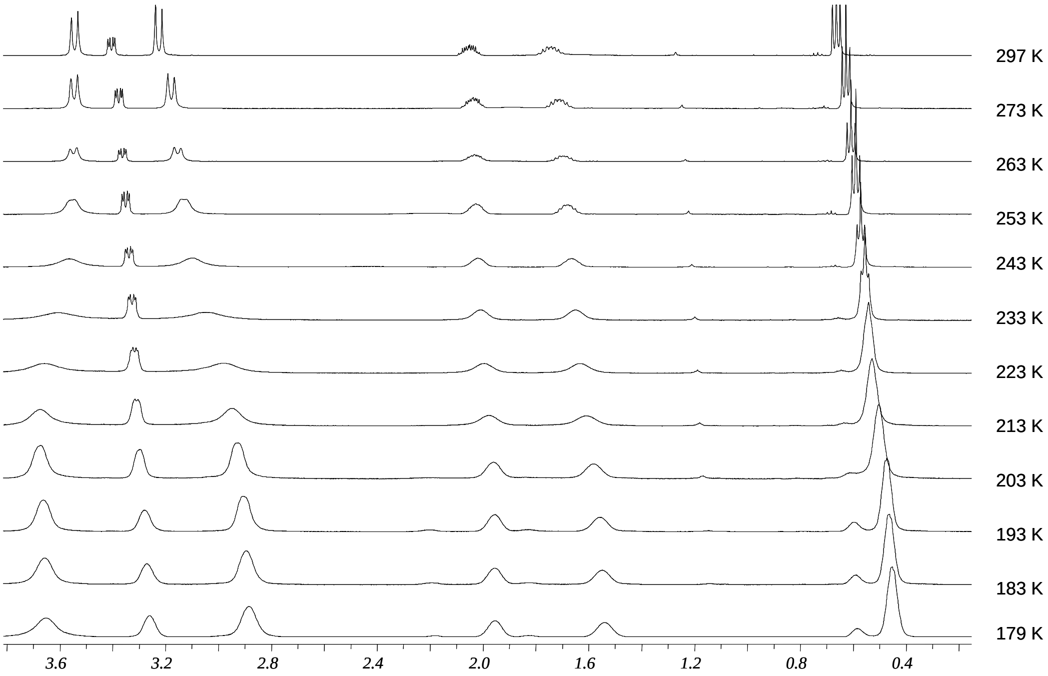
*^{1}H VT NMR (400 MHZ, CD_2Cl_2, 295-193 K, 4.1-0.9 ppm) of **1b**:*



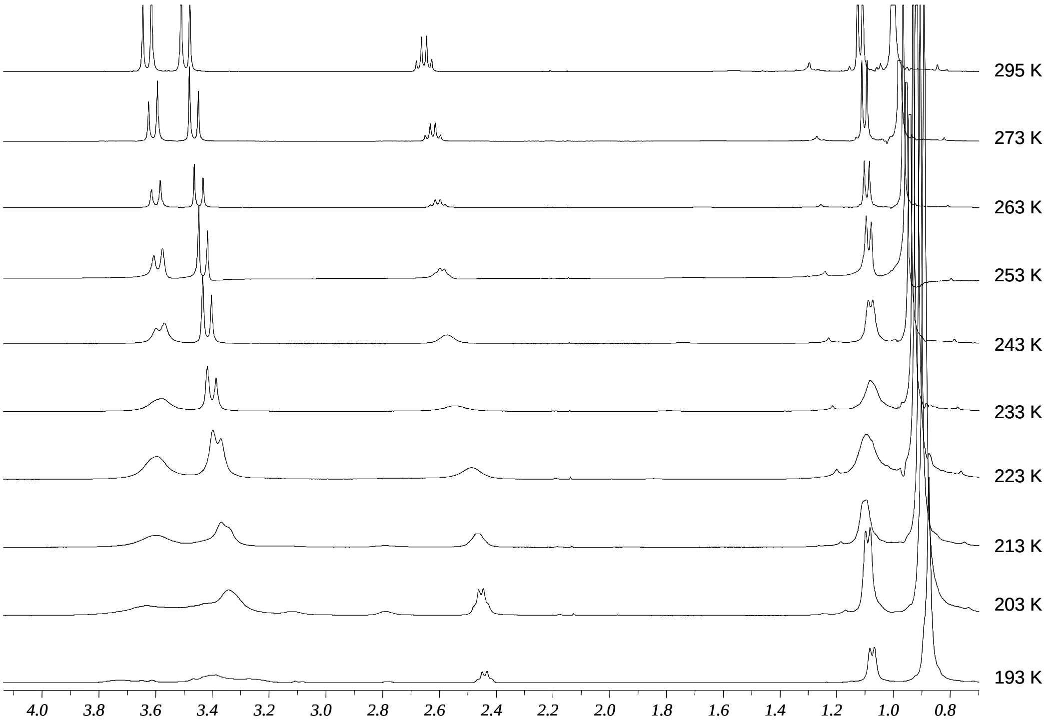
^{1}H VT NMR (400 MHZ, CD_2Cl_2, 295-183 K, 4.1-0.6 ppm) of ***1d**:*



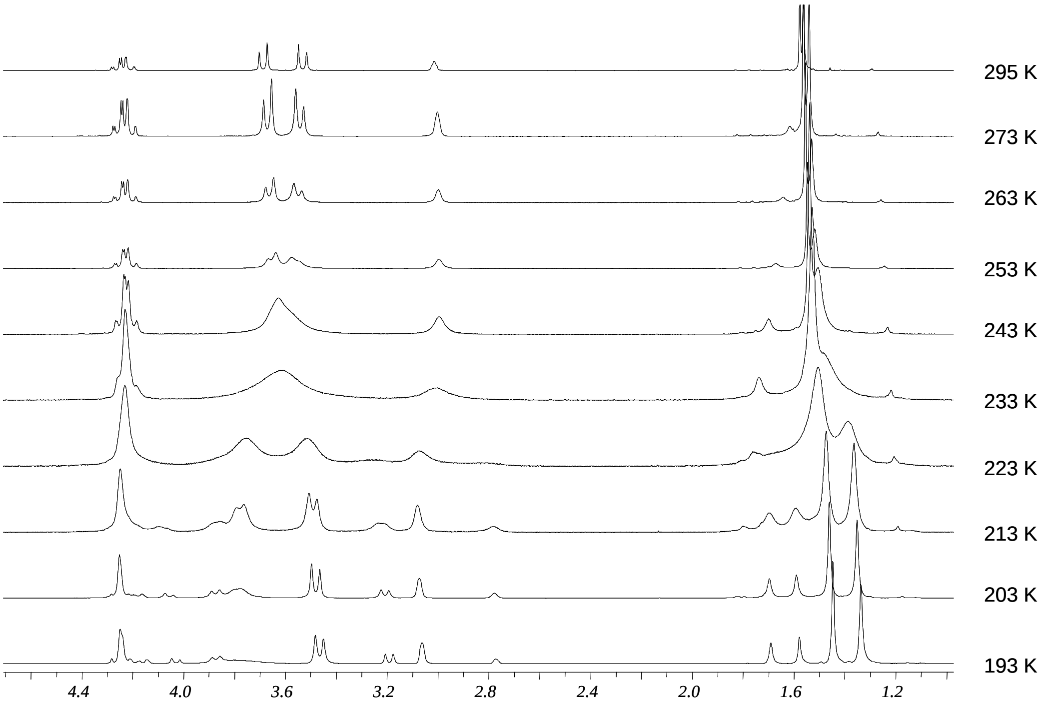
^{1}H VT NMR (400 MHZ, CD_2Cl_2, 297-179 K, 3.8-0.2 ppm) of ***1e**:*



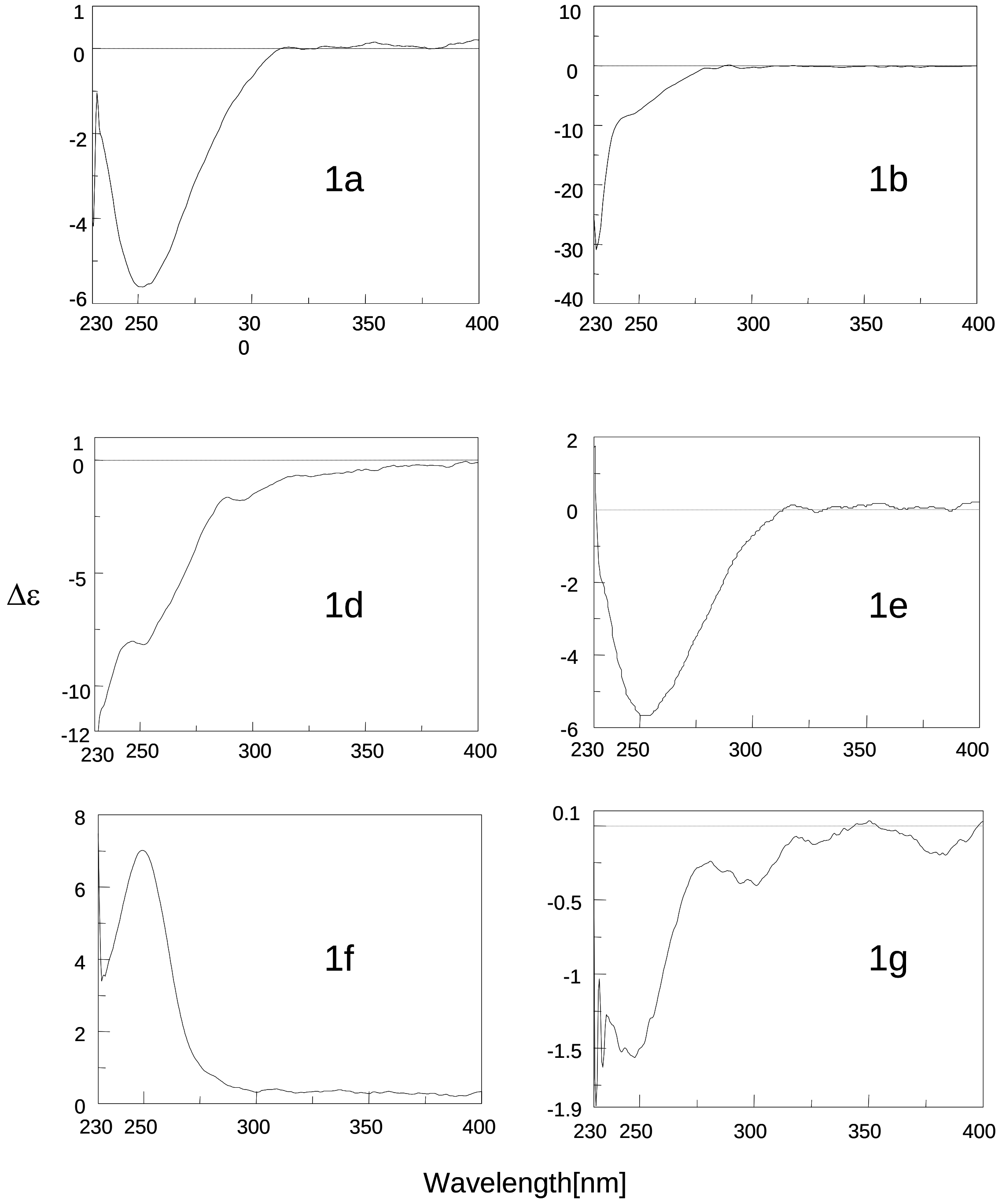
^{1}H VT NMR (400 MHZ, CD_2Cl_2, 295-193 K, 4.1-0.7 ppm) of ***1f****:*



^{1}H VT NMR (400 MHZ, CD_2Cl_2, 295-193 K, 4.7-1.0 ppm) of ***1g****:*

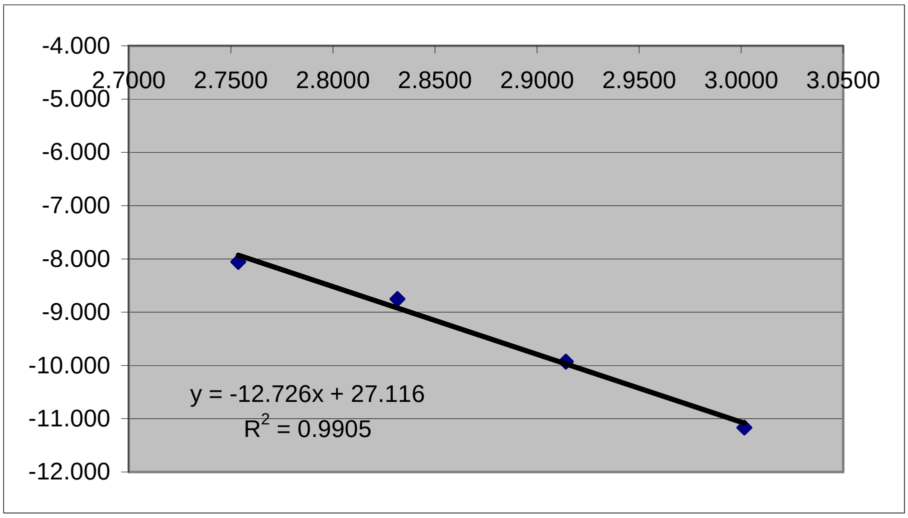


Circular Dichroism of ***1a****,* ***1b****,* ***1d****,* ***1e****,* ***1f*** *and* ***1g*** *(c ~ 1.10^{-5} M, DCM):*



Activation parameters of ***4b****:*

T [K]	1000/T	k	ln(k)
333	3.002	1.42E-05	-11.164
343	2.914	4.87E-05	-9.929
353	2.832	0.000158	-8.754
363	2.754	0.000316	-8.059



ln(k)= f(1000/T)

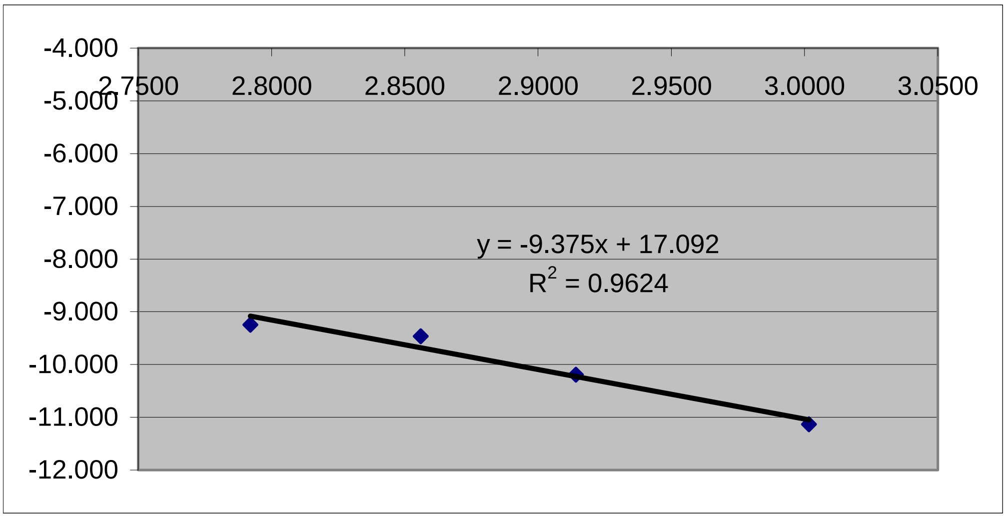
slope=	-12.726	(- Ea/R)
intercept=	27.116	(Ln(A))

T	20	°C		
Ea	**106.138**	**kJ/mol**	**R^2 =**	**0.991**
A	**5.97E+11**	**s^{-1}**		

ΔH$^{\neq}$ = Ea-RT	24.807	kcal/mol
ΔS$^{\neq}$ = R[ln(h.A/k.T)-1]	-6.614	cal/(mol.K)
ΔG$^{\neq}$	26.746	kcal/mol

*Activation parameters of **4e**:*

T [K]	1000/T	k	ln(k)
333	3.002	1.46E-05	-11.133
343	2.914	3.74E-05	-10.194
350	2.856	7.74E-05	-9.466
358	2.792	9.63E-05	-9.248



ln(k)= f(1000/T)		
slope=	-9.374959	(- Ea/R)
intercept=	17.09232	(Ln(A))

T 20 °C

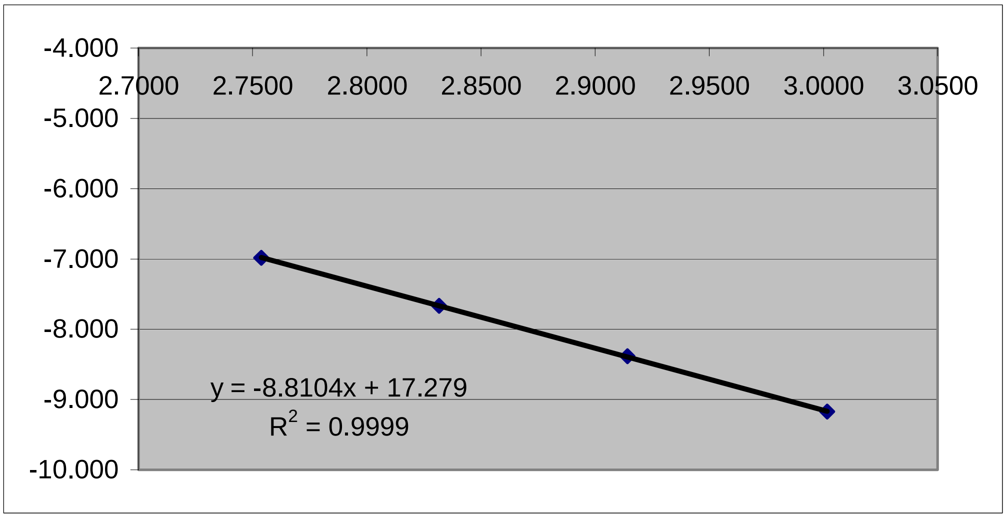
Ea 78.187 kJ/mol **R^2 = 0.962**

A 2.64E+07 s^{-1}

$\Delta H^{\neq}$ = Ea-RT	18.120	kcal/mol
$\Delta S^{\neq}$ = R[ln(h.A/k.T)-1]	-26.550	cal/(mol.K)
$\Delta G^{\neq}$	25.903	kcal/mol

Activation parameters of ***4f****:*

T [K]	1000/T	k	ln(k)
333	3.002	1.04E-04	-9.173
343	2.914	2.28E-04	-8.386
353	2.832	4.68E-04	-7.667
363	2.754	9.25E-04	-6.986



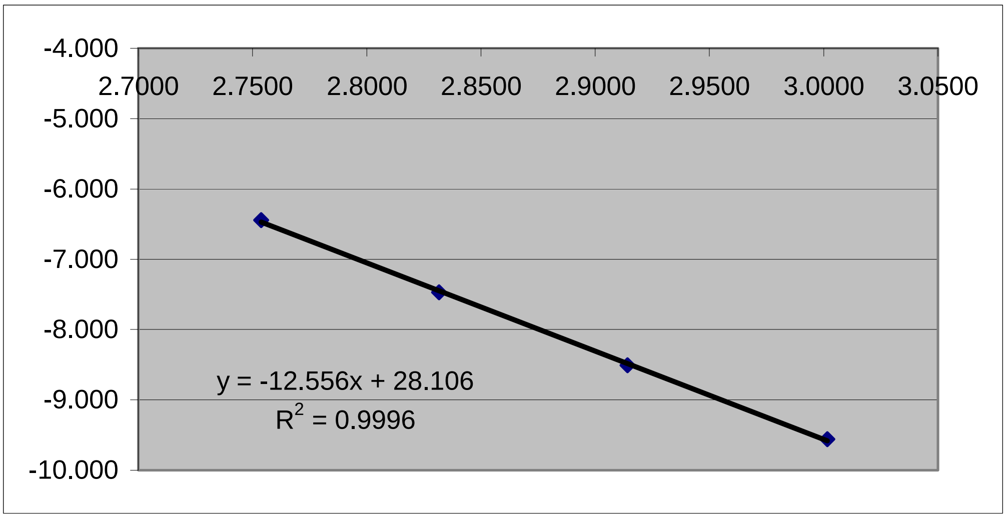
ln(k)= f(1000/T)		
slope=	-8.810	(- Ea/R)
intercept=	17.279	(Ln(A))

T	20	°C		
Ea	**73.479**	**kJ/mol**	**R^2 =**	**0.999**
A	**3.19E+07**	**s^{-1}**		

ΔH[≠] = Ea-RT	16.994	kcal/mol
ΔS[≠] = R[ln(h.A/k.T)-1]	-26.178	cal/(mol.K)
ΔG[≠]	24.668	kcal/mol

*Activation parameters of **4g**:*

T [K]	1000/T	k	ln(k)
333	3.002	7.06E-05	-9.558
343	2.914	0.000202	-8.507
353	2.832	0.000571	-7.469
363	2.754	0.00159	-6.444



ln(k)= f(1000/T)		
slope=	-12.556	(- Ea/R)
intercept=	28.106	(Ln(A))

T 20 °C

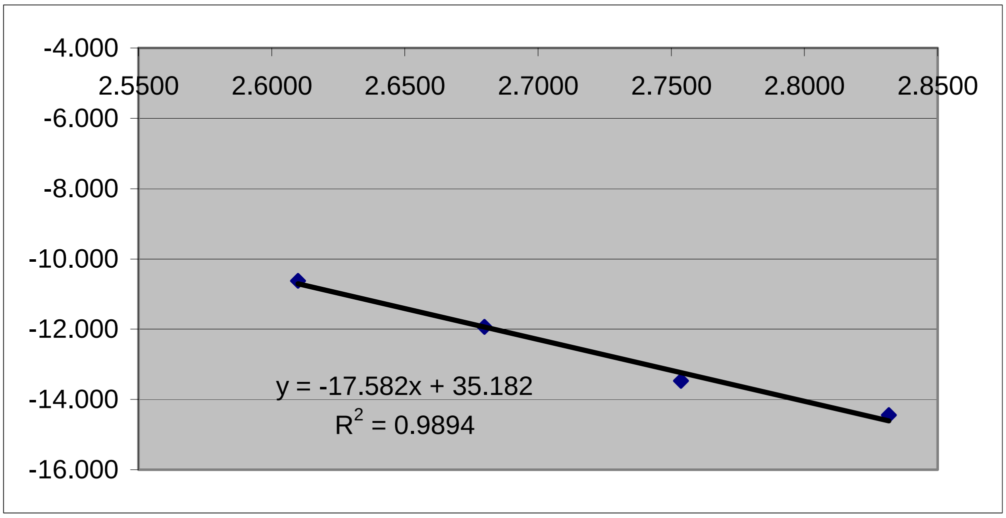
Ea 104.714 kJ/mol **R^2 = 0.999**

A 1.61E+12 s^{-1}

ΔH[≠] = Ea-RT	24.466	kcal/mol
ΔS[≠] = R[ln(h.A/k.T)-1]	-4.643	cal/(mol.K)
ΔG[≠]	25.827	kcal/mol

Activation parameters of ***10b****:*

T [K]	1000/T	k	ln(k)
353	2.832	5.32E-07	-14.447
363	2.754	1.41E-06	-13.475
373	2.680	6.57E-06	-11.933
383	2.610	2.44E-05	-10.622

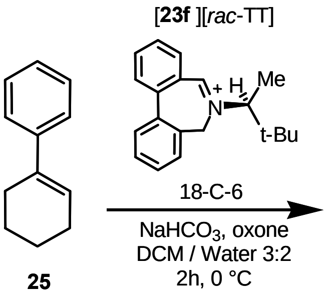


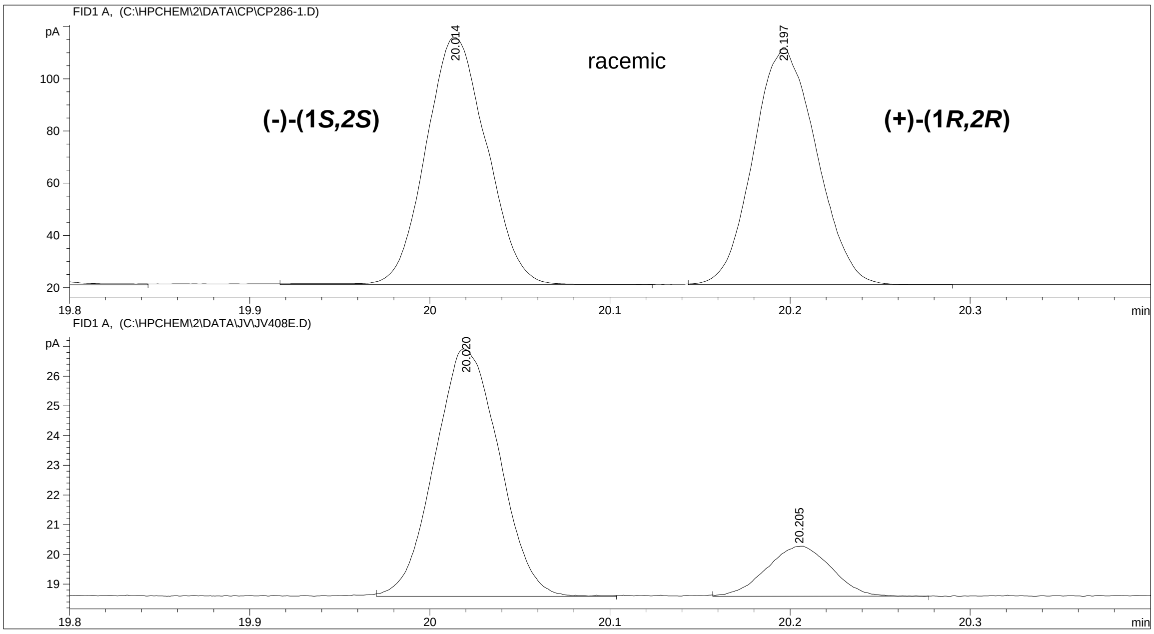
ln(k)= f(1000/T)		
slope=	-17.582	(- Ea/R)
intercept=	35.182	(Ln(A))

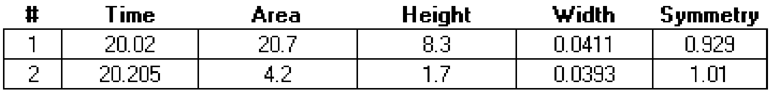
T	20	°C		
Ea	**146.632**	**kJ/mol**	**R^2 =**	**0.989**
A	**1.9E+15**	**s^{-1}**		

$\Delta H^{\neq}$ = Ea-RT	34.495	kcal/mol
$\Delta S^{\neq}$ = R[ln(h.A/k.T)-1]	9.430	cal/(mol.K)
$\Delta G^{\neq}$	31.730	kcal/mol

*Epoxidation of **25** with iminium salt catalyst [**23f**][rac-TT]:*



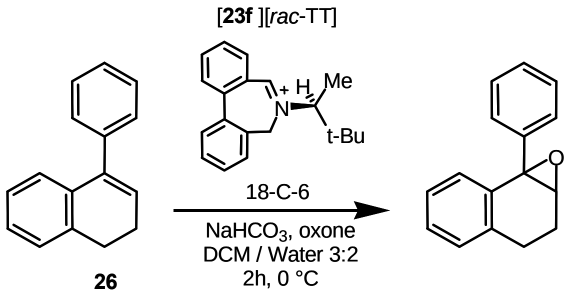


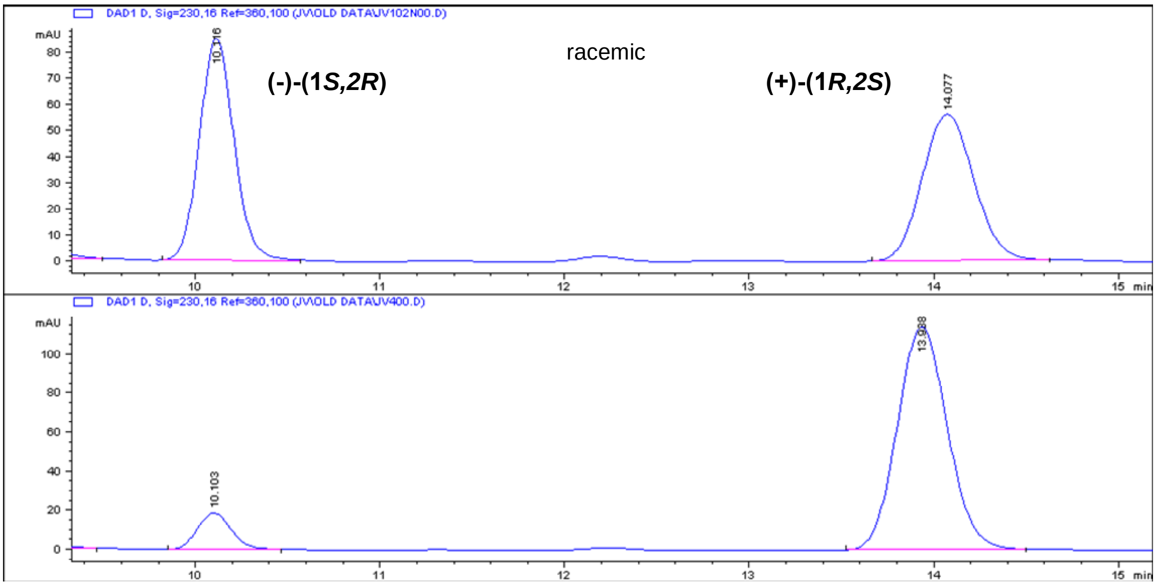


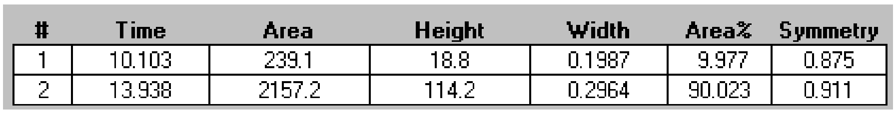
#	Time	Area	Height	Width	Symmetry
1	20.02	20.7	8.3	0.0411	0.929
2	20.205	4.2	1.7	0.0393	1.01

Determined by CSP-GC (Chiraldex Hydrodex β–3P), T_{inj} 250 °C, P = 0.842 bar;
Conditions: 80 °C, 5 min, then progression to 180 °C in 20 min, then 180 °C for 5 min.

*Epoxidation of **26** with iminium salt catalyst [**23f**][rac-TT]:*



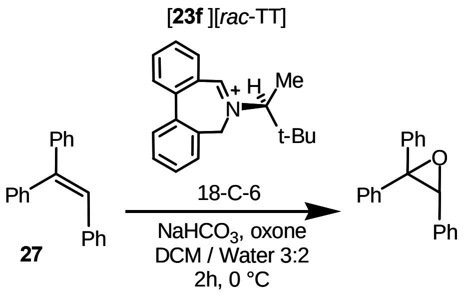


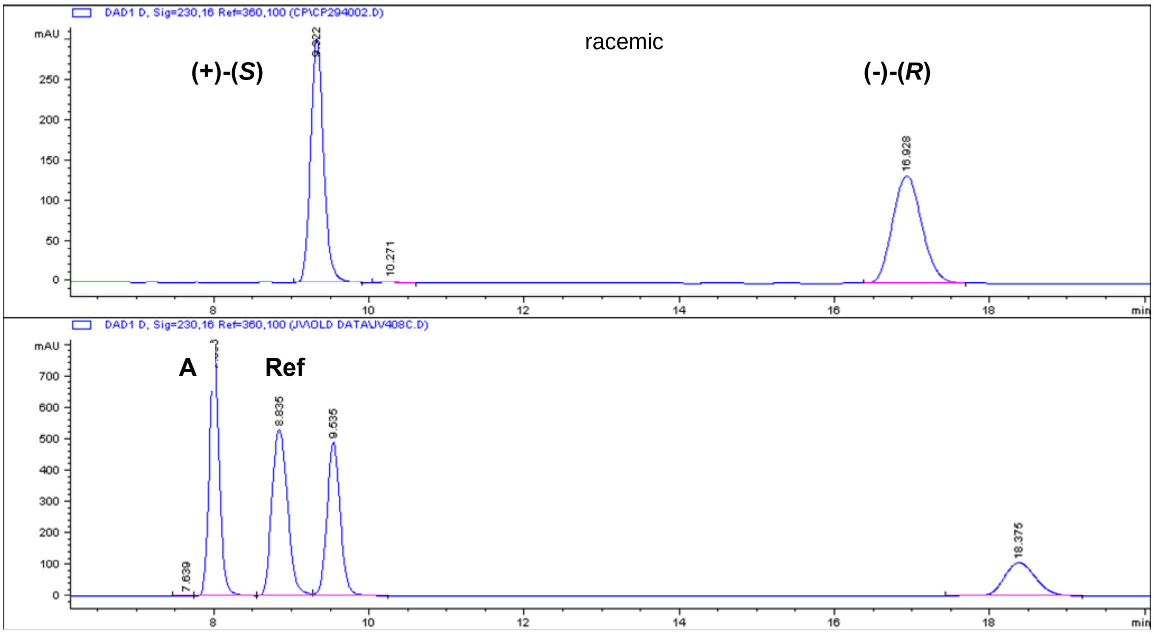


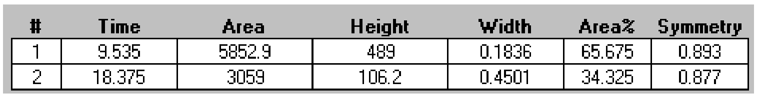
#	Time	Area	Height	Width	Area%	Symmetry
1	10.103	239.1	18.8	0.1987	9.977	0.875
2	13.938	2157.2	114.2	0.2964	90.023	0.911

Determined by CSP-HPLC (Chiralcel OD-H); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}

*Epoxidation of **27** with iminium salt catalyst [**23f**][rac-TT]:*





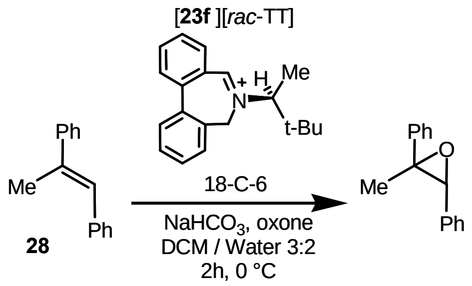


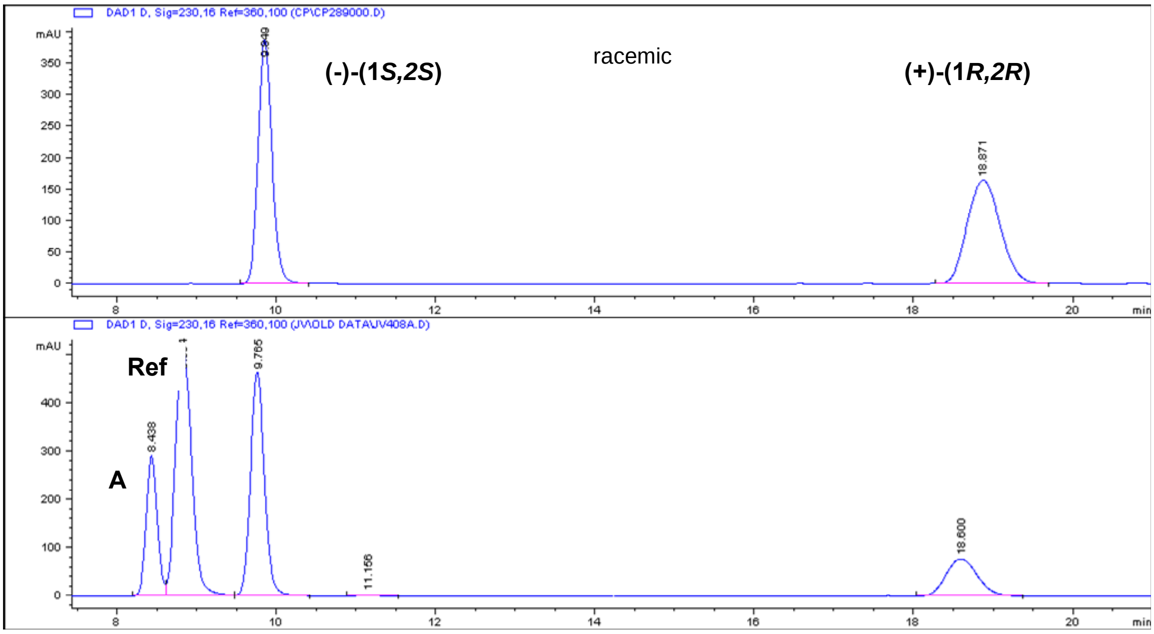
#	Time	Area	Height	Width	Area%	Symmetry
1	9.535	5852.9	489	0.1836	65.675	0.893
2	18.375	3059	106.2	0.4501	34.325	0.877

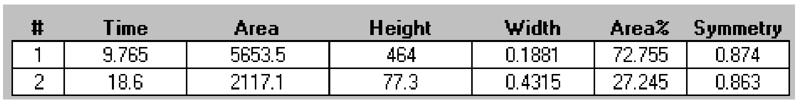
A: Alkene, Ref: naphthalene

Determined by CSP-HPLC (Chiralcel OD-H); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}

*Epoxidation of **28** with iminium salt catalyst [**23f**][rac-TT]:*





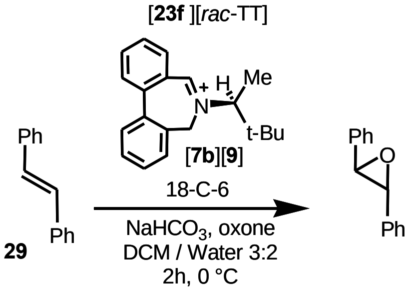


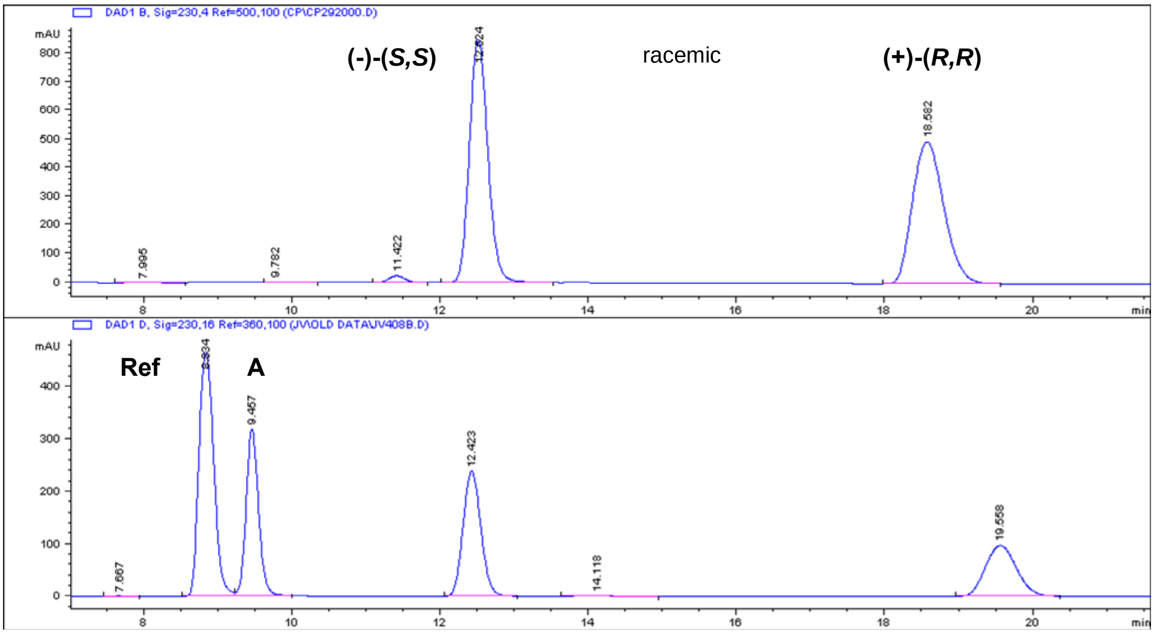
#	Time	Area	Height	Width	Area%	Symmetry
1	9.765	5653.5	464	0.1881	72.755	0.874
2	18.6	2117.1	77.3	0.4315	27.245	0.863

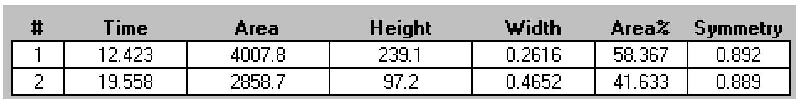
A: Alkene, Ref: naphthalene

Determined by CSP-HPLC (Chiralcel OD-H); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}

Epoxidation of ***29*** *with iminium salt catalyst [****23f****][rac-TT]:*





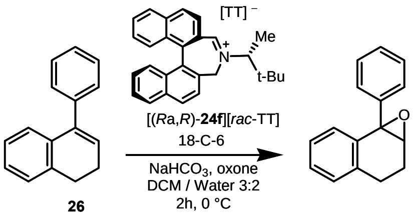


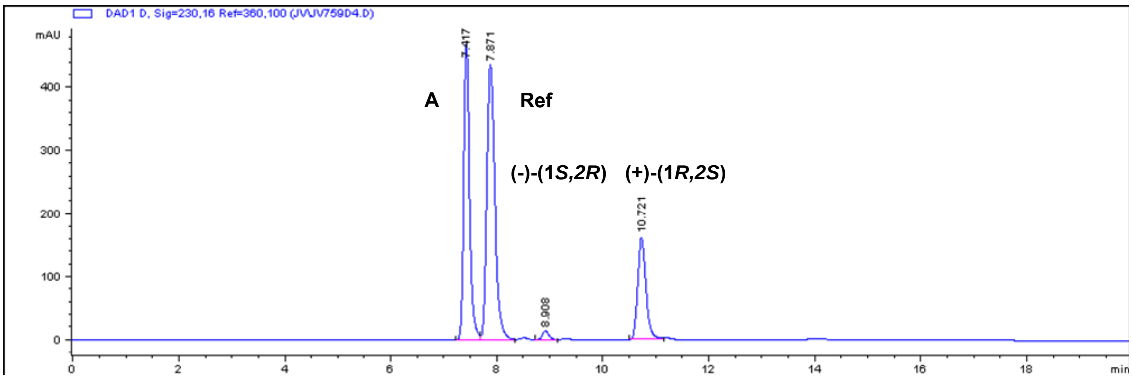
#	Time	Area	Height	Width	Area%	Symmetry
1	12.423	4007.8	239.1	0.2616	58.367	0.892
2	19.558	2858.7	97.2	0.4652	41.633	0.889

A: Alkene, Ref: naphthalene

Determined by CSP-HPLC (Chiralcel OD-H); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}

*Epoxidation of **26** and **27** with iminium salt catalyst [(Ra,R)-**24f**][rac-TT]*

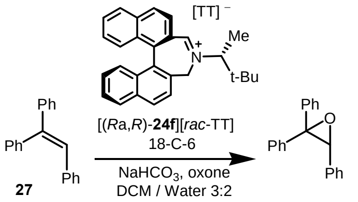


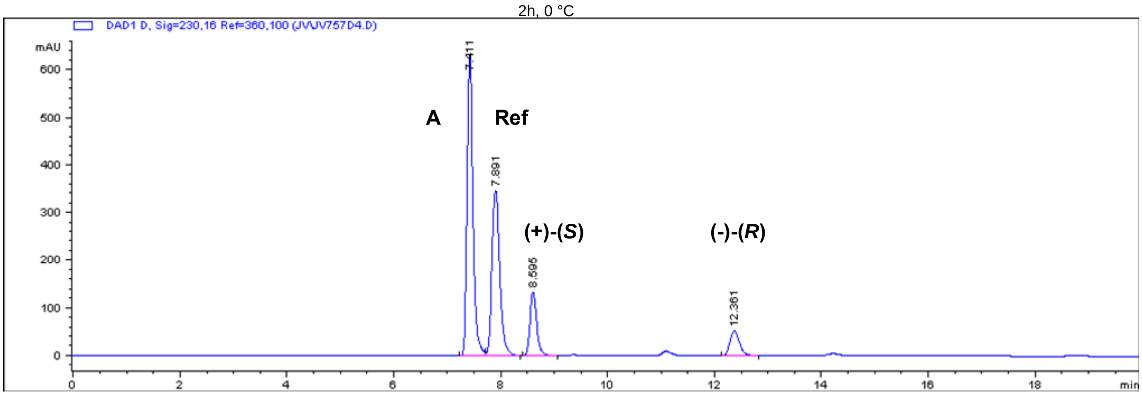


A: Alkene, Ref: naphthalene

#	Time	Area	Height	Width	Area%	Symmetry
1	7.417	3629.2	471.3	0.1158	35.793	0.781
2	7.871	4631.6	436.4	0.1678	45.680	0.745
3	8.908	125	13.8	0.1375	1.233	0.826
4	10.721	1753.5	162.1	0.1662	17.294	0.783

Determined by CSP-HPLC (Chiralpack® IB); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}



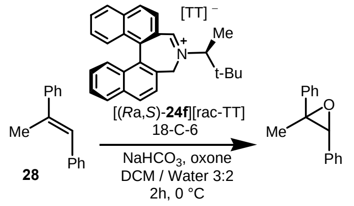


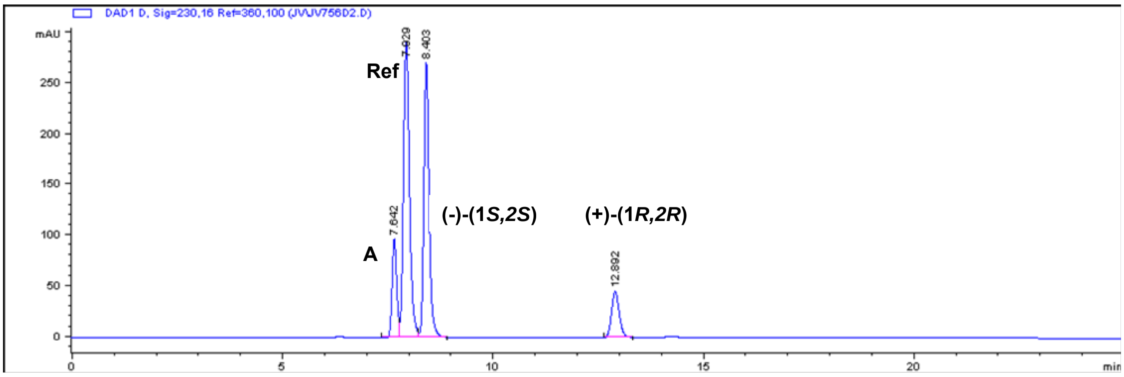
A: Alkene, Ref: naphthalene

#	Time	Area	Height	Width	Area%	Symmetry
1	7.411	4843.5	632.7	0.1173	47.351	0.756
2	7.891	3559.2	347.2	0.1616	34.795	0.776
3	8.595	1179.1	134.3	0.1344	11.527	0.774
4	12.361	647.2	51.8	0.1918	6.327	0.787

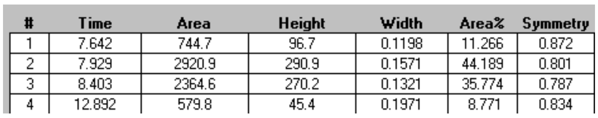
Determined by CSP-HPLC (Chiralpack® IB); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}

*Epoxidation of **28** and **29**with iminium salt catalyst [(Ra,S)-**24f**][rac-TT]*



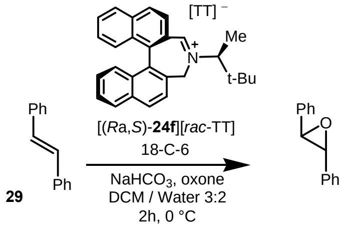


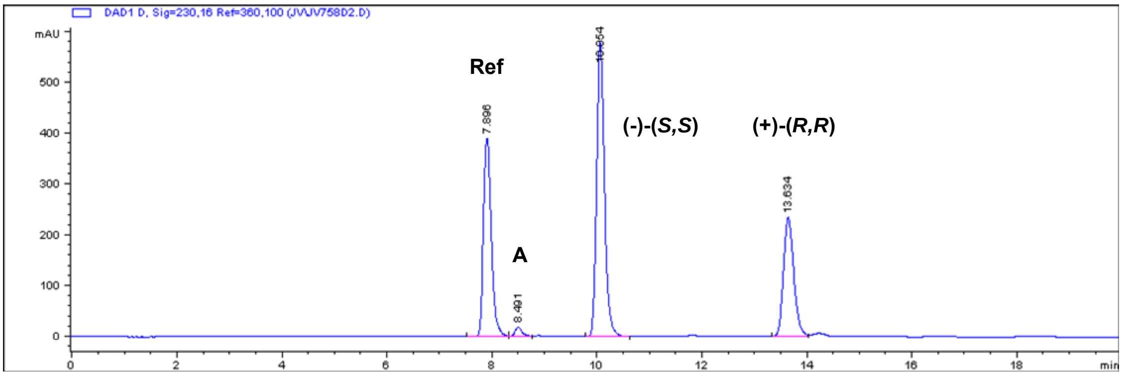
A: Alkene, Ref: naphthalene



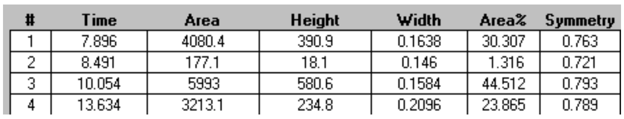
#	Time	Area	Height	Width	Area%	Symmetry
1	7.642	744.7	96.7	0.1198	11.266	0.872
2	7.929	2920.9	290.9	0.1571	44.189	0.801
3	8.403	2364.6	270.2	0.1321	35.774	0.787
4	12.892	579.8	45.4	0.1971	8.771	0.834

Determined by CSP-HPLC (Chiralpack® IB); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}





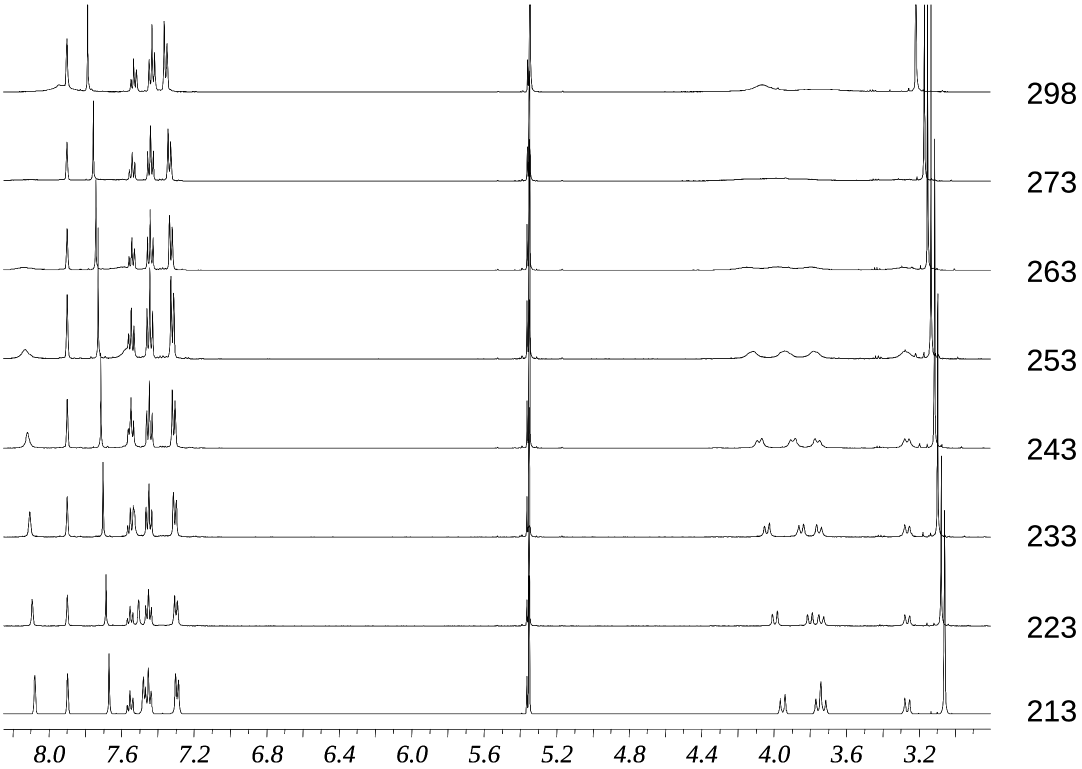
A: Alkene, Ref: naphthalene



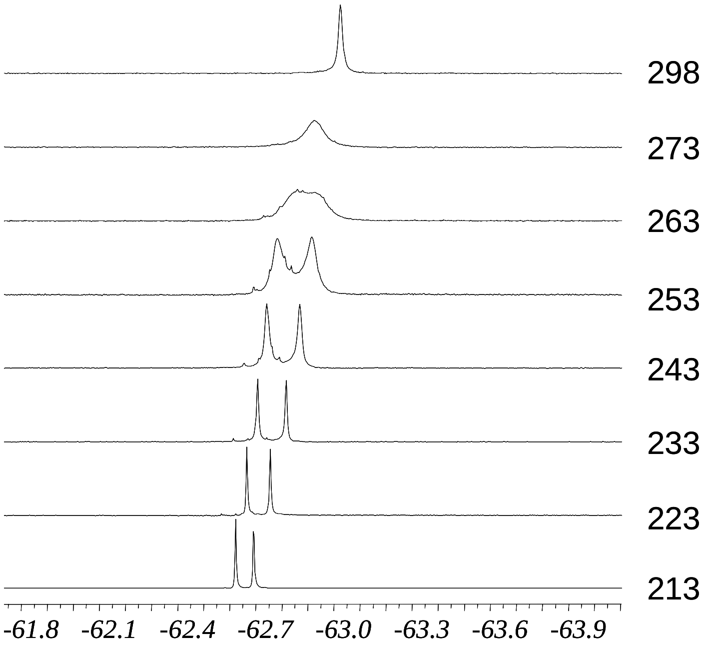
#	Time	Area	Height	Width	Area%	Symmetry
1	7.896	4080.4	390.9	0.1638	30.307	0.763
2	8.491	177.1	18.1	0.146	1.316	0.721
3	10.054	5993	580.6	0.1584	44.512	0.793
4	13.634	3213.1	234.8	0.2096	23.865	0.789

Determined by CSP-HPLC (Chiralpack® IB); Hexane / iPrOH 95 : 5 ; 0.5 mL.min^{-1}

*^{1}H VT NMR (500 MHZ, CD_2Cl_2, 298-213 K, 8.2-3.0 ppm) of **78**:*

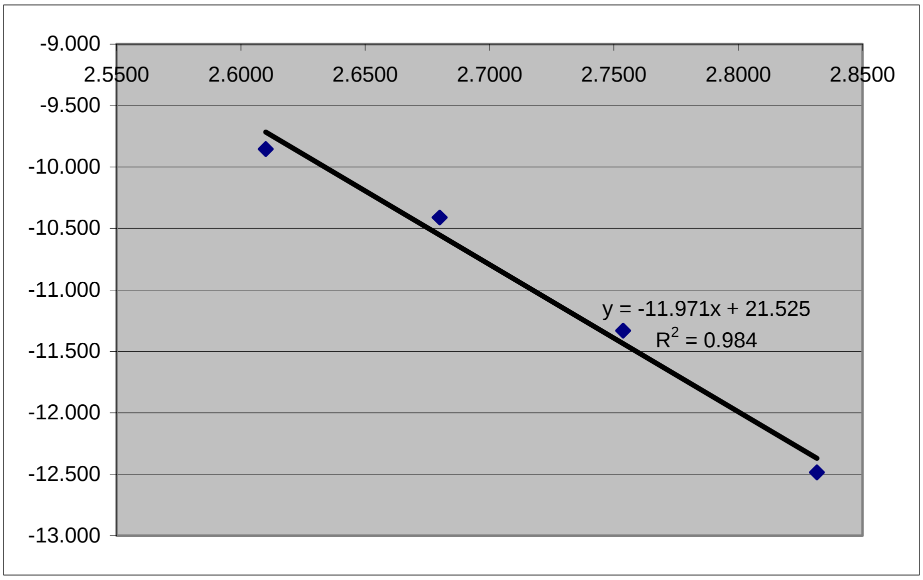


*^{19}F VT NMR (471 MHZ, CD_2Cl_2, 298-213 K, –61.8 - –63.9 ppm) of **78**:*



Activation parameters of ***67****:*

T [K]	1000/T	k	ln(k)
353	2.832	3.78E-06	-12.485
363	2.754	1.2E-05	-11.331
373	2.680	3.01E-05	-10.410
383	2.610	5.26E-05	-9.853



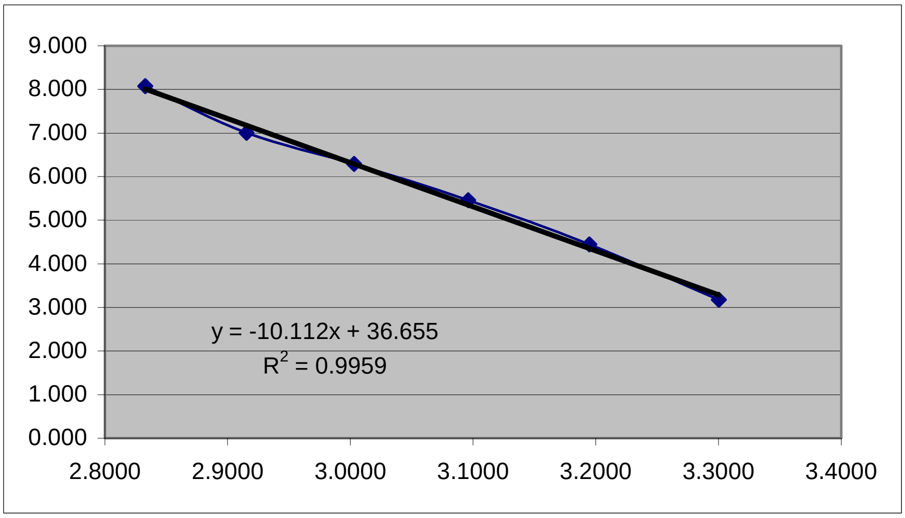
ln(k)= f(1000/T)		
slope=	-11.971	(- Ea/R)
intercept=	21.525	(Ln(A))

T	20	°C	**R^2= 0.984**
Ea	99.834	**kJ/mol**	
A	2.23E+09	**s^{-1}**	

Δ**H**$^{\neq}$ = Ea - RT	23.299	kcal/mol
Δ**S**$^{\neq}$ = R [ln(h*A/k*T)-1]	-17.733	cal/(mol.K)
Δ**G**$^{\neq}$	28.497	kcal/mol

*Activation parameters of **79** (CF_3 region):*

T [K]	1000/T	k	ln(k)
303	3.300	24	3.178
313	3.195	85	4.443
323	3.096	234.5	5.457
333	3.003	540	6.292
343	2.915	1105	7.008
353	2.833	3221	8.077



ln(k)= f(1000/T)

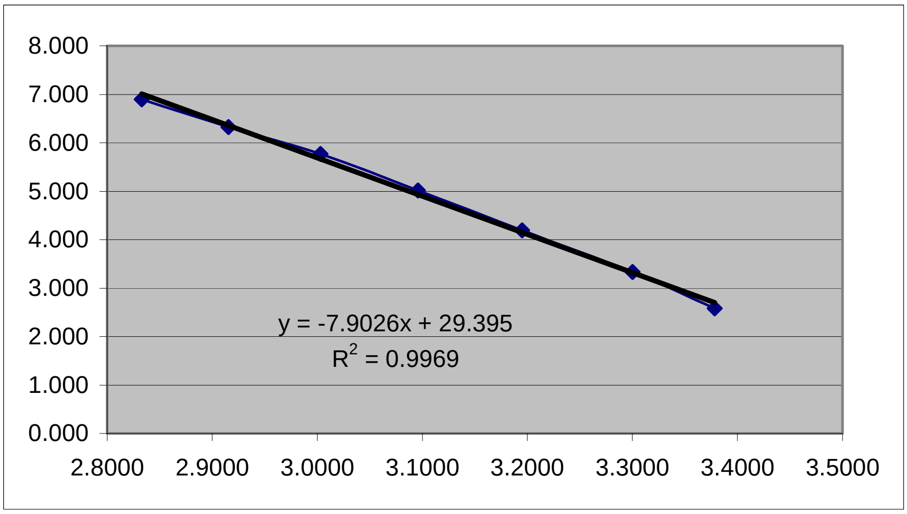
slope=	-10.11187	(- Ea/R)
intercept=	36.655	(Ln(A))

T	25	°C		
Ea	**84.333**	**kJ/mol**	**R^2 =**	**0.996**
A	**8.3E+15**	**s^{-1}**		

$\Delta H^{\neq}$ = Ea-RT	19.580	kcal/mol
$\Delta S^{\neq}$ = R[ln(h.A/k.T)-1]	12.357	cal/(mol.K)
$\Delta G^{\neq}$	15.905	kcal/mol

*Activation parameters of **79** (CH_2 region):*

T [K]	1000/T	k	ln(k)
296	3.378	13.2	2.580
303	3.300	28.1	3.336
313	3.195	65.9	4.188
323	3.096	150.9	5.017
333	3.003	319.9	5.768
343	2.915	557.9	6.324
353	2.833	991.9	6.900



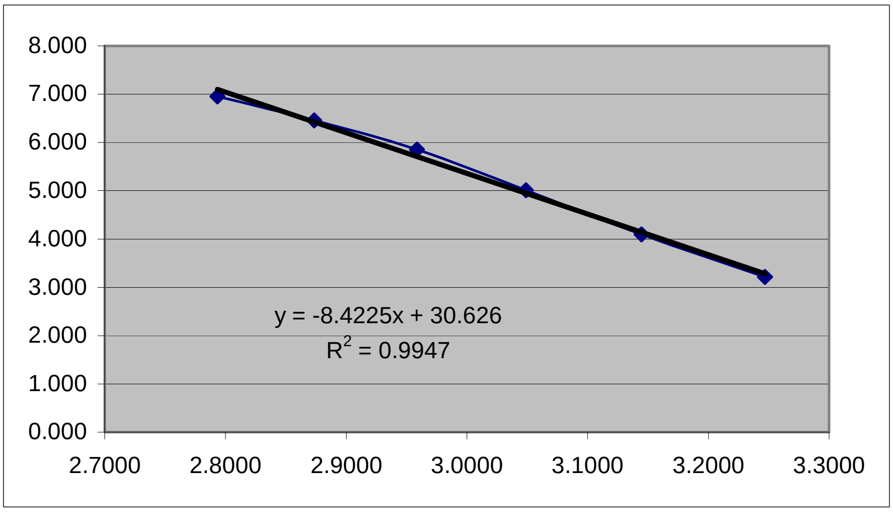
ln(k)= f(1000/T)		
slope=	-7.903	(- Ea/R)
intercept=	29.395	(Ln(A))

T	25	°C		
Ea	**65.908**	**kJ/mol**	**R^2 =**	**0.997**
A	**5.83E+12**	**s^{-1}**		

$\Delta H^{\neq}$ = Ea-RT	15.173	kcal/mol
$\Delta S^{\neq}$ = R[ln(h.A/k.T)-1]	-2.114	cal/(mol.K)
$\Delta G^{\neq}$	15.803	kcal/mol

Activation parameters of ***80*** *(CF_3 region):*

T [K]	1000/T	k	ln(k)
358	2.793	1050	6.957
348	2.874	639	6.460
338	2.959	350	5.858
328	3.049	150	5.011
318	3.145	60	4.094
308	3.247	25	3.219



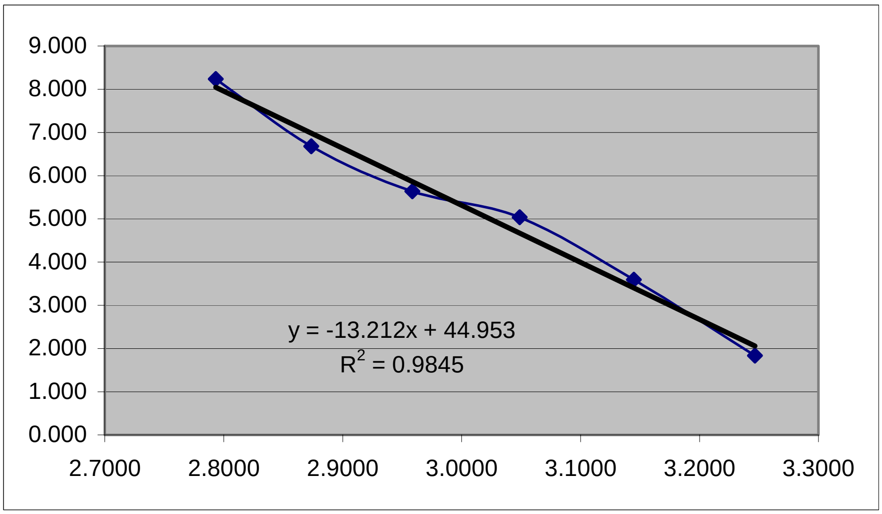
ln(k)= f(1000/T)		
slope=	-8.198	(- Ea/R)
intercept=	29.972	(Ln(A))

T	25	°C		
Ea	**68.368**	**kJ/mol**	**R^2 =**	**0.995**
A	**1.04E+13**	**s^{-1}**		

$\Delta H^{\neq}$ = Ea-RT	15.761	kcal/mol
$\Delta S^{\neq}$ = R[ln(h.A/k.T)-1]	-0.967	cal/(mol.K)
$\Delta G^{\neq}$	16.049	kcal/mol

*Activation parameters of **80** (CH_2 region):*

T [K]	1000/T	k	ln(k)
358	2.793	3780.3	8.238
348	2.874	799.3	6.684
338	2.959	281.3	5.639
328	3.049	154.3	5.039
318	3.145	36.3	3.592
308	3.247	6.3	1.841



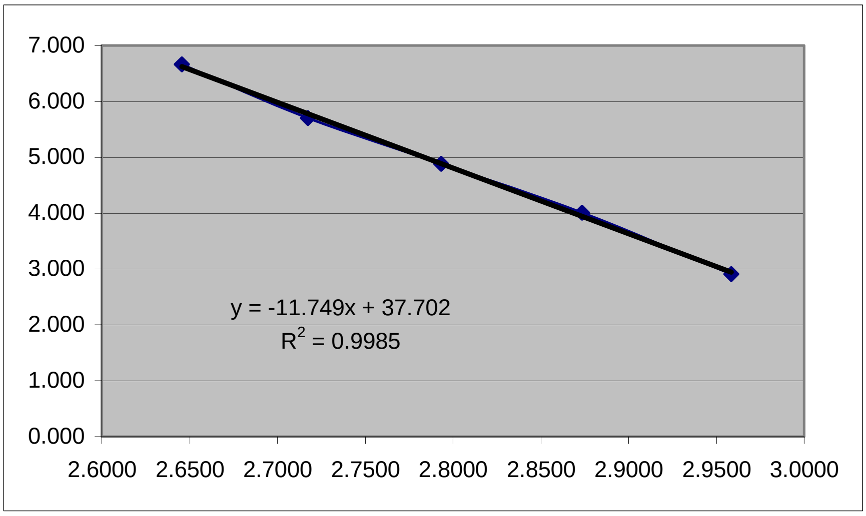
ln(k)= f(1000/T)		
slope=	-12.421	(- Ea/R)
intercept=	42.652	(Ln(A))

T	25	°C		
Ea	**103.592**	**kJ/mol**	**R^2 =**	**0.984**
A	**3.34E+18**	**s^{-1}**		

$\Delta H^{\neq}$ = Ea-RT	24.188	kcal/mol
$\Delta S^{\neq}$ = R[ln(h.A/k.T)-1]	24.253	cal/(mol.K)
$\Delta G^{\neq}$	16.957	kcal/mol

*Activation parameters of **82** (CF_3 region):*

T [K]	1000/T	k	ln(k)
388	2.577	1439	7.272
378	2.646	782	6.662
368	2.717	299	5.700
358	2.793	132	4.883
348	2.874	55	4.007
338	2.959	18.4	2.912



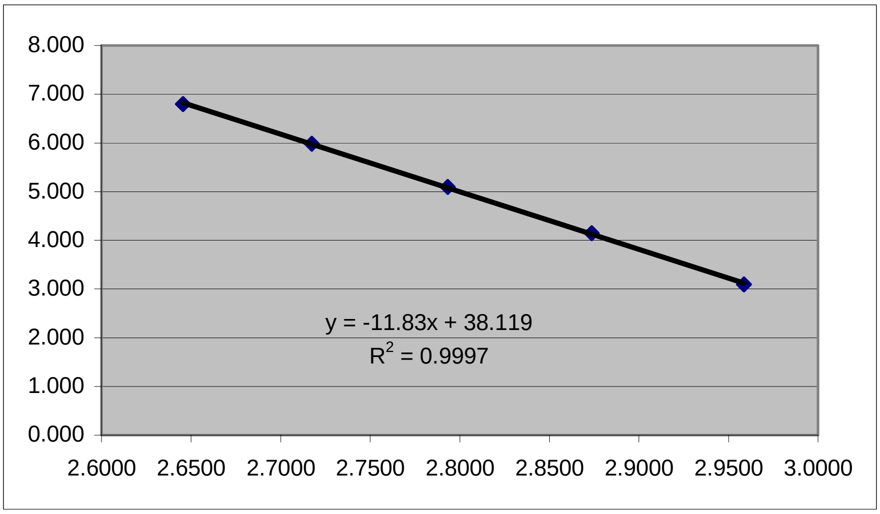
ln(k)= f(1000/T)		
slope=	-11.478	(- Ea/R)
intercept=	36.9295	(Ln(A))

T	25	°C		
Ea	**95.726**	**kJ/mol**	**R^2 =**	**0.999**
A	**1.09E+16**	**s^{-1}**		

$\Delta H^{\neq}$ = Ea-RT	22.306	kcal/mol
$\Delta S^{\neq}$ = R[ln(h.A/k.T)-1]	12.872	cal/(mol.K)
$\Delta G^{\neq}$	18.468	kcal/mol

Activation parameters of ***82*** *(H_{arom} region):*

T [K]	1000/T	k	ln(k)
378	2.646	895	6.797
368	2.717	396	5.981
358	2.793	164	5.100
348	2.874	63	4.143
338	2.959	22	3.091



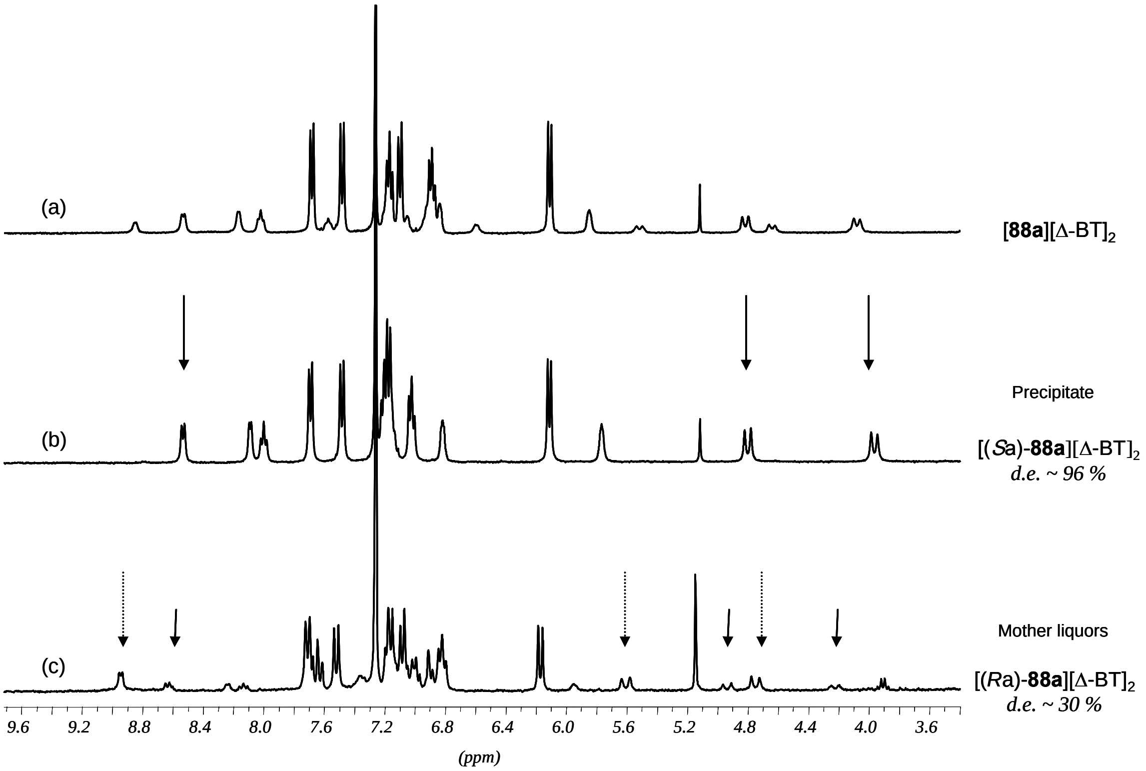
ln(k)= f(1000/T)

slope=	-11.830	(- Ea/R)
intercept=	38.119	(Ln(A))

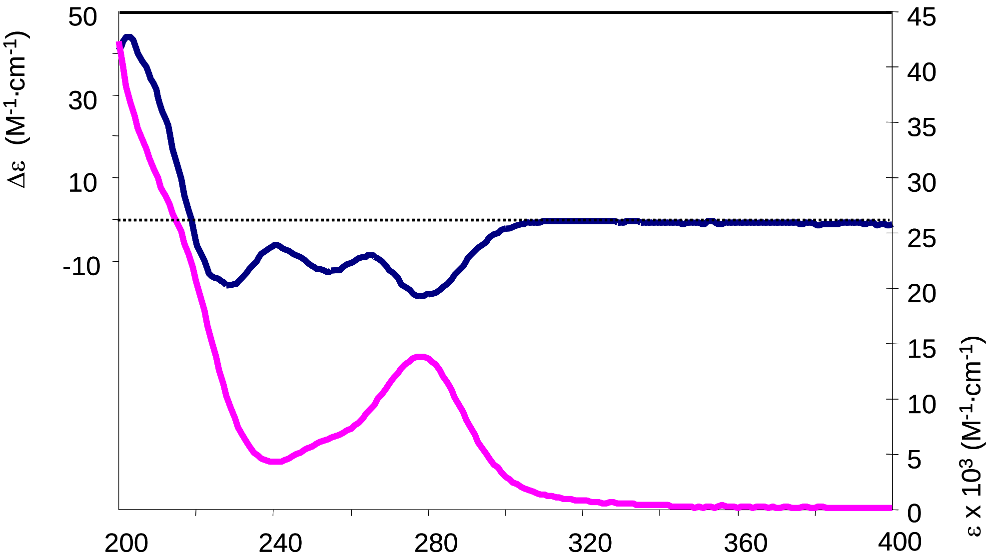
T	25	°C		
Ea	**98.664**	**kJ/mol**	**R^2 =**	**0.999**
A	**3.59E+16**	**s^{-1}**		

ΔH$^{\neq}$ = Ea-RT	23.009	kcal/mol
ΔS$^{\neq}$ = R[ln(h.A/k.T)-1]	15.239	cal/(mol.K)
ΔG$^{\neq}$	18.465	kcal/mol

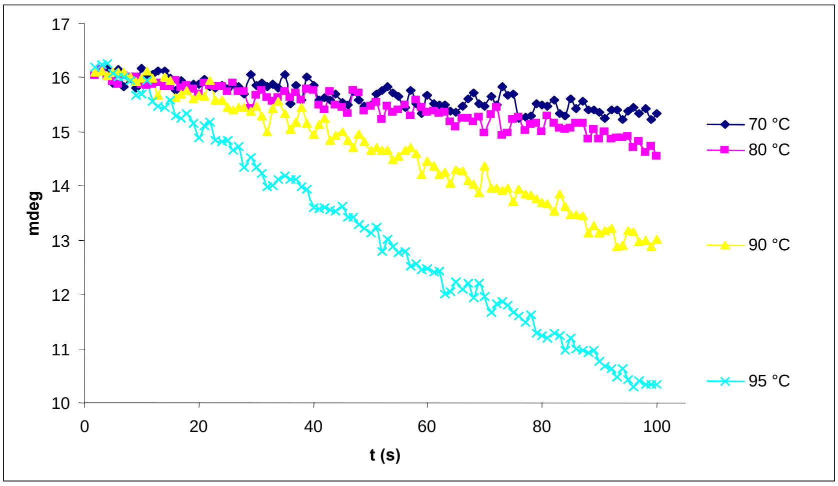
*^{1}H NMR (400 MHz, 14% DMSO-d_6 in $CDCl_3$) of (a) 1:1 mixture of the two diastereomers of **[88a]**[Δ-BT]$_2$, (b) [(Sa)-**88a**][Δ-BT]$_2$ coming from the precipitate and (c) [(Ra)-**88a**][Δ-BT]$_2$ coming from the mother liquors after the separation of the two diastereomers*



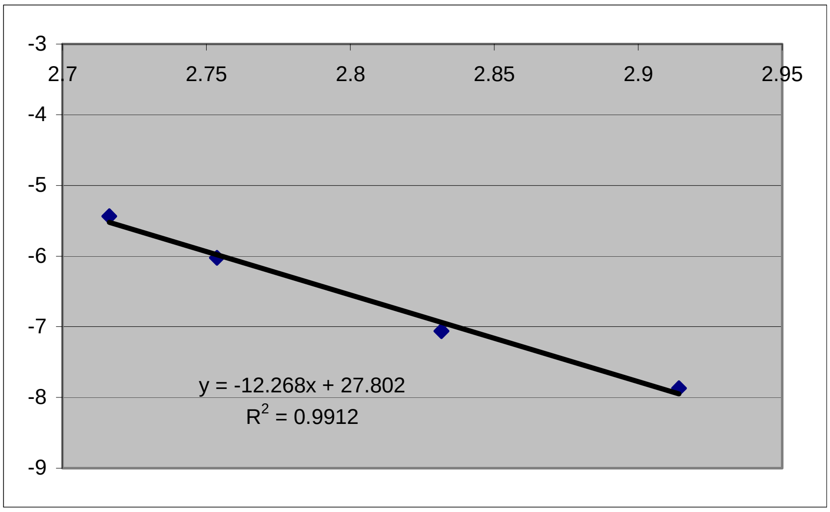
*Circular Dichroism (CD) and UV of [(Sa)-**88a**][PF_6]$_2$ (c ~ 3.10^{-5} M, H_2O, 20 °C)*



*CircularDichroism "Time course measurement" of [**88a**][PF$_6$]$_2$ (c ~ 3.10^{-5} M, H$_2$O) at 70 °C, 80 °C, 90 °C, 95°C during 100 s:*



*Activation parameters of [**88a**][PF$_6$]$_2$:*



T [K]	1000/T	k	ln(k)
343	2.914	0.000382	-7.870
353	2.832	0.000859	-7.060
363	2.754	0.002419	-6.024
368	2.716	0.004359	-5.436

ln(k)= f(1000/T)

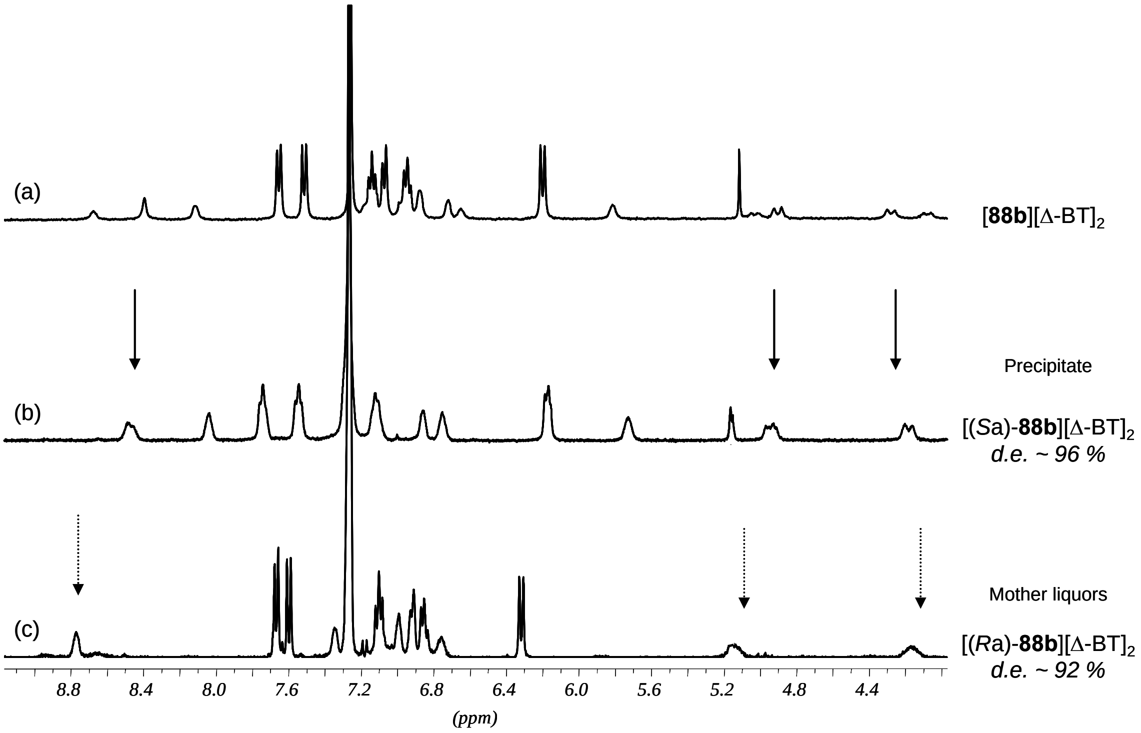
slope=	-12.2683	(- Ea/R)
intercept=	27.80215	(Ln(A))

T	20	°C
Ea	**102.318**	**kJ/mol**
A	**1.19E+12**	**s^{-1}**

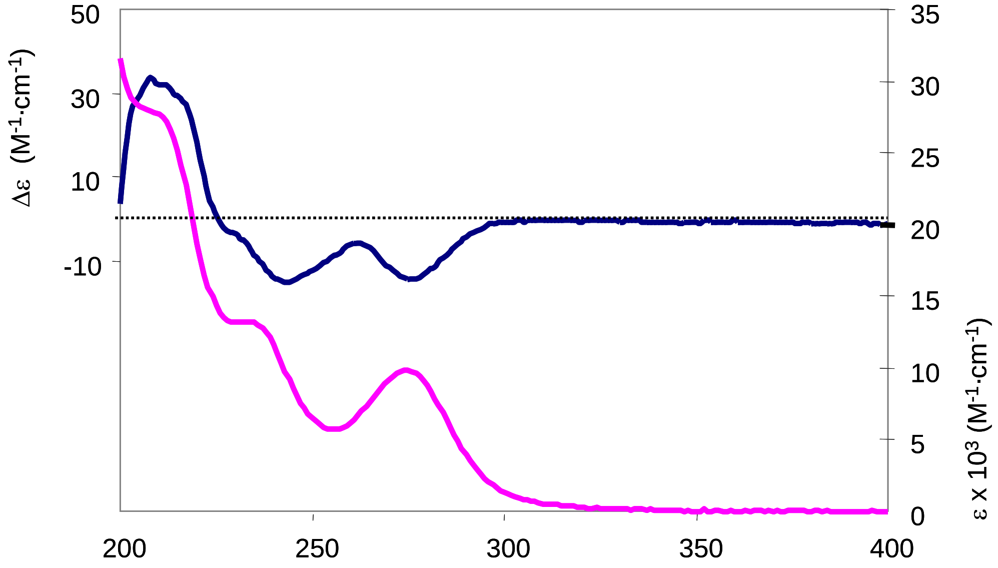
R^2 = **0.991**

ΔH$^{\neq}$ = Ea-RT	23.893	kcal/mol
ΔS$^{\neq}$ = R[ln(h.A/k.T)-1]	-5.249	cal/(mol.K)
ΔG$^{\neq}$	25.432	kcal/mol

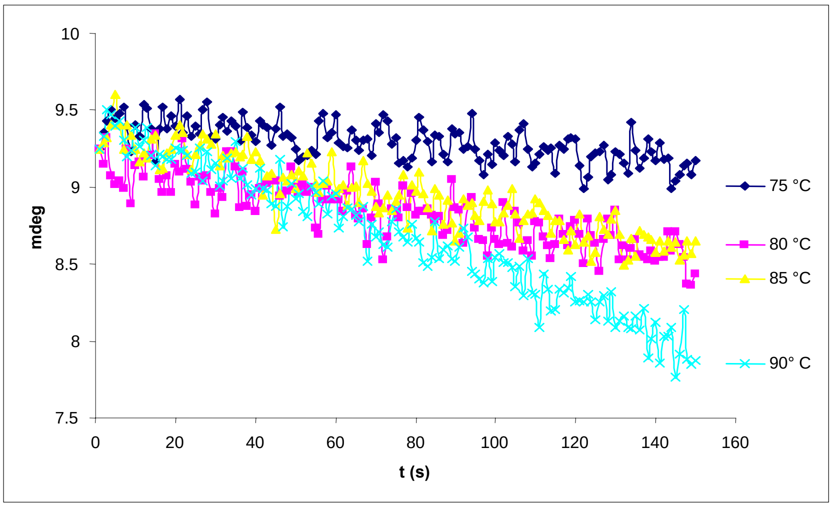
*^{1}H NMR (400 MHz, 14% DMSO-d_6 in $CDCl_3$) of (a) ~1:1 mixture of the two diastereomers of [**88b**][Δ-BT]$_2$, (b) [(Sa)-**88b**][Δ-BT]$_2$ coming from the precipitate and (c) [(Ra)-**88b**][Δ-BT]$_2$ coming from the mother liquors after the separation of the two diastereomers*



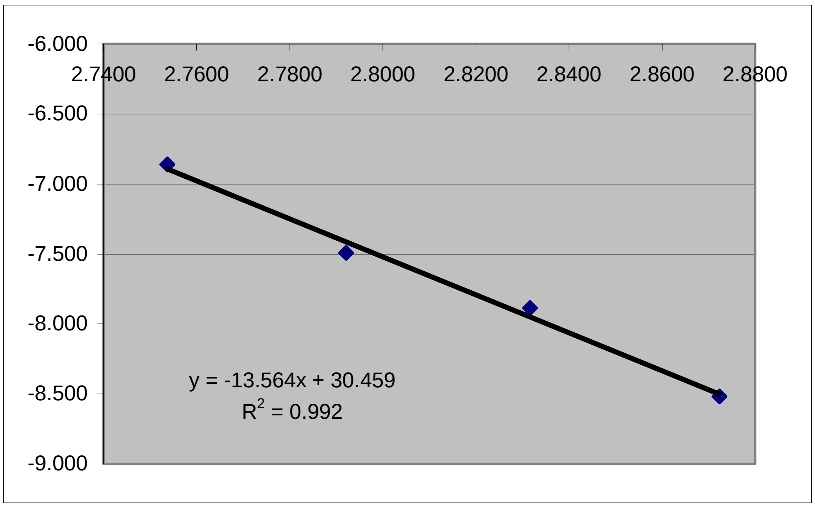
*CD and UV analysis of [(Sa)-**88b**][PF_6]$_2$ (c ~ 3.10^{-5} M, H_2O, 20 °C)*



*CircularDichroism "Time course measurement" of [**88b**][PF$_6$]$_2$ (c ~ 3.10^{-5} M, H$_2$O) at 70 °C, 80 °C, 85 °C, 90°C during 150 s:*



*Activation parameters of [**88b**][PF$_6$]$_2$:*

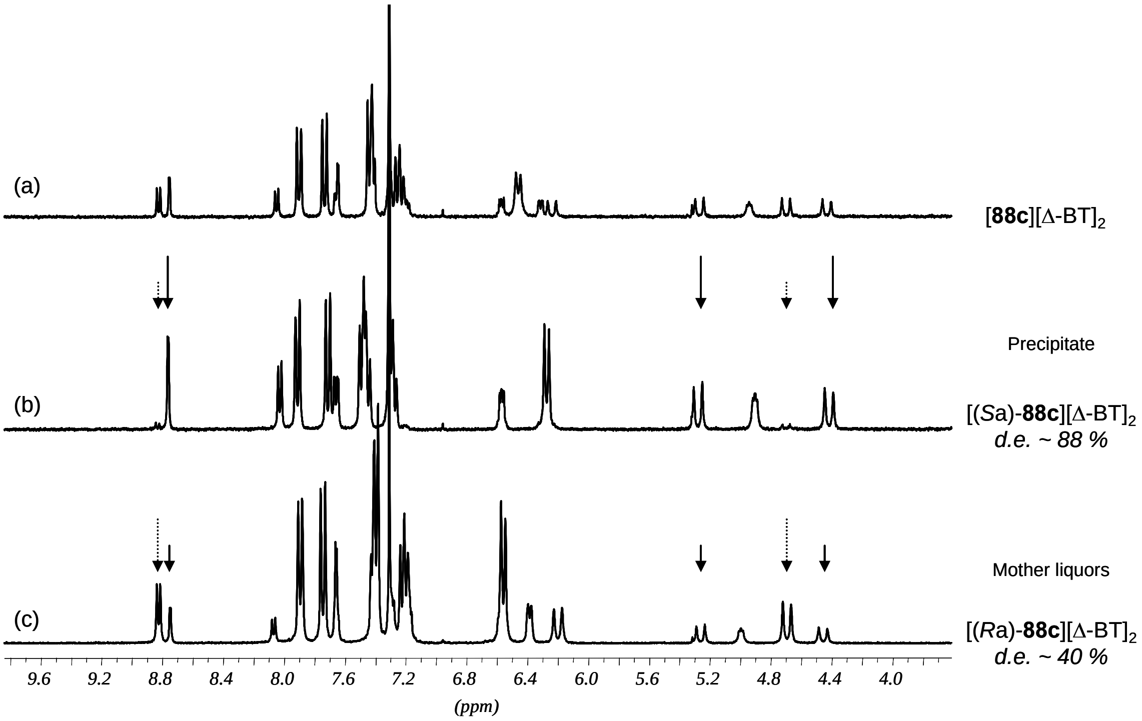


T [K]	1000/T	k	ln(k)
348	2.872	0.0002	-8.517
353	2.832	0.000376	-7.886
358	2.792	0.000557	-7.493
363	2.754	0.001049	-6.860

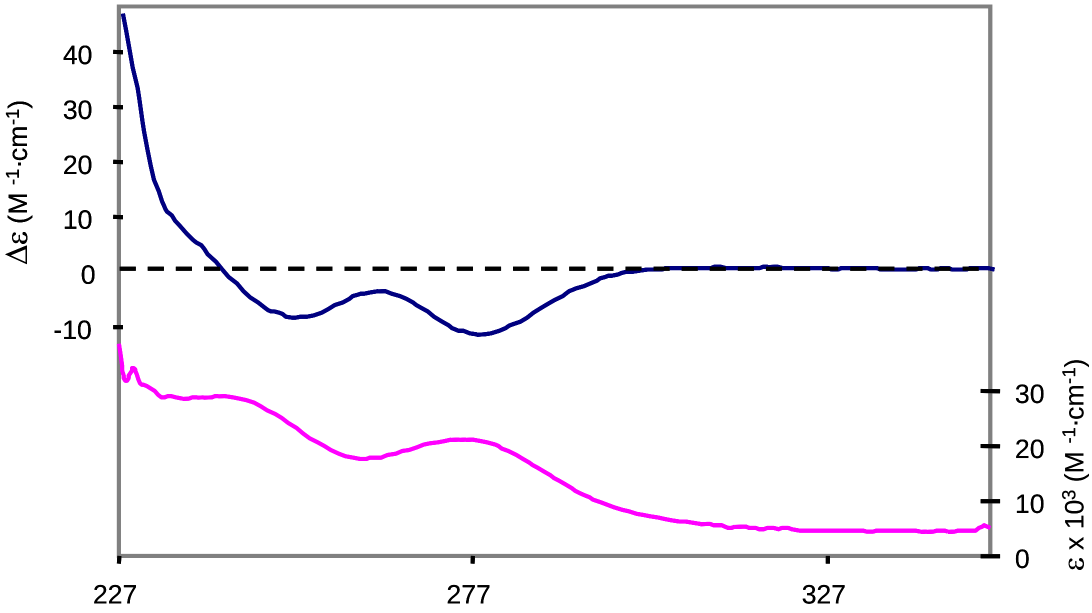
ln(k)= f(1000/T)			
slope=	-13.564		(- Ea/R)
intercept=	30.459		(Ln(A))
T	20	°C	
Ea	**113.123**	**kJ/mol**	
A	**1.69E+13**	**s^{-1}**	
R^2 =	**0.992**		

ΔH$^{\neq}$ = Ea-RT	26.478	kcal/mol
ΔS$^{\neq}$ = R[ln(h.A/k.T)-1]	0.036	cal/(mol.K)
ΔG$^{\neq}$	26.468	kcal/mol

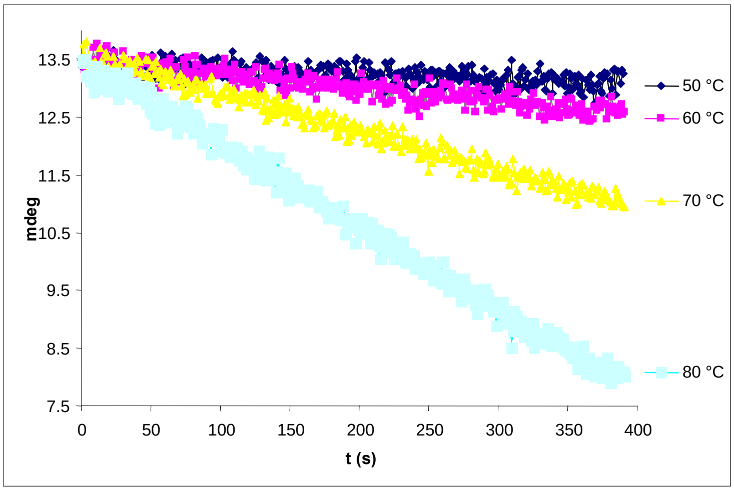
*^{1}H NMR (400 MHz, 3% CD_3CN in $CDCl_3$) of (a) ~1:1 mixture of the two diastereomers of [**88c**][Δ-BT]$_2$, (b) [(Sa)-**88c**][Δ-BT]$_2$ coming from the precipitate and (c) [(Ra)-**88c**][Δ-BT]$_2$ coming from the mother liquors after the separation of the two diastereomers*



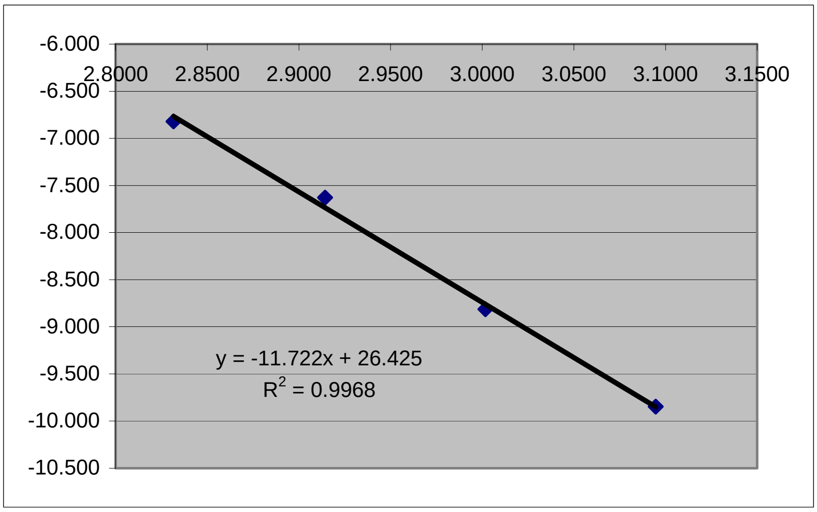
*CD and UV analysis of [(Sa)-**88c**][PF_6]$_2$ (c ~ 10^{-5} M, CH_2Cl_2, 20 °C)*



*CircularDichroism “Time course measurement” of [**88c**][PF$_6$]$_2$ (c ~ 3.10^{-5} M, H$_2$O) at 70 °C, 80 °C, 85 °C, 90°C during 150 s:*



*Activation parameters of [**88c**][PF$_6$]$_2$:*



T [K]	1000/T	k	ln(k)
323	3.095	5.29E-05	-9.847
333	3.002	0.000149	-8.814
343	2.914	0.000486	-7.630
353	2.832	0.001091	-6.821

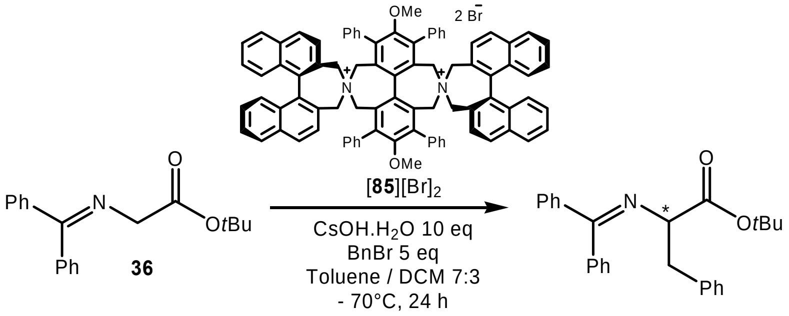
ln(k)= f(1000/T)		
slope=	-11.722	(- Ea/R)
intercept=	26.425	(Ln(A))

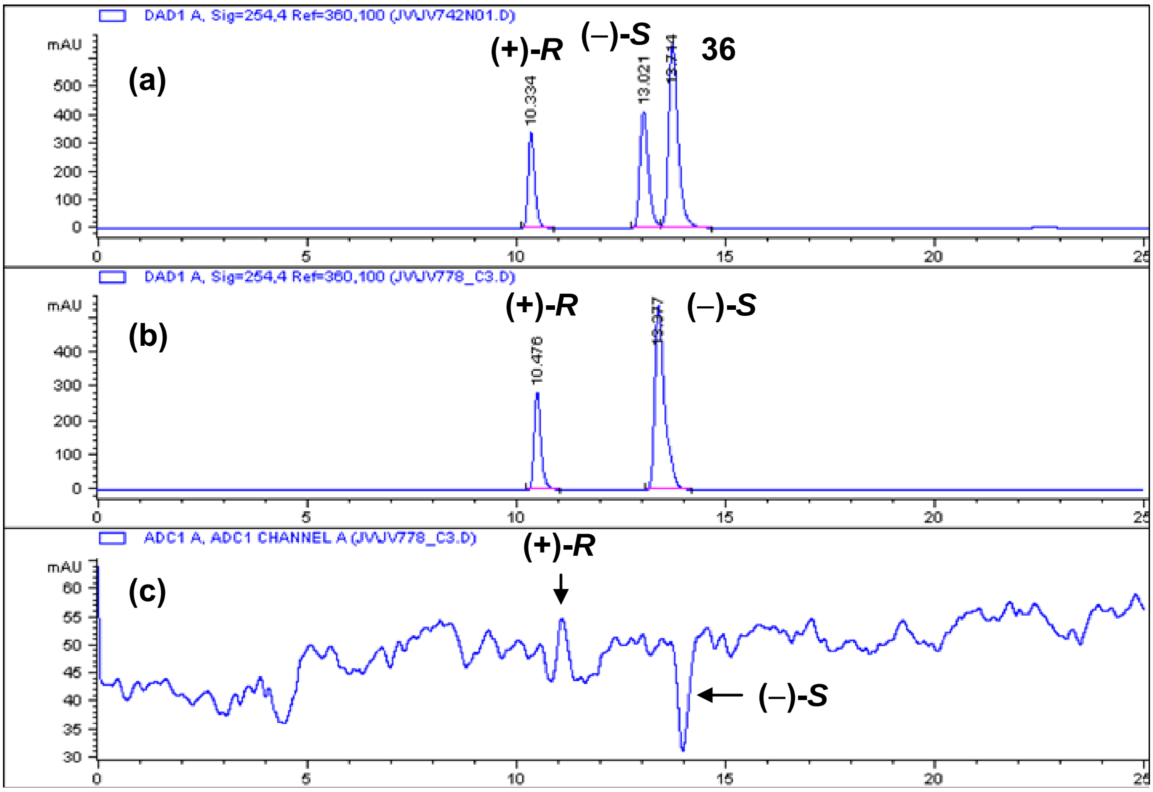
T	20	°C
Ea	**97.762**	**kJ/mol**
A	**2.99E+11**	**s^{-1}**

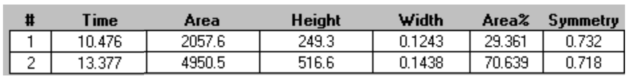
R^2 = **0.997**

ΔH$^{≠}$ = Ea-RT	22.803	kcal/mol
ΔS$^{≠}$ = R[ln(h.A/k.T)-1]	-7.987	cal/(mol.K)
ΔG$^{≠}$	25.144	kcal/mol

*Benzylation of **36** with ammonium salt catalyst [**85**][Br]$_2$:*







#	Time	Area	Height	Width	Area%	Symmetry
1	10.476	2057.6	249.3	0.1243	29.361	0.732
2	13.377	4950.5	516.6	0.1438	70.639	0.718

Determined by CSP-HPLC (Chiralcel IB); Hex / iPrOH 99:1; 0.5 mL.min^{-1} with:
(a): racemic product and starting material **36**
(b): product with 41% ee
(c): ORD signal

CRYSTALLOGRAPHIC DATA:

Compound [(*S*a)-**88c**][Δ-TT]$_2$

Date: 19.9.2006	**Requérant**:	J. Vachon	**code**: LA/48/822
		cpid: JVAC	

Formule brute:	$[C_{26}H_{32}N_2]^{2+}$ $2(C_{18}O_6Cl_{12}P)^-$ $(C_3H_6O)_5$
Poids moléculaire:	2200.1
Coefficient d'absorption linéaire	μ = 0.79 mm^{-1} (Mo (Kα))
Solvant de recristallisation	Acetone / Hexane
Densité Do = ?	Dx = 1.548 (gr.cm^{-3})
Diffractomètre	STOE IPDS

Géométrie de la maille

Système cristallin: Orthorhombique	Groupe d'espace: $P\,2_12_12_1$
a = 13.5436 (5) (Å)	α = 90°
b = 16.5758 (8)(Å)	β = 90°
c = 42.0510 (16)(Å)	γ = 90°
V = 9440.3 (7)(Å^3)	Z = 4
Nombre de réflexions pour l'affinement des paramètres:	7996 (7.3° < 2θ < 49.9°)

Forme et dimensions du cristal

Forme: prisme; Couleur:

Dimensions: 0.07 x 0.21 x 0.27 mm

Mode de fixation: RS3000

Conditions expérimentales pour la collection des intensités

Température:	200 K	Longueur d'onde	0.7107(Å)
Mode de balayage	φ-scan	$\Delta\varphi$ / image	0.6 (°)
T Irradiation / image	5 (min)	φ min, max =	0 - 270 (°)
Distance cristal / IP	75 (mm)	Nombre d'images	450
EMS	0.007	Moyenne (I/σ(I))	5.81
Limites angulaires	3.9° < 2θ < 49.9°		
Limites d'indices	-16 < h < 16 ; -19 < k < 19 ; -49 < ℓ < 50		

Nombre de réflexions mesurées: 90'383

Réduction des données

Corrections : LP ☒

Disp. anomale	☒	
Absorption	☒	T min. , max. = 0.8559 , 0.9539

Nombre de réflexions observables	9802	**$|Fo| > 3\sigma(Fo)$**
Nombre de réflexions non-observables	6813	
Nombre de réflexions uniques	16615	R_{int} pour 73664 réfl. équivalentes = 0.071

Statistique des réflexions

Facteur de température global	3.67 (Å^2)
Distribution des $<E^2>$: acentrique	$<E^2-1>$ = 0.762

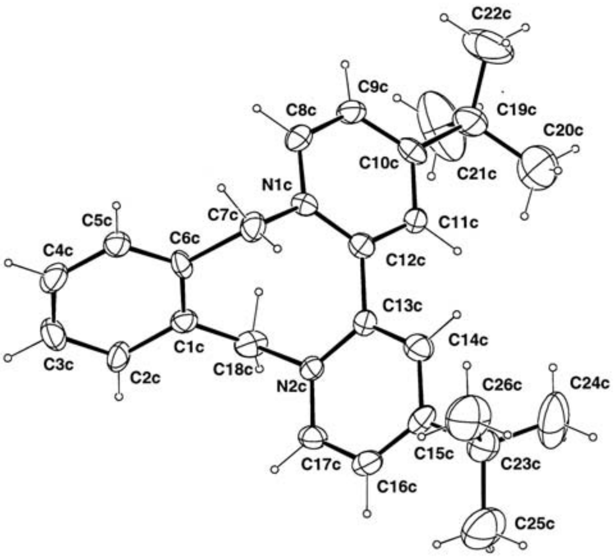
Résolution et affinement de la structure

Résolution:	Méthodes directes (SIR97)
Fonction minimisée :	Σ (ω (Fo-Fc)^2)
Fonction de poids :	$\omega = 1/[\sigma^2(Fo) + 0.0002\ (Fo^2)]$
Nombre d'atomes affinés "iso" :	-
Nombre d'atomes affinés "aniso":	122
Coordonnées des atomes d'hydrogène:	calculées
Programme	XTAL 3.2

Valeurs obtenues en fin d'affinement

Nombre de variables:	1100
Nombre de réflexions :	9942
Nbe reflexions / Nbe de variables	9.0
Affinement par moindres carrés:	Full matrix
"shift/error":	moyen : 0.35 10^{-4} , Maximum : 0.10 10^{-2}
Résidus (delta F) (eÅ^{-3}):	-0.48 , 0.47
Configuration absolue:	x = -0.02(6)
"Goodness of fit": S =	1.22(1)

Facteur résiduel final	**R = 0.037**
Facteur résiduel pondéré	**ωR = 0.034**



$[C_{26}H_{32}N_2]^{2+}$ $2(C_{18}O_6Cl_{12}P)^{-}$ $(C_3H_6O)_5$ LA/48/822 $P\ 2_12_12_1$ 200K IPDS

Bond Distances (Angstroms)

N1c-C7c	1.49(1)	N1c-C8c	1.337(9)
N1c-C12c	1.34(1)	N2c-C13c	1.36(1)
N2c-C17c	1.330(9)	N2c-C18c	1.51(1)
C1c-C2c	1.42(1)	C1c-C6c	1.40(1)
C1c-C18c	1.51(1)	C2c-C3c	1.40(1)
C3c-C4c	1.39(1)	C4c-C5c	1.36(1)
C5c-C6c	1.38(1)	C6c-C7c	1.57(1)
C8c-C9c	1.38(1)	C9c-C10c	1.37(1)
C10c-C11c	1.40(1)	C10c-C19c	1.52(1)
C11c-C12c	1.36(1)	C12c-C13c	1.51(1)
C13c-C14c	1.35(1)	C14c-C15c	1.40(1)
C15c-C16c	1.37(1)	C15c-C23c	1.53(1)
C16c-C17c	1.38(1)	C19c-C20c	1.52(2)
C19c-C21c	1.48(2)	C19c-C22c	1.46(1)
C23c-C24c	1.45(2)	C23c-C25c	1.54(1)
C23c-C26c	1.53(2)	O1d-C1d	1.21(2)
C1d-C2d	1.44(2)	C1d-C3d	1.45(2)
O1e-C1e	1.53(3)	C1e-C2e	1.21(3)
C1e-C3e	1.40(2)	O1f-C1f	1.21(1)
C1f-C3f	1.44(2)	C1f-C2f	1.46(2)
O1g-C1g	1.25(2)	C1g-C2g	1.37(3)
C1g-C3g	1.41(2)	O1h-C1h	1.22(3)
C1h-C2h	1.39(3)	C1h-C3h	1.40(3)

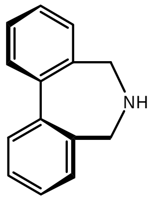
Bond Angles (degrees)

C7c-N1c-C8c	118.7(6)	C7c-N1c-C12c	120.7(6)
C8c-N1c-C12c	120.0(7)	C13c-N2c-C17c	121.0(7)
C13c-N2c-C18c	121.7(6)	C17c-N2c-C18c	117.2(6)
C2c-C1c-C6c	119.0(8)	C2c-C1c-C18c	116.1(7)
C6c-C1c-C18c	124.8(7)	C1c-C2c-C3c	119.1(8)
C2c-C3c-C4c	119.9(8)	C3c-C4c-C5c	120.9(9)
C4c-C5c-C6c	120.5(8)	C1c-C6c-C5c	120.6(8)
C1c-C6c-C7c	122.1(7)	C5c-C6c-C7c	117.0(7)
N1c-C7c-C6c	114.3(6)	N1c-C8c-C9c	120.2(8)
C8c-C9c-C10c	122.0(7)	C9c-C10c-C11c	115.4(7)
C9c-C10c-C19c	121.5(7)	C11c-C10c-C19c	123.0(8)
C10c-C11c-C12c	121.4(8)	N1c-C12c-C11c	120.9(7)
N1c-C12c-C13c	119.5(7)	C11c-C12c-C13c	119.6(7)
N2c-C13c-C12c	117.8(7)	N2c-C13c-C14c	119.3(6)
C12c-C13c-C14c	122.9(7)	C13c-C14c-C15c	121.9(8)
C14c-C15c-C16c	116.2(8)	C14c-C15c-C23c	120.6(8)
C16c-C15c-C23c	123.2(7)	C15c-C16c-C17c	121.4(7)
N2c-C17c-C16c	120.2(7)	N2c-C18c-C1c	112.9(7)
C10c-C19c-C20c	112.3(8)	C10c-C19c-C21c	108(1)
C10c-C19c-C22c	113.2(9)	C20c-C19c-C21c	104(1)
C20c-C19c-C22c	111(1)	C21c-C19c-C22c	108(1)
C15c-C23c-C24c	111.3(9)	C15c-C23c-C25c	111.0(8)
C15c-C23c-C26c	107.6(8)	C24c-C23c-C25c	111(1)
C24c-C23c-C26c	110(1)	C25c-C23c-C26c	106.1(9)

Dihedral Angles (degrees)

C8c-N1c-C7c-C6c	91.2(8)	C12c-N1c-C7c-C6c	-97.5(8)
C7c-N1c-C8c-C9c	171.1(8)	C12c-N1c-C8c-C9c	0(1)
C7c-N1c-C12c-C11c	-168.7(8)	C7c-N1c-C12c-C13c	13(1)
C8c-N1c-C12c-C11c	3(1)	C8c-N1c-C12c-C13c	-175.3(7)
C17c-N2c-C13c-C12c	177.6(7)	C17c-N2c-C13c-C14c	-1(1)
C18c-N2c-C13c-C12c	0(1)	C18c-N2c-C13c-C14c	-179.3(7)
C13c-N2c-C17c-C16c	1(1)	C18c-N2c-C17c-C16c	179.4(7)
C13c-N2c-C18c-C1c	-93.9(8)	C17c-N2c-C18c-C1c	87.9(8)
C6c-C1c-C2c-C3c	0(1)	C18c-C1c-C2c-C3c	-175.2(7)
C2c-C1c-C6c-C5c	0(1)	C2c-C1c-C6c-C7c	174.1(7)
C18c-C1c-C6c-C5c	175.8(7)	C18c-C1c-C6c-C7c	-10(1)
C2c-C1c-C18c-N2c	-123.9(7)	C6c-C1c-C18c-N2c	60.4(9)
C1c-C2c-C3c-C4c	-1(1)	C2c-C3c-C4c-C5c	0(1)
C3c-C4c-C5c-C6c	0(1)	C4c-C5c-C6c-C1c	0(1)
C4c-C5c-C6c-C7c	-175.0(7)	C1c-C6c-C7c-N1c	49.4(9)
C5c-C6c-C7c-N1c	-136.6(7)	N1c-C8c-C9c-C10c	-3(1)
C8c-C9c-C10c-C11c	3(1)	C8c-C9c-C10c-C19c	-179.5(8)
C9c-C10c-C11c-C12c	0(1)	C19c-C10c-C11c-C12c	-178.2(8)
C9c-C10c-C19c-C20c	170(1)	C9c-C10c-C19c-C21c	-76(1)
C9c-C10c-C19c-C22c	44(1)	C11c-C10c-C19c-C20c	-12(1)
C11c-C10c-C19c-C21c	101(1)	C11c-C10c-C19c-C22c	-139(1)
C10c-C11c-C12c-N1c	-2(1)	C10c-C11c-C12c-C13c	175.9(8)
N1c-C12c-C13c-N2c	62(1)	N1c-C12c-C13c-C14c	-119(1)
C11c-C12c-C13c-N2c	-115.8(9)	C11c-C12c-C13c-C14c	63(1)
N2c-C13c-C14c-C15c	0(1)	C12c-C13c-C14c-C15c	-178.1(8)
C13c-C14c-C15c-C16c	0(1)	C13c-C14c-C15c-C23c	-180.0(8)
C14c-C15c-C16c-C17c	0(1)	C23c-C15c-C16c-C17c	179.9(8)
C14c-C15c-C23c-C24c	-46(1)	C14c-C15c-C23c-C25c	-169.4(9)
C14c-C15c-C23c-C26c	75(1)	C16c-C15c-C23c-C24c	134(1)
C16c-C15c-C23c-C25c	11(1)	C16c-C15c-C23c-C26c	-105(1)
C15c-C16c-C17c-N2c	0(1)		

List of Principal Compounds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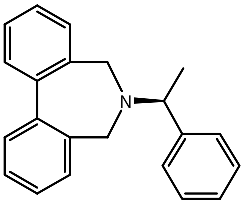
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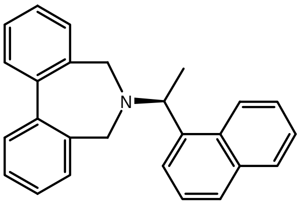
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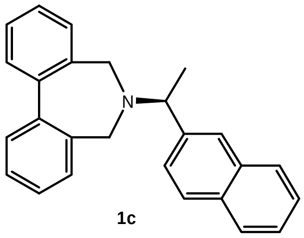
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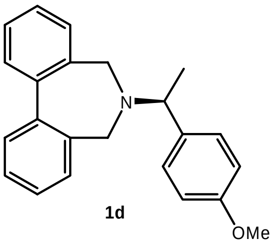

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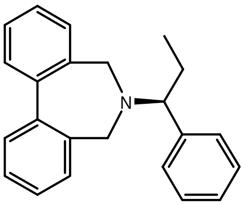
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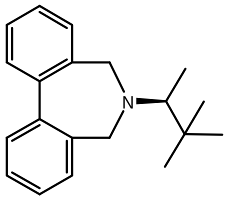
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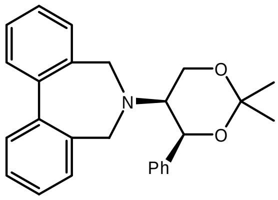
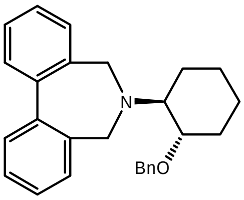
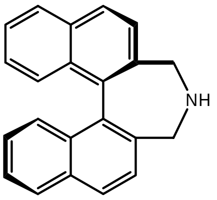
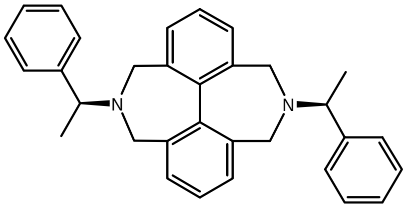


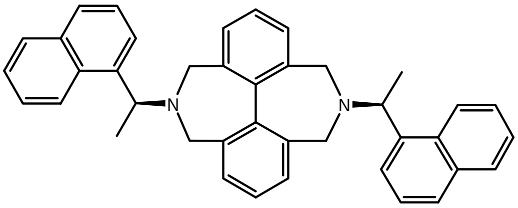
1g



1h


(R_a)-**2**


4a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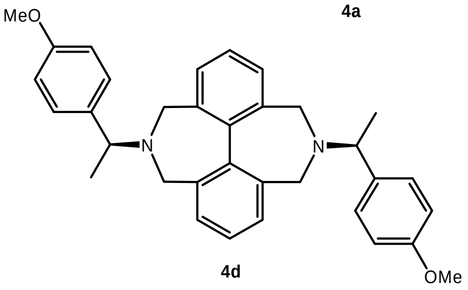

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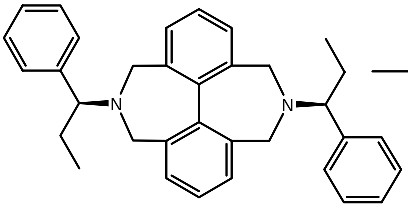
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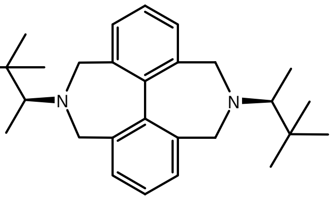
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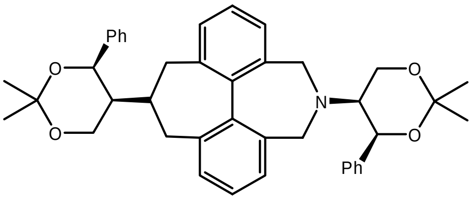

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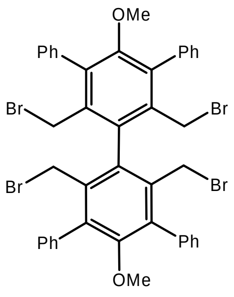

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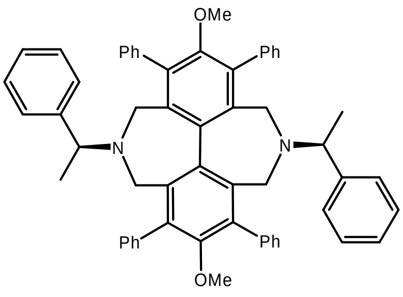

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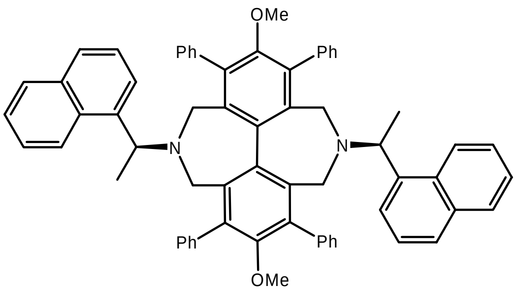

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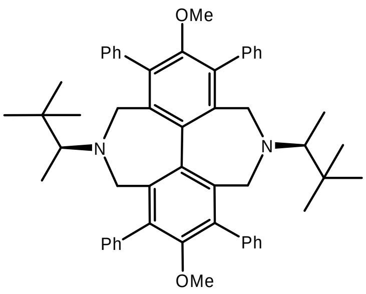

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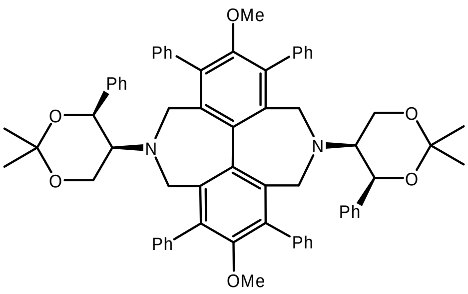

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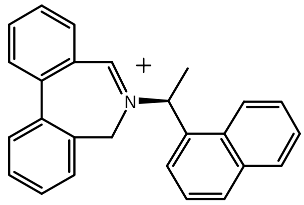

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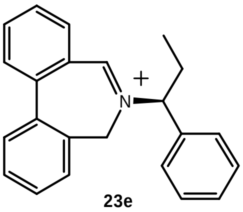

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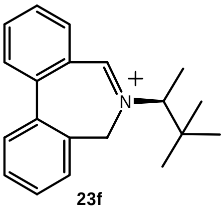

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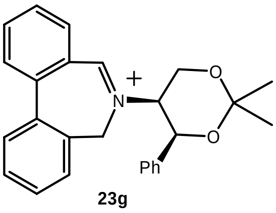

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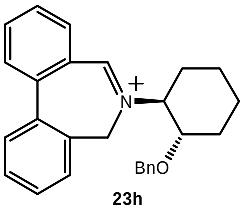

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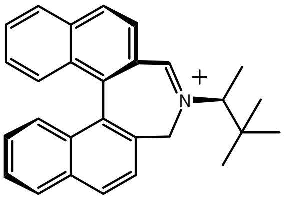
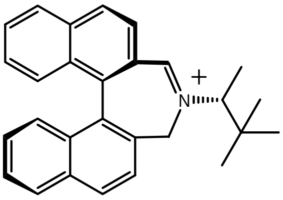


(*R*a,*S*)-24f



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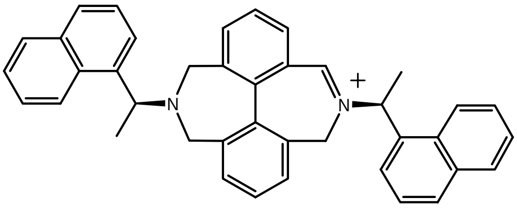

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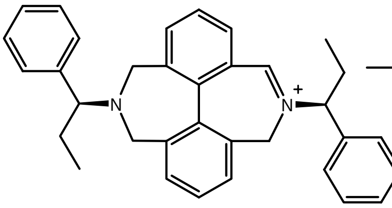

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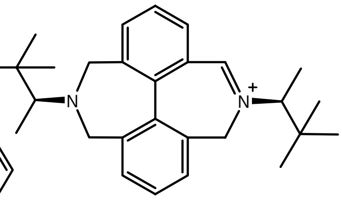

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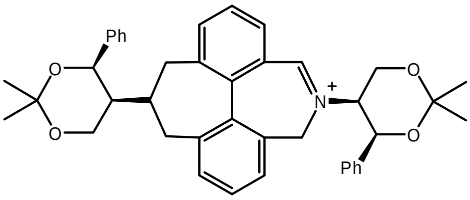

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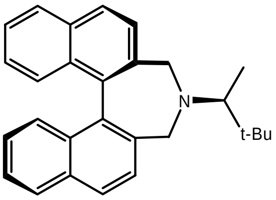
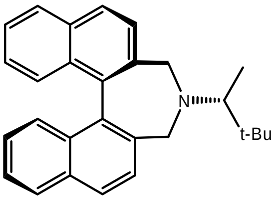


(R_a,*S*)-**35f**



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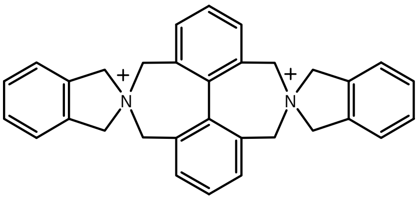

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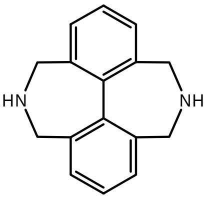

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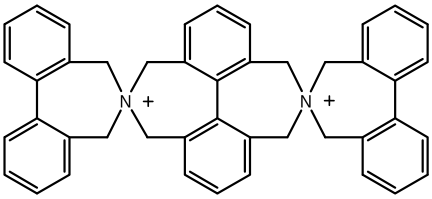

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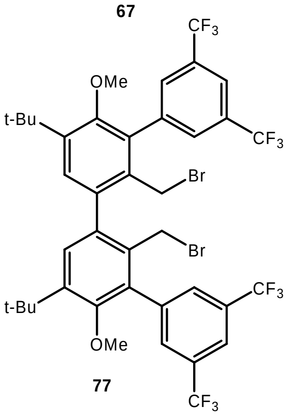

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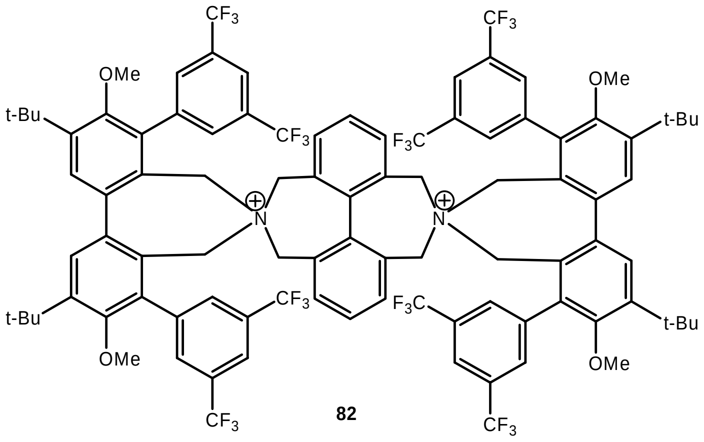

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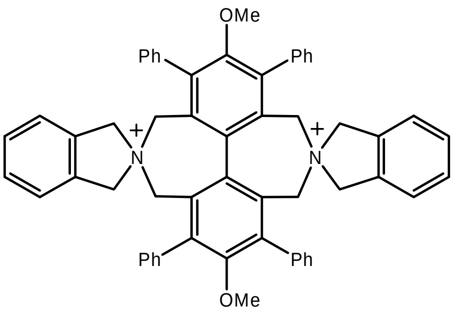

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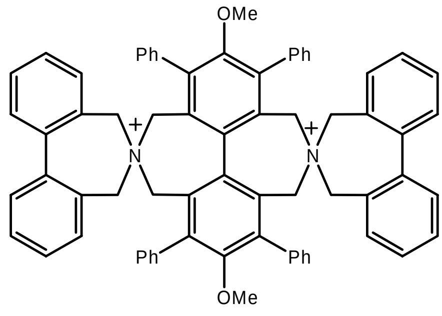

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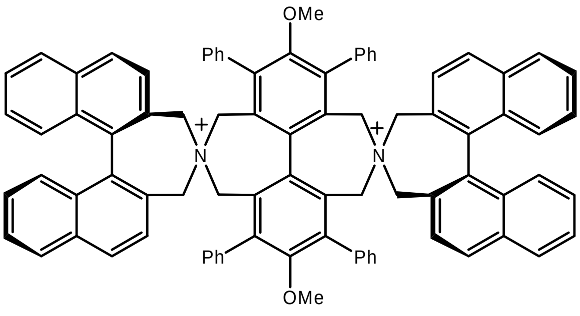

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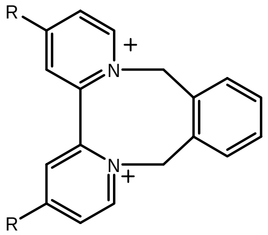
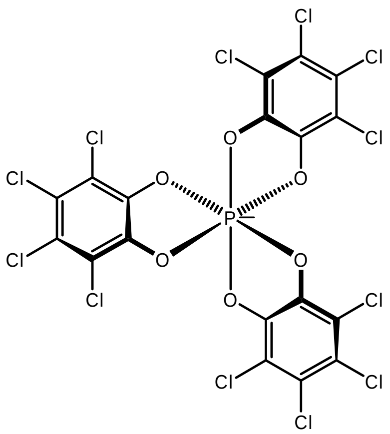
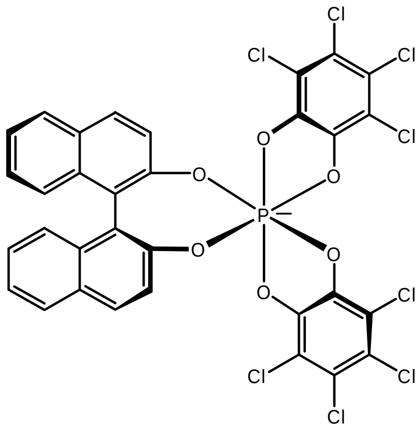


88a (R = H)
88b (R = Me)
88c (R = ^{t}Bu)



Δ–TRISPHAT



Δ–BINPHAT