# Recent developments on the enantioselective [1,2]-Stevens rearrangement

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# Recent Developments on the Enantioselective [1,2]-Stevens Rearrangement

THÈSE

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par

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La Faculté des sciences, sur le préavis de Messieurs J. LACOUR, professeur ordinaire et directeur de thèse (Département de chimie organique), I. COLDHAM, docteur (University of Sheffield – Departement of Chemistry – Sheffield, England), et Madame K. VELONIA, docteur (Département de chimie), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

Genève, le 16 janvier 2008

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**Le Doyen**, Jean-Marc TRISCONE

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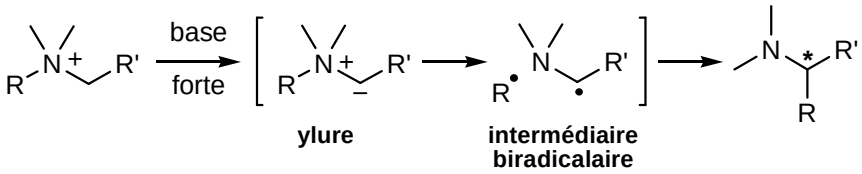
# RÉSUMÉ

Le réarrangement de Stevens-[1,2] est une réaction où un ammonium quaternaire (non-allylique), traité par une base forte, génère un ylure d'ammonium intermédiaire. Dans une deuxième étape, la migration de l'un des substituants de l'azote vers ce carbone activé forme une amine tertiaire avec la création d'une nouvelle liaison C−C et, le plus souvent, d'un centre stéréogène en $\alpha$ de l'azote (Schéma ci-dessous).




Depuis sa découverte en 1928,[1] cette transformation a été souvent étudiée pour son mécanisme intéressant qui implique probablement un intermédiaire biradicalaire[2] et pour son potentiel synthétique qui a été appliqué de nombreuses fois en synthèse de produit naturels (alcaloïdes).[3] De plus, diverses réactions de réarrangement de Stevens-[1,2] asymétriques, diastéréosélectives[4] ou énantiospécifiques[5] ont été développées. Cependant, à notre connaissance, aucun exemple de réarrangement de Stevens strictement énantiosélectif n'a été rapporté dans la littérature, c'est-à-dire sans la formation préalable d'un composé possédant un atome d'azote stéréogène.[5]

Par conséquent, le but de ce travail de thèse fût de développer une nouvelle stratégie pour le réarrangement de Stevens-[1,2] énantiosélectif. Pour cela, notre étude s'est portée sur l'utilisation de cations «diphénylazépiniums» conformationnellement labiles de type **1**. Ces composés possèdent un cycle à 7 chainons *tropos* de type dibenzo[*c*,*e*]azepinium ainsi qu'un second cycle

[1] Stevens, T. S.; Creigton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193-3197

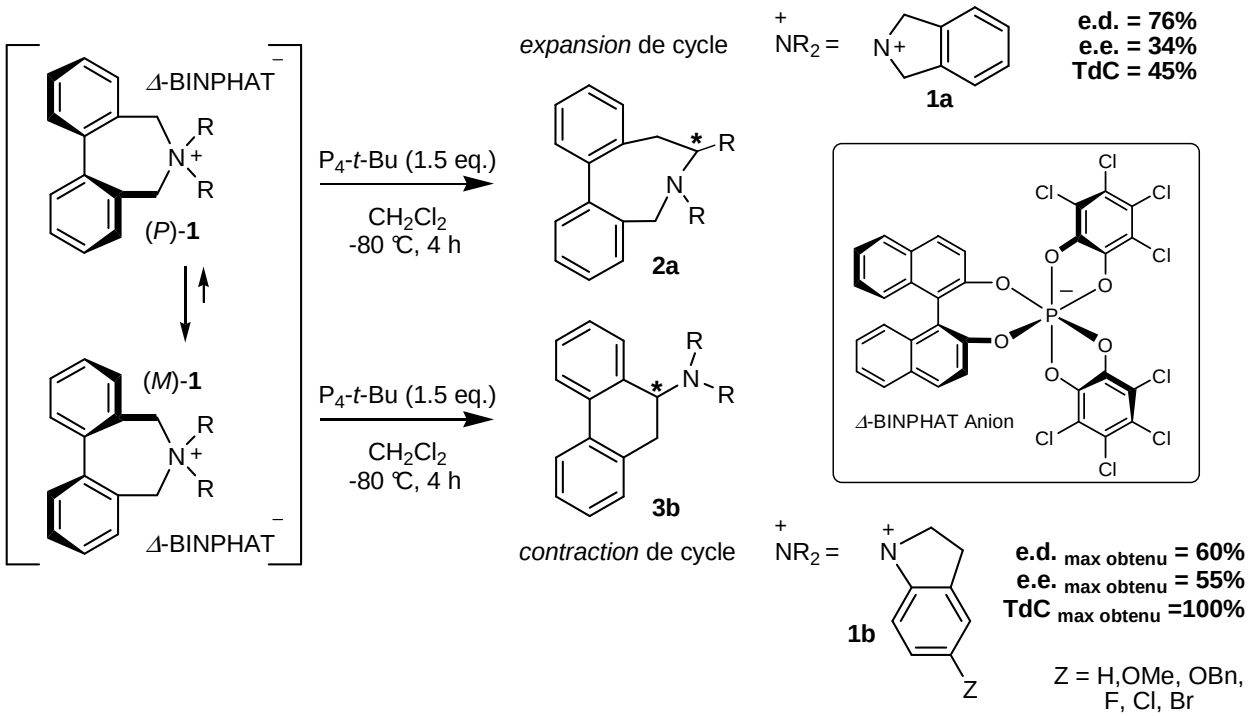
[2] Maeda, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1491-1493. Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009-1027. Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049-1061

[3] Hanessian, S.; Parthasarathy, S.; Mauduit, M.; Payza, K. *J. Med. Chem.* **2003**, *46*, 34-48. Hanessian, S.; Mauduit, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3810-3813. Liou, J.-P.; Cheng, C.-Y. *Tetrahedron Lett.* **2000**, *41*, 915-918. Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565-16574. West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420-8421

[4] Stará, I. G.; Starý, I.; Tichý, M.; Závada, J.; Hanuš, V. *J. Am. Chem. Soc.* **1994**, *116*, 5084-5088. Joshua, H.; Gans, R.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4884-4892

[5] Tayama, E.; Nanbara, S.; Nakai, T. *Chem. Lett.* **2006**, *35*, 478-479.Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31-33

rigide de type -isoindolinium **1a** ou -indolinium **1b** qui portent différent substituents en position 5 (Z = H, OMe, OBn, F, Cl, Br). Ces cations sont *chiraux* du fait de la chiralité axiale du cycle à 7 chainons mais ils existent en solution sous deux conformations atropoisomériques *P* et *M* en libre échange ($\Delta G^{\neq}$ ~ 12-14 kcal.mol$^{-1}$, $t_{½}$ ~ $10^{-4}$ s à 25 °C). Ces cations ont été synthétisés sous forme de sels de bromure ou d'iodure, puis ils ont été associés avec un anion du phosphore hexacoordiné énantiopur de type BINPHAT (*e.g.* *Δ*) dont la synthèse et les applications ont été développées au sein du groupe du Professeur Lacour depuis 1995. Il en résulte deux paires d'ions diastéréoisomériques [(*P*)-**1**][*Δ*-BINPHAT] et [(*M*)-**1**][*Δ*-BINPHAT] dont le rapport est différent de 1. En effet, l'anion BINPHAT est connu pour être un excellent agent d'énantiodifférentiation RMN ainsi qu'un inducteur d'asymétrie efficace en présence d'espèces cationiques chirales (effet *Pfeiffer*, en particulier avec certains ammoniums quaternaires).[6] L'association de l'anion BINPHAT avec un cation de type **1** conduit donc à un stéréocontrôle supramoléculaire permettant la prédominance d'une des paires d'ions diastéréoisomères avec un excès diastéréomérique (e.d.) allant jusqu'à 76% pour le cation **1a** ($CD_2Cl_2$, –40 °C).




[6] Lacour, J.; Vial, L.; Herse, C. *Org. Lett.* **2002**, *4*, 1351-1354. Lacour, J.; Londez, A.; Goujon-Ginglinger, C.; Buss, V.; Bernardinelli, G. *Org. Lett.* **2000**, *2*, 4185-4188

L'originalité de ce travail a été de montrer que le traitement à basse température (–80 °C) des sels [**1**][*Δ*-BINPHAT] avec une base phosphazène de Schwesinger, la $P_4$-*t*-Bu,[7] mène dans le cas du sel **1a** à la formation d'une amine tertiaire **2a** avec *expansion* de cycle et, dans le cas de **1b**, à une amine tertiaire **3b** par un réarrangement de Stevens-[1,2] *endocyclique*; les deux processus formant les amines chirales sous forme non-racémiques.

Il a été montré au cours de ce travail que l'une ou l'autre des amines est obtenue exclusivement en fonction (1) de la régiosélectivité de la déprotonation (cycle à 7 *vs* cycle rigide, géométrie axiale ou équatoriale de l'ylure généré) et (2) de la régiosélectivité de la migration du fragment carboné (fragmentation *exocyclique* ou *endocyclique* et recombinaison menant à une *expansion* ou une *contraction* de cycle respectivement). Cette dernière sélectivité est intrinsèquement liée à la nature du groupe migrant.

Dans le cas du réarrangement de Stevens-[1,2] des sels [**1b**][*Δ*-BINPHAT], les amines tertiaires non-racémiques de type **3b** ont été obtenues avec des excès enantiomériques (e.e.) hautement reproductibles allant jusqu'à 55% pour Z = Cl et surtout avec d'excellents transferts de chiralité (TdC = 100% pour Z = H et OBn). De plus, de nombreuses expériences mécanistiques ont été réalisées au cours de cette thèse afin de mieux comprendre le mécanisme du réarrangement de Stevens-[1,2]. Les résultats obtenus ont permis de conclure que (1) la déprotonation du cation n'est pas *a priori* énantiosélective, (2) la déprotonation n'est pas l'étape cinétique déterminante et enfin (3) que la nature des deux cycles est à prendre en compte pour déterminer la sélectivité du réarrangement de Stevens.

[7] Vial, L.; Gonçalves, M.-H.; Morgantini, P.-Y.; Weber, J.; Bernardinelli, G.; Lacour, J. *Synlett* **2004**, 1565-1568. Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 1167-1169

**Abbreviations**

br s: broad singlet signal
d: doublet
*Maj*: Major
*min*: minor
m: multiplet
NMR: Nuclear Magnetic Resonance
ppm: part per million
s: singlet
t: triplet
VT: Variable Temperature

aq.: aqueous
cat.: catalyst
conc.: concentration
conf.: conformation
conv.: conversion
D: Deuterium atom
d.e.: diastereomeric excess
d.r.: diastereomeric ratio
DBB: Double Bridged Biphenylazepinium
e.e.: enantiomeric excess
e.r.: enantiomeric ratio
endo: endocyclic
equiv.: equivalent
exo: exocyclic
H: Hydrogen atom
*rac*: racemic
R.T.: Room Temperature
Ts: tosyl
ToC: Transfer of Chirality
Tf: trifluoro

CSP: Chiral Stationary Phase
CD: Circular Dichroism
DFT: Density Functional Theory
ES-MS: Electrospray Mass Spectra
IR: InfraRed
M.p.: Melting point
ORD: Optical Rotation Dispersion
UV: Ultraviolet

$CH_3CN$: acetonitrile
AIBN: azobisisobutyronitrile
NBS: *N*-bromosuccinimide
$CHCl_3$: chloroform
DBU: 1,8-diazabicyclo[5.4.0]undec-7ene
$CH_2Cl_2$: dichloromethane
$Et_2O$: diethyl ether
NDMBA: *N*,*N*'-dimethylbarbituric acid
DMF: *N*,*N*-dimethylformamide
DMSO: dimethylsulfoxide
dppp: 1,3-bis(diphenylphosphino)-propane
HCl: hydrogen chloride
*i*-PrOH: isopropanol
MeOH: methanol
PhLi: phenyllithium
*t*-BuOK: potassium *tert*-butoxide
KBr: potassium bromide
$K_2CO_3$: potassium carbonate
KI: potassium iodide
NaOH: sodium hydroxide
THF: tetrahydrofuran
Tol: toluene
TFA: trifluoroacetic acid

**Symbols**

δ: chemical shift

ΔΔδ: difference of magnitude

$\Delta G^{\neq}$: energy of activation

$\Delta H^{\neq}$: enthalpy of activation

$\Delta S^{\neq}$: entropy of activation

ε: extinction coefficient

λ: wavelength

*c*: concentration

*J*: coupling constant

$t_{1/2}$: half life

$t_R$: retention time

T: Temperature

**Units**

°: degree

°C: degree Celsius

K: Kelvin

Hz: Hertz

J: Joule

kcal: kilocalorie

µl: microliter

mL: milliliter

µmol: micromole

mmol: millimole

mg: milligrams

M: Molarity

Å: Angstrom

nm: nanometers

s: second

min: minute

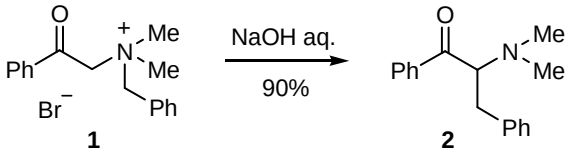
h: hour

# Chapter I

# On the [1,2]-STEVENS REARRANGEMENT

## Introduction

In 1928, Stevens and co-workers[1] discovered a novel [1,2]-shift reaction of ammonium ylides while investigating amine-protecting groups. Stevens reported the first example of a reaction, in which the treatment of a quaternary ammonium salt **1** (the phenacylbenzyldimethyl-ammonium bromide) with sodium hydroxide provided the tertiary amine product **2** (the 2-(dimethylamino)-3-phenylpropiophenone) by migration of the benzyl group from the nitrogen atom towards the adjacent carbon and this, in a good yield (90%, *Equation I-1*).




**1** **2**

*Equation I-1*: First example of the Stevens rearrangement.

This type of reaction, now commonly referred to as the [1,2]-Stevens rearrangement, has been extended to many non-allylic quaternary ammoniums[2] and has the unique ability to generate many different types of nitrogen containing compounds. Since its discovery, this spontaneous transformation has been extensively studied for its interesting mechanism and for its synthetic utility.[3] Examples of such a rearrangement have been chosen to illustrate the wide use of this reaction for the synthesis of biologically active compounds,[4] especially natural products belonging to different classes of alkaloids.

[1] Stevens, T. S.; Creigton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193-3197

[2] For allylic quaternary ammoniums see some examples of the [2,3]-Stevens rearrangement: Somfai, P.; Panknin, O. *Synlett* **2007**, 1190-1202. Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, 4214-4223. Armstrong, A.; Challinor, L.; Cooke, R. S.; Moir, J. H.; Treweeke, N. R. *J. Org. Chem.* **2006**, *71*, 4028-4030. Tayama, E.; Tanaka, H.; Nakai, T. *Heterocycles* **2005**, *66*, 95-99. Roberts, E.; Sancon, J. P.; Sweeney, J. B. *Org. Lett.* **2005**, *7*, 2075-2078. Rowlands, G. J.; Kentish Barnes, W. *Tetrahedron Lett.* **2004**, *45*, 5347-5350. Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3312-3324. Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. J. *J..Chem. Soc., Perkin Trans. 1* **2001**, 3325-3337. Arbore, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236-238. Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2951-2952

[3] Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043-1062. Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M.;Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. 3, pp 913-974. Lepley, A. R.; Giumanini, A. G. In Thygarajan, B. S., Ed.; *Mechanisms of Molecular Migrations*; Interscience: New York, **1971**; Vol. 3, pp 297-440. Pine, S. H. *Org. React.* **1970**, *18*, 403-464

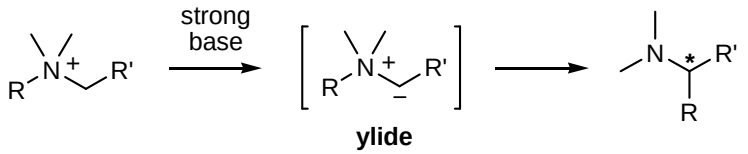
[4] Some of these examples could have also been selected for the later mechanistic discussions, and *vice-versa*.

# I-1 Synthetic applications of the [1,2]-Stevens rearrangement of ammonium ylides

### *I-1.1 Some examples of [1,2]-Stevens rearrangements induced by the base*

I-1.1.a Base-induced ylide generation

The earliest and most commonly used methods for the ylide generation which is necessary for the [1,2]-Stevens rearrangement, were conducted by treating quaternary ammonium ions with a strong base (*Scheme I-1*). This approach provides the formation of new C−C bonds and a new stereogenic centre adjacent to nitrogen through a [1,2]-shift of one of the quaternary ammonium substituents to the neighbouring ylide carbon. This way has been often applied for the synthesis of several heterocyclic compounds presenting considerable biological interests.




*Scheme I-1*: Principle of the [1,2]-Stevens rearrangement from quaternary ammonium cations.

I-1.1.b Approaches to the morphine core and isopavines

For instance, Cheng[5] and Hanessian[6] have both employed the Stevens rearrangement in their respective approaches to morphine and isopavines. Recently, Liou and Cheng[5] used such a rearrangement in their synthetic novel route to related desoxycodeine-D, a potent analgesic alkaloid containing a rigid pentacyclic skeleton of morphine (*Figure I-1*).

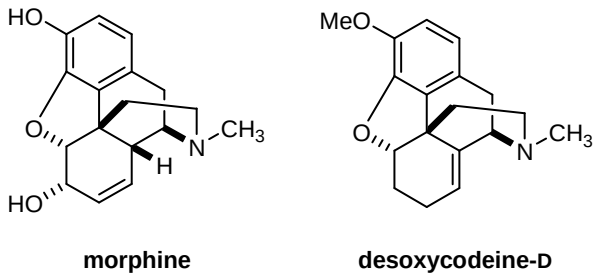
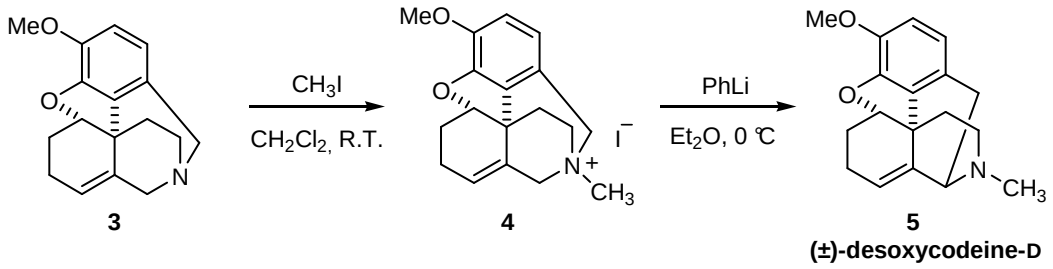



*Figure I-1*

[5] Liou, J.-P.; Cheng, C.-Y. *Tetrahedron Lett.* **2000**, *41*, 915-918
[6] Hanessian, S.; Parthasarathy, S.; Mauduit, M.; Payza, K. *J. Med. Chem.* **2003**, *46*, 34-48. Hanessian, S.; Mauduit, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3810-3813

Prompted by Kametani's[7] important prior works concerning the Stevens rearrangement of quaternary tetrahydroisoquinoline alkaloids, compound **3** was first converted by alkylation into the corresponding *N*-methylammoniumiodide **4** which was then treated with phenyllithium in ether (*Scheme I-2*). Much to the delight of Liou and Cheng,[5] quaternary ammonium cation **4** underwent the anticipated Stevens rearrangement and provided (±)-desoxycodeine-D **5** possessing the morphine core (83% yields in two-steps).




*Scheme I-2*: Approach to the morphine core by Cheng.

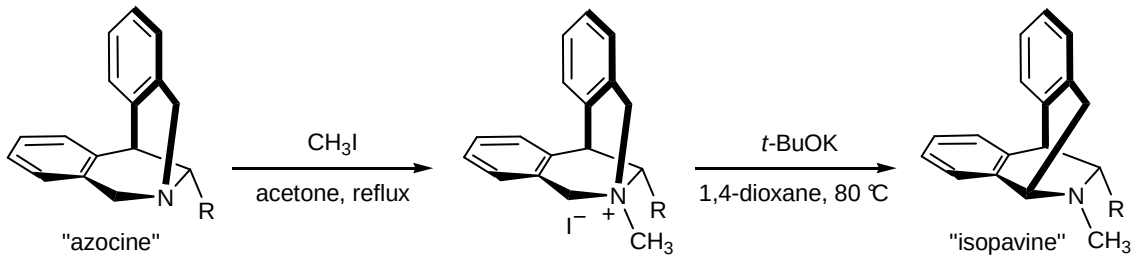
Hanessian and Mauduit[6] applied the Stevens rearrangement in a similar manner in their approach to the asymmetric synthesis of isopavine alkaloids. Isopavines and pavines have been associated with varying pharmacological properties[8,9] pertaining to Alzheimer disease, Parkinson disease and Down's syndrome.

First, the authors have reported several examples of highly stereocontrolled, diastereoselective [1,2]-Stevens rearrangements of 13-substituted dihydro methanodiarylazocines **6a–h**, which are readily available from *α*-amino acids to give 6-substituted enantiopure isopavines **8a–h** (*Scheme I-3*). The methylation of the individual azocine analogues **6a–h** afforded the corresponding quaternary ammonium salts **7a–h**. Subsequently, treatment under basic conditions led to the formation of the desired [1,2]-shift rearranged products **8a–h**. In general, moderate to good yields were obtained for the two-step process.

[7] Kametani, T.; Ujiie, A.; Huang, S.-P.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 394-397. Kametani, T.; Huang, S.-P.; Koseki, C.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1977**, *42*, 3040-3046. Kametani, T.; Huang, S. P.; Koseki, C.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1977**, *42*, 3040-3046. Kametani, T.; Huang, S.-P.; Ujiie, A.; Ihara, M.; Fukumoto, K. *Heterocycles* **1976**, *4*, 1223-1228. Kametani, T.; Kobari, T.; Fukumoto, K.; Fujihara, M. *J. Chem. Soc.* **1971**, 1796-1800

[8] Nomoto, T.; Takayama, H. *Chem. Commun.* **1982**, 1113-1115. Takayama, H.; Nomoto, T.; Suzuki, T.; Takamoto, M.; Okamoto, T. *Heterocycles* **1978**, *9*, 1545-1548

[9] Monn, J. A.; Schoepp, D. D. *Annu. Rep. Med. Chem.* **1994**, *29*, 53-64. Gee, K. R.; Barmettler, P.; Rhodes, M. R.; McBurney, R. N.; Reddy, N. L.; Hu, L. Y.; Cotter, R. E.; Hamilton, P. N.; Weber, E.; Keana, J. F. W. *J. Med. Chem.* **1993**, *36*, 1938-1946




**a**: R=Me, 85%; **b**: R=iPr, 88%; **c**: R=$CH_2CH(CH_3)_2$, 78%; **d**: R=benzyl, 75%; **e**: R=$CH_2OH$, 55%; **f**: R=$CH_2CH_2OH$, 57%; **g**: R=$CH_2CH_2CH_2OH$, 65%; **h**: R=3-indolyl, 28% (yields over two steps).

*Scheme I-3*: Asymmetric syntheses of functionalised isopavines as morphinomimetics.

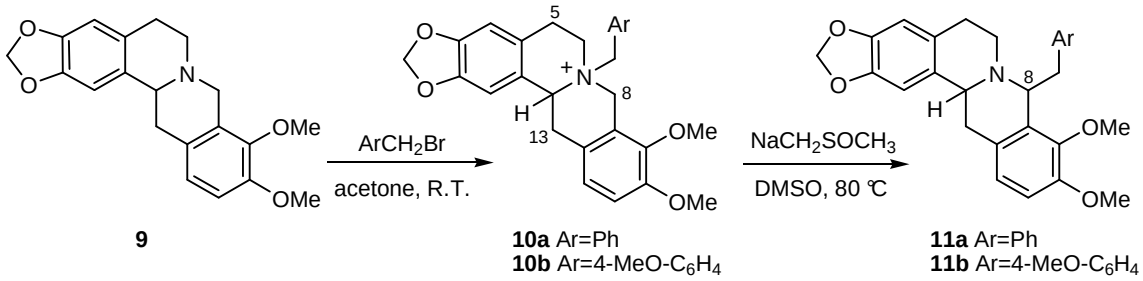
The same authors also developed the synthesis of more highly functionalised substrates with variations in the aromatic positions in an effort to determine the effect that aromatic substitution would have on this desired transformation. Thus, they obtained corresponding isopavines under the same conditions, in good yields, like previously. Furthermore, due to the structural similarity of the isolated isopavines to the morphine backbone, the authors chose to further extend this chemistry towards the synthesis of morphinomimetics.[10] The highly diastereoselective nature of the [1,2]-shift seen by Hanessian exemplifies the powerful nature of this rearrangement providing a ready access to pharmacologically interesting alkaloid natural products.

### I-1.1.c Synthesis of benzyltetrahydroprotoberberine alkaloids

Valpuesta and co-workers[11] have developed a short and efficient synthetic approach to 8-arylmethylberbines by using a regio- and stereoselective [1,2]-Stevens rearrangement (*Scheme I-4*). These 8-arylmethylberbine or tetrahydroprotoberberine alkaloids substituted in ring position 8 (like **11a–b**) constitute an uncommon group of isoquinoline alkaloids that have been isolated from several achiral sources and presenting a variety of biological activities.

[10] Filizola, M.; Villar, H. O.; Loew, G. H. *Bioorg. Med. Chem.* **2001**, *9*, 69-76. Hruby, V.; Gehrig, C. A. *Med. Res. Rev.* **1989**, *9*, 343-401

[11] Valpuesta, M.; Diaz, A.; Suau, R.; Torres, G. *Eur. J. Org. Chem.* **2004**, 4313-4318




*Scheme I-4*: Diastereoselective [1,2]-Stevens rearrangement of benzyltetrahydro-protoberberinium cations.

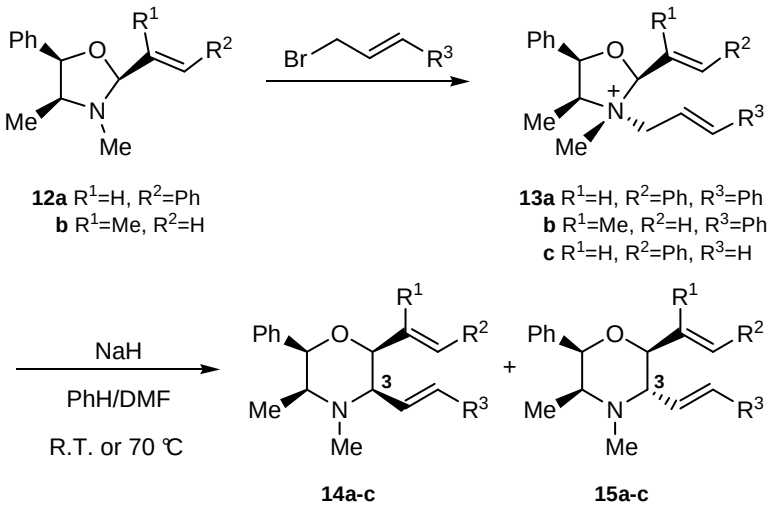
The syntheses of these *N*-arylmethylberberinium salts **10a–b** were achieved following standard conditions from (±)-canadine **9** (alkylation with benzyl bromides and subsequent base treatment). Both products were obtained as a mixture of *cis* and *trans* diastereomers (*cis*-**10a**/*trans*-**10a**, 8:1; *cis*-**10b**/*trans*-**10b**, 4:1, *Scheme I-4*). The major *cis* diastereomers were separated by fractional crystallisation.

Treatment of these *N*-arylmethylberberinium salts **10a–b** with a strong base, dimsylsodium in highly polar non-protic solvent DMSO, afforded the formation of tertiary amines **11a–b** through a nitrogen ylide formed at C-8 and a [1,2]-Stevens rearrangement. This method avoided the competition of alternative reactions such as Hofmann elimination which would occur by hydrogen removal at C-5 and C-13. Interestingly, the diastereomers were isolated in a ratio similar to the *cis*/*trans* ratio of the starting material as predicted by stereochemical control of the rearrangement. Thus, two new non-natural 8-arylmethylberbines **11a–b** were obtained stereoselectively by Stevens rearrangement of the corresponding quaternary ammonium ylides.

### I-1.1.d Synthesis of enantiopure morpholines from oxazolidines

A recent publication by Pedrosa and co-workers[12] has provided a novel entry to enantiopure morpholines (*Scheme I-5*) by the diastereoselective Stevens rearrangement of chiral 1,3-oxazolidinium salts.

[12] Pedrosa, R.; Andres, C.; Delgado, M. *Synlett* **2000**, 893-895




**12a** $R^1$=H, $R^2$=Ph
**b** $R^1$=Me, $R^2$=H

**13a** $R^1$=H, $R^2$=Ph, $R^3$=Ph
**b** $R^1$=Me, $R^2$=H, $R^3$=Ph
**c** $R^1$=H, $R^2$=Ph, $R^3$=H

**14a-c** **15a-c**

*Scheme I-5*: Diastereoselective [1,2]-Stevens rearrangement to access enantiopure morpholines.

(–)-Ephedrine-derived oxazolidines **12a–b** were first converted into oxazolidinium bromides as 3:1 mixture of diastereomers at the nitrogen centre. The major quaternary ammonium isomers, the *trans* **13a–c**, isolated and purified, were then treated under basic conditions to lead to the rearranged products **14a–c** and **15a–c**. However, these *ring-expanded* morpholine derivatives were obtained in moderate yields (60-65%) as a 2:1 mixture of diastereomers at C-3. This methodology presented by Pedrosa and co-workers[12] represents a stereoselective way to enantiopure morpholines through regioselective formation of ylides and chirality transfer from nitrogen to carbon in 1,3-oxazolidinium salts.

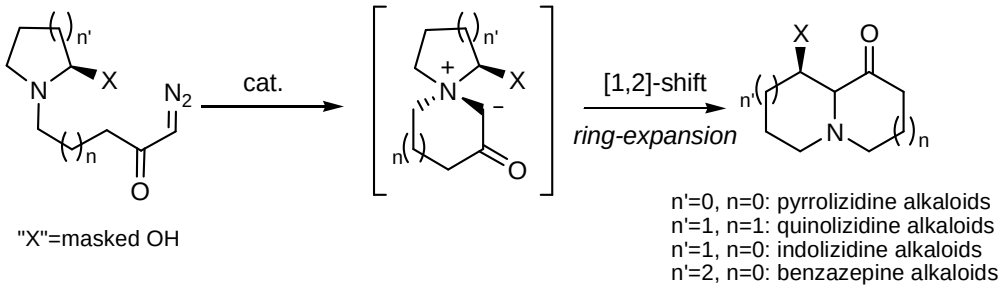
### *I-1.2 Some examples of [1,2]-Stevens rearrangements via metallocarbenes*

#### I-1.2.a Ylide generation via metallocarbenes

Another efficient protocol to access a variety of amine-containing natural products is the formation of metallocarbenoid/spirocyclic ammonium ylides and the subsequent *ring-expansion* occurring with [1,2]-Stevens rearrangement (*Scheme I-6*).[13] It is a viable alternative to base-promoted ammonium ylide formation. Here the ammonium ylides are generated by reaction of tertiary amines with metallocarbenes produced by the decomposition of diazo

[13] (a) West, F. G.; Clark, J. S. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. S., Ed.; Oxford University Press: Oxford, **2002**; pp 115–134. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, **1998**. (c) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263-309. (d) For reviews regarding metallocarbene-mediated processes, see: Padwa, A. *Molecules* **2001**, *6*, 1-12. Padwa, A. *J. Organomet. Chem.* **2000**, *610*, 88-101. Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121-158. Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223-269

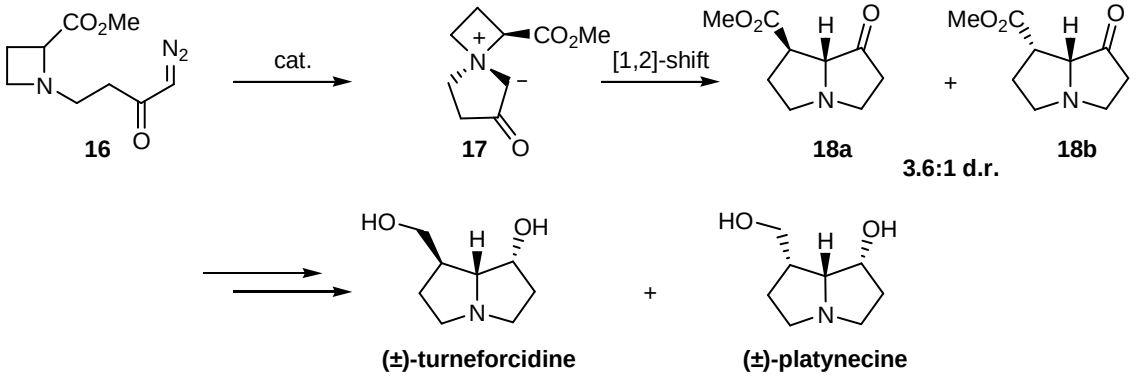
compounds and transition metal catalysts, $Rh(OAc)_4$ or $Cu(acac)_2$ in particular. This methodology has been also nicely exploited for the synthesis of a number of alkaloids.




*Scheme I-6*: Principle of the [1,2]-Stevens rearrangement from metallocarbenoids.

I-1.2.b Synthesis of pyrrolizidine alkaloids

West and Vanecko[14] have for instance employed this *ring-expansion* methodology for a rapid access to the pyrrolizidine ring system (*Scheme I-7*). Azetidinecarboxylate ester **16** reacted readily with rhodium or copper catalysts to generate a metallocarbene intermediate. Attack of the electrophilic metallocarbene by the nucleophilic tertiary amine provided the azetidinium ylide **17**, after dissociation of the metal. Efficient [1,2]-shift of the ester-substituted carbon furnished *ring-expanded* pyrrolidine products **18a** and **18b** in excellent yields, as a 3.6:1 mixture of diastereomers. Subsequent reactions provided access to the pyrrolizidine alkaloids (±)-turneforcidine and (±)-platynecine *via* a high-yield five-step sequence starting with readily available methyl 1-benzylazetidine-2-carboxylate.



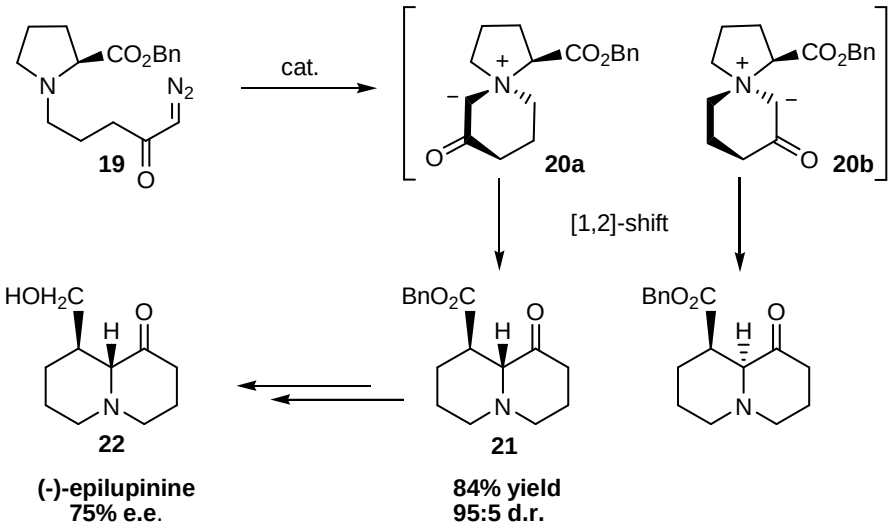

*Scheme I-7*: Synthesis of pyrrolizidine alkaloids.

[14] Vanecko, J. A.; West, F. G. *Org. Lett.* **2005**, *7*, 2949-2952

I-1.2.c Synthesis of quinolizidine alkaloids

• **Synthesis of epilupinine**

In this context, West and Naidu[15] applied the Stevens *ring-expansion* methodology described in the previous paragraph, in an efficient total synthesis of a quinolizidine alkaloid: the epilupinine (*Scheme I-8*).

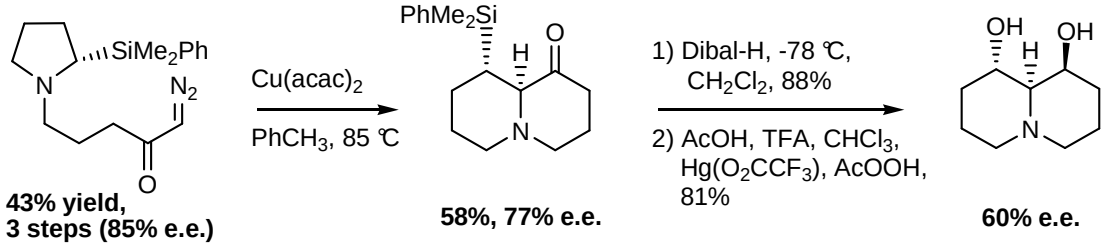



*Scheme I-8*: Synthesis of (–)-epilupinine from *L*-proline benzyl ester.

As described in *Scheme I-8*, diazoketone **19** available in two-steps from *L*-proline benzyl ester was treated with copper and rhodium catalysts to preferentially form the diastereomeric spiro-cyclic ylide **20a** over **20b**. This, following a [1,2]-Stevens rearrangement provided the desired quinolizidine ring system **21**, in high yield (84%) and with good diastereoselectivity (95:5). Having achieved high levels of diastereoselectivity, the authors examined the enantiomeric excess (e.e.) of this major diastereomer. Using a NMR chiral-solvating reagent, the resulting quinolizidine **22** was obtained after three-steps with an enantiomeric excess of 75%.

**• Hydroxylated quinolizidines via silyl-directed Stevens [1,2]-shift**

Recently, West and Vanecko[16] developed a variation of the just detailed methodology.[15] The authors were interested in finding a directing group for the regioselective [1,2]-Stevens rearrangement, other than a carboxylate ester, that could serve as a hydroxyl group surrogate. They chose to examine silyl groups as potential [1,2]-shift directing moieties based on previous examples showing that silyl groups can stabilise adjacent radical centres;[17] subsequent Fleming–Tamao[18] oxidation reaction converting possibly the silanes to hydroxyl groups (*Scheme I-9*). Moreover, synthesis of the necessary silyl substituted pyrrolidines could rely on the asymmetric lithiation chemistry.[19]




*Scheme I-9*: Silyl groups as potential [1,2]-shift directing groups.

With this method, West and Vanecko achieved a novel silyl-directed Stevens rearrangement and applied it to the stereoselective construction of hydroxylated quinolizidines (*Scheme I-9*).

I-1.2.d Approach to indolizidine alkaloids

Saba and co-workers[20] recently utilised the same tandem metallocarbenoid/ammonium ylide/ [1,2]-Stevens rearrangement in their approach to swansonine analogues which belong to an important class of biologically active natural and unnatural chiral polyhydroxylated alkaloids (*Scheme I-10*).

[15] Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565-16574. West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420-8421

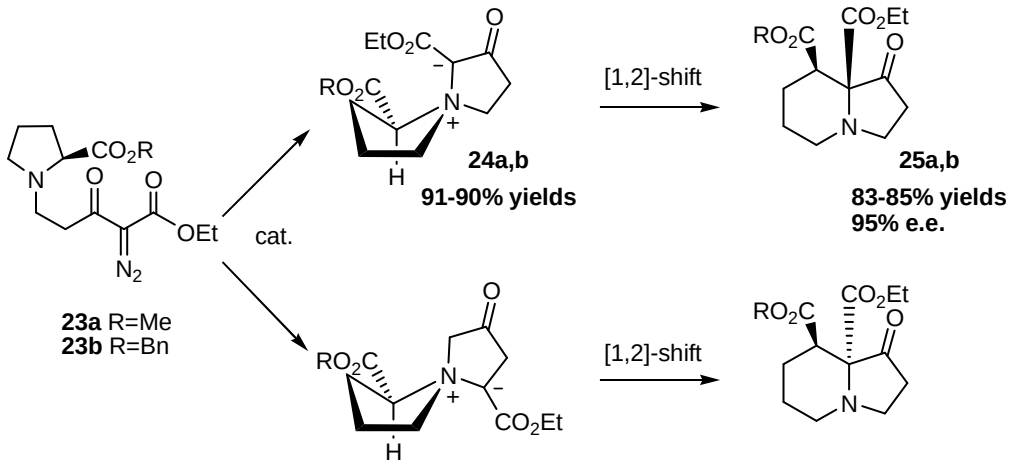
[16] Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813-2816

[17] Manabe, T.; Yanagi, S.-i.; Ohe, K.; Uemura, S. *Organometallics* **1998**, *17*, 2942-2944. Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281-287

[18] Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599-7662. Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1-64

[19] Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139-176. Clayden, J. *Top. Organomet. Chem.* **2003**, *5*, 251-286. Hodgson, D. M.; Tomooka, K.; Gras, E. *Top. Organomet. Chem.* **2003**, *5*, 217-250. Normant, J. F. *Top. Organomet. Chem.* **2003**, *5*, 287-310. Toru, T.; Nakamura, S. *Top. Organomet. Chem.* **2003**, *5*, 177-216

[20] Muroni, D.; Saba, A.; Culeddu, N. *Tetrahedron* **2006**, *62*, 1459-1466. Muroni, D.; Saba, A.; Culeddu, N. *Tetrahedron: Asymmetry* **2004**, *15*, 2609-2614




*Scheme I-10*: Saba's approach to indolizidine alkaloids.

*L*-Proline derived substrates **23a–b** bearing the nitrogen atom tethered to an $\alpha$-diazoketoester chain, were converted into stable isolable [5,5]-spirocyclic ammonium ylides **24a** and **24b** in very good yields (91-90% respectively) but with moderate diastereoselectivity, using two transition metal catalysts and various reaction conditions. The thermal reaction for each of the ylides **24a** and **24b** afforded the *ring-expanded* indolizidines **25a** and **25b** as pure diastereomers, in good yields (83-85%) and high enantiomeric excess (95%).

I-1.2.e Synthesis of benzazepine alkaloids

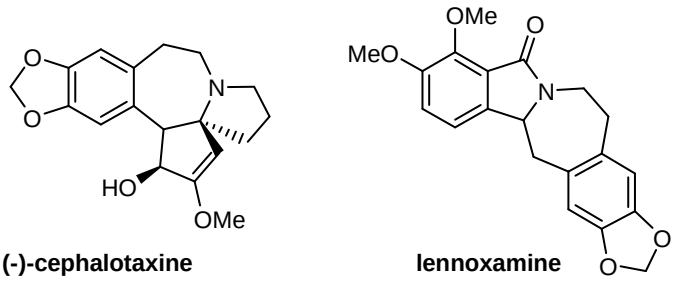
Over the past few years, the group of Prof. Padwa[21] has developed facile routes for the synthesis of tetrahydroisoquinoline and benzazepine ring systems containing fused five-membered rings present in many natural products. Tandem intramolecular formation of metallocarbenoids and [1,2]-Stevens rearrangement of spirocyclic ammonium ylides have been examined for the synthesis of 5,7-fused benzazepine skeletons and particularly in cephalotaxine **26** (*Figure I-2* and *Scheme I-11*).

Cephalotaxine is the major alkaloid constituent isolated from *Cephalotaxus harringtonia*[22] and is of considerable interest due to the biological activity of its ester derivatives.[23]

[21] Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414-2421. Beall, L. S.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4159-4162

[22] Wickremesinhe, R. M.; Arteca, R. N. J. *Liq. Chrom. & Rel. TechnoL* **1996**, 19, 889

[23] Hudlicky, T.; Kwart, L. D.; Reed, J. W. In *Alkaloids. Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer Verlag: New York, **1987**; Vol. 5, Chapter 5

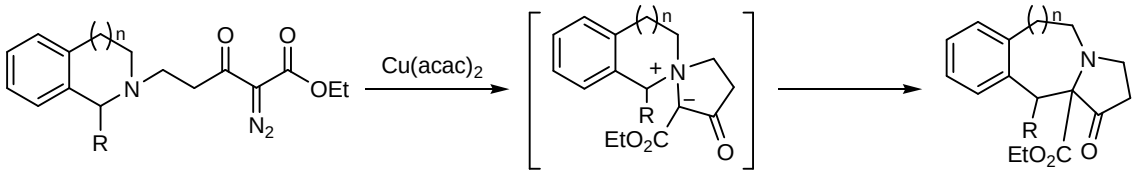



**(-)-cephalotaxine** **26**

**lennoxamine** **30**

*Figure I-2*

Treatment of diazoacetate compounds **27a–d** with $Cu(acac)_2$ as catalyst furnished the rearranged 5,7-fused systems **28a–d** in good yields (68%-77%), both compounds **29c** and **29d** consisted of a 1:1 mixture of diastereomers. The formation of these *ring-expanded* products can be attributed to the initial formation of intermediate ammonium ylide **28** followed by a preferential Stevens [1,2]-shift of the benzylic carbon atom.[24]




**27a** n=0, R=H
**b** n=1, R=H
**c** n=1, R= $CH_3$
**d** n=1, R=($CH=CHCH_3$)

**28**

**29a** 68%
**b** 73%
**c** 77%
**d** 77%

*Scheme I-11*: Padwa's approach to benzazepine alkaloids.

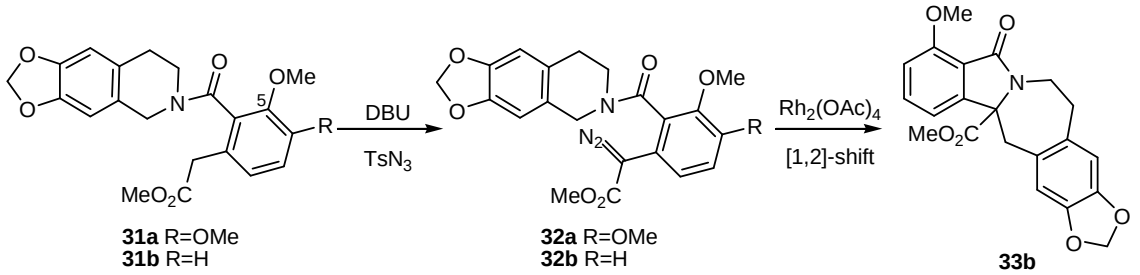
Padwa and co-workers[21] also carried out model studies toward the synthesis of lennoxamine **30**, an interesting member of the isoindolobenzazepine family of alkaloids, which was isolated from the Chilean barberries (*Figure I-2*).

Initial efforts to convert **31a** to the corresponding diazo compound **32a** were unsuccessful (*Scheme I-12*). The authors attribute this lack of reactivity to the diminished acidity of the benzylic protons due to the methoxy group in the 5-position of the aromatic ring.

Indeed, conversion of the related amide **31b** provided the desired amido diazoester **32b** in 88% yield without any of the difficulties associated with the previous series. Treatment of **32b** with $Rh_2(OAc)_4$ furnished the desired *ring-expanded* lactam **33b** in good yield (75%).

[24] For a similar reaction in the 6,6-system, see: Zaragoza, F. *Synlett* **1995**, 237-238

Although **33b** lacks the additional methoxy group necessary for the synthesis of lennoxamine, the examples substantiate the utility of this transformation in the formation of 5,7-fused nitrogen heterocyclic natural products.

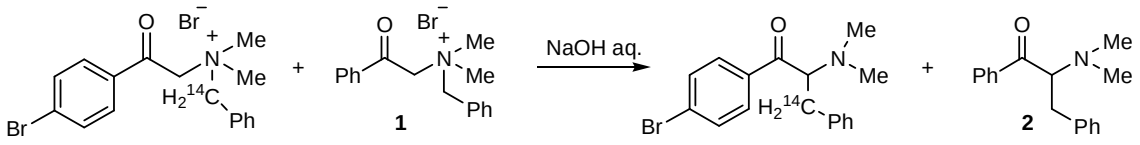



*Scheme I-12*: New route for the synthesis of 5,7-fused nitrogen heterocyclic natural products.

## I-2 Mechanism of the [1,2]-Stevens Rearrangement

Having seen the usefulness of the [1,2]-Stevens rearrangement, we will now detail the current knowledge on its mechanism. Indeed, over the years, several hypotheses have been considered for this one and we will present in a chronological order, key examples that have allowed chemists to test these assumptions.

First, mechanistic investigations using a $^{14}C$-labeled starting material with the quaternary ammonium salt **1**, found in the first example of the [1,2]-Stevens rearrangement, as well as *cross-over* experiments, demonstrated the reaction to be intramolecular because two products were isolated instead of four (*Scheme I-13*).[25]



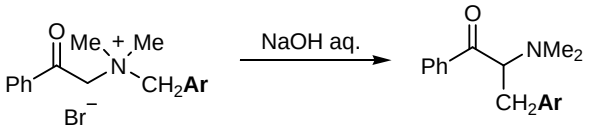

*Scheme I-13*: *Cross-over* experiment.

A variety of groups including allyl, propargyl and phenacyl were also shown to be good migrating groups in the Stevens rearrangement.[26] Moreover, subsequent studies of the effect of substituents on the phenyl ring of the benzyl group of compound **1** have demonstrated that

[25] Johnstone, R. A. W.; Stevens, T. S. *J. Chem. Soc.* **1955**, 4487-4488. Stevens, T. S.; Snedden, W. W.; Stiller, E. T.; Thomson, T. *J. Chem. Soc.* **1930**, 2119-2125. Stevens, T. S. *J. Chem. Soc.* **1930**, 2107-2119

[26] Dunn, J. L.; Stevens, T. S. *J. Chem. Soc.* **1934**, 279-282. Thomson, T.; Stevens, T. S. *J. Chem. Soc.* **1932**, 1932-1940

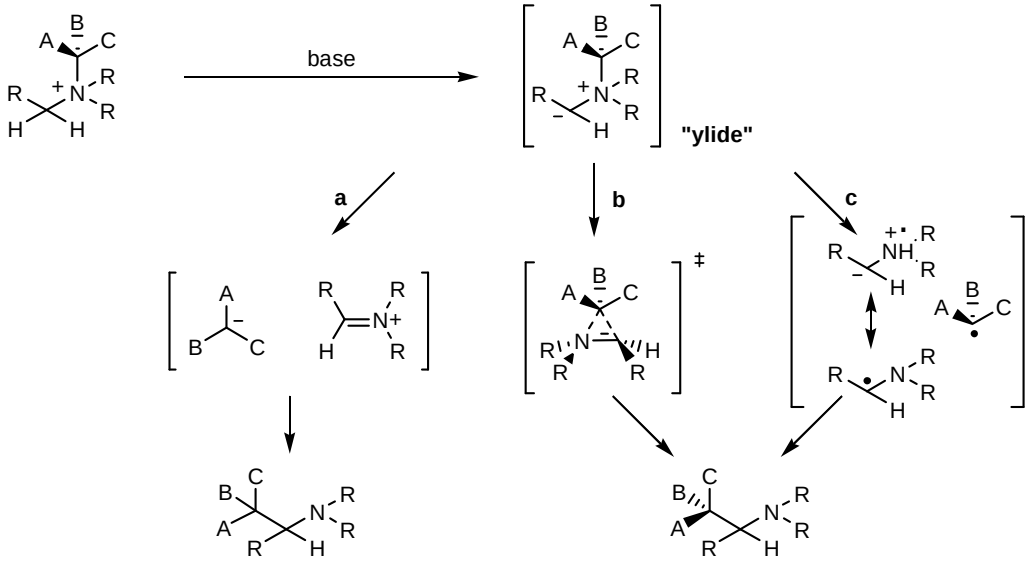
the migrating ability increases when electron-poor substrates rather than electron-rich are present. The following order of reactivity was determined: *p*-$NO_2$ > *p*-Cl > *p*-Me > *p*-OMe (*Figure I-3*).[27]




| **Ar** | 4-methoxyphenyl | phenyl | 4-methylphenyl | 4-chlorophenyl | 4-nitrophenyl |
|---|---|---|---|---|---|
| **relative rate** | 0.76 | 1.00 | 1.06 | 2.65 | 73.0 |

*Figure I-3*: Substituent effect on the rate of the Stevens rearrangement.

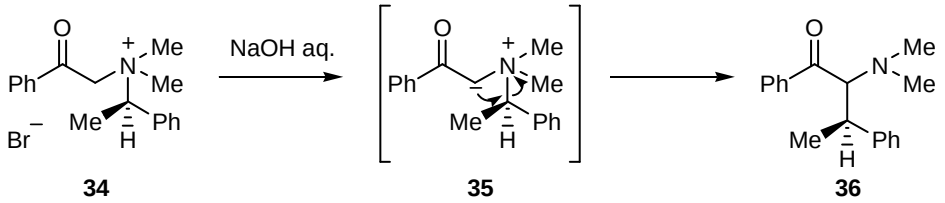
These observations led Stevens to postulate that the reaction proceeds by initial formation in $\alpha$ to the nitrogen, of an ylide which then gives an anion and an iminium ion after a heterolytic fragmentation. A recombination of this ion pair provides the observed product in *Scheme I-14* (path **a**).




*Scheme I-14*: Possible pathways concerning the mechanism of the [1,2]-Stevens rearrangement.

[27] Thomson, T.; Stevens, T. S. *J. Chem. Soc.* **1932**, 55-69. Dunn, J. L.; Stevens, T. S. *J. Chem. Soc.* **1932**, 1926-1931

In 1947, Kenyon[28] showed that the migrating stereogenic group retained its configuration during the course of the rearrangement. The optically-active ammonium salt **34** was converted into an enantiopure amine **36** with retention of configuration at the stereogenic benzylic carbon atom (*Scheme I-15*).



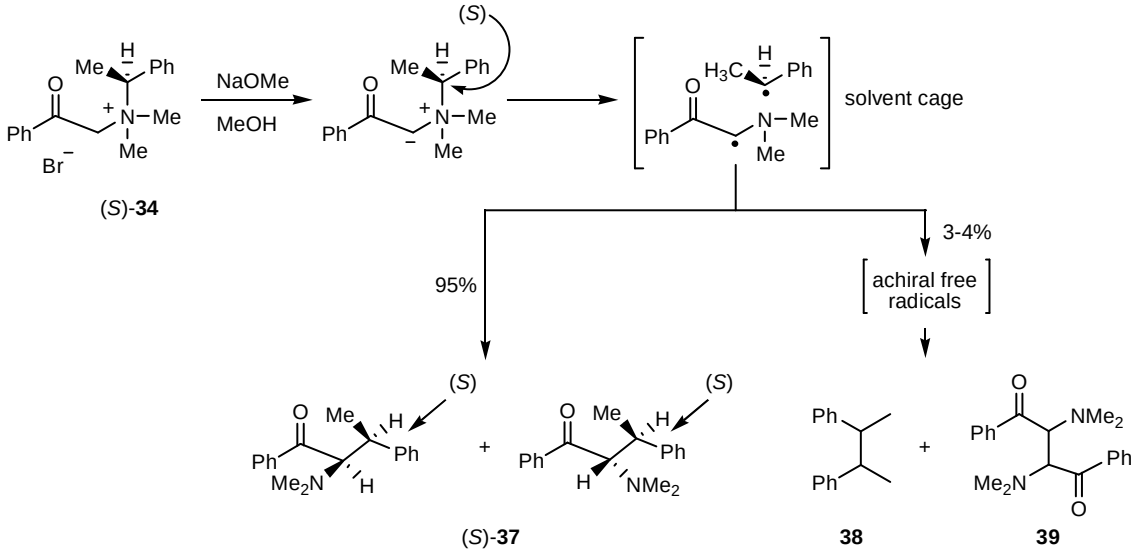

*Scheme I-15*: First stereoselective Stevens rearrangement.

Wittig[29] and Hauser[30] proposed that the reaction was a concerted intramolecular displacement of the migrating group by the carbanionic centre of the ylide **35** (*Scheme I-15* and *Scheme I-14*, path **b**). Therefore, the hypothesis of an ion pair intermediate was turned down because according to them, this implicated a full loss of the chiral information on the shifted carbon.

However, if the Stevens rearrangement was a concerted reaction, then according to the Woodward and Hoffmann rules of conservation of orbital symmetry, it should be a symmetry-forbidden reaction.[31,32] Indeed, if the reaction proceeded *via* a *suprafacial-antarafacial* mode, inversion of configuration at the migrating centre should result, which was against Kenyon's observations. In fact, a high degree of retention of configuration was observed not only by Kenyon[28], but by Brewster[33] as early as 1952. Schollkopf[34] and Stevens[35] performed the reaction again and found it to advance with at least 95% of enantiomeric excess. The same conclusion was reached by Lown[36] several years later using optically-active benzylamine.
This assumption that the *antarafacial* mode of reactivity ought to be translated into a change of configuration of the migrating group, only came from this period of time. It will be reassessed at the end of this Ph.D.

[28] Campbell, A.; Houston, A. H. J.; Kenyon, J. *J. Chem. Soc.* **1947**, 93-95
[29] Wittig, G.; Mangold, R.; Felletschin, G. *Justus Liebig Ann. Chem.* **1948**, *560*, 116-127
[30] Hauser, C. R.; Kantor, S. W. *J. Am. Chem. Soc.* **1951**, *73*, 1437-1441
[31] Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781. Woodward, R.B.; Hoffman, R. *The Conservation of the Orbital Symmetry*; Academic Press: New-York; **1970**
[32] Dewar, M. J. S.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1839-1844
[33] Brewster, J. H.; Kline, M. W. *J. Am. Chem. Soc.* **1952**, *74*, 5179-5182
[34] Schollko.U; Ludwig, U.; Osterman.G; Patsch, M. *Tetrahedron Lett.* **1969**, 3415
[35] Millard, B. J.; Stevens, T. S. *J. Chem. Soc.* **1963**, 3397
[36] Lown, J. W.; Akhtar, M. H. *J. Chem. Soc., Chem. Com.* **1973**, 511-513

Later on, Ollis re-examined the reaction and demonstrated in a very elegant manner that the Stevens rearrangement can also happen by a non-concerted mechanism, involving radical pair intermediates. Indeed, Ollis proposed this mechanism after observations of Chemically Induced Dynamic Nuclear Polarisation[37] (CIDNP) effects and the studies of the secondary products of Stevens rearrangement.[38] Ollis remarked that the enantiomeric ammonium salt (*S*)-**34** rearranged to form three products **37**, **38**, **39** in an 80:11:5 ratio (*Scheme I-16*). The retention of the configuration (95%) on the amine **37** was confirmed and the secondary products (alkane **38** and diamine **39**) have been described as a mixture of racemate and meso adducts.




*Scheme I-16*: Radical pair mechanism, determination of secondary products generated during Stevens rearrangement.

After ylide generation, Ollis' mechanism involved a homolytic cleavage of the carbon-nitrogen bond to the most potentially carbon-centred radical, producing a radical pair held tightly together by a solvent cage. This step was followed by a rapid recombination to provide the major Stevens [1,2]-product **37**, where the migrating centre has retained its absolute stereochemistry (*Scheme I-16* and *Scheme I-14*, path **c**).

[37] Lowry, T.H.; Schueller Richardson, K. *Mechanism and Theory in Organic Chemistry*; 3rd Ed.; Harper International Edition; **1987**

[38] Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009-1027. Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049-1061. Ollis, W. D.; Rey, M.; Sutherland, I. O.; Closs, G. L. *J. Chem. Soc., Chem. Commun.* **1975**, 543-545

This solvent cage/rapid recombination pathway would also account for the high degree of intramolecularity and stereoselectivity observed in this rearrangement. Radical escape provided achiral free radicals that combined to give racemic products **38** and **39**, their random recombination leading to the loss of the stereochemical information.

Nevertheless, nothing prevents us from thinking about the possible intervention of a solvent cage for the first heterolytic mechanism, proposed by Stevens. In this case, the retention of the configuration would occur if the recombination of the intermediates, iminium and benzylic anion, is fast.[39] So, we can consider that two types of intermediates – radical and/or ionic – can be implicated in the [1,2]-Stevens rearrangement depending on substrates and reaction conditions. However, Ollis' hypothesis in favour of a radical cleavage–recombination mechanism remains the most probable and the most considered in the literature, most chemists adhering to this theory.

## I-3 Selectivity of the [1,2]-Stevens Rearrangement

### *I-3.1 Preamble*

As just mentioned, the mechanism of the [1,2]-Stevens rearrangement is not trivial and a clear understanding has not been reached despite all the investigations and studies carried out on the process for the past decades; the mechanism of the [1,2]-Stevens rearrangement still being the subject of debates.

Furthermore, asymmetric versions of this reaction still remain a challenge probably reflecting the mechanistic difficulties of the process.[38,39] In fact, strict enantioselective [1,2]-Stevens rearrangements of quaternary ammonium ions have not been reported[40] so far, whereas many effective diastereoselective processes have been developed,[41] some of them being detailed in part I of this chapter.

[39] For mechanism involving ion pair see: Maeda, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1491-1493. Pine, S. H.; Catto, B. A.; Yamagish.Fg *J. Org. Chem.* **1970**, *35*, 3663

[40] For tertiary amines and in the context of *Lewis* acid-mediated enantioselective [2,3]-Stevens rearrangements, it was recently shown that competing [1,2]-rearrangements occur with decent enantioselectivity: Blid, J.; Panknin, O.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 1294-1300. Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352-9353

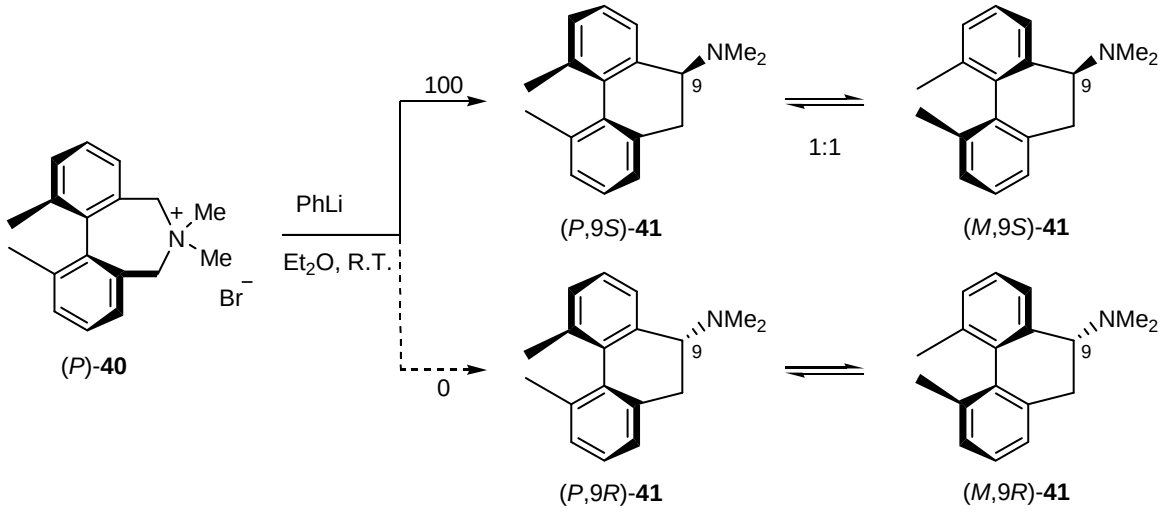
[41] See references in Chapter I-1: 2, 3, 8, 9, 14, 15, 16, 20, 22b. Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, 4214-4223. Harada, M.; Nakai, T.; Tomooka, K. *Synlett* **2004**, 365-367. Couty, F.; Durrat, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2004**, *45*, 7525-7528. Glaeske, K. W.; Naidu, B. N.; West, F. G. *Tetrahedron: Asymmetry* **2003**, *14*, 917-920. West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051-6056

### *I-3.2 Diastereoselective [1,2]-Stevens Rearrangements*

Two further examples of diastereoselective Stevens rearrangements, which are key for this Ph.D., are detailed below.

Previously, Mislow and al.[42] reported the [1,2]-Stevens rearrangement of *configurationally stable* bridged biphenylazepinium cation (*P*)-**40** (*Scheme I-17*). The enantiopure bromide salt of this quaternary ammonium cation reacted with a strong base (PhLi, in $Et_2O$, at 25 °C) to produce two optically-active diastereomers in a 1:1 ratio of (*P*,9*S*)-**41** and (*M*,9*S*)-**41**, whereas four products were theoretically possible.[43]

In fact, this reaction was diastereoselective and it involved a complete asymmetric transfer, the transfer of the axial chirality of the $C_2$-symmetric diphenylazepinium cation (*P*)-**40** to the stereogenic centre of tertiary amines **41**. However, the occurring ring-*contraction* decreased the level of the energetic barrier between the two biaryl atropisomers, leading to the formation of a mixture of two diastereomers, at room temperature, by rapid interconversion around the biphenyl pivot bound axis.[44] The configuration of the stereogenic centre created $\alpha$ to the nitrogen atom remained however constant.



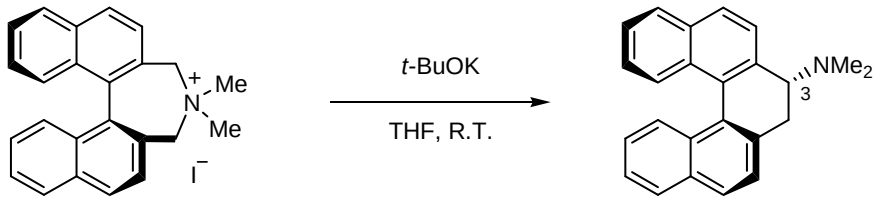

*Scheme I-17*: Diastereoselective Stevens Rearrangement of biphenyl ammonium cation.

[42] Joshua, H.; Gans, R.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4884-4892

[43] The other diastereomers are (*P*,9*R*)-**41** and (*M*,9*R*)-**41**.

[44] The presence of the stereogenic centre at C-9 carries out no control of the axial chirality.

Twenty-five years later, another example of [1,2]-Stevens rearrangement transforming a *configurationally stable* biarylazepinium ylide into a tertiary amine was described by Závada and co-workers[45] (*Equation I-2*). Treatment of the iodide salt of the binaphthyl ammonium cation (*P*)-**42** with a strong base (*t*-BuOK, in THF, at 25 °C) resulted in the exclusive formation (100% d.e.) of the corresponding rearranged product (*M*,3*R*)-**43**, revealing a total transfer of chirality. A full transfer of chirality has thus taken place from the biaryl axis of the diarylazepinium precursor **42** to the new $sp^3$ stereogenic centre. It was noted that the presence of naphthalenic cores induces, in this case, a high barrier of interconversion between the atropisomers.




(*P*)-**42** (*M*,3*R*)-**43**

*Equation I-2*: Diastereoselective Stevens Rearrangement of binaphthyl ammonium cation.

It is interesting to underline that in the two studies led by Mislow[42] and Závada,[45] biaryl ammonium ions with the same sense of axial chirality (*P* configuration) were used. Surprisingly, amines with exactly opposite stereochemistry for the newly-formed carbon-centre were obtained. This may be taken as a consequence of a *mechanistic dichotomy*. Furthermore, this observation may indicate that two stereochemically different pathways can participate in the Stevens rearrangement and that it can come from the structural differences between the substrates. Závada[45] suggested an explanation in terms of rotation around simple bonds and steric strains between the biaryl cycles. In the case of Mislow, the mechanism transfers the biaryl chirality with *configurational retention* (**40**→**41**) whereas in the case of Závada it occurs with *inversion* (**42**→**43**). Indeed, the former result would be due to a *suprafacial-suprafacial* concerted mechanism and the latter to a *suprafacial-antarafacial* non-concerted (radical and/or ion pair) mechanism.

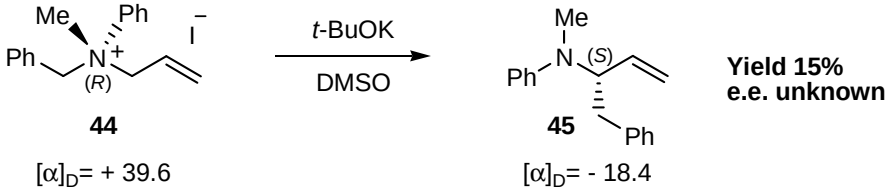
[45] Stará, I. G.; Starý, I.; Tichý, M.; Závada, J.; Hanuš, V. *J. Am. Chem. Soc.* **1994**, *116*, 5084-5088

### *I-3.3 Enantiospecific [1,2]-Stevens Rearrangements*

Although strict enantioselective [1,2]-Stevens rearrangements of quaternary ammonium ions are unknown so far,[40] enantiospecific transformations have been studied. Below, we present the examples of the literature.

The first example dates from 1966 by Hill and al.,[46] in which he demonstrated that the Stevens rearrangement of (+)-(*R*)-allylbenzylmethylphenylammonium cation **44** with *t*-BuOK in DMSO gave optically active (–)-(*S*)-3-(*N*-methylanilino)-4-phenylbutene-1 **45**, in low yield (15%, *Equation I-3*).

This example shows the first transfer of asymmetry from a stereogenic quaternary nitrogen atom to an adjacent carbon. Unfortunately, the degree of stereospecificity of the process was unknown as the enantiomeric excess of **45** was not determined during the course of the study.



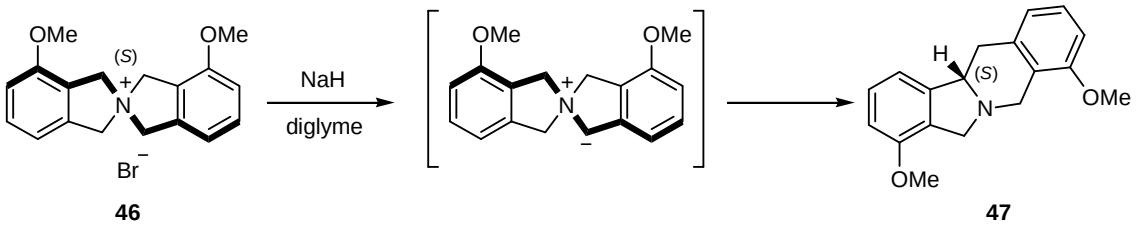

**44** $[\alpha]_D$= + 39.6

**45** $[\alpha]_D$= - 18.4

*Equation I-3*: First example of enantiospecific [1,2]-Stevens rearrangement of a quaternary ammonium cation containing a chiral centre on the nitrogen.

Later, Brewster[47] established that the pure (*S*)-isomer of the spiro quaternary ammonium **46** (*Scheme I-18*) treated under basic conditions (NaH in diglyme), underwent a [1,2]-Stevens rearrangement, to provide the optically-active tertiary amine **47** with an (*S*) absolute configuration. Bond-breaking and bond-making phases of Stevens rearrangement have happened on the two different rings of the spiro system, with a transfer of chirality from the stereogenic centre on the nitrogen to the newly-formed stereogenic carbon atom. Also in this case, the enantiomeric excess of the product **47** was unknown.

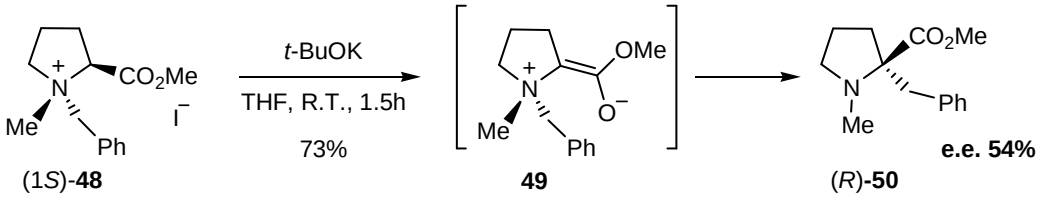
[46] Hill, R. K.; Chan, T. H. *J. Am. Chem. Soc.* **1966**, *88*, 866-867
[47] Brewster, J. H.; Jones, R. S. *J. Org. Chem.* **1969**, *34*, 354-358




**46** **47**

*Scheme I-18*: Enantiospecific transformation of a spiro quaternary ammonium ion.

In 1999, West and Glaeske[48] reported the [1,2]-Stevens rearrangement of proline-derived salts and of the (1*S*,2*S*)-*N*-benzylproline methyl ester–derived ammonium salt (1*S*)-**48**, in particular (*Scheme I-19*). This diastereomerically pure salt was synthesised from *N*-benzylproline methyl ester by a moderate selective alkylation with methyl iodide followed by three recrystallisations. Treatment of this quaternary ammonium salt (1*S*)-**48** under basic conditions with *t*-BuOK in THF afforded, *via* the planar ammonium ylide intermediate **49**, the rearranged product (*R*)-**50** by migration of the *N*-benzylic substituent to the adjacent carbon in a good yield (73%) and a moderate enantiomeric excess (54%).




(1*S*)-**48** **49** (*R*)-**50**

*Scheme I-19*: Asymmetric [1,2]-Stevens rearrangement of a proline derived cation.

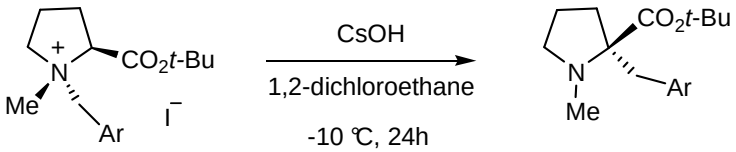
This enantiospecific transformation established clearly for the first time the occurrence of a loss of stereochemical information during the [1,2]-Stevens rearrangement. This methodology provided nevertheless an interesting stereoselective route to $\alpha$-quaternary amino acid derivatives albeit with a moderate level of N-to-C chirality transmission.

More recently, Tayama[49] applied the method described by West[48] to the [1,2]-Stevens rearrangement of the more hindered (1*S*,2*S*)-*N*-benzylproline *t*-butyl ester–derived ammonium

[48] Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31-33
[49] Tayama, E.; Nanbara, S.; Nakai, T. *Chem. Lett.* **2006**, *35*, 478-479

salt (1*S*)-**51a** (*Table I-1*). Using West's conditions (*t*-BuOK, THF) and diastereomerically pure (1*S*)-**51a**, the Stevens product (*R*)-**52a** was obtained in 80% yield and 72% of enantiomeric excess (e.e.). This already effective result was improved by applying biphasic (solid/liquid) conditions to the present rearrangement; CsOH as base and 1,2-dichloroethane solvent affording the best outcome (73% yield and 92% e.e.).

*Table I-1*: Enantiospecific [1,2]-Stevens rearrangement of *N*-(arylmethyl)proline ammonium cations induced by biphasic conditions.




(1*S*)-**51** (*R*)-**52**

| Ar | Product | Yield %[a] | e.e. %[b] |
|---|---|---|---|
| **51a**-$C_6H_5$ | **52a** | 73 | 92 |
| **51b**-*p*-Me-$C_6H_4$ | **52b** | 77 | 84 |
| **51c**-*p*-MeO-$C_6H_4$ | **52c** | 56 | 86 |
| **51d**-*p*-F-$C_6H_4$ | **52d** | 69 | 90 |
| **51e**-*p*-*t*-BuOCO-$C_6H_4$[c] | **52e** | 42[d] | >99 |

[a]Determined by $^1$H-NMR assay using mesitylene or diphenylmethane as an internal standard; [b]Determined by chiral HPLC analysis after reduction of **52** with $LiAlH_4$; [c]Performed at 0 °C; [d]*t*-Butyl *p*-toluate was isolated in 55% yield.

With this optimised biphasic procedure in hand, the rearrangements of several other *N*-(arylmethyl)proline ammonium salts (1*S*)-**51b**–**e** were carried out and the corresponding rearranged products (*R*)-**52b**–**e** were obtained with variable yields (42%-77%) and good enantiomeric excesses (84-99%), depending on the nature of the aryl substituent (*Table I-1*).
The enantioselectivity of the transfer of chirality thus depends upon the ionisation conditions and, to some extent, upon the migrating group. Therefore, when performed under proper biphasic conditions, the [1,2]-Stevens rearrangement exhibits an enhanced level of the

chirality transmission to afford the $\alpha$-substituted proline derivatives in high enantiopurities.[50] It is important to note that in all cases, recrystallisations are necessary at the stage of the formation of the stereogenic quaternary ammonium ions in order to remove minor diastereomeric salts. Without the purification prior to the Stevens rearrangement, lower levels of enantioselectivity are achieved.

West[48] and Tayama[49] proposed that after the formation of the ylide by deprotonation of the $\alpha$ stereogenic proton, the mechanism of [1,2]-Stevens rearrangement was followed by a homolytic fragmentation giving rise to a radical pair which recombines more rapidly in a solvent cage and hence more preferentially in the stereo-retentive fashion. Depending on the substrate and condition, the rate of radical pair recombination of the benzyl group from the same face is in competition with that of the diffusion to the opposite face or out of the solvent cage entirely.

### *I-3.4 Scope*

As already mentioned in this chapter, many useful diastereoselective and enantiospecific [1,2]-Stevens rearrangements of quaternary ammonium ions occurred with high asymmetric transfer. However strict enantioselective [1,2]-Stevens rearrangements have not been reported so far.

The goal of this thesis was to study a novel enantioselective approach that would not require the formation of any stereogenic quaternary nitrogen atom. This strategy allowed to reach possibly high levels of transfer of chirality and of enantioselectivity altogether, in the [1,2]-Stevens rearrangement.

[50] For preparations of $\alpha$-substituted proline derivatives, see: Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012-13013. Ferey, V.; Vedrenne, P.; Toupet, L.; LeGall, T.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 7244-7245

# Chapter II

# TOWARDS AN ENANTIOSELECTIVE [1,2]-STEVENS REARRANGEMENT

## II-1 A novel approach towards the realisation of enantioselective [1,2]-Stevens rearrangements

### *II-1.1 Problematic*

As just mentioned in chapter I, the development of an enantioselective variant of the [1,2]-Stevens rearrangement was a highly challenging task, in particular if one considers the most probable mechanism[1] of the reaction that involves diradical intermediates and the consequent risk of some loss of the chiral information, during the transformation. Despite these facts, the goal of this Ph.D. was to achieve such an enantioselective [1,2]-shift rearrangement. Considering the lack of previous success, it was necessary to develop a novel strategy.

### *II-1.2 Looking for a different approach*

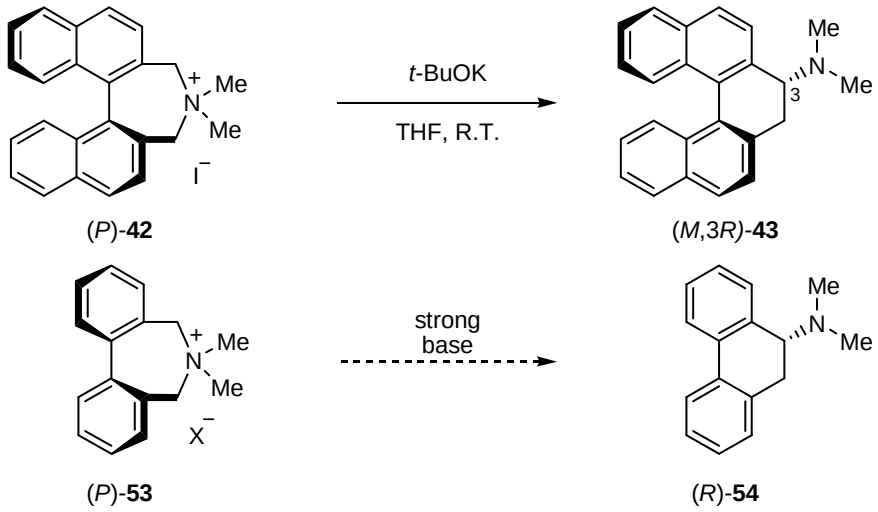
For the development of an enantioselective [1,2]-Stevens rearrangement, we considered that the effective diastereoselective processes of *configurationally stable* biaryl quaternary ammonium ylides, carried out by Mislow[2] and Závada[3] in particular, could be a good base to start our investigations (See chapter I-3.2). Indeed, during these studies, the authors have shown that [1,2]-Stevens rearrangement of *configurationally stable* biarylazepinium cations occurs readily upon ylide formation.[2,3] The reaction proceeds with high selectivity as, for instance, cations of type **42** (*Scheme II-1*) react with strong bases (PhLi, *t*-BuOK, etc.) to produce dihydrohelicenes of type **43** as single diastereomers (99% yield).[3] The transfer of chirality from the biaryl axis of the diarylazepinium percursor to the new $sp^3$ stereogenic centre is complete (*e.g.*, (*P*)-**42** to (*M*,3*R*)-**43**).

[1] Maeda, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1491-1493. Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009-1027. Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049-1061. Ollis, W. D.; Rey, M.; Sutherland, I. O.; Closs, G. L. *J. Chem. Soc., Chem. Commun.* **1975**, 543-545

[2] Joshua, H.; Gans, R.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4884-4892

[3] Stará, I. G.; Starý, I.; Tichý, M.; Závada, J.; Hanuš, V. *J. Am. Chem. Soc.* **1994**, *116*, 5084-5088

With this established precedent, it occurred to us that any other twisted biarylazepinium entity of analogous structure and geometry could react similarly and selectively in [1,2]-Stevens rearrangements – and "simple" diphenylazepinium cations of type **53** (*Scheme II-1*) in particular. If the reaction happened as Závada described, the *P* configuration induced onto quaternary ammonium cation (*P*)-**53** ought to be translated into the *R* configuration of the rearranged product (*R*)-**54**, during the [1,2]-Stevens rearrangement.



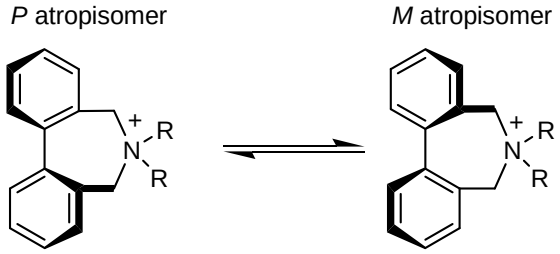

*Scheme II-1*: Stereoselective [1,2]-Stevens rearrangement of diarylazepinium cations.

However, the problem with this type of diphenylazepinium cations is their *configurational lability* at ambient and low temperatures (*Scheme II-2*). In fact, studies performed on several diphenylazepines or diphenylazepinium cations have revealed that the 7-membered dibenzo[*c*,*e*]azepinium ring presents an axial chirality with a low kinetic barrier of enantiomerisation ($\Delta G^{\neq}$ ~ 12-14 kcal.mol$^{-1}$).[4,5] These diphenylazepinium cations exist thus in solution as a 1:1 mixture of freely interconverting *P* and *M* atropisomers by simple rotation around the biphenyl axis.

[4] Superchi, S.; Bisaccia, R.; Casarini, D.; Laurita, A.; Rosini, C. *J. Am. Chem. Soc.* **2006**, *128*, 6893-6902. Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551-1554. Rashidi-Ranjbar, P.; Taghvaei-Ganjali, S.; Wang, S. L.; Liao, F. L.; Heydari, A. *J. Chem. Soc. Perkin Trans. 2* **2001**, 1255-1260. Saudan, L. A.; Bernardinelli, G.; Kundig, E. P. *Synlett* **2000**, 483-486. Tichy, M.; Budesinsky, M.; Gunterova, J.; Zavada, J.; Podlaha, J.; Cisarova, I. *Tetrahedron* **1999**, *55*, 7893-7906. Kiupel, B.; Niederalt, C.; Nieger, M.; Grimme, S.; Vögtle, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 3031-3034. Sutherland, I. O.; Ramsay, M. V. J. *Tetrahedron* **1965**, *21*, 3401-3408

[5] Considering first-order kinetics, this corresponds to half-lives in the range of the $10^{-4}$ s and minutes at 25 °C and –80 °C respectively.

As such, these *tropos*[6] derivatives were not used in stereoselective [1,2]-Stevens rearrangements because tertiary amines (reaction products) would have been obtained in racemic form only.




*Scheme II-2*: Conformational equilibrium of atropisomeric 7-membered dibenzo[*c*,*e*]azepiniums.

At this stage, the possibility of an asymmetric process was considered and it would require the configuration control of this particular type of dibenzo[*c*,*e*]azepinium cations. To reach this goal, we decided to use an enantiopure anion as counterion, applying thus a novel supramolecular asymmetric ion pairing strategy.[7,8,9] In fact, the association of an enantiopure anion with *configurationally labile* cations was interesting for the stereocontrol. It could result in a predominance of one diastereomeric ion pair over the other which should itself be translated in the preferential formation of one enantiomer of rearranged product over the other. In other words, it was considered that any stereoselective induction by the anionic counterion on the axial chirality of the quaternary ammonium cation ought to be possibly transferred – as in the case of Mislow[2] and Závada[3] – to the new $sp^3$ stereogenic centre.

For the chiral anionic auxiliary, we decided to use a hexacoordinated phosphorus anion. Over the past few years, the group of Prof. Jérôme Lacour has actively developed the synthesis and the use of chiral anionic auxiliaries, belonging to the family of hexacoordinated phosphate anions.[10]

[6] Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561-1578
[7] Lacour, J.; Frantz, R. *Org. Biomol. Chem.* **2005**, *3*, 15-19 and references therein
[8] For recent examples of asymmetric processes mediated by chiral anions, see: Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562-4565. Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496-499. Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193-4195. Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 3689-3692
[9] Macchioni, A. *Chem. Rev.* **2005**, *105*, 2039-2073. Macchioni, A. *Eur. J. Inorg Chem.* **2003**, 195-205
[10] Lacour, J.; Linder, D. *Chem Rec* **2007**, *7*, 275-285. Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373-382 and references therein

## II-2 Chiral hexacoordinated phosphate anions

### *II-2.1 Generalities*

In terms of chirality, hexacoordinated phosphate anions are of particular interest, since a simple triple chelation of symmetrical bidentate ligands to an octahedral phosphorus is sufficient to create $D_3$ or $C_2$-symmetric chiral structures.[11] As such, these compounds exist either as *Δ* (*P*) or *Λ* (*M*) enantiomers of respectively right- or left-handed "propeller" shape (*Figure II-1*).

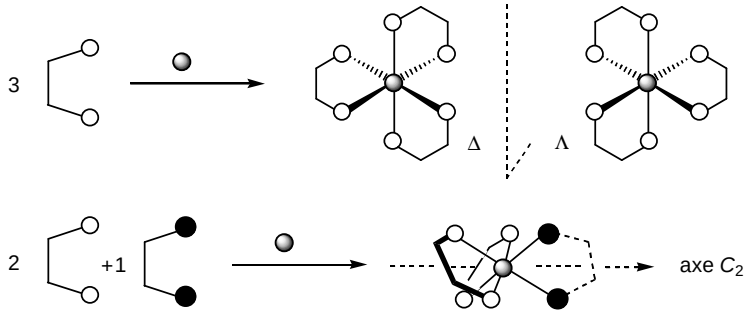
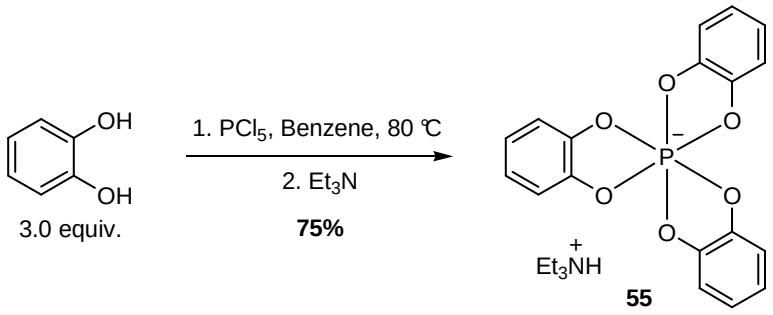



*Figure II-1*: Representation of the triple chelation of a bidentate ligand around a phosphorus atom.

Following the first studies of Hellwinkel in the 1960s about the synthesis of non-racemic tris(biphenyl)phosphate(V) anion and of a *configurationally labile* tris(benzenediolato)-phosphate(V) anion **55**,[12,13] Munoz and co-workers proposed milder conditions to access these hexacoordinated phosphorus compounds. The direct reaction of three equivalents of pyrocatechol with one equivalent of $PCl_5$ followed by the addition of triethylamine affords the racemic- triethylammonium phosphate salt [$Et_3NH$][**55**] with good yield (75%) and excellent purity (*Equation II-1*).[14]

[11] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; 1st ed.; John Wiley & Sons: New York, USA, **1994**;
[12] Hellwinkel, D. *Angew. Chem.* **1965**, *77*, 378-379. Hellwinkel, D. *Chem. Ber.* **1965**, *98*, 576-587
[13] Hellwinkel, D.; Wilfinger, H. J. *Phosphorus* **1972**, *2*, 87-90. Hellwinkel, D. *Chem. Ber.* **1966**, *99*, 3628-3641
[14] Koenig, M.; Klaebe, A.; Munoz, A.; Wolf, R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 40-44




*Equation II-1*: Preparation of tris(benzenedioalato)phosphate(V) anion (Munoz, 1979).

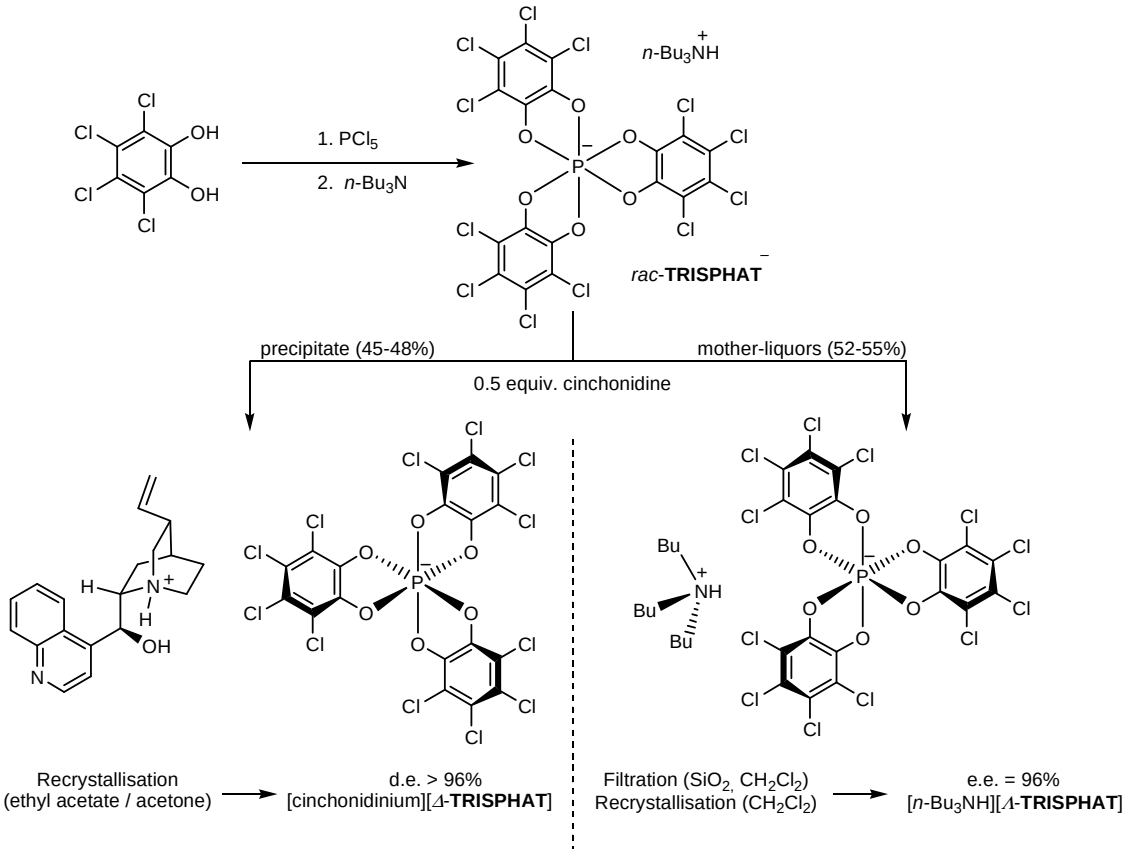
Unfortunately, this particular anion **55** is *configurationally labile* as an ammonium salt. Indeed, when an enantiopure amine – the brucine – is used instead of triethylamine, the [brucinium][**55**] salt is obtained in a diastereomerically enriched form. However, the dissolution of this salt leads to rapid racemisation of the anion, especially in low polarity solvents. One hypothesis concerning the racemisation mechanism was then studied in Prof. Jérôme Lacour's laboratory. It was assumed that the racemisation pathway of this anion involves the protonation of one of the oxygen atoms of the catecholate ligands by the acidic proton of the ammonium counterion.[15] The instability of this oxonium intermediate leads to a P-O bond cleavage 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.

### *II-2.2 Synthesis of hexacoordinated phosphorus anions*

#### II-2.2.a The TRISPHAT anion

Based on this analysis, it was then shown that the introduction of electron-withdrawing atoms such as chlorines, on the aromatic nuclei of the catecholate ligands, increases the configurational (and chemical) stability of the resulting tris(tetrachlorobenzenediolato)-phosphate(V) derivative, commonly called TRISPHAT (*Scheme II-3*).[16] The racemic salt [*n*-$Bu_3NH$][*rac*-TRISPHAT] can be easily synthesised on a multigram scale, following the method of Munoz, by "simple" replacement of the pyrocatechol by tetrachloropyrocatechol.

[15] Cavezzan, J.; Etemadmoghadam, G.; Koenig, M.; Klaebe, A. *Tetrahedron Letters* **1979**, 795-798
[16] The electronic density of the oxygen atom being lower, this decreases their ability to be protonated in acidic medium.




*Scheme II-3*: Synthesis and resolution of the TRISPHAT anion.

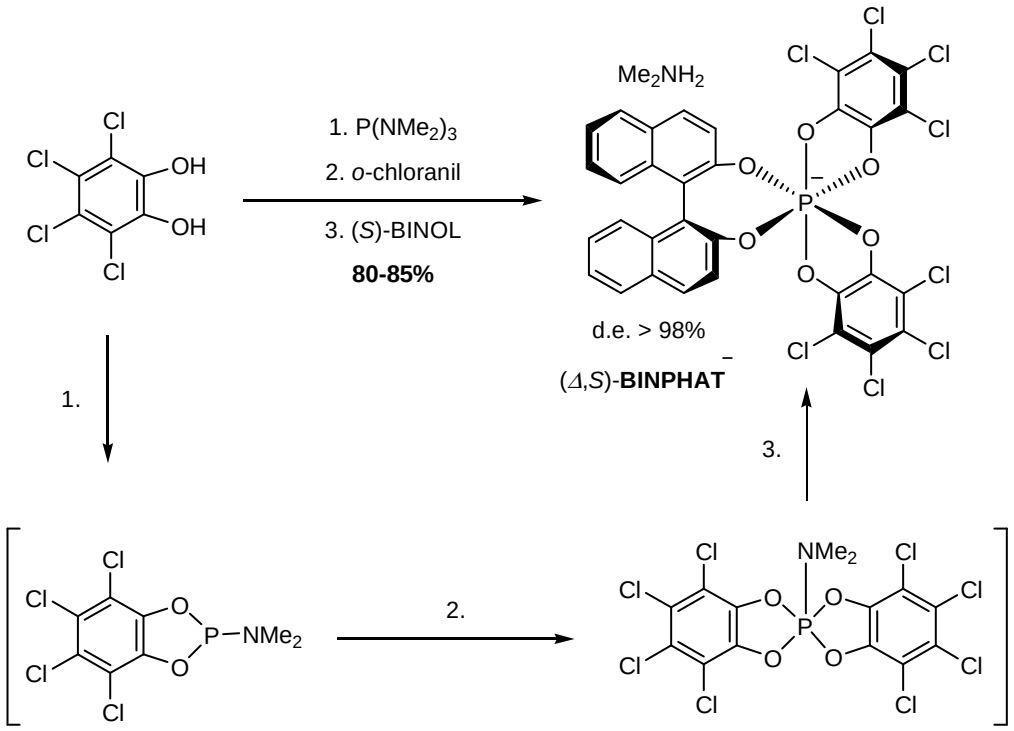
This $D_3$-symmetric TRISPHAT anion can be resolved by a classical association with a chiral ammonium cation: the cinchonidine (*Scheme II-3*). This technique allows a rapid access to both enantiomers of the TRISPHAT anion with good optical purities and the procedure can also be realised on a multigram scale in a straightforward manner.[17] The geometry, as well as the absolute configuration of the TRISPHAT anion was determined by structural X-ray diffraction analysis.[18] To confirm this assessment in solution, an analysis by Circular Dichroism (CD), both Electronical (ECD) and Vibrational (VCD) were recently performed.[19]

[17] Favarger, F.; Goujon-Ginglinger, C.; Monchaud, D.; Lacour, J. *J. Org. Chem.* **2004**, *69*, 8521-8524
[18] Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 608-610
[19] Bas, D.; Buergi, T.; Lacour, J.; Vachon, J.; Weber, J. *Chirality* **2005**, *17*, S143-S148

II-2.2.b The BINPHAT anion

In the group, it was however demonstrated that the TRISPHAT anion is efficient as a NMR-chiral solvating, resolving and asymmetry-inducing agent for cationic metallo-organic and organometallic substrates only.[20] Therefore, in view of an application as anionic chiral auxiliary for the enantioselective [1,2]-Stevens rearrangement, this anion was less than ideal.

We thus turned our attention to the more electron-rich $C_2$-symmetric hexacoordinated phosphate anion, namely the BINPHAT anion, derived from the enantiopure BINOL (*Scheme II-4*). The stereoselective synthesis of this bis(tetrachlorobenzenediolato)mono(1,1'-dinaphthyl-2,2'-diolato)phosphate(V) anion, can be realised by a general one-pot three-step-process in good yield (80-85%, *Scheme II-4*) and excellent diastereoselectivity (d.e.≥96%). If the BINOL used in the synthesis has a *S* or *R* configuration, the phosphate anion resulting, will respectively present a *Δ* or *Λ* configuration (determined by X-ray diffraction analysis).[21]




*Scheme II-4*: Diastereoselective synthesis of BINPHAT anion.

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

### *II-2.3 Application of the BINPHAT anion to N-based cations*

II-2.3.a As an agent of NMR enantiodifferentiation of chiral quaternary ammonium cations

As mentioned before, TRISPHAT is known to be an efficient NMR chiral solvating and resolving agent for, above all, cationic metallo-organic and organometallic substrates. Since there are only few simple methods available to determine with precision the enantiomeric purity of purely organic cations, it was interesting to see whether BINPHAT anion could display superior NMR chiral solvating properties when associated with chiral N-based cations. Several solutions of chiral racemic ammonium iodide salts were previously prepared in NMR tubes and then titrated with a lipophilic tetrabutylammonium *Δ*-BINPHAT salt. The two enantiomers of these cations were directly detected in $^{1}$H-NMR spectroscopy (*Figure II-2*).[22]

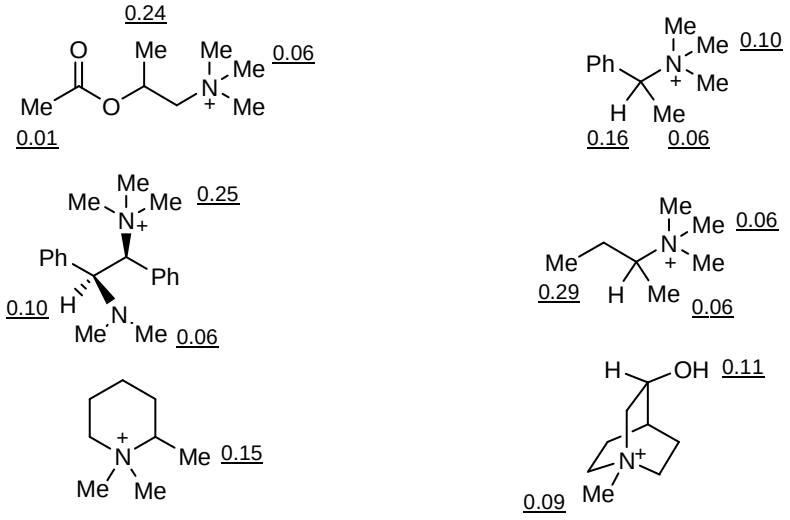



*Figure II-2*: Chiral quaternary ammoniums studied for $^{1}$H-NMR enantiodifferentiation with the difference of magnitude (underlined $\Delta\Delta\delta$ values) for the well-separated signals of the BINPHAT salts.

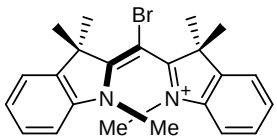
In fact, this anion forms with chiral cations tightly associated diastereomeric ion pairs, leading to short-range interactions and consequently efficient $^{1}$H-NMR enantiodifferentiation. Well-separated signals are usually observed on the spectra of the diastereomeric salts. Several chiral quaternary ammonium cations have been accordingly analysed with success (*Figure II-2*).
The figure above represents the difference of magnitude in chemical shifts – underlined $\Delta\Delta\delta$ values (in ppm) – of the well-separated signals of the diastereomeric salts of BINPHAT.

II-2.3.b As an asymmetry inducer onto *configurationally labile* quaternary ammonium cations

Chiral compounds are sometimes *configurationally stable* as solids and c*onfigurationally labile* in solution. When optically active samples of such derivatives are solubilised, a racemisation 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 can happen and favour one of the equilibrating diastereomers. If the chiral compounds are charged like in our case with the diphenylazepinium cations, an alternative strategy is to consider their ion pairing with chiral counterions, such as BINPHAT. The stereoselectivity can then be controlled through *intermolecular* – rather than intramolecular – diastereoselective interactions. This type of asymmetric induction has been observed as early as 1931 and is generally called the *Pfeiffer* effect.[23] The NMR chiral solvating shift efficiency of the BINPHAT anion was more over found to be an excellent analytical tool to provide accurate measurements of the induced selectivity, for chiral quaternary ammoniums in particular.[24]

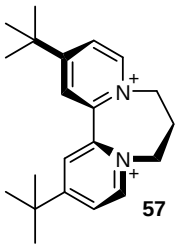
This asymmetric supramolecular approach has been extended to other *configurationally labile* quaternary ammonium cations for which the barrier of interconversion is in the order or higher than the NMR time-scale. For instance, monomethinium dyes **56**, diquats **57** and singly bridged biphenyl ammonium cation **58** were studied with success in conjunction with enantiopure BINPHAT anion (*Figure II-3*).[25] In essentially all cases, a stereoselective recognition between the chiral cations and anions was observed after the integration of the split signals revealing the preferential occurrence of one diastereomeric salt over the other. The diastereomeric excesses (d.e.) were calculated after the signal integration of each diastereomer.

[22] Lacour, J.; Vial, L.; Herse, C. *Org. Lett.* **2002**, *4*, 1351-1354
[23] Pfeiffer, P.; Quehl, K. *Chem. Ber.* **1931**, *64*, 2667-2671
[24] Vial, L.; Lacour, J. *Org. Lett.* **2002**, *4*, 3939-3942
[25] See references 21, 22 and Pasquini, C.; Desvergnes-Breuil, V.; Jodry, J. J.; Dalla Cort, A.; Lacour, J. *Tetrahedron Lett.* **2002**, *43*, 423-426



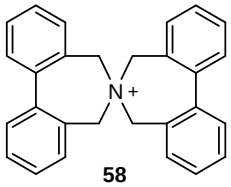

**56**

d.e.= 27% with *Δ*-BINPHAT in $CDCl_3$ at 295 K
d.e.= 40% with *Δ*-BINPHAT in $C_6D_6$ at 295 K




**57**

d.e.= 36% with *Δ*-BINPHAT
in 8% acetone-$d_6$ / $CDCl_3$ at 295 K




**58**

d.e.= 65% with *Δ*-BINPHAT in $CDCl_3$ at 233 K
d.e.= 23% with *Δ*-BINPHAT in $CD_2Cl_2$ at 233 K

*Figure II-3*: Examples of *configurationally labile* N-based cations with the d.e. of the diastereomeric salts of *Δ*-BINPHAT.

The hexacoordinated phosphorus anion BINPHAT has therefore proven to be a general and efficient NMR chiral solvating, resolving and asymmetry-inducing reagent for organic cationic species and quaternary ammoniums in particular. For these reasons, it appeared to us that it should be the "best" enantiopure anion for the association with the *configurationally labile* quaternary ammonium cations foreseen for our studies concerning the asymmetric version of the [1,2]-Stevens rearrangement.

At this stage, the skeleton of diphenylazepinium cation remained to be chosen to enable: (i) the association with the enantiopure BINPHAT anion (*Δ* and *Λ* enantiomers) and (ii) the test of the resulting ammonium salts in the enantioselective [1,2]-Stevens rearrangement.

## II-3 Choice of a *configurationally labile* quaternary ammonium cation for the enantioselective [1,2]-Stevens rearrangement

### *II-3.1 Previous studies*

Previous studies in the Lacour group have shown that spirobi[dibenzazepinium] cation **58**,[26] which contained two *tropos*[6] dibenzo[*c*,*e*]azepinium rings with a rather low kinetic barrier of enantiomerisation of $\Delta G^{\neq} \sim 12.87$ kcal.mol$^{-1}$,[4,5] preferred to adopt enantiomeric $D_2$-symmetric (*P*,*P*) and (*M*,*M*) conformations.[24,27] Association of **58** with enantiopure BINPHAT anion (*e.g.*, *Δ*) led to the preferred formation of one diastereomeric salt, [(*M*,*M*)-**58**][*Δ*-BINPHAT],

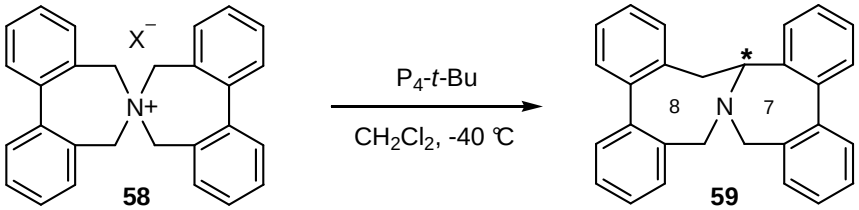
[26] Vial, L.; Gonçalves, M.-H.; Morgantini, P.-Y.; Weber, J.; Bernardinelli, G.; Lacour, J. *Synlett* **2004**, 1565-1568

[27] For a recent study on the stereodynamics of $D_2$- and $S_4$-symmetric conformers of tetraisopropylmethane and tetracyclopropylmethane, see: Anderson, J. E.; de Meijere, A.; Kozhushkov, S. I.; Lunazzi, L.; Mazzanti, A. *J. Am. Chem. Soc.* **2002**, *124*, 6706-6713

as determined by circular dichroism and NMR spectroscopy with 23% and 65% diastereomeric excesses (d.e.) in $CD_2Cl_2$ and $CDCl_3$ respectively.

The [(*M*,*M*)-**58**][*Δ*-BINPHAT] salt and its enantiomer [(*P*,*P*)-**58**][*Λ*-BINPHAT] were treated with a strong Schwesinger's phosphazene base,[28a] $P_4$-*t*-Bu ($CH_2Cl_2$, –40 °C).[28b] This induced a [1,2]-Stevens rearrangement affording the exclusive formation of *ring-expanded* amines (+)-**59** and (–)-**59** respectively,[29] in good yields (74%-80%). Unfortunately, only a low enantiomeric excess (e.e.) of 11% was determined by Chiral Stationary Phase (CSP)-HPLC (*Table II-1*, entries 3 and 4), showing a moderate level of transfer of chirality (47% ToC). The ToC value is defined as the ratio of the enantioselectivity (e.e.) over the diastereoselectivity (d.e.). In order to measure the exact influence of the BINPHAT anion, reactions of salts [**58**][*rac*-TRISPHAT] and [**58**][*Δ*-TRISPHAT] with $P_4$-*t*-Bu were performed and gave the tertiary amine **59** in good yield and in racemic form only (*Table II-1*, entries 1 and 2).

*Table II-1*: [1,2]-Stevens rearrangement of the spirobi[dibenzazepinium] cation **58**.[a]




| entry | Anion | Yield % | d.e. %[b] | e.e. %[c] | $[\alpha]_D$[d] | ToC %[e] |
|---|---|---|---|---|---|---|
| 1 | [*rac*-TRISPHAT] | 76 | - | 0 | - | - |
| 2 | [*Δ*-TRISPHAT] | 71 | 0 | 0 | - | 0 |
| 3 | [*Δ*-BINPHAT] | 74 | 23 (*M*,*M*) | 11 | (+) | 47 |
| 4 | [*Λ*-BINPHAT] | 80 | 23 (*P*,*P*) | 11 | (–) | 47 |

[a]Conditions: $P_4$-*t*-Bu (1M in Hexane, 1.5 equiv.), $CH_2Cl_2$, -40 °C, 4h; [b]Diastereoselectivity of the ion pairing determined by $^1$H-NMR spectroscopy at 233 K, in $CD_2Cl_2$; (*M*,*M*) and (*P*,*P*) indicate the induced absolute configuration of **58**; [c]Average of two runs, enantiomeric purity of **59** determined by CSP-HPLC (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C); [d]Sign of the optical rotation of the enantiomers of **59**; [e]Transfer of Chirality defined as the ratio of the enantioselectivity (e.e.) over the ionic stereoinduction (d.e.): ToC = e.e. / d.e. × 100.

[28] (a) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 1167-1169. (b) Strongly basic conditions ($^{MeCN}pK_a$ > 26.5) are needed to induce the [1,2]-Stevens rearrangement of diarylazepinium moieties (see chapter II-4.2).

[29] Wittig, G.; Koenig, G.; Clauss, K. *Liebigs Ann. Chem.* **1955**, *593*, 127-156

### *II-3.2 Choice of a* "new" *ammonium skeleton*

In view of these previous results concerning the [1,2]-Stevens rearrangement of the *configurationally labile* quaternary ammonium cation **58**, there was a need to (i) increase the diastereoselectivity of the asymmetric induction between the BINPHAT anion and the ammonium cation in the solvent of choice, the $CD_2Cl_2$ and (ii) enhance the stereoselectivity of the transfer of chirality after the ylide formation – from 23% and 47% respectively.[30]
At this stage, two solutions seemed possible:

- to change the chiral anion,
- or to modify the chemical structure of the *configurationally labile* ammonium cation.

Since the BINPHAT anion has been the "best" enantiopure anionic counterion with chiral organic cationic species for close to a decade, a change of anion was not decided. We rather envisaged new cationic structures assuming that an increase of the ammonium skeleton rigidity would be favourable for a chiral recognition.
As a negative proof of this hypothesis, a first experiment was carried out with the dibenzylated cation **60** (*Figure II-4*) which was prepared in one step by condensation of 2,2'-bis(bromomethyl)biphenyl and dibenzylamine ($K_2CO_3$, $CH_3CN$, 80 °C, 87%). Cation **60** appeared to be a good model as it is close to compound **58** structures. The break of one biphenyl bond provided a higher flexibility to this molecule. The association of the enantiopure BINPHAT anion with cation **60** showed a lower asymmetric induction of the anion onto the cation. Diastereomeric excesses (d.e.) of 9% and 13% in $CD_2Cl_2$ and $CDCl_3$ respectively were found in this case, against d.e. of 23% and 65% in $CD_2Cl_2$ and $CDCl_3$ for the spiro cation **58**, demonstrating that an increase in flexibility led to a decrease in supramolecular stereocontrol. Besides, the energetic barrier of **60** was slightly lower than the one obtained for **58** ($\Delta G^{\neq}$ = 12.77 kcal.mol$^{-1}$ *vs* $\Delta G^{\neq}$ = 12.87 kcal.mol$^{-1}$).

[30] The global enantioselectivity is the product of the diastereoselectivity by the transfer of chirality: e.e. = d.e. × ToC.

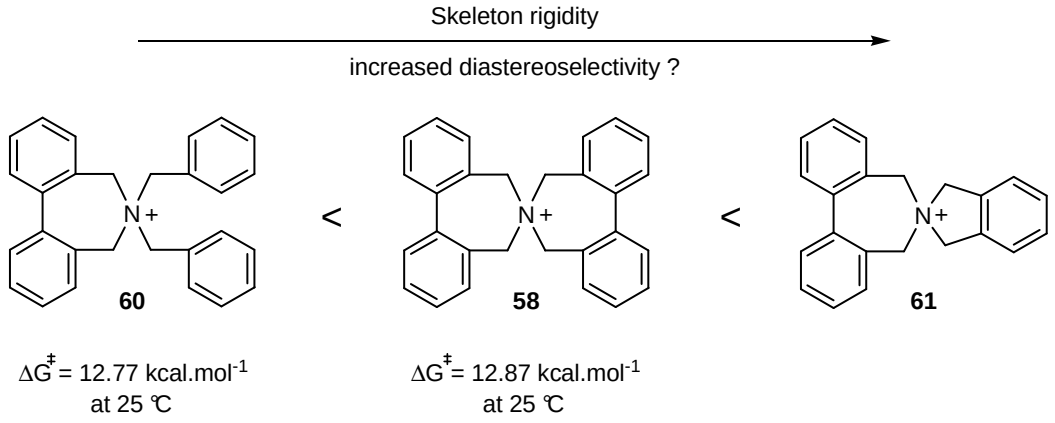



*Figure II-4*: Increase of *configurational stability* of some spiro ammoniums with smaller ring sizes.

In order to move in the "other direction" and increase the rigidity of the cation instead, we envisaged the synthesis of the diphenylazepinium cation **61**. This cation is constituted of the 7-membered ring and a ring-constrained 5-membered ring. The presence of the latter ring-system should limit the number of possible conformations and increase the rigidity of the skeleton of the cation (*Figure II-4*). An extended study was performed on the salts of cation **61** and the results are described in the next chapter.

## II-4 Isoindanyl-dibenzoazepinium cation and [1,2]-Stevens rearrangement

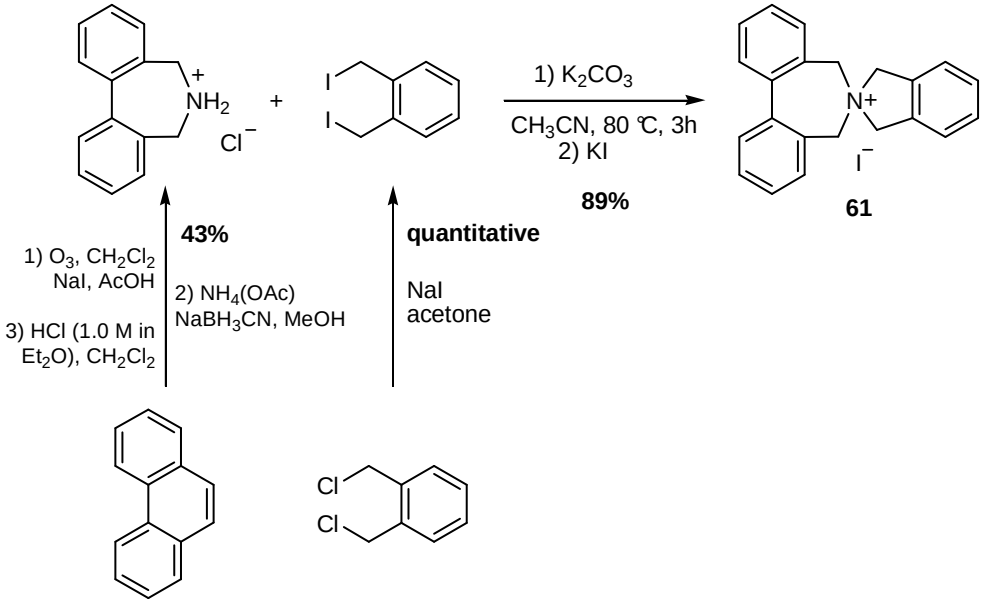
### *II-4.1 Studies on the* "new" *diphenylazepinium cation*

II-4.1.a Synthesis of the iodide salt of the isoindanyl-dibenzoazepinium cation

The new target, the 6,6-isoindanyl-6,7-dihydro-5H-dibenzo[*c*,*e*]azepinium iodide salt [**61**][I] was easily synthesised by condensation of 1,2-bis(iodomethyl)benzene with the 6,7-dihydro-5H-dibenzo[*c*,*e*]azepinium chloride, in good yield (1. $K_2CO_3$, $CH_3CN$, 80 °C; 2. KI, 89%, *Scheme II-5*). This latter compound was prepared in a relatively straightforward fashion in three steps, from the commercially available phenanthrene.[31] Ozonolysis of this tricyclic derivative followed by a reductive amination and a treatment with HCl (1.0 M in $Et_2O$) provided the desired chloride salt (43% in three steps).

[31] Ahmed, S. R.; Hall, D. M. *J. Chem. Soc.* **1958**, 3043-3047. Wenner, W. *J. Org. Chem.* **1951**, *16*, 1475-1480

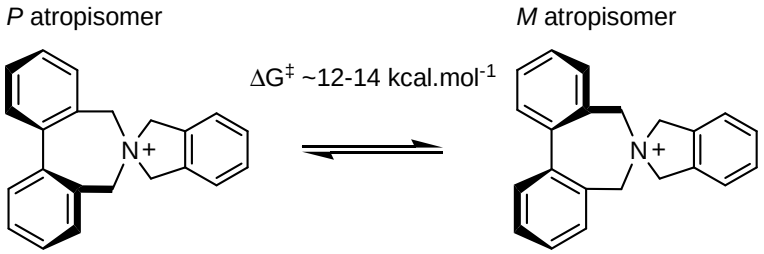
The other partner, the 1,2-bis(iodomethyl)benzene was obtained quantitatively by simple exchange of the chlorine atoms of the 1,2-bis(chloromethyl)benzene with sodium iodide following a Finkelstein reaction.[32]




*Scheme II-5*: Synthesis of the isoindanyl-dibenzoazepinium iodide salt [**61**][I].

II-4.1.b Stereodynamic studies

As just said, this spiro cation **61** is constituted of one stereogenic 7-membered dibenzo[*c*,*e*]azepinium ring and a rigid 5-membered isoindolinium ring that are joined together at the charged nitrogen atom (*Scheme II-6* and *Figure II-5*). This diphenylazepinium cation exists then in just two *P* and *M* atropisomeric conformations due to the axial chirality of the 7-membered dibenzo[*c*,*e*]azepinium ring (*Scheme II-6*).[4,5,6]




*Scheme II-6*: Atropisomerism of cation 61.

[32] Baughman, T. W.; Sworen, J. C.; Wagener, K. B. *Tetrahedron* **2004**, *60*, 10943-10948. Bordwell, F. G.; Brannen, W. T. *J. Am. Chem. Soc.* **1964**, *86*, 4645. Streitwieser, A. *Chem. Rev.* **1956**, *56*, 571-752

II-4.1.c Asymmetric induction

Following these results, the [**61**][*Δ*-BINPHAT] salt was prepared and studied by NMR spectroscopy. The desired ion pairing was realised by mixing a solution of the iodide salt with that of [$Me_2NH_2$][*Δ*-BINPHAT] (or its enantiomer, 1.2 equiv.) in $CH_2Cl_2$/acetone. Chromatographic filtration of the crude mixture on basic alumina with $CH_2Cl_2$ as eluent afforded the compound [**61**][*Δ*-BINPHAT] as the only eluted salt (90% yield).[38]

For this salt, $^1$H-NMR analyses at –40 °C (and lower temperatures) showed that the enantiopure *Δ*-BINPHAT acted as a NMR chiral solvating agent. NMR signals of the benzylic protons were completely split in two sets, one for each of the atropisomers of **61** (*Figure II-7*). More importantly, these experiments also revealed an asymmetric induction of the chiral anion onto the cation and that one of the diastereoisomeric ion pairs, [(*P*)-**61**][*Δ*-BINPHAT] or [(*M*)-**61**][*Δ*-BINPHAT], is thermodynamically favoured in solution.[24,39] As previously mentioned, such behaviour is called the *Pfeiffer* effect.[23,40] The integration of the signals gave 7.5:1 and 13.3:1 ratios in pure $CD_2Cl_2$ and $CDCl_3$ respectively, corresponding to diastereomeric excesses of 76% and 86%. The slightly higher diastereoselectivity in chloroform is probably the result of a tighter ion pairing in this lower polarity solvent.[41]

[38] Hexacoordinated phosphate anions of type BINPHAT confer to their salts a poor affinity for polar chromatographic phases as they elute rapidly over silica gel / alumina. See: Desvergnes-Breuil, V.; Hebbe, V.; Dietrich-Buchecker, C.; Sauvage, J.-P.; Lacour, J. *Inorg. Chem.* **2003**, *42*, 255-257. Monchaud, D.; Jodry, J. J.; Pomeranc, D.; Heitz, V.; Chambron, J.-C.; Sauvage, J.-P.; Lacour, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2317-2319. Lacour, J.; Barchéchath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567-570

[39] Winkelmann, O.; Linder, D.; Lacour, J.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2007**, 3687-3697. Laleu, B.; Bernardinelli, G.; Chauvin, R.; Lacour, J. *J. Org. Chem.* **2006**, *71*, 7412-7416. Vignon, S. A.; Wong, J.; Tseng, H.-R.; Stoddart, J. F. *Org. Lett.* **2004**, *6*, 1095-1098. Martínez-Viviente, E.; Pregosin, P. S.; Vial, L.; Herse, C.; Lacour, J. *Chem. Eur. J.* **2004**, *10*, 2912-2918. Hiraoka, S.; Harano, K.; Tanaka, T.; Shiro, M.; Shionoya, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5182-5185

[40] Yeh, R. M.; Raymond, K. N. *Inorg. Chem.* **2006**, *45*, 1130-1139. Bonnot, C.; Chambron, J.-C.; Espinosa, E. *J. Am. Chem. Soc.* **2004**, *126*, 11412-11413. Owen, D. J.; VanDerveer, D.; Schuster, G. B. *J. Am. Chem. Soc.* **1998**, *120*, 1705-1717. Green, M. M.; Khatri, C.; Peterson, N. C. *J. Am. Chem. Soc.* **1993**, *115*, 4941-4942. Kirschner, S.; Ahmad, N.; Munir, C.; Pollock, R. J. *Pure Appl. Chem.* **1979**, *51*, 913-923

[41] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; 2nd ed.; VCH: Weinheim, **1988**

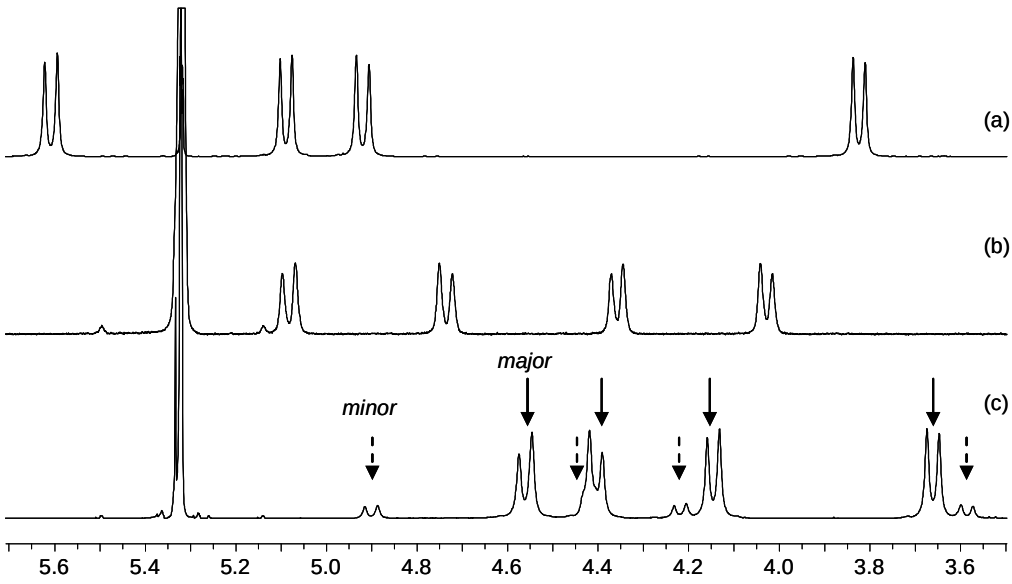



*Figure II-7*: $^{1}$H-NMR (500 MHz, 233 K) of salts (a) [**61**][I], $CD_2Cl_2$; (b) [**61**][*rac*-TRISPHAT], $CD_2Cl_2$; (c) [**61**][*Δ*-BINPHAT], $CD_2Cl_2$, 76% d.e.

II-4.1.d Circular dichroism analysis

The assignment of the preferred configuration of cation **61** in the [**61**][*Δ*-BINPHAT] salt was attempted by circular dichroism (CD). Mislow and Sandström have shown that positive and negative *Cotton* effects at ~ 250 nm in ECD spectra of twisted biphenyl moieties can be used to prove the predominance of respective *M* or *P* torsions of a biphenyl ring.[42] The UV spectrum of [**61**][I] salt was recorded and revealed the absorption characteristic of the biphenyl moiety – including the A band – at 249 nm in $CH_2Cl_2$. The CD spectrum of salt [**61**][*Δ*-BINPHAT] was then measured, showing such a *Cotton* effect. However, care had to be taken due to the presence of the *Δ*-BINPHAT and its aromatic chromophores which were masking the induced CD spectrum of the A band of **61**. A sample of [$Bu_4N$][*Δ*-BINPHAT] was then prepared and its CD spectrum was subtracted from that of [**61**][*Δ*-BINPHAT], in order to observe the induced CD of the cation **61** itself. The resulting spectrum is presented on the *Figure II-8*, and clearly a negative Cotton effect is observed.

[42] Loncar-Tomascovic, L.; Sarac-Arneri, R.; Hergold-Brundic, A.; Nagl, A.; Mintas, M.; Sandstrom, J. *Helv. Chim. Acta* **2000**, *83*, 479-494. Borecka, B.; Cameron, T. S.; Linden, A.; Rashidiranjbar, P.; Sandstrom, J. *J. Am. Chem. Soc.* **1990**, *112*, 1185-1190. Mislow, K.; Djerassi, C.; Records, R.; Bunnenberg, E.; Wellman, K. *J. Am. Chem. Soc.* **1963**, *85*, 1342-1349. Bunnenberg, E.; Mislow, K.; Moscowitz, A.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 2823-2826

The same measurements were performed in variable mixtures of $CHCl_3$ (0-75%) in $CH_2Cl_2$ (*Figure II-8*). As expected, an absorbance in the region of the A band was detected on the calculated spectra ([**61**][*Δ*-BINPHAT]–[$Bu_4N$][*Δ*-BINPHAT]). Its intensity raised with the increase of the chloroform content (lower polarity), its positive sign indicating a preferred *M* torsion of the biphenyl chromophore of **61**. Salt [(*M*)-**61**][*Δ*-BINPHAT] is then the more thermodynamically stable diastereomeric ion pair in solution.

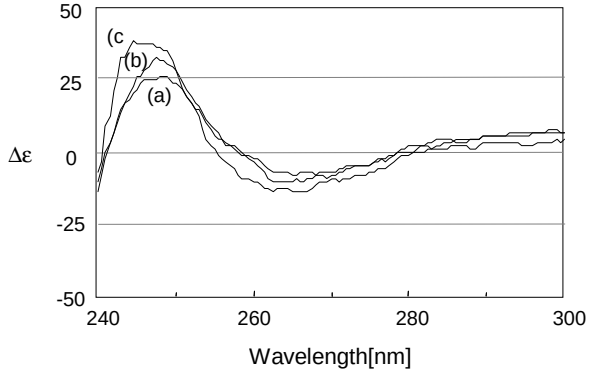



*Figure II-8*: Calculated CD spectra of {[**61**][*Δ*-BINPHAT]–[$Bu_4N$][*Δ*-BINPHAT]} in variable mixtures of $CHCl_3$ in $CH_2Cl_2$: (a) 0%; (b) 25% $CHCl_3$; (c) 75% $CHCl_3$; Concentration $2.13 \times 10^{-6}$ M.

Our initial hypothesis concerning the advantage of an increase of the ammonium skeleton rigidity on the chiral recognition phenomenon was confirmed by the NMR experiments. The next step was therefore to examine the [1,2]-Stevens rearrangement. For the initial attempt, the racemic isoindanyl-dibenzoazepinium salt [**61**][*rac*-TRISPHAT] was selected as a substrate, for its higher solubility in the low polarity solvents, such as dichloromethane, compared to the iodide salt [**61**][I]. This was deemed beneficial for the progress of the reaction. In case of success, the asymmetric version of the [1,2]-Stevens rearrangement would then be tested on the [**61**][*Δ*-BINPHAT] salt in order to determine the existence (or not) of an enantioselectivity and the efficiency of the transfer of chirality during the reaction.

### *II-4.2 [1,2]-Stevens rearrangement of cations of isoindanyl-dibenzoazepinium type*

II-4.2.a Choice of base for the [1,2]-Stevens rearrangement

For the Stevens rearrangement, care was also taken to select a base that will readily generate the initial ylide of ammonium **61**. Among possible neutral bases, Schwesinger's phosphazene bases[28] were considered and $P_4$-*t*-Bu (*Figure II-9*) was chosen for the following reasons:

- It is commercially available.
- Its neutral nature is ideal not to upset the possible asymmetric ion pairing situation by addition of another salt.
- It is also a very strong base ($^{MeCN}pK_{BH+}$ = 41.9).[43] In fact, strongly basic conditions ($^{MeCN}pK_a$>26.5) are needed to induce the [1,2]-Stevens rearrangement of the diaryl/diphenyl-azepinium moieties.[26]
- $P_4$-*t*-Bu is soluble in all organic solvents and after addition of one proton, the positive charge of the conjugated acid is delocalised on a volume of *ca.* 500 angstroms, resulting in the formation of very reactive anionic species.

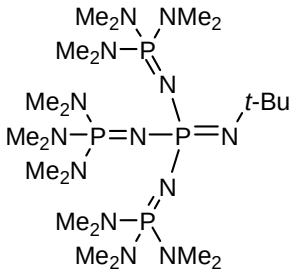



*Figure II-9*: A Schwesinger's phosphazene base: the $P_4$-*t*-Bu.

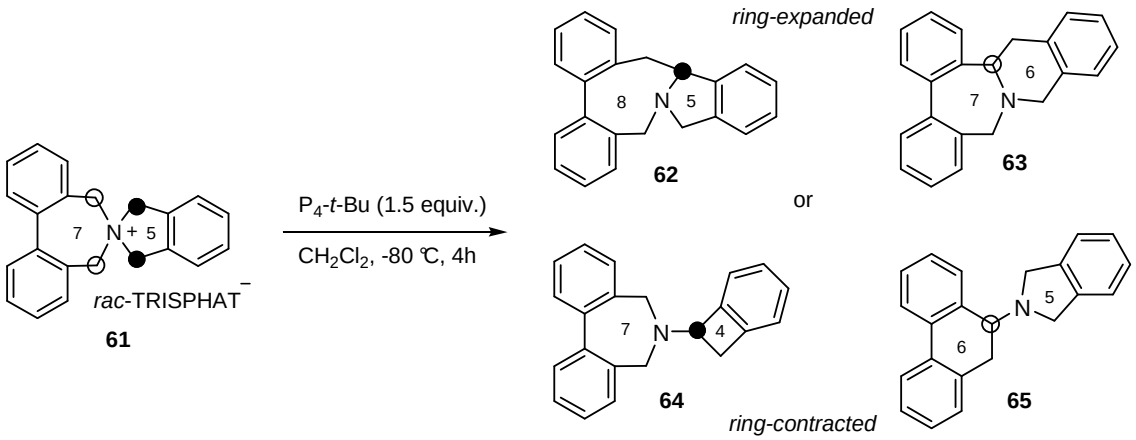
II-4.2.b Preliminary experiments

Treatment of salt [**61**][*rac*-TRISPHAT] with $P_4$-*t*-Bu in $CH_2Cl_2$ at –80 °C,[44] followed by a quench of the reaction with MeOH (also at –80 °C), afforded the exclusive formation of a single (racemic) tertiary amine, albeit in low yield (15%). This compound is the *ring-expanded* amine **62** (*Scheme II-7*). We detail below the process for the structure determination, this one being not as trivial as it may look.

[43] Zhang, X. M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968-972

[44] The same reaction was also performed at –40 °C and R.T., giving a single tertiary amine as a rearrangement product with 21% and 33% respective yields.

Indeed, depending on the regioselectivity of the deprotonation (7- *vs* 5-membered ring) and the regioselectivity of the [1,2]-shift (exocyclic or endocyclic fragmentation and recombination), four different (racemic) products **62**, **63**, **64** and **65** can theoretically result from the reaction of [**61**][*rac*-TRISPHAT] with $P_4$-*t*-Bu (*Scheme II-7* and *Scheme II-8*).

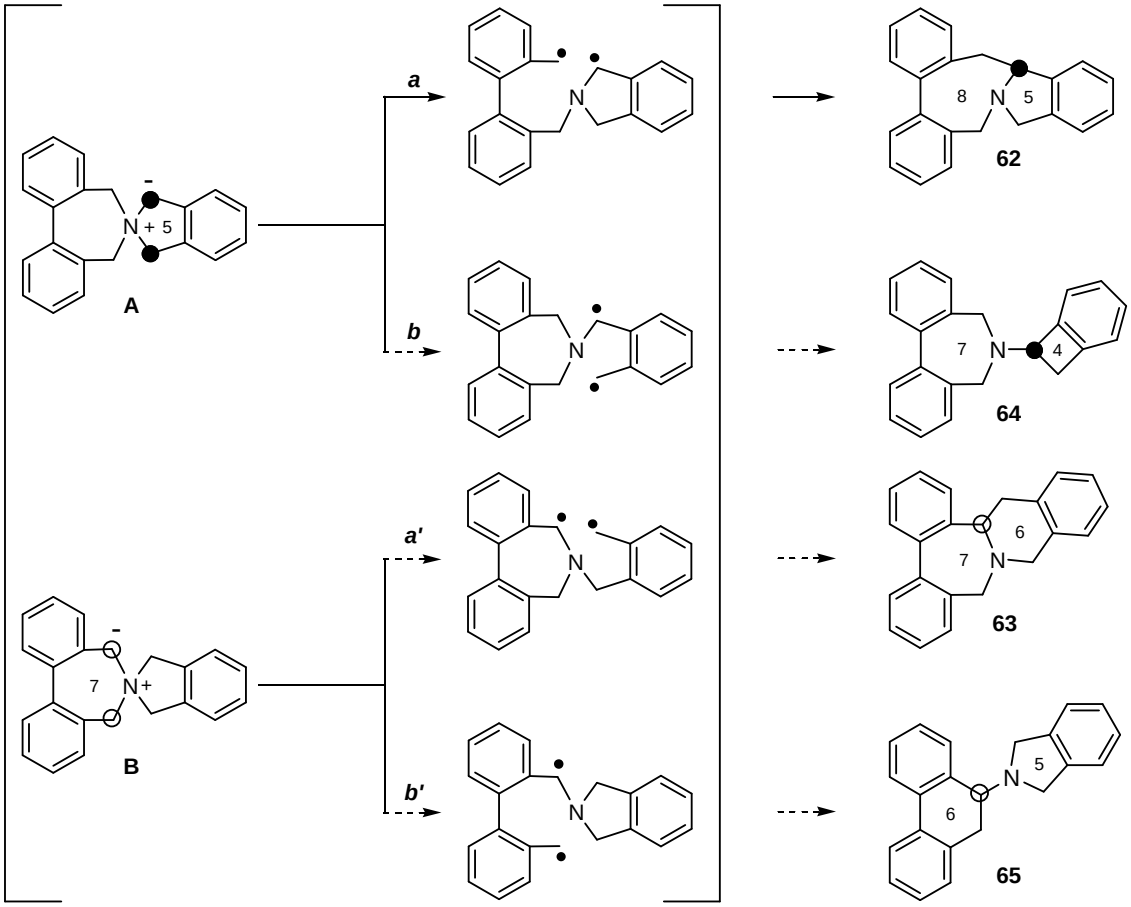



<u>*Scheme II-7*</u>: Stevens rearrangement from salt [**61**][*rac*-TRISPHAT]; four possible products.

In fact, cation **61** contains eight benzylic protons which can all be possibly removed by the strong base, four protons on the 5-membered isoindolinium ring and four protons on the 7-membered dibenzo[*c*,*e*]azepinium ring.

Analysis of the mechanism[1] of the reaction indicated that the strong base could induce the deprotonation on the 5-membered ring to generate ylide **A**, providing then two possible tertiary amines **62** or **64** (*Scheme II-8*, pathways ***a*** and ***b***). Indeed, after this deprotonation, two homolytic fragmentations could *a priori* occur during the [1,2]-Stevens rearrangement. One biradical intermediate, generated by an exocyclic nitrogen-carbon bond cleavage, would give after recombination the fused 8- and 5-membered ring system **62** (path ***a***). The recombination of the other biradical, formed by the endocyclic cleavage, would lead to the formation of the non-fused 7- and 4-membered ring system **64** (path ***b***). In a same fashion, two distinct rearranged products **63** or **65** could be obtained during the Stevens rearrangement, if we considered the deprotonation on the 7-membered ring, creating thus the ylide **B** instead of **A** (*Scheme II-8*, pathways ***a'*** and ***b'***). Tertiary amine **63** would thus come from a rearrangement with a cleavage of an exocyclic bond and would then be constituted of a fused 7- and 6-membered ring system (path ***a'***), as in the case of the spirobi[dibenzazepinium] cation **58**.[26]

The ylide **B** could also decompose to provide another diradical which would couple to give "classical" 6-membered ring derivative **65** (path ***b'***), as in the previous studies by Mislow[2] and Závada.[3]




*Scheme II-8*: Possible pathways for the [1,2]-Stevens rearrangement of the cation **61**.

At this stage, it was necessary to determine which of these four structures **62** to **65** was formed during the synthesis. Fortunately, NMR experiments indicated rapidly that the [1,2]-Stevens rearrangement of cation **61** arose following a *ring-expansion* process. Indeed, only a *ring-expanded* structure could account for seven clearly distinct resonances at 20 °C (293 K) in the benzylic region (*Figure II-10*); compound **62** or **63** being then the two possible remaining structures. Indeed, if a *ring-contracted*-derivative **64** or **65** was then synthesised, only five separated signals would be seen on the NMR spectrum. This regioselectivity and the origin of this particular reactivity would be traced back to the geometry of the ylide intermediate.

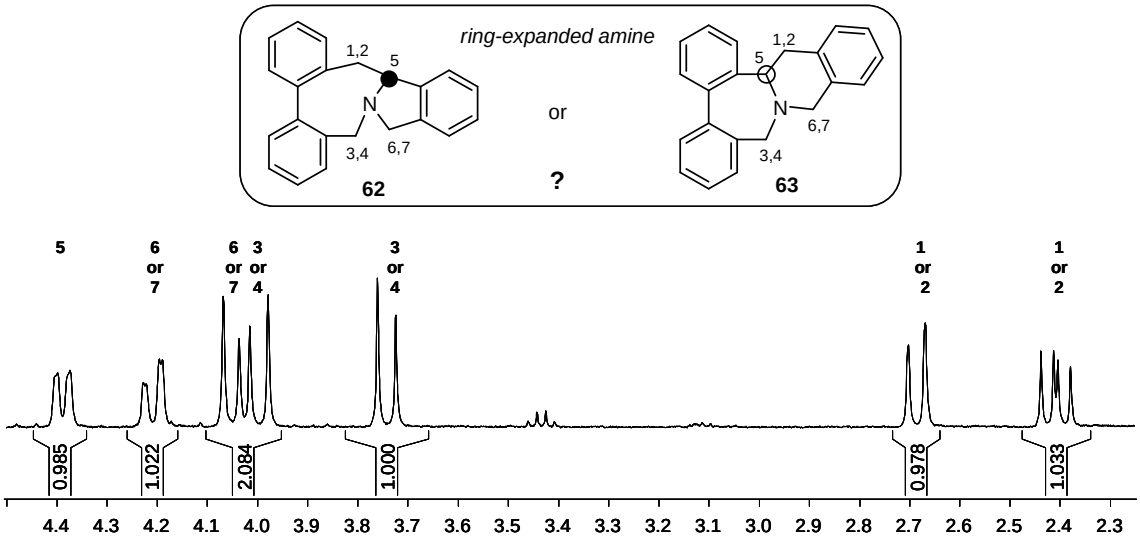


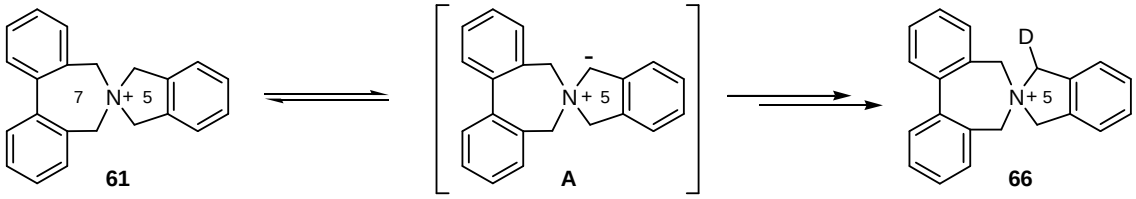

*Figure II-10*: $^{1}$H-NMR (500 MHz, $CD_2Cl_2$, 293 K) spectrum of the benzylic protons of the *ring-expanded* rearrangement product (**62** or **63**).

The next task was then to establish which of the two *ring-expanded* amines was formed during the [1,2]-shift transformation, **62** or **63**? A series of experiments, described in the next paragraph, were necessary to make the distinction; other elaborated NMR experiments being insufficient.

II-4.2.c Regioselectivity of the deprotonation

Experiments performed on [**61**][*rac*-TRISPHAT] salt with $P_4$-*t*-Bu (1.5 equiv.) as a base showed a fugace yellow coloration (~5 s) in solution ($CH_2Cl_2$), which we assumed to be the indication of the formation of ylide **A** or **B** (*Scheme II-8*). Experimentally, the "trapping" of the ylide could only be realised at very low temperature (–90 °C) by the immediate addition of a proton or deuterium source after the phosphazene base. In fact, the instantaneous addition of an excess of MeOH (3.0 equiv.) led to the complete recovery of the starting material. In the case of a direct addition of MeOH-$d_4$ in excess (3.0 equiv.), the monodeuterated compound **66**, containing one deuterium atom on the 5-membered ring, was obtained. The integration of the benzylic protons on the skeleton of ammonium **66** indicated the presence of 4 protons on the 7-membered ring against 3 on the 5-membered ring (*Figure II-11*); the deuterium atom

being distributed evenly between the axial and equatorial positions due to the rapid interconversion of the atropisomers of **66** on all positions.[45]




*Scheme II-9*: Formation of the ammonium ylide **A**.

First, this important experiment demonstrated that the benzylic protons on the 5-membered ring of cation **61** are more acidic than those on the 7-membered ring. Second, this result also constituted an experimental proof of the initial and quantitative formation of the ylide (**A**) and this, even at low temperature. Third and foremost, it showed that the deprotonation is not the kinetically determining step of the reaction because the starting compound **61** can be entirely regenerated by addition of a proton source, before the proceeding of the[1,2]-Stevens rearrangement (*Scheme II-9*).

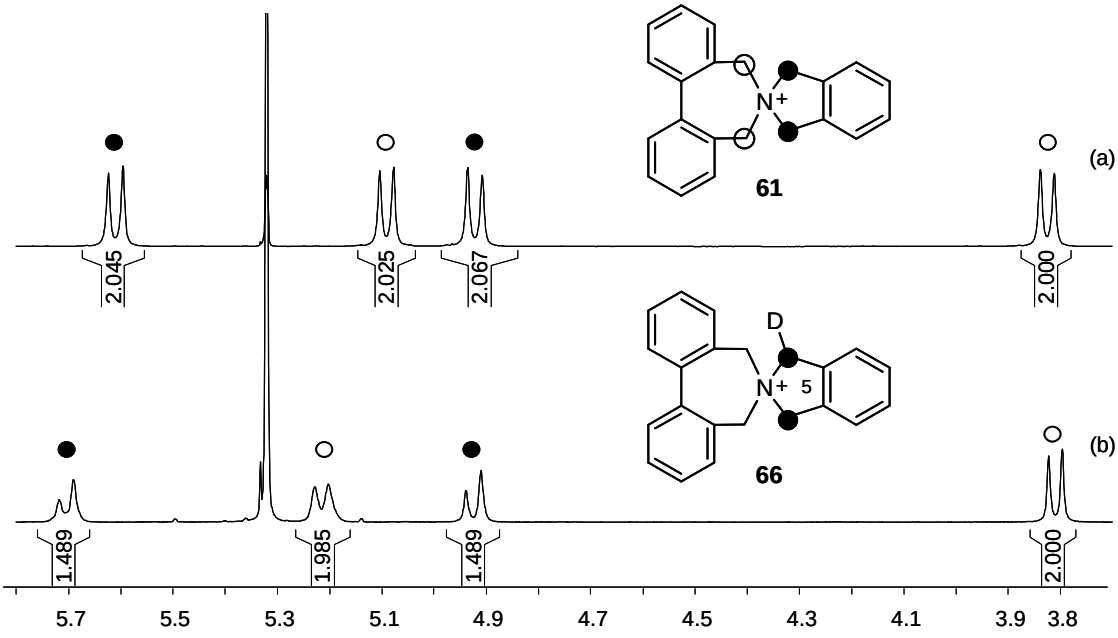


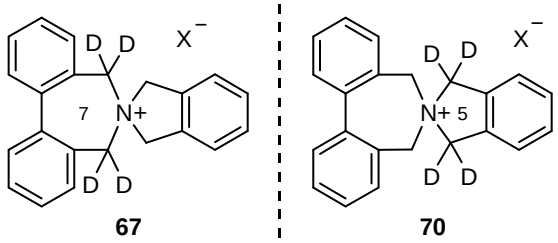

*Figure II-11*: $^{1}$H-NMR (500 MHz, $CD_2Cl_2$, 233 K) of cations: (a) **61** and (b) **66**.

[45] The racemic nature of TRISPHAT anion does not allow us to determine if the benzylic proton comes back exclusively or not to the preferential axial (the most probable) or equatorial position.

Consequently, considering the probable mechanism (*Scheme II-8*, path ***a***), the existence of the ylide intermediate **A** and all the $^{1}$H-NMR analyses (*Figure II-10* and *Figure II-11*), the [1,2]-Stevens rearrangement product for the dibenzo[*c,e*]azepinium cation **61** can only be the *ring-expanded* amine **62**, characterised by fused 8- and 5-membered rings. Besides, other experiments detailed in the following paragraphs have been carried out to confirm this deduction.

II-4.2.d Studies of the [1,2]-Stevens rearrangement on the "half-deuterated" cations

As just said, to confirm that the rearrangement product was indeed the *ring-expanded* amine **62**, one obvious series of experiments was performed, using a "half-deuterated" version of the isoindanyl-dibenzoazepinium cation **61**: the alternatively deuterated cations **67** and **70** (*Figure II-12*). These two adducts should *a priori* rise to a tetra- and tri-deuterated version of tertiary amine **62** respectively, after the [1,2]-Stevens rearrangement. These rearranged products ought to be then easily distinguished by simple NMR and Mass measurements.



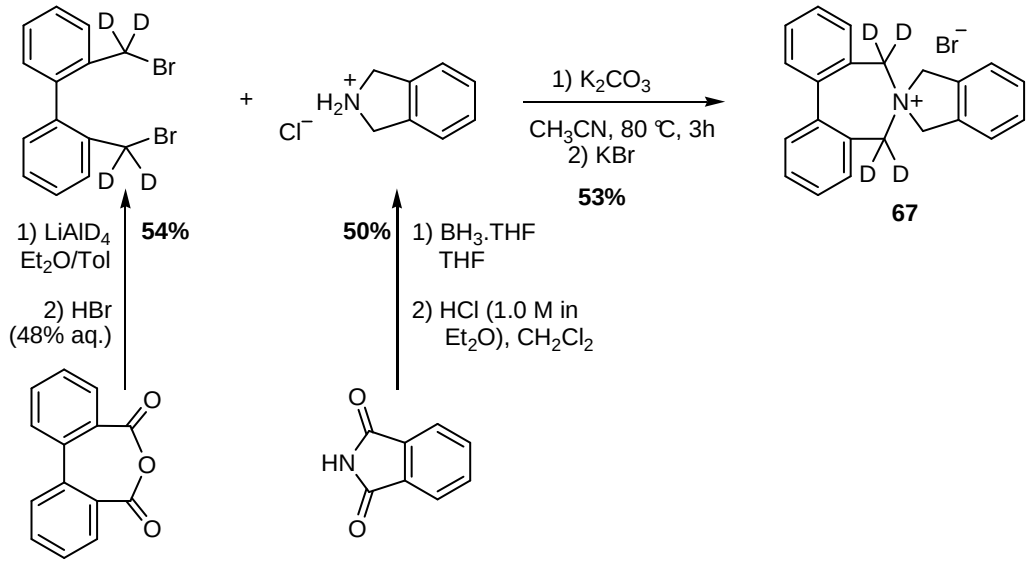

**67** **70**

*Figure II-12*: The "half-deuterated" isoindanyl-dibenzoazepinium cations.

First, for these studies, we decided to consider the cation **67** with 4 benzylic deuterium atoms (D) on the 7-membered ring and 4 benzylic hydrogen atoms (H) on the 5-membered ring (*Scheme II-10*). 6,6-isoindanyl-6,7-dideuterio-5H-dibenzo[*c,e*]azepinium bromide salt [**67**][Br] was synthesised by alkylation of the 1,3-dihydroisoindolium chloride with the 2,2'-bis(bromo-dideuterio-methyl)biphenyl (1. $K_2CO_3$, $CH_3CN$, 80 °C; 2. KBr, 53% yield). The latter compound was simply prepared by reduction of diphenic anhydride with lithium aluminium deuteride followed by a bis-bromination with hydrogen bromide (54%, in two steps).[46] On the other hand, the 1,3-dihydroisoindolium chloride was obtained by reduction of

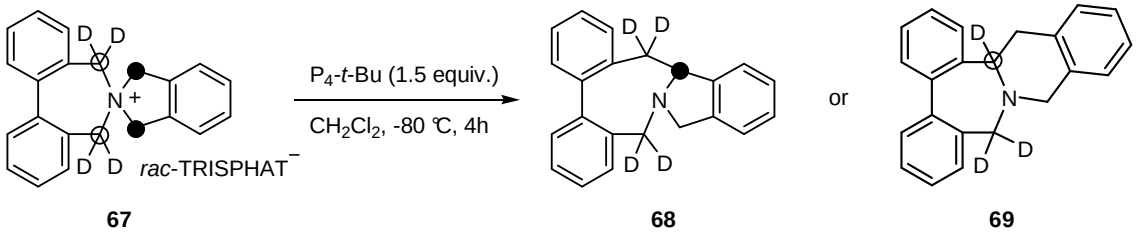
[46] Yachandra, V. K.; Hare, J.; Moura, I.; Spiro, T. G. *J. Am. Chem. Soc.* **1983**, *105*, 6455-6461

the phthalimide with a 1.0 M solution of borane–THF (50% yield), followed by a treatment with HCl (1.0 M in $Et_2O$).[47]




*Scheme II-10*: Synthesis of the isoindanyl-dideuterio-dibenzoazepinium bromide salt [**67**][Br].

The [1,2]-Stevens rearrangement of the [**67**][*rac*-TRISPHAT] salt,[48] under the same conditions as previously described ($P_4$-*t*-Bu, $CH_2Cl_2$, –80 °C)[49] generated one racemic *ring-expanded* amine (18% yield) exclusively. In fact, two possible *ring-expanded* structures could be produced: **68** having 3 H and 4 D or **69** containing 4 H and 3 D (*Scheme II-11*). The result ought to be immediately given by the NMR and Mass measurements.




*Scheme II-11*: Possible products of the Stevens rearrangement of salt [**67**][*rac*-TRISPHAT].

[47] Wang, Q.; Lucien, E.; Hashimoto, A.; Pais, G. C. G.; Nelson, D. M.; Song, Y.; Thanassi, J. A.; Marlor, C. W.; Thoma, C. L.; Cheng, J.; Podos, S. D.; Ou, Y.; Deshpande, M.; Pucci, M. J.; Buechter, D. D.; Bradbury, B. J.; Wiles, J. A. *J. Med. Chem.* **2007**, *50*, 199-210. Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.* **1988**, *53*, 5381-5383

[48] The counter-ion TRISPHAT was used in the experiments because it conferred to the cation with which it was associated, a good solubility in the low polarity solvents such as dichloromethane.

[49] The reaction has been realised at R.T., affording the formation of one *ring-expanded* product with 36% yield.

In fact, the $^{1}$H-NMR analysis revealed the presence of only 3 benzylic protons (*Figure II-13*), providing thus, evidence for the exclusive formation of tertiary amine **68** over **69**. On the positive Electrospray Mass Spectrum ((+)-ES-MS), a molecular peak of *m/z* 302.5 with a relative intensity of 100% was detected, corresponding to the molecular weight (plus one proton) of compound **68** ([$M_{\mathbf{68}}$+1]). All these results corroborated to the fact that the rearrangement product is the fused 8- and 5-membered ring system and the deprotonation with the strong base occurs on the 5-membered ring during the [1,2]-Stevens rearrangement.

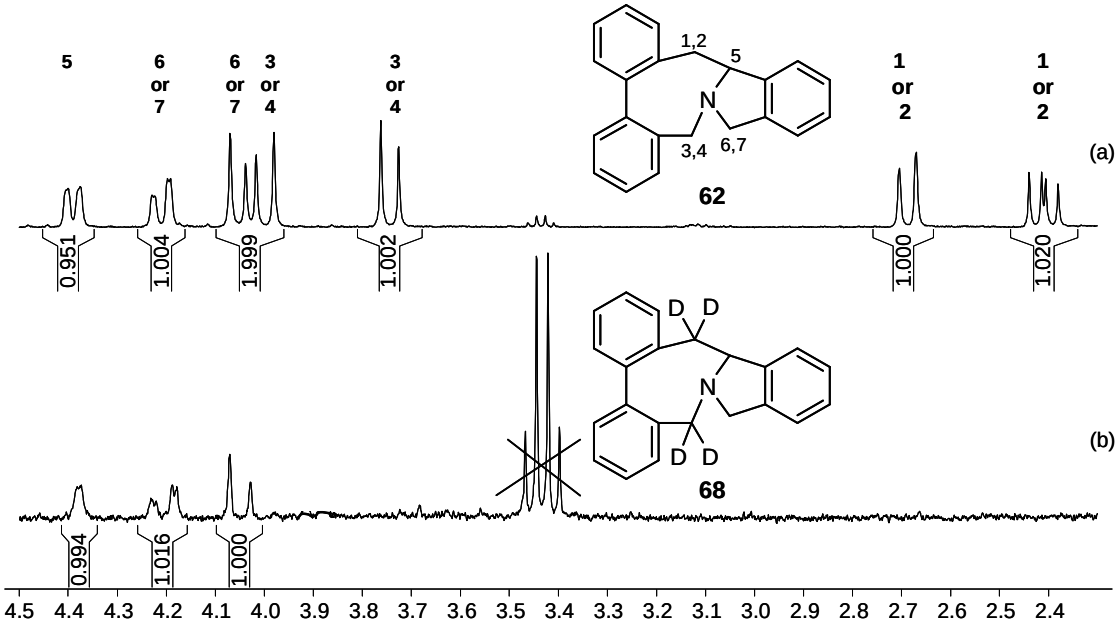
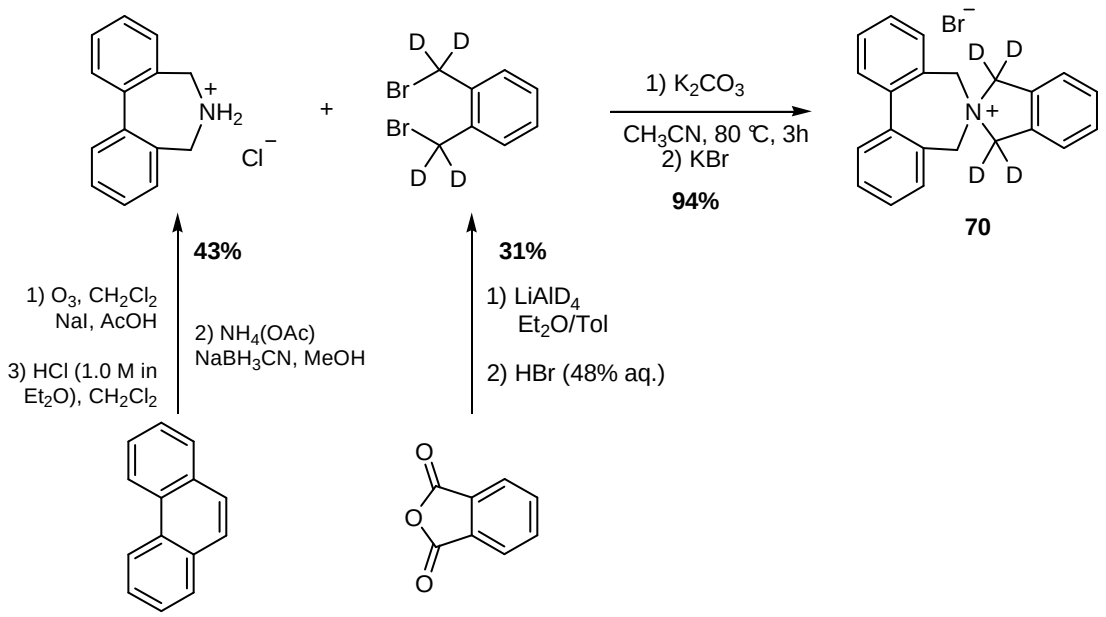


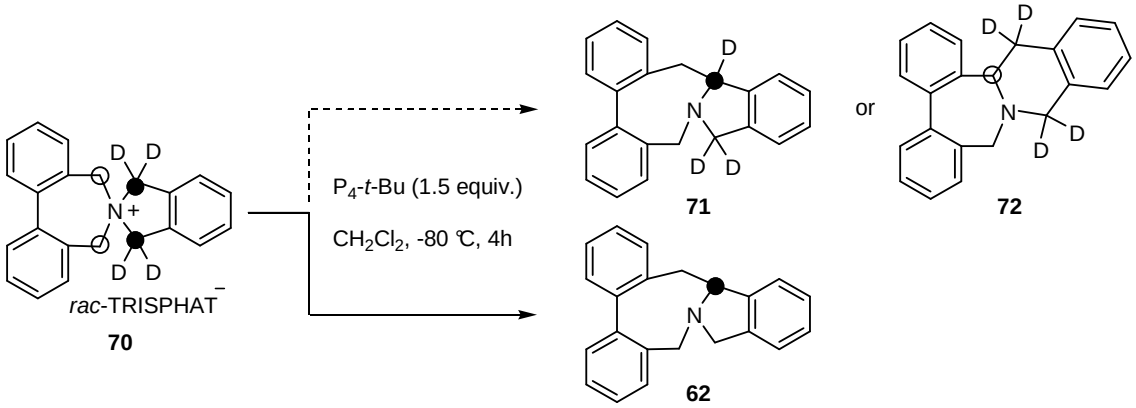

*Figure II-13*: $^{1}$H-NMR (400 MHz, $CD_2Cl_2$, 293 K) spectra showing the benzylic protons of the *ring-expanded* rearrangement products (a) **62** and (b) **68**.

With these considerations in mind, we decided to synthesise the other "half-deuterated" cation: the 6,6-dideuterio-isoindanyl-6,7-dihydro-5H-dibenzo[*c,e*]azepinium bromide salt [**70**][Br], having all benzylic deuterium atoms on the 5-membered ring instead of on the 7-, compared to the [**67**][Br] salt. The [**70**][Br] salt was easily prepared by condensation of 6,7-dihydro-5H-dibenzo[*c,e*]azepinium[31] chloride with the 1,2-bis(bromo-dideuterio-methyl)-benzene[46] in very good yield (1. $K_2CO_3$, $CH_3CN$, 80 °C; 2. KBr, 94%, *Scheme II-12*).




*Scheme II-12*: Synthesis of the dideuterio-isoindanyl-dibenzoazepinium bromide salt [**70**][Br].

So, following the same procedure as before, it was expected that the treatment of the [**70**][*rac*-TRISPHAT] salt with $P_4$-*t*-Bu ($CH_2Cl_2$, –80 °C)[50] should lead to the formation of the racemic *ring-expanded* amine **71** over the tertiary amine **72**, with 4 H and 3 D benzylic atoms (*Scheme II-13*). However, much to our surprise, the rearrangement product resulting from this [1,2]-shift reaction corresponded to neither of the tertiary amines expected. The product obtained was the original fused 8- and 5-membered rings, the amine **62** (20% yield), in which all evidence of previous deuterium atoms had vanished.




*Scheme II-13*: Stevens rearrangement of salt [**70**][*rac*-TRISPHAT].

[50] The Stevens rearrangement at R.T. of this same salt provided amine **62** with 41% yield.

This compound was identified by $^1$H-NMR spectroscopy in which 7 benzylic protons were apparent. On the (+)-ES-MS, a molecular peak of *m/z* 298.1 with a relative intensity of 100% was detected, corresponding to the molecular weight (plus one proton) of compound **62** ([$M_{\mathbf{62}}$+1]).

At this stage, the observed loss of deuterium atoms is essentially mysterious. It might be due to a rapid exchange of deuterium/hydrogen atoms with the solvent of the reaction – dichloromethane in this case – after the deprotonation. If so, it would indicate that the initial deprotonation of **61** is reversible, which would partially validate our assumption that the deprotonation is not the kinetically determining step of the reaction.

In any case, these experiments have produced interesting insight and have confirmed that the amine **62** was the product of rearrangement.

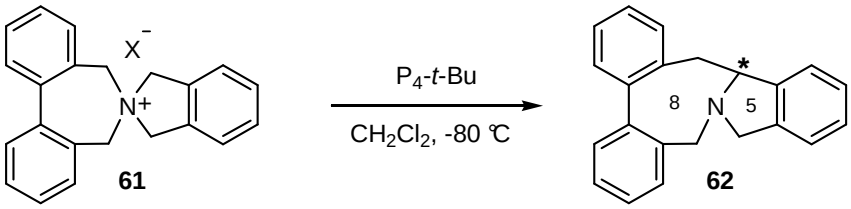
### *II-4.3 Towards an enantioselective [1,2]-Stevens rearrangement and transfer of chirality*

II-4.3.a Enantioselective *ring-expanding* [1,2]-Stevens rearrangement of the isoindanyl-dibenzoazepinium cation

The association of the *configurationally labile* quaternary ammonium cation **61** with the enantiopure *Δ* or *Λ* BINPHAT anion, led to the preferred formation of one diastereomeric ion pair [(*M*)-**61**][*Δ*-BINPHAT] and [(*P*)-**61**][*Λ*-BINPHAT] respectively (76% d.e. in $CD_2Cl_2$, see chapter II-4.1.c and d).[24,39] The [**61**][BINPHAT] salts were then engaged for an asymmetric version of the [1,2]-Stevens rearrangement.

With the reaction conditions in hand, salt [**61**][*Δ*-BINPHAT] and its enantiomer [**61**][*Λ*-BINPHAT] were treated with $P_4$-*t*-Bu (1.5 equiv., $CH_2Cl_2$, –80 °C, 4h) to yield two non-racemic amines (+)-**62** and (–)-**62** respectively (28%); the reaction proceeding therefore stereospecifically. The CSP-HPLC revealed an enantiomeric purity of 34% for both (*Figure II-14*) and a moderate transfer of chirality of 45% was thus reached (*Table II-2*, entries 2 and 3). Obviously, no enantiomeric excess was obtained from the racemic reagent (*Table II-2*, entry 1).

*Table II-2*: Enantioselectivity of the [1,2]-Stevens rearrangement of the isoindanyl-dibenzoazepinium cation **61**[a] in the presence of chiral anionic auxiliaries.




| entry | Anion | Yield %[51] | d.e. %[b] | e.e. %[c] | $[\alpha]_D$[d] | ToC %[e] |
|---|---|---|---|---|---|---|
| 1 | [*rac*-TRISPHAT] | 15 | - | 0 | - | - |
| 2 | [*Δ*-BINPHAT] | 28 | 76 (*M*) | 34 | (+) | 45 |
| 3 | [*Λ*-BINPHAT] | 28 | 76 (*P*) | 34 | (–) | 45 |

[a]Conditions: $P_4$-*t*-Bu (1M in Hexane, 1.5 equiv.), $CH_2Cl_2$, -80 °C, 4h; [b]Diastereoselectivity of the ion pairing determined by $^1$H-NMR spectroscopy at 233 K, in $CD_2Cl_2$, (*M*) and (*P*) indicate the induced absolute configuration of **61**; [c]Average of two runs, enantiomeric purity of **62** determined by CSP-HPLC (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C); [d]Sign of the optical rotation of the enantiomers of **62**; [e]Transfer of Chirality defined as the ratio of the enantioselectivity (e.e.) over the ionic stereoinduction (d.e.): ToC = e.e. / d.e. × 100.

Unfortunately, [1,2]-Stevens rearrangements could not be performed in $CHCl_3$ due to an immediate reaction of the $P_4$-*t*-Bu with this acidic solvent. In all probability, a higher enantioselectivity would have been expected with the use of $CHCl_3$ because the asymmetric induction of the BINPHAT anion onto cation **61** was a bit stronger in $CHCl_3$ (solvent of lower polarity) than in $CH_2Cl_2$ which was the solvent chosen for our rearrangement reactions (d.e.= 86% *vs*. 76%).

[51] The low or moderate yields obtained during the Stevens rearrangements of cation **61** can be explained by the formation of another more polar product which was isolated. Unfortunately, complex and "messy" NMR spectra did not allow a determination of its structure.

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 14.419 | 4595.8 | 303.4 | 0.2327 | 32.782 | 0.862 |
| 2 | 17.477 | 9423.6 | 514.2 | 0.2838 | 67.218 | 0.916 |

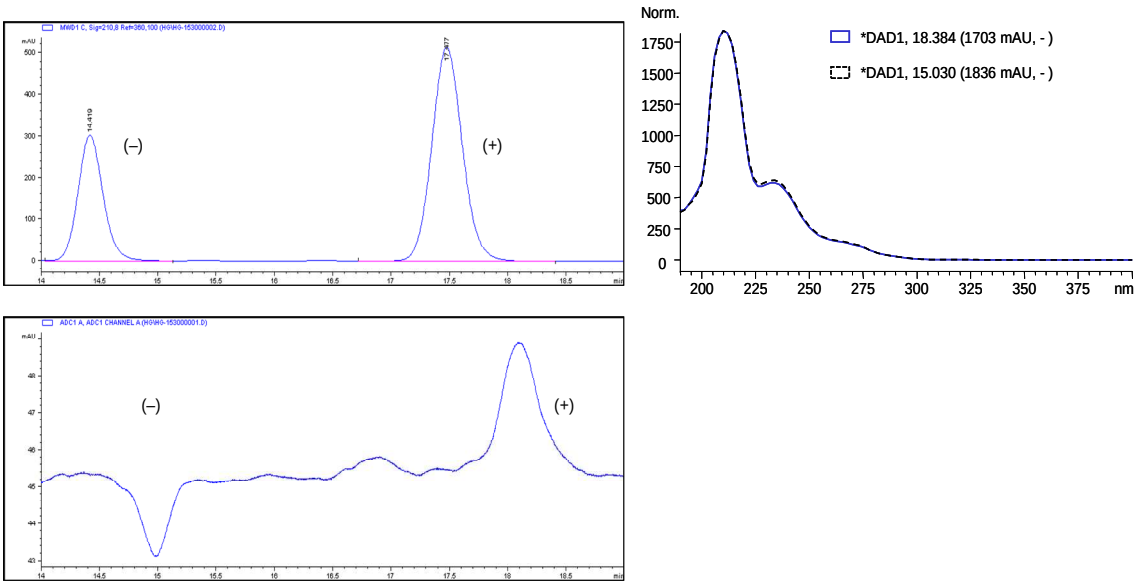



*Figure II-14:* HPLC trace (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C) of amines **62** from salt [**61**][*Δ*-BINPHAT] with 34% e.e. and Optical Rotation Dispersion (ORD) trace of the two enantiomers (*left*); Respective UV spectra of the two enantiomers of **62** (*right*); (+) and (–) indicate the respective signs of the optical rotation.

### II-4.3.b Influence of the temperature on the enantioselectivity

The optimised conditions (*i.e.* highest enantiomeric excess of 34% achieved at –80 °C) for the [1,2]-Stevens rearrangement of the cation **61** were identified, by varying the temperature of the reaction from –85 to –50 °C (188 to 223 K).[52]

This study allowed us to note clearly that the temperature has an influence on both enantiomeric excess (e.e.) and yields. Indeed, we found that the reaction product **62** is obtained with the highest e.e. by carrying out the reaction at –80 °C (193 K), whilst the enantioselectivity drops upon going both to lower and higher temperatures as shown in *Figure II-15* (a). As an alternative way to present this result, an Eyring diagram,[53] plotting ln(*S*/*R*) (*S*/*R* = product enantiomer ratio) *versus* the inverse of the absolute temperature, is displayed

[52] It is to be noticed that the rearrangement transformation of the cation **61** has also been performed at -40 °C and R.T. The rearrangement product **62** has been respectively isolated with 37% and 46% yield and more importantly with 0% e.e. for both.

below in *Figure II-15* (b). Such non-linear temperature dependence for the enantioselectivity has been previously observed.[54] In a detailed analysis of this phenomenon, Hale and Ridd concluded that the observation of a maximum in a ln(S/R) *versus* 1/T may be taken as evidence for two selectivity determining stages in a reaction.[55] However, it remains to be seen whether this occurs in our reaction of [1,2]-Stevens rearrangement.[56]

Moreover, as we can see in *Figure II-15* (c), between –85 and –70 °C (188 and 203 K), the yield followed the same behaviour as the e.e, giving the highest value at –80 °C (193 K). However, from –70 to –50 °C (203 to 223 K), the yield of the reaction increased whereas the e.e. stayed almost constant.

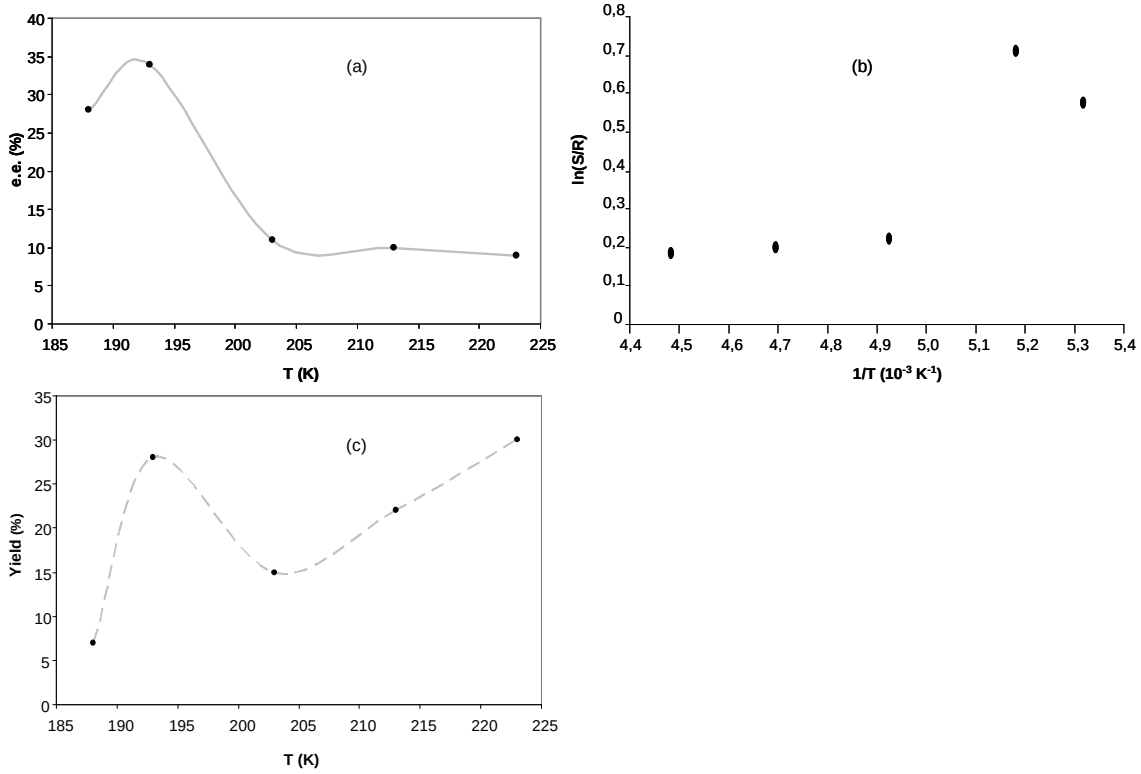



*Figure II-15:* (a) Temperature dependence on the enantiomeric excess (e.e. *vs* temperature); (b) Eyring diagram (ln(S/R) *vs* 1/T); (c) Temperature dependence on the yield (yield *vs* temperature).

[53] S. Glasstone, K. J. Laidler, H. Eyring, The Theory of Rate Processes, McGraw-Hill, New York, **1941**, Chapter 4

[54] Haag, D.; Runsink, J.; Scharf, H.-D. *Organometallics* **1998**, *17*, 398-409. Enders, D.; Gielen, H.; Breuer, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3571-3574

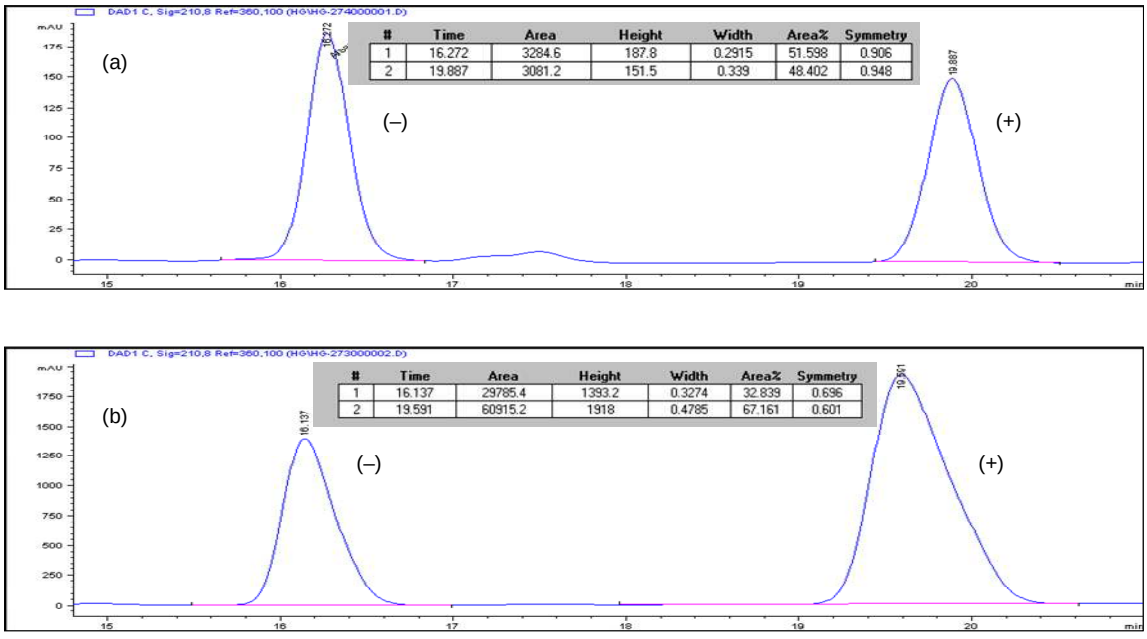
[55] Hale, K. J.; Ridd, J. H. *J. Chem. Soc., Chem. Commun.* **1995**, 357-358. Hale, K. J.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1601-1605

[56] Indeed, to have a better correlation, there is a need to increase the number of measurements to have more points on the graphics.

II-4.3.c Isotope labelling and enantioselectivity of the [1,2]-Stevens rearrangement of the "half-deuterated" cations

Finally, it occurred to us that the "half-deuterated" cations **67** and **70** with 4 deuterium atoms (D) on the 7- and 5-membered rings respectively, associated with the enantiopure BINPHAT anion (*e.g.* *Δ*), could be wonderful probes to study further the mechanism of the[1,2]-Stevens rearrangement. Very surprising but interesting results were obtained when these BINPHAT salts were treated with $P_4$-*t*-Bu. They are detailed below.

In fact, treatment of the [**67**][*Δ*-BINPHAT] salt[57,38] under the "classical" reaction conditions ($P_4$-*t*-Bu 1.5 equiv., $CH_2Cl_2$, –80 °C, 4h), resulted in the formation of the tertiary amine **68** (chapter II-4.2.d), in 18% yield and **no** enantiomeric excess (*Figure II-16*). However, the enantioselective [1,2]-Stevens rearrangement performed on the [**70**][*Δ*-BINPHAT] salt[57,38] gave the dextrorotatory amine (+)-**62** (chapter II-4.2.d) in 25% yield and 34% e.e. (determined by polarimetry and CSP-HPLC, *Figure II-16*).




| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 16.272 | 3284.6 | 187.8 | 0.2915 | 51.598 | 0.906 |
| 2 | 19.887 | 3081.2 | 151.5 | 0.339 | 48.402 | 0.948 |

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 16.137 | 29785.4 | 1393.2 | 0.3274 | 32.839 | 0.696 |
| 2 | 19.591 | 60915.2 | 1918 | 0.4785 | 67.161 | 0.601 |

*Figure II-16*: HPLC trace (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C) of amines: (a) **68** from salt [**67**][*Δ*-BINPHAT] with 0% e.e.; (b) **62** from salt [**70**][*Δ*-BINPHAT] with 34% e.e.

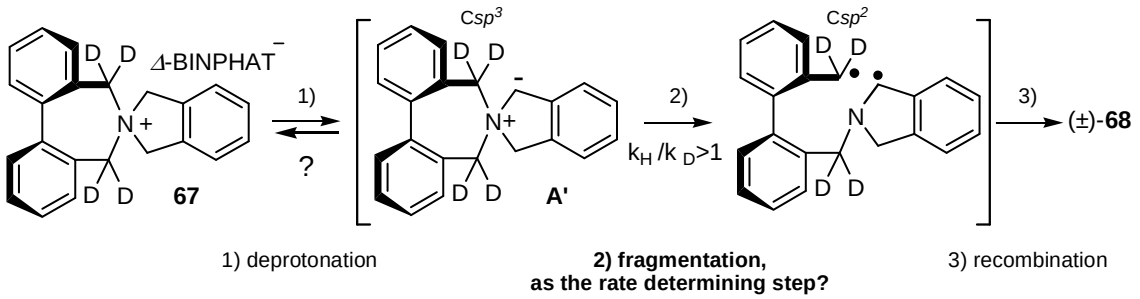
[57] These ion pairings were realised in the same way as the previous salt [**61**][*Δ*-BINPHAT], by mixing a solution of the corresponding bromide salt with that of [$Me_2NH_2$][*Δ*-BINPHAT] in $CH_2Cl_2$/acetone. Chromatographic filtration of the crude mixture on basic alumina with $CH_2Cl_2$ as eluent afforded the desired pair [**67**][*Δ*-BINPHAT] and [**70**][*Δ*-BINPHAT] as the only eluted salt respectively (99% and 88% respective yields).

In these two reactions, the presence of the BINPHAT anion instead of the racemic TRISPHAT did not modify the global reactivity; amine **68** (the product from cation **67**) being still tetradeuterated and amine **62** (the product from cation **70**) losing again all its deuterium (D) atoms during the reaction (most probably at the ylide formation stage). The yields of formation of these tertiary amines **68** and **62** are virtually the same from two hexacoordinated phosphorus salts (**68**: [*rac*-TRISPHAT] yield 15% *vs* [*Δ*-BINPHAT] yield 18% and **62**: [*rac*-TRISPHAT] yield 28% *vs* [*Δ*-BINPHAT] yield 25%).

Clearly and unexpectedly, the presence of the D atoms on the benzylic postions of the 7-membered ring (cation **67**) had a dramatic effect on the enantioselectivity of the [1,2]-Stevens rearrangement (**68**: e.e. 0% *vs* **62**: e.e. 34%). As the diastereoselectivity of the chiral recognition was not perturbed by the presence of the D atoms, the effect had to occur during the [1,2]-shift transformation. The fact that these deuterium atoms were not exchanged by hydrogen atoms (unlike for **70**) indicates that the isotopic effect is not of primary nature, which gives some information on the nature of the mechanism of the reaction.[58]

Moreover, the presence of D atoms on the migrating carbon modifies the kinetic of one or more of the elemental steps. Obviously, the loss of selectivity in the case of the [1,2]-Stevens rearrangement of the [**67**][*Δ*-BINPHAT] salt, shows that these elemental steps are slowed rather than accelerated in the presence of the D atoms. Therefore, considering that (1) the ratio $k_H / k_D$ is greater than 1 and (2) the isotopic effect is a secondary kinetic effect, then it would mean that a change of hybridisation from $sp^3$ to $sp^2$ arises in the rate determining step for the carbon atom bearing the H/D atoms. Only the elemental fragmentation step sees the change of carbon atom hybridisation (the C$sp^3$ on the ylide **A'** becoming C$sp^2$ on the biradical intermediate, see *Scheme II-14*) and so, the cleavage of the N–C bond. Consequently, the fragmentation would then be the kinetically determining step because of compatiblility with our explanation. Finally, as far as **62** is concerned, the lack of change in the enantioselectivity and the yield of the [1,2]-Stevens rearrangement of the [**70**][*Δ*-BINPHAT] salt would confirm that the deprotonation of the 5-membered ring would not be the rate determining step (chapter II-4.2.c).

[58] Carrol, F.A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole Publishing Compagny: Pacific Grove, **1998**




*Scheme II-14*: Mechanistic evaluation: possible pathway and intermediates for the [1,2]-Stevens rearrangement of the [**67**][*Δ*-BINPHAT] salt, the cation containing 4 benzylic deuterium atoms on the 7-membered ring.

### *II-4.4 Summary*

Introducing the 5-membered ring in the ammonium skeleton, the chiral recognition between the enantiopure BINPHAT anion and the cation has significantly increased. Indeed, a diastereomeric excess of 76% in $CD_2Cl_2$ was found for the BINPHAT salts of cation **61** *versus* 23% for those of the spirobi[dibenzazepinium] cation **58**. The enantioselectivity of the [1,2]-Stevens rearrangement was improved, thanks to the more effective supramolecular stereocontrol (e.e. 34% for **61** *vs* 11% for **58**). The transfer of chirality (ToC) remained moderate, with values of 45% and 47% for the cations **61** and **58** respectively.

Although the enantioselectivity of the reaction was only 34%, this constituted an interesting example of double transmission of chirality: (i) first by an efficient supramolecular transfer of the helical chirality of the BINPHAT anion to the axial chirality of cation **61** (76% d.e., in $CD_2Cl_2$) and (ii) secondly by the partial control of the centred chirality of amine **62** (45% ToC) during the [1,2]-Stevens rearrangement.

At this stage, having demonstrated with the isoindanyl-dibenzoazepinium cation **61** that an increase of the rigidity of the ammonium skeleton was beneficial, we decided to confirm this observation. That's why, we envisaged another "rigid" diarylazepinium cation, namely **73**, constituted of the 7-membered ring with a 6-membered ring including a naphthalene group (*Figure II-17*). This cation under bromide salt was prepared and then associated with enantiopure BINPHAT anion. The results of the [1,2]-Stevens rearrangements of these latter salts will be presented in the following chapter.

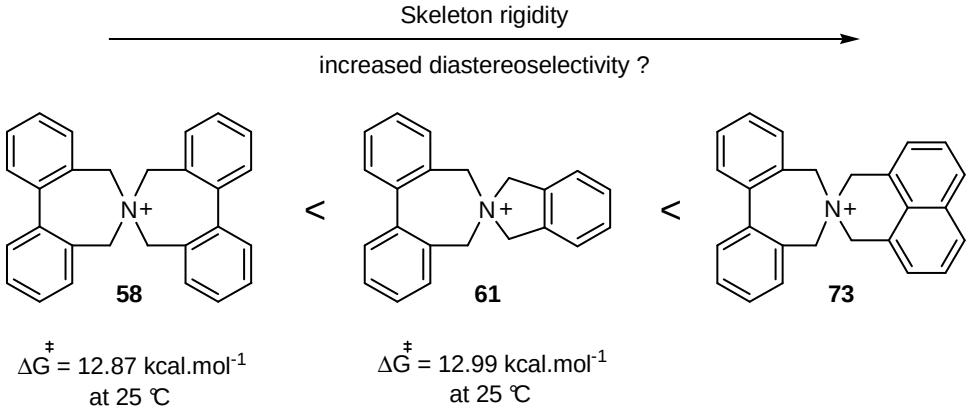


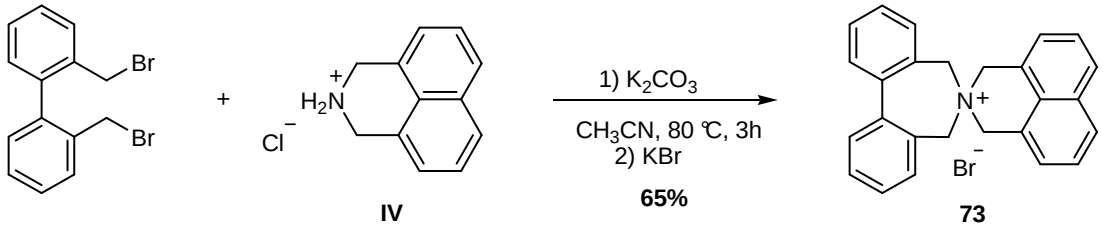

*Figure II-17*: Increase of c*onfigurational stability* of some spiro ammoniums.

## II-5 Isoquinoline-dibenzoazepinium cation and the [1,2]-Stevens rearrangement

### *II-5.1 Studies on this other diphenylazepinium cation*

II-5.1.a Synthesis of the bromide salt of the isoquinoline-dibenzoazepinium cation

The 6,6-isoquinoline-6,7-dihydro-5H-dibenzo[*c*,*e*]azepinium bromide salt [**73**][Br] was synthesised by alkylation of the 2,3-dihydro-1H-benz[*de*]isoquinolinium chloride **IV** with the 2,2'-bis(bromomethyl)biphenyl (1. $K_2CO_3$, $CH_3CN$, 80 °C; 2. KBr, 65% yield, *Scheme II-15*). The latter compound was prepared by reduction of diphenic anhydride with lithium aluminium hydride followed by a bis-bromination with hydrogen bromide (82%, in two steps).




*Scheme II-15*: Synthesis of the isoquinoline-dibenzoazepinium bromide salt [**73**][Br].

Plotting the data into the following equation: ln(k) = f(1000/T), allowed access to the values of the enthalpy and the entropy of activation for cation **73**: $\Delta H^{\neq}$ = 12.51 ±0.5 kcal.mol$^{-1}$, $\Delta S^{\neq}$ = -3.65 ±0.5 cal.(K.mol)$^{-1}$ at 25 °C (See appendix, chapter II).[35,36,60]

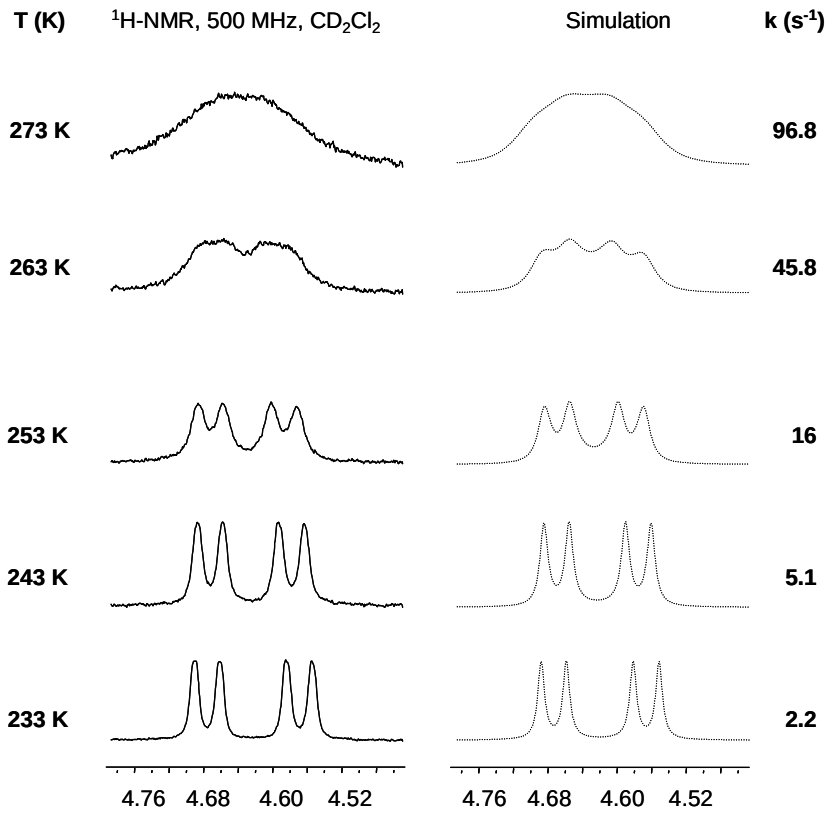



*Figure II-20*: Stereodynamics of salt [**73**][Br] as evidenced by variable temperature (VT)-NMR experiments (273-233 K); Experimental $^1$H-NMR spectra (500 MHz, $CD_2Cl_2$, *left*) and calculated (WinDNMR, *right*).

II-5.1.c Asymmetric induction

Following these results, cation **73** was then associated with the enantiopure BINPHAT anion to form the salt [**73**][*Δ*-BINPHAT][61,38] which was studied by NMR spectroscopy. For this salt, $^1$H-NMR analyses, at –40 °C (and lower temperatures) showed that the *Δ*-BINPHAT

[60] The values of the entropy of activation for the cation **73** being almost equal to zero ($\Delta S^{\neq}$ = -3.65 ±0.5 cal.(K.mol)$^{-1}$ at 25 °C), shows the unimolecular nature of the transition state.

[61] This ion pairing was realised in the same way as the previous [**61**][*Δ*-BINPHAT] salt, by mixing a solution of the bromide salt with that of [$Me_2NH_2$][*Δ*-BINPHAT] in $CH_2Cl_2$/acetone. Chromatographic filtration of the crude mixture on basic alumina with $CH_2Cl_2$ as eluent afforded the desired pair [**73**][*Δ*-BINPHAT] as the only eluted salt (82% yield).

acted as a NMR chiral-solvating agent. NMR signals of the benzylic protons were completely split in two sets, one for each of the atropisomers of **73** (*Figure II-21*). More importantly, these experiments also revealed an asymmetric induction of the chiral anion onto the cation and the fact that one of the diastereomeric ion pairs, [(*P*)-**73**][*Δ*-BINPHAT] or [(*M*)-**73**][*Δ*-BINPHAT], is thermodynamically favoured in solution.[23,24,39,40] The integration of the signals gave a 2.6:1 ratio in pure $CD_2Cl_2$, corresponding to diastereomeric excesses of 44%.

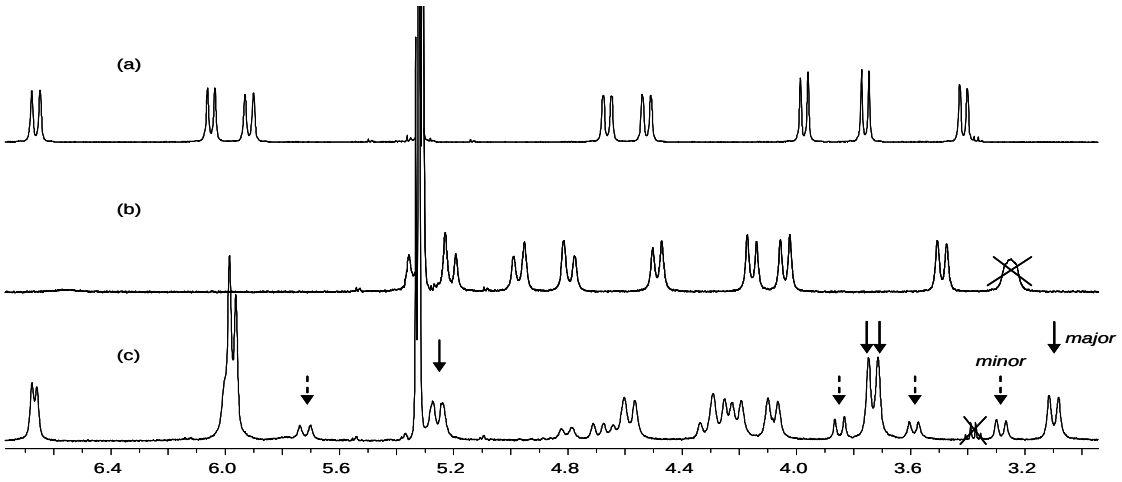



*Figure II-21*: $^1$H-NMR (500 MHz, 233 K) of salts (a) [**73**][Br], $CD_2Cl_2$; (b) [**73**][*rac*-TRISPHAT], $CD_2Cl_2$; (c) [**73**][*Δ*-BINPHAT], $CD_2Cl_2$, 44% d.e.

Clearly, our hypothesis that an increase of the ammonium skeleton rigidity would involve a better chiral recognition is not fulfilled with the cation **73**. The higher barrier of interconversion between the *P* and *M* atropisomers of **73** is not translated into a better chiral recognition with the BINPHAT anion, in this case.

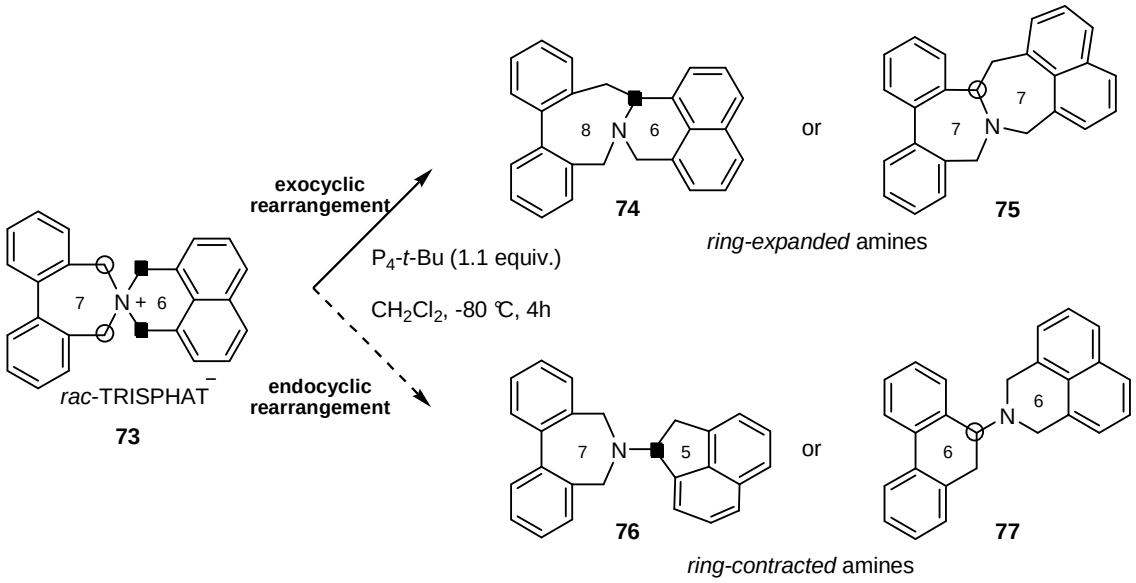
Whereas the restriction in the degrees of freedom of the cation **73** is still favourable, the increased hindrance of the 6-membered ring (including a naphthalene group) most probably generates negative interactions with the anion, disfavouring the chiral recognition.

The next step was then to test the [1,2]-Stevens rearrangement on various salts of the isoquinoline-dibenzoazepinium cation **73**.

### *II-5.2 [1,2]-Stevens rearrangement of the isoquinoline-dibenzoazepinium cation.*

II-5.2.a Preliminary experiments

The [**73**][*rac*-TRISPHAT][62] salt was then treated with the $P_4$-*t*-Bu in $CH_2Cl_2$ at –80 °C,[63] followed by a quench of the reaction with MeOH (also at –80 °C), to give exclusively a single (racemic) tertiary amine in very good yield (92%), whereas four different (racemic) products **74**, **75**, **76** and **77** can be theoretically generated (*Scheme II-17*).




*Scheme II-17*: Stevens rearrangement from [**73**][*rac*-TRISPHAT] salt and possible rearrangement products.

Indeed, considering the probable mechanism[1] of the reaction, four distinct products from the Stevens rearrangement can be formed during the reaction, as also noted in the previous case of the [1,2]-shift transformation involving the isoindanyl-dibenzoazepinium cation **61** (See chapter II-4.2.b). In fact, either *ring-expanded* or *ring-contracted* tertiary amines can be obtained, depending on (1) the regioselectivity of the deprotonation (7- *vs* 6-membered ring), *i.e.* the nature of the ylide generated and (2) the nature of the homolytic fragmentation,

[62] As previously, the [**73**][*rac*-TRISPHAT] was selected as a substrate, for its higher solubility in the low polarity solvents, such as dichloromethane, compared to the bromide salt [**73**][Br].
[63] The same reaction has been also performed at R.T., giving one *ring-expanded* amine as rearrangement product with 89% yield.

(exocyclic or endocyclic) which occurs after the ylide formation, followed by a recombination.

Fortunately, NMR experiments rapidly indicated that the [1,2]-Stevens rearrangement of cation **73** arose following a *ring-expansion* process. Indeed, in the $^{1}$H-NMR spectrum in particular, seven clearly separated signals for the benzylic protons were exhibited at 20 °C (293 K), allowing thus the assignment of the *ring-expanded* structure for the possible amine **74** or **75** (*Figure II-22*). Only five benzylic protons would be expected for the *contracted* derivatives (**76** or **77**).

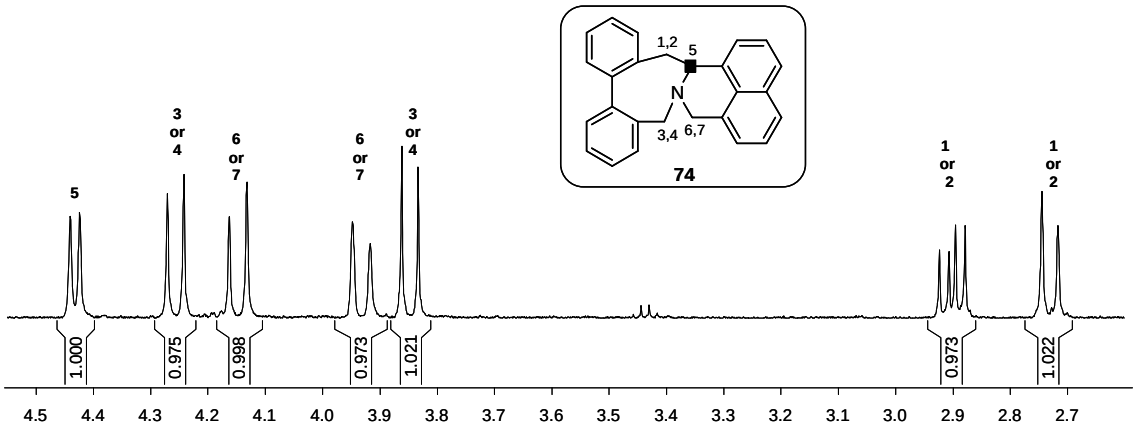
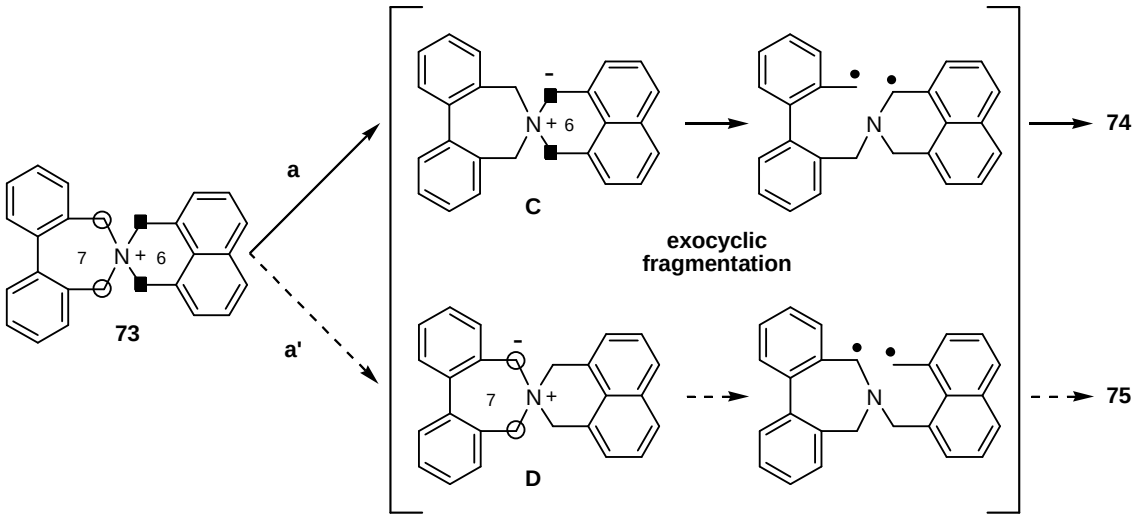



*Figure II-22*: $^{1}$H-NMR (500 MHz, $CD_2Cl_2$, 293 K) spectrum of the benzylic protons of the *ring-expanded* rearrangement product (**74** or **75**).

In fact, if the phosphazene base induced the deprotonation on the 6-membered ring, ylide **C** would then be generated, leading to the formation of the amine **74** constituted of fused 8- and 6-membered rings, after an exocylic N–C bond cleavage and a recombination of the corresponding biradical intermediate (*Scheme II-18*, path **a**). On the other hand, if the deprotonation occurred on the 7-membered ring, the ylide **D** would then be created, resulting in the formation of product **75** composed of two fused 7-membered rings, after the same exocyclic fragmentation/recombination pathway (*Scheme II-18*, path **a'**).




*Scheme II-18*: Two possible ylide intermediates for the [1,2]-Stevens rearrangement of the cation **73**, followed by the exocyclic fragmentation/recombination pathway.

At this stage, to establish which of the two *ring-expanded* amines was formed during the [1,2]-shift transformation (**74** or **75** ?), it was necessary to proceed in the same fashion as for the cation **61**. That's why, the experiment of the characterisation of the ylide for cation **73** was carried out and described in the next paragraph; other elaborated NMR experiments being unsufficient.

II-5.2.b Characterisation of the ylide intermediate

As just mentioned, experiments were performed to prove the formation of the ylide and to determine with precision the regioselectivity of the deprotonation, as in the case of cation **61**. Thus, at –90 °C, after the addition of the $P_4$-*t*-Bu (1.1 equiv.) as a base to a solution of [**73**][*rac*-TRISPHAT] salt in $CH_2Cl_2$, a fugace red coloration (~5 s) appeared, which was assumed to be the indication of the formation of ylide **C** or **D**. The immediate addition of MeOH-$d_4$ in excess (2.2 equiv.) led to the formation of the deuterated compound **78**, containing not one but two deuterium atoms on the 6-membered ring. Indeed, as shown in the $^1$H-NMR spectrum, the integration of the benzylic protons indicated the presence of 4 protons on the 7-membered ring against 2 on the 6-membered ring of **73** (*Figure II-23*); the deuterium atom being evenly distributed between the axial and equatorial positions due to the rapid interconversion of the atropisomers of **73** on all positions.[45]

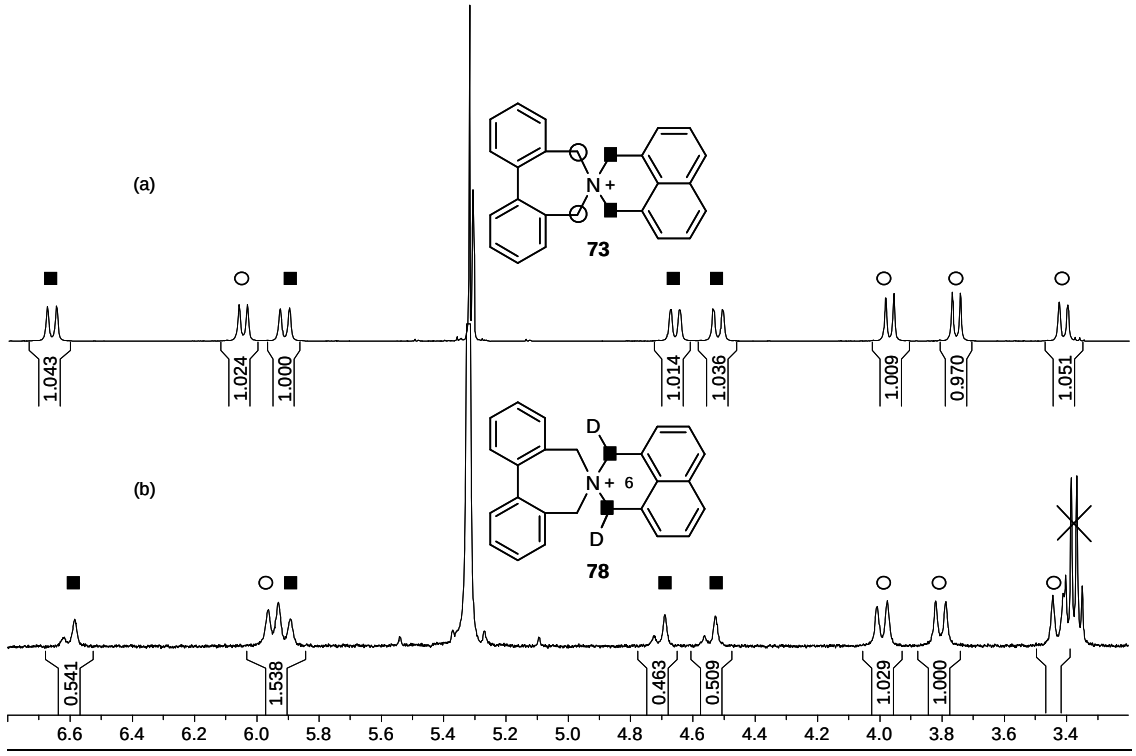



*Figure II-23*: $^{1}$H-NMR (500 MHz, $CD_2Cl_2$, 233 K) of cations: (a) **73** and (b) **78**.

Therefore, this experiment proves that the 6-membered ring of cation **73** is deprotonated not once but twice during the (5 s) reaction time, this result remaining unexplained at this stage. The benzylic protons on the 6-membered ring are certainly more acidic than those located on the 7-membered ring. Following the results obtained for the isoquinoline-dibenzoazepinium cation **73** and those achieved for the isoindanyl-dibenzoazepinium cation **61**, the rearrangement product must be the tertiary amine **74**, constituted of fused 8- and 6-membered rings.

II-5.2.c Attempts for an enantioselective [1,2]-Stevens rearrangement

The association of the *configurationally labile* quaternary ammonium cation **73** with the enantiopure *Δ*-BINPHAT anion, led to the predominance of one diastereomeric ion pair over the other, *e.g.* [(*M*)-**73**][*Δ*-BINPHAT] over [(*P*)-**73**][*Δ*-BINPHAT] (44% d.e., in $CD_2Cl_2$, see chapter II-5.1.c)[24,39]

Furthermore, with the established precedent on the enantioselective [1,2]-Stevens rearrangement of the isoindanyl-dibenzoazepinium cation [**61**[BINPHAT] salt and the spirobi[dibenzazepinium] cation **58**,[26] we decided to test the reactivity of the [**73**][*Δ*-BINPHAT] salt. However, its treatment with $P_4$-*t*-Bu (1.1 equiv., $CH_2Cl_2$, 4h) at three different temperatures: –80 °C, –40 °C and R.T. provided the racemic amine **74** only, albeit in good to excellent yields (96%, 94% and 87% respectively). This lack of selectivity was evidenced by the CSP-HPLC analysis (*Figure II-24*).

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 14.727 | 17897.8 | 986.8 | 0.2796 | 50.343 | 0.734 |
| 2 | 17.709 | 17653.6 | 830.7 | 0.3279 | 49.657 | 0.865 |

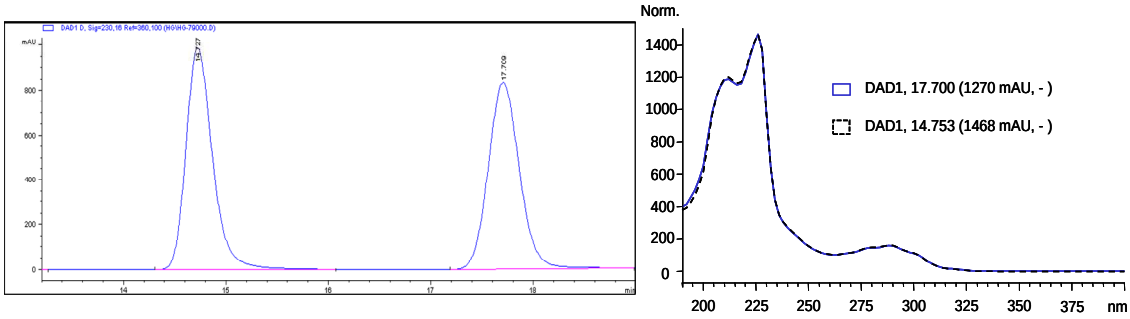


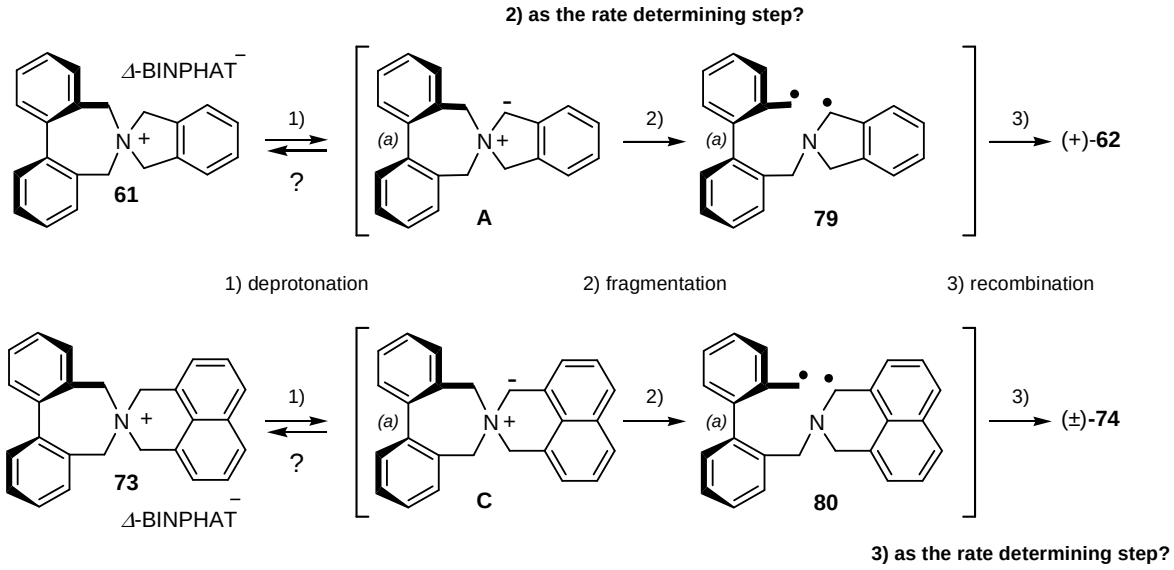

*Figure II-24*: Example of one HPLC trace (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C) of amines **74** from [**73**][*Δ*-BINPHAT] salt with 0% e.e. (*left*); Respective UV spectra of the two enantiomers of **74** (*right*).

## II-6 Conclusion

Comparing the "behaviour" of the cations **61** and **73** in the [1,2]-Stevens rearrangement, we can notice that the 7-membered ring is never deprotonated by the base, the other ring moiety being deprotonated. Interestingly, protons on the 5/6-membered ring are more acidic than of the 7-membered ring. This might be due to a stronger participation of the *2s* atomic orbital of the carbon atoms in these acidic C–H bonds of the 5/6-membered ring. As usual, the smaller the ring, the stronger the *s* participation gives the higher acidity.

The reaction is then always following an exocyclic fragmentation/ recombination pathway and generates a *ring-expanded* tertiary amine over a *ring-contracted* one. At first glance, the mechanism of the Stevens rearrangement should be quite similar for these two cations (*Scheme II-19*). However, we have observed that the selectivity of the reaction is moderate from the [**61**][*Δ*-BINPHAT] salt (34% e.e. and 45% ToC) and null for the [**73**][*Δ*-BINPHAT]

salt. The loss of selectivity, partial with **61** and complete with **73**, can be explained considering the "classical" diradical pathway of Ollis.[1] In fact, as previously described, the [1,2]-Stevens rearrangement of **61** and/or **73** should involve principally two successive intermediates. The first is a zwitterionic ylide **A** or **C** generated by deprotonation. The second intermediate is a radical pair **79** or **80** produced by homolytic fragmentation with an exocyclic bond cleavage (*Scheme II-19*). All compounds **A**/**79** or, **C**/**80** are neutral and should enable the *Δ*-BINPHAT anion to diffuse out of the reaction pocket. Loss of amine enantiomeric purity can then occur by rotation around the biaryl axis of **A**/**79** or **C**/**80** (See *(a)* in *Scheme II-19*).




*Scheme II-19:* Possible intermediates **A**/**C** and **79**/**80** in the rearrangement of **61** to **62** and **73** to **74**; Loss of chirality may occur by rotation of the biaryl C–C bond *(a)*.[64]

A clear-cut mechanism can be proposed to rationalise some of the results. For both cations **61** and **73**, it is clear that the benzylic protons on respectively the 5- and 6-membered ring are highly acidic. There exists in the two cases a rapid exchange of deuterium/hydrogen atoms in solution prior to the [1,2]-Stevens rearrangement. This would indicate that the initial deprotonation of **61** and **73** is probably reversible and that the deprotonation is not the kinetically determining step of the reaction.

In both cases, the biradical intermediates would be generated by an exocyclic N–C bond fragmentation. For the cation **61**, as discussed in chapter II-4.3.c, this fragmentation might be the kinetically determining step. However, for the cation **73**, the rate determining step might actually be the recombination. A slow C–C bond forming reaction would give ample time to the ylide **C** and the radical pair intermediate **80** to undergo racemisation by faster rotation *(a)* around the biaryl axis.

[64] Configurations for **73**, **C** and **80** are assumed by analogy with the results obtained for the cation **61**.

# Chapter III

# ENANTIOSELECTIVE [1,2]-STEVENS REARRANGEMENT AND EXCELLENT TRANSFER OF CHIRALITY

## Introduction

Our aim was still to achieve an enantioselective [1,2]-Stevens rearrangement that would occur, after asymmetric ion pairing,[1,2,3] with excellent chirality transfer after ylide formation. At this point of our study, we realised that two basic mechanistic questions had to be at least considered to reach our goal:

- Can the deprotonation of the ammonium cation be enantioselective and, if so, does it matter?
- Does the configuration of the 7-membered ring determine solely the selectivity of the Stevens rearrangement?

In fact, understanding more deeply the mechanism of the reaction would allow us to design better the skeleton of the *configurationally labile* quaternary ammonium cations to study and hopefully to achieve decent enantiomeric excesses and excellent selectivity for the transfer of chirality.

## III-1 Further mechanistic aspects

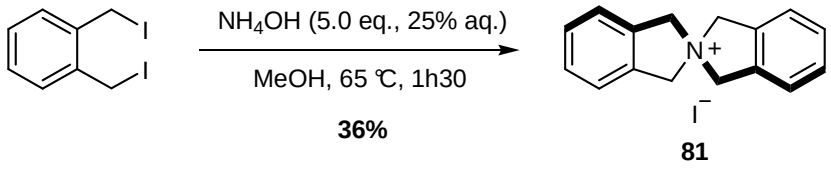
### *III-1.1 Enantioselectivity in the deprotonation of the [1,2]-Stevens rearrangement ?*

III-1.1.a Strategy to follow

In fact, association of *configurationally labile* cations with enantiopure counterions transforms the benzylic enantiotopic protons of the quaternary ammonium cations into diastereotopic ones giving hence the possibility, at least formal, of an enantioselective deprotonation.

[1] Lacour, J.; Linder, D. *Chem Rec* **2007**, *7*, 275-285. Lacour, J.; Frantz, R. *Org. Biomol. Chem.* **2005**, *3*, 15-19
[2] Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562-4565. Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496-499. Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193-4195. Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 3689-3692
[3] Macchioni, A. *Eur. J. Inorg Chem.* **2003**, 195-205

To study this enantioselective possibility of a deprotonation, occurring during the Stevens rearrangement, the quaternary tetrahydrospiro[isoindole-isoindolium] cation **81** was chosen (*Scheme III-1*).[4] This cation was considered ideal for the study as it is achiral (it contains two planes of symmetry) and conformationally rigid. It was prepared as its iodide salt from the reaction of the 1,2-bis(iodomethyl)benzene with $NH_4OH$ (5.0 equiv., MeOH, 65 °C) in moderate yield (36%).[5]




*Scheme III-1*: Synthesis of the tetrahydrospiro[isoindole-isoindolium] iodide salt [**81**][I].

As just mentioned, upon association of the spiro ammonium cation **81** with chiral anions, like the *Δ*-BINPHAT anion, the enantiotopic protons will become diastereotopic and possibly distinguishable by the Schwesinger's phosphazene base (the $P_4$-*t*-Bu).[6] In such cases, a [1,2]-Stevens rearrangement could, at least formally, happen with some enantioselectivity. This possibility was quite unlikely, considering the equilibrium occurring at the deprotonation stage, as demonstrated in the previous chapter. It nevertheless had to be tested.

III-1.1.b Effect of enantiopure BINPHAT and TRISPHAT anions on the achiral spiro ammonium cation

Salt [**81**][*Δ*-BINPHAT] was synthesised by solubilising the iodide salt [**81**][I] and the [$Me_2NH_2$][*Δ*-BINPHAT] (1.2 equiv.) together in methanol. Upon addition of water and cooling to 0 °C, a solid corresponding to the desired ion pairing, was afforded and collected by filtration (56% yield).

[4] Brewster, J. H.; Jones, R. S. *J. Org. Chem.* **1969**, *34*, 354-358
[5] Scholz, M. *Ber.* **1891**, *24*, 2402
[6] Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 1167-1169

For this salt, in $^1$H-NMR analysis at 20 °C (293 K), the influence of the enantiopure *Δ*-BINPHAT anion was easily seen. Indeed, the singlet signal of the eight equivalent (enantiotopic) benzylic protons of salt [**81**][I] (*Figure III-1*, (a)), is clearly shifted to lower frequency and split in two sets (two doublets), one for each diastereotopic set (*Figure III-1*, (c)). Moreover, the aromatic protons of the cation **81** in this *Δ*-BINPHAT salt are also shifted to lower frequency (*Figure III-1*, (c)).

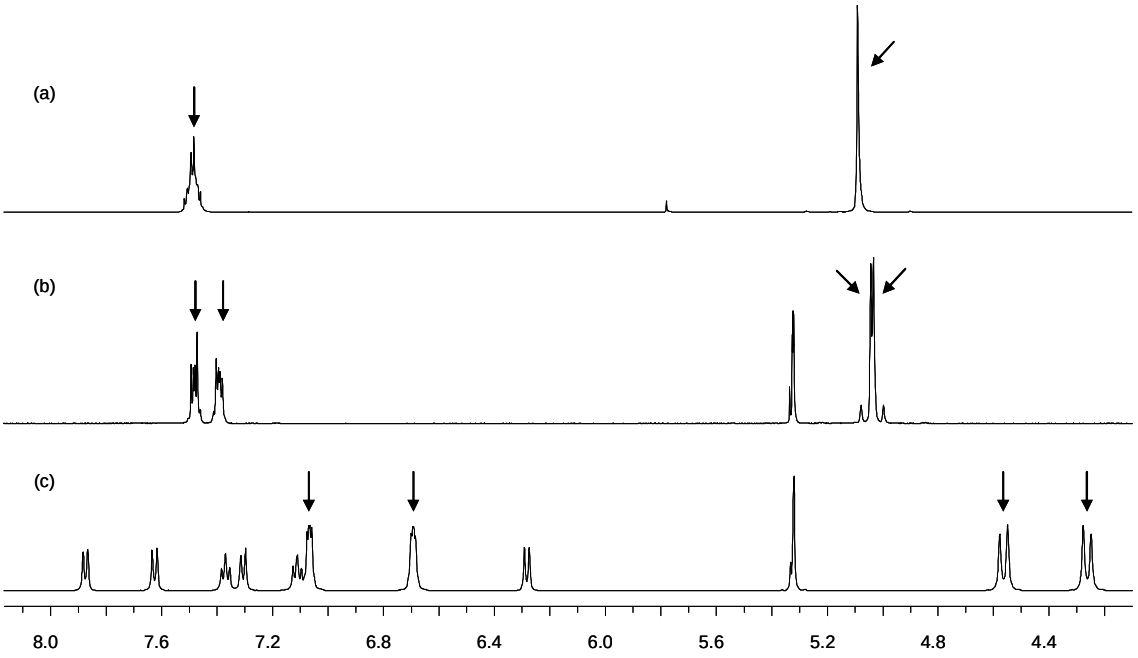
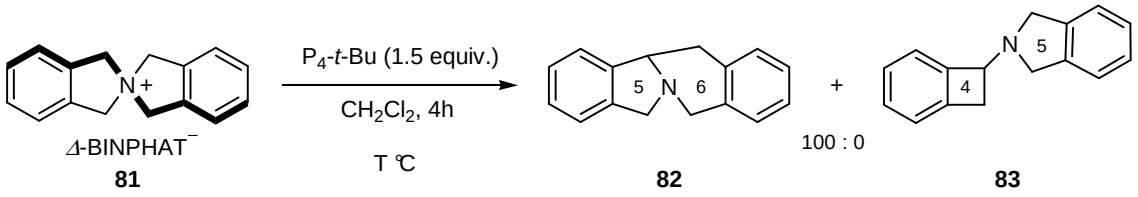



*Figure III-1*: $^1$H-NMR (400 MHz, 293 K) of salts (a) [**81**][I], DMSO-$d_6$; (b) [**81**][*Δ*-TRISPHAT], $CD_2Cl_2$; (c) [**81**][*Δ*-BINPHAT], $CD_2Cl_2$.

To check if the BINPHAT anion was indeed the best NMR chiral-solvating agent, salt [**81**][*Δ*-TRISPHAT] was also prepared, by mixing solutions of the iodide salt in $CH_2Cl_2$/MeOH mixture with [cinchonidinium][*Δ*-TRISPHAT] (1.2 equiv.) in water/acetone mixture. Flash chromatography of the crude on basic alumina, with $CH_2Cl_2$ as eluent, afforded the desired pair [**81**][*Δ*-TRIPHAT] as the single eluted salt (75% yield). A much reduced enantioseparation of the benzylic protons of cation **81** was obtained, validating the choice of the BINPHAT anion (*Figure III-1*, (b)).

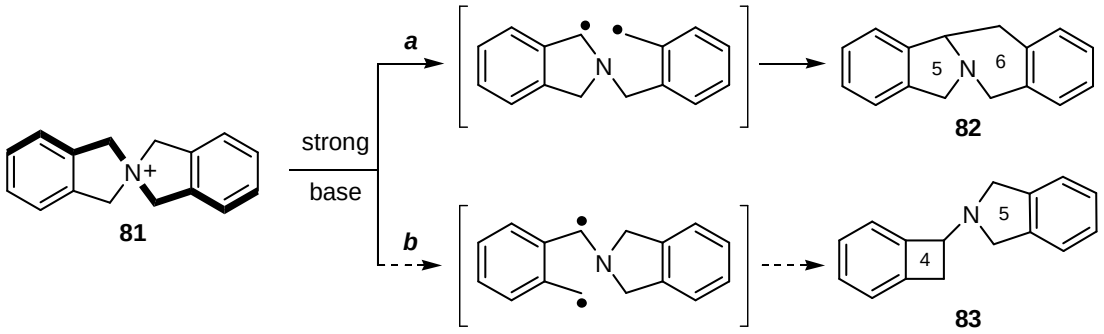
III-1.1.c [1,2]-Stevens rearrangement of the tetrahydrospiro[isoindole-isoindolium] cation

Treatment of salt [**81**][*Δ*-BINPHAT] with the $P_4$-*t*-Bu base (1.5 equiv.) in $CH_2Cl_2$ at various temperatures led to the formation of the tertiary amine **82**.[7] Although two products **82** and **83** were theoretically possible, the *ring-expanded* amine **82** was obtained stereoselectively over the *ring-contracted* one **83** (*Scheme III-2*).




*Scheme III-2*: Stevens rearrangement of [**81**][*Δ*-BINPHAT] salt.

Analysis of the mechanism[8] of the reaction indicated indeed that two distinct rearrangement products could be formed during the reaction (*Scheme III-3*, pathways ***a*** and ***b***). Each position being isoelectronic, two biradical intermediates could be formed after generation of the ylide, during the [1,2]-Stevens rearrangement.[9] One biradical intermediate with an exocyclic nitrogen-carbon bond would give after recombination the fused 5- and 6-membered ring system **82** (path ***a***). The coupling of the other biradical would provide the non-fused 4- and 5-membered ring system **83**, corresponding to the endocyclic rearrangement (path ***b***).




*Scheme III-3*: Possible pathways for the [1,2]-Stevens rearrangement of the cation **81**.

[7] Wittig, G.; Tenhaeff, H.; Schoch, W.; Koenig, G. *Annalen Der Chemie-Justus Liebig* **1951**, *572*, 1-22
[8] Maeda, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1491-1493. Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009-1027. Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049-1061. Ollis, W. D.; Rey, M.; Sutherland, I. O.; Closs, G. L. *J. Chem. Soc., Chem. Commun.* **1975**, 543-545
[9] Vial, L.; Gonçalves, M.-H.; Morgantini, P.-Y.; Weber, J.; Bernardinelli, G.; Lacour, J. *Synlett* **2004**, 1565-1568

The structure of **82** was confirmed by $^{1}$H-NMR analysis at 20 °C (293 K) showing seven separated signals for the benzylic protons (only five would be expected for derivative **83**) (*Figure III-2*).

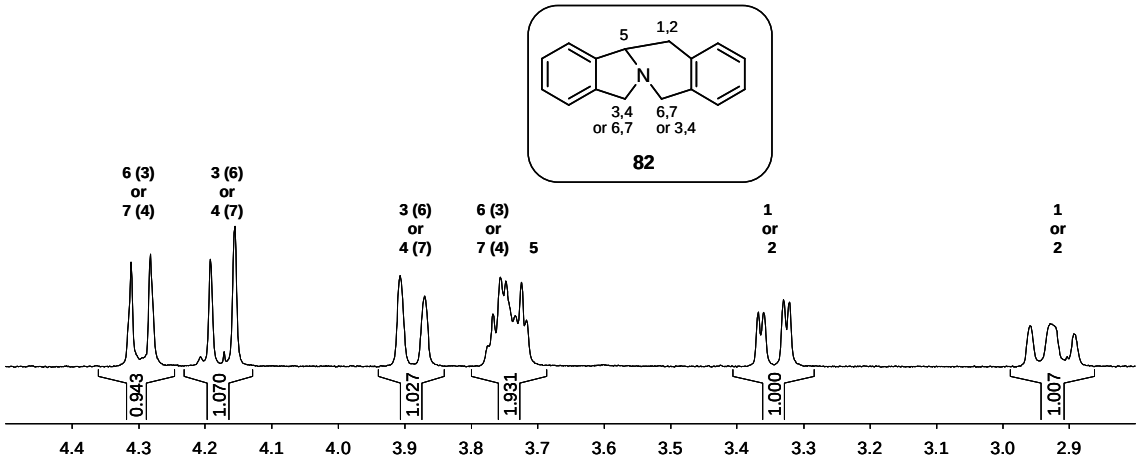
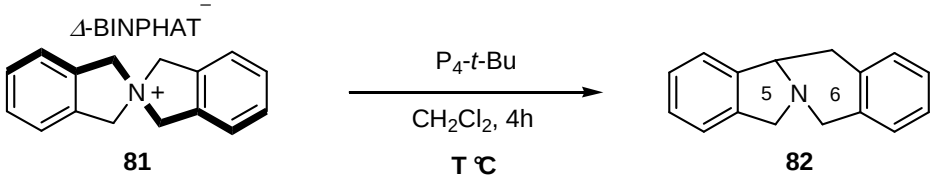



*Figure III-2*: $^{1}$H-NMR (400 MHz, $CD_2Cl_2$, 293 K) spectrum of the benzylic protons of the *ring-expanded* rearrangement product **82**.

But, the main result of this study was that the [1,2]-Stevens rearrangement of the [**81**][*Δ*-BINPHAT] salt always afforded tertiary amine **82** in racemic form, at various temperatures between –80 and 25 °C (193 to 298 K) (*Table III-1*). An enantiomeric excess of 0% for each reaction was determined by CSP-HPLC (*Figure III-3*). This seems to confirm our intuition, that the deprotonation of the 5-membered ring of ammonium **81** is not enantioselective in the Stevens rearrangement process.

*Table III-1*: [1,2]-Stevens rearrangement of the tetrahydrospiro[isoindole-isoindolium] BINPHAT salt [**81**][*Δ*-BINPHAT] [a] at various temperatures.



| **T °C** | Yield % | e.e. %[b] |
|---|---|---|
| -80 | 12 | 0 |
| -60 | 13 | 0 |
| -40 | 15 | 0 |
| -20 | 23 | 0 |
| +25 | 54 | 0 |

[a]Conditions: $P_4$-*t*-Bu (1M in Hexane, 1.5 equiv.), $CH_2Cl_2$, 4h; [b]Average of two runs, enantiomeric purity of **82** determined by CSP-HPLC (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C).

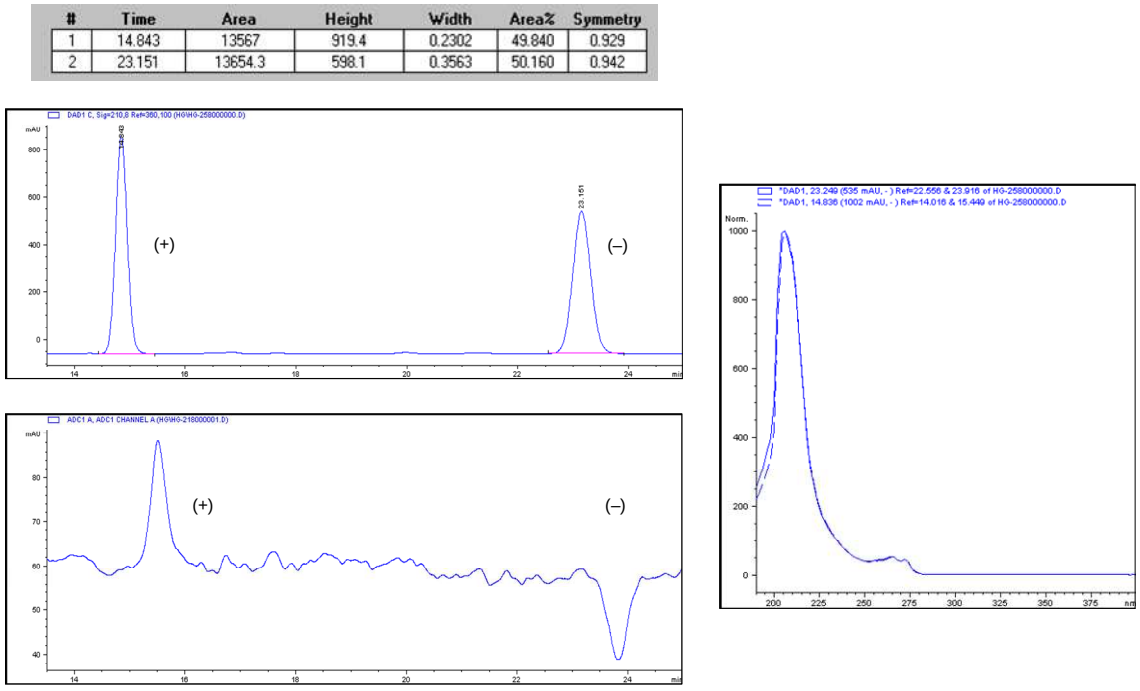


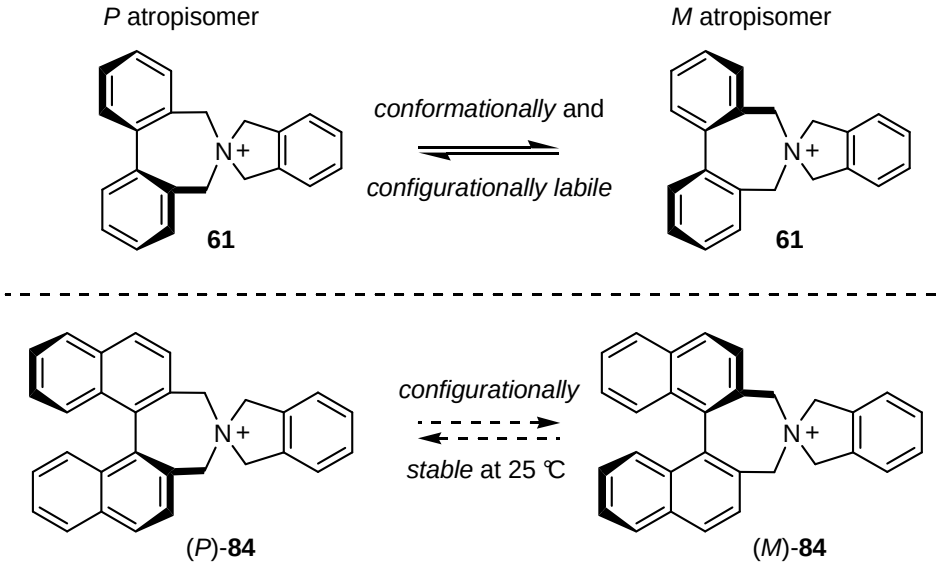

*Figure III-3*: Example of one HPLC trace (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C) of amines **82** from salt [**81**][*Δ*-BINPHAT] with 0% e.e. and ORD trace of the two enantiomers (*left*); Respective UV spectra of the two enantiomers of **82** (*right*).

### *III-1.2 Importance of the 7-membered ring configuration in the selectivity of the Stevens rearrangement*

III-1.2.a Scope

To test decisively the importance of the stereochemistry of the 7-membered ring, we decided to replace the *configurationally labile* 7-membered dibenzo[*c*,*e*]azepinium ring included in the cation **61**, by a *configurationally stable* dinaphth[*c*,*e*]azepinium ring. In this context, the chiral isoindanyl-dinaphthazepinium cation (*P*)-**84** and its enantiomer (*M*)-**84** were prepared (*Scheme III-4*).

These cations **84** would then be tested in the [1,2]-Stevens rearrangement with either an iodide or a BINPHAT as counterions. If the amine product is obtained predominantly or exclusively as one stereoisomer, this will be the proof that indeed, the configuration of the 7-membered ring determines the selectivity of the Stevens rearrangement. Depending on the *P* or *M* configuration of the dinaphth[*c*,*e*]azepinium ring, enantiomeric products should also result.

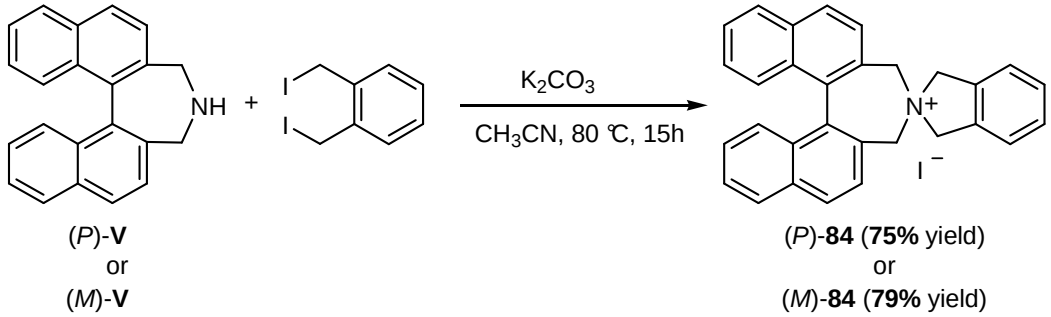



*Scheme III-4*: Comparison between the diphenylazepinium **61** and the diarylazepiniums **84**.

III-1.2.b Synthesis of the iodide salt of (*P*) and (*M*) isoindanyl-dinaphthazepinium cations

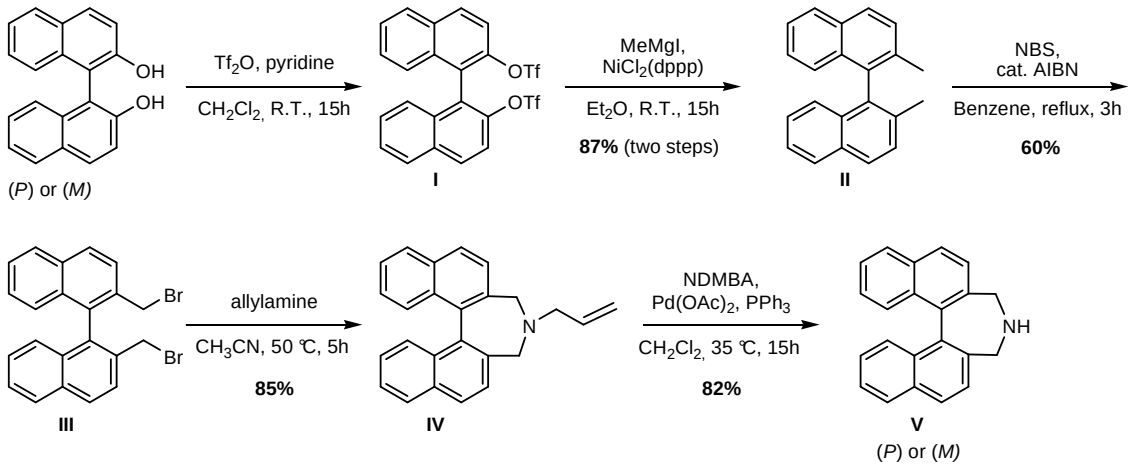
The (*P*)- or (*M*)-6,6-isoindanyl-3,5-dihydro-4H-dinaphth[2,1-*c*;1',2'-*e*]azepinium iodide salts [**84**][I] were synthesised by alkylation of the secondary amines (*P*)- or (*M*)-3,5-dihydro-4H-

dinaphth[2,1-c;1',2'-e]azepine **V** with 1,2-bis(iodomethyl)benzene ($K_2CO_3$, $CH_3CN$, 80 °C) in 75% and 79% respective yields (*Scheme III-5*).




*Scheme III-5*: Synthesis of the isoindanyl-dinaphthazepinium iodide salts [(*P*)-**84**][I] and [(*M*)-**84**][I].

Amines **V** were synthesised from commercially available or simply prepared (*P*)- or (*M*)-1,1'-bi-2-naphthol (BINOL) in a five-step sequence as shown in *Scheme III-6*.[10] A bis *O*-triflation of this diol followed by a Kumada's Ni(0)-catalysed cross-coupling with MeMgI gave **II** in 87% yield over two steps; the reactions were completely stereospecific. Radical bromination of **II** afforded the dibromide compound **III** (60% yield) which reacted with allylamine to form tertiary amines **IV** (85% yield). Finally, a Pd(0)-catalysed *N*-deallylation provided the (*P*)- or (*M*)-3,5-dihydro-4H-dinaphth[2,1-*c*;1',2'-*e*]azepine **V** in 82% yield.

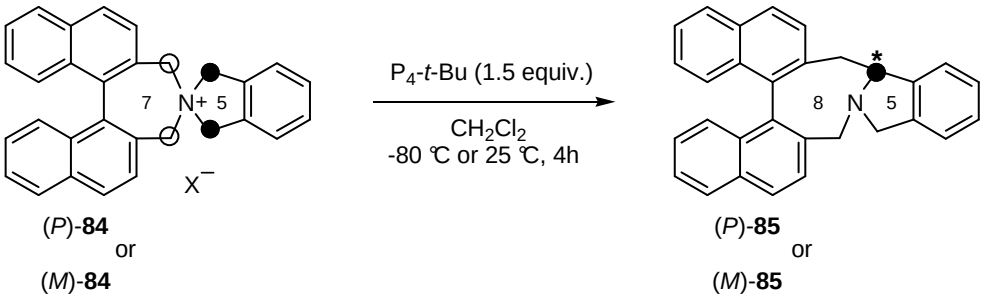



*Scheme III-6*: Synthesis of (*P*)- or (*M*)-3,5-dihydro-4H-dinaphth[2,1-*c*;1',2'-*e*]azepine **V**.

[10] Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139-5151. Ikunaka, M.; Maruoka, K.; Okuda, Y.; Ooi, T. *Org. Process Res. Dev.* **2003**, *7*, 644-648. Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519-6520

III-1.2.c Diastereoselective [1,2]-Stevens Rearrangement of the isoindanyl-dinaphthazepinium cations

The iodide and *Δ*-BINPHAT salts[11] of the ammonium cations (*P*)- and (*M*)-**84** were then treated with the Schwesinger's base[6] $P_4$-*t*-Bu (1.5 equiv.) in $CH_2Cl_2$ at –80 °C or 25 °C to yield exclusively the *ring-expanded* tertiary amines (*P*)-**85** and (*M*)-**85** (*Scheme III-7*, *Table III-2*, *Table III-3*).




(*P*)-**84** or (*M*)-**84** → (*P*)-**85** or (*M*)-**85**

*Scheme III-7*: Stevens rearrangement of salts [(*P*)-**84**][I] / [(*P*)-**84**][*Δ*-BINPHAT] and [(*M*)-**84**][I] / [(*M*)-**84**][*Δ*-BINPHAT].

The structure of this amine **85** was established by comparison of the NMR data with those of **62**, previously obtained by the [1,2]-Stevens rearrangement of the related isoindanyl-dibenzoazepinium cation **61** (See chapter II-4.2). Amine **85** is constituted of a fused 8- and 5-membered ring system and its formation can be explained by the probable mechanism[8] described in chapter II-4.2.b. This involves one deprotonation of the 5-membered ring, generating the corresponding ylide intermediate, followed by a homolytic exocyclic fragmentation and a recombination of the biradical intermediate.

[11] The ion pairings were realised by mixing a solution of the iodide salt with that of [$Me_2NH_2$][*Δ*-BINPHAT] in $CH_2Cl_2$/acetone. Chromatographic filtration of the crude mixture on basic alumina with $CH_2Cl_2$ as eluent afforded respectively the desired pair [(*P*)-**84**][*Δ*-BINPHAT] or [(*M*)-**84**] ][*Δ*-BINPHAT] as the only eluted salt (92% and 99% respective yields).

In all cases, the $^1$H-NMR spectra of the product were identical and showed signals corresponding to a single diastereomer. Seven clear and distinct resonances at 20 °C (293 K) are noticed, corresponding to the signals of the seven benzylic protons of compound **85** (*Figure III-4*).

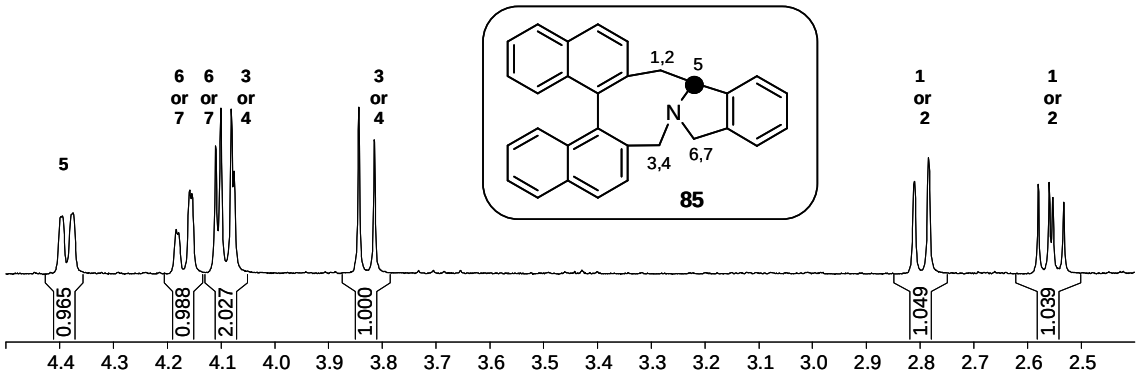
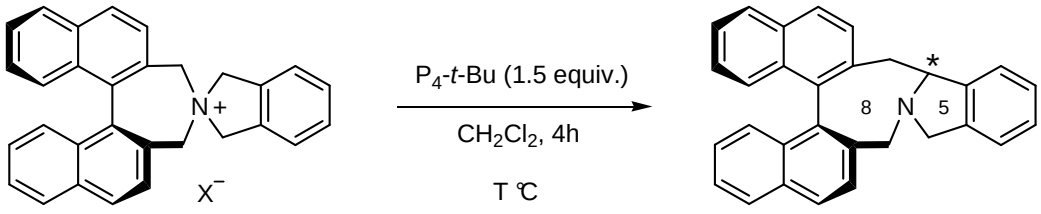



*Figure III-4*: $^1$H-NMR (500 MHz, $CD_2Cl_2$, 293 K) spectrum of the benzylic protons of the *ring-expanded* rearrangement product **85**.

Salts [(*P*)-**84**][I] and [(*P*)-**84**][*Δ*-BINPHAT] afforded (+)-(*P*)-**85**, whereas [(*M*)-**84**][*I*] and [(*M*)-**84**][*Δ*-BINPHAT] gave (–)-(*M*)-**85**. To conclude, it is clear from these results that the configuration of the 7-membered ring is key for the stereoselectivity of the process – as shown previously by Mislow[12] and Závada.[13] The presence of a single diastereomer also indicates that the transfer of chirality is complete even if the [1,2]-Stevens rearrangement occurs with *ring-expansion* rather than *ring-contraction*. Interestingly, the yields are virtually the same in both series – [(*P*)-**84**][I] and [(*M*)-**84**][I] – [(*P*)-**84**][*Δ*-BINPHAT] and [(*M*)-**84**][*Δ*-BINPHAT] in particular. The configuration of the anion has no effect in the present case, which is completely logical.

[12] Joshua, H.; Gans, R.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4884-4892
[13] Stará, I. G.; Starý, I.; Tichý, M.; Závada, J.; Hanuš, V. *J. Am. Chem. Soc.* **1994**, *116*, 5084-5088

*Table III-2*: [1,2]-Stevens rearrangement of the isoindanyl-dinaphthazepinium cation (*P*)-**84**.[a]

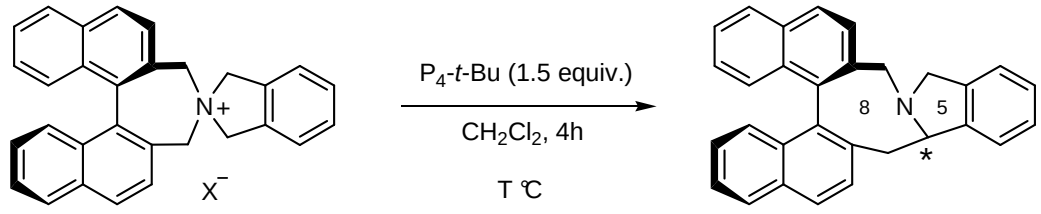



(*P*)-**84** (*P*)-**85**

| Anion | T °C | Yield % | d.e. %[b] | $[\alpha]_D$[c] | ToC % |
|---|---|---|---|---|---|
| I | -80 | 42 | >99 | (+) | 100 |
| I | +25 | 20 | >99 | (+) | 100 |
| [*Δ*-BINPHAT] | -80 | 32 | >99 | (+) | 100 |
| [*Δ*-BINPHAT] | +25 | 23 | >99 | (+) | 100 |

[a]Conditions: $P_4$-*t*-Bu (1M in Hexane, 1.5 equiv.), $CH_2Cl_2$, 4h; [b]Average of two runs, diastereoselectivity of the amine (*P*)-**85** determined by $^1$H-NMR at 293 K; [c]Sign of the optical rotation of (*P*)-**85**.

*Table III-3*: [1,2]-Stevens rearrangement of the isoindanyl-dinaphthazepinium cation (*M*)-**84**.[a]




(*M*)-**84** (*M*)-**85**

| Anion | T °C | Yield % | d.e. %[b] | $[\alpha]_D$[c] | ToC % |
|---|---|---|---|---|---|
| I | -80 | 42 | >99 | (–) | 100 |
| I | +25 | 21 | >99 | (–) | 100 |
| [*Δ*-BINPHAT] | -80 | 33 | >99 | (–) | 100 |
| [*Δ*-BINPHAT] | +25 | 23 | >99 | (–) | 100 |

[a]Conditions: $P_4$-*t*-Bu (1M in Hexane, 1.5 equiv.), $CH_2Cl_2$, 4h; [b]Average of two runs, diastereoselectivity of the amine (*M*)-**85** determined by $^1$H-NMR at 293 K; [c]Sign of the optical rotation of (*M*)-**85**.

## III-2 Dibenzoazepine-indolinium cations and [1,2]-Stevens rearrangement

### *III-2.1 Description of our strategy*

III-2.1.a Envisaged methods to improve our results

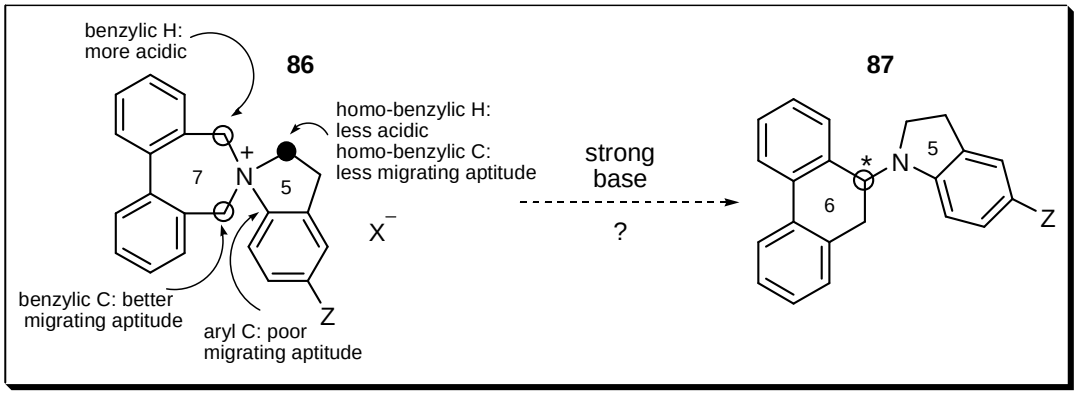
At this stage, we wondered what had to be done to improve the enantioselectivity of the [1,2]-Stevens rearrangement of *configurationally labile* quaternary ammonium cations. It was clear that a ToC of 45% from the diphenylazepinium **61** to amine **62** (See chapter II-4.3.a) was far too limiting – in particular, in view of the results just obtained for the *configurationally stable* dinaphthazepiniums **84**, leading to amine **85** with perfect transfer of chirality.

Looking back at the results of Mislow[12] and Závada,[13] in which diarylazepinium cations of type **42** have yielded *ring-contracted* amines of type **43** (See chapter II-1.2), we wondered if such endocyclic [1,2]-Stevens rearrangements would not occur more rapidly than the exocyclic ones. Moreover, we wondered if the presence in the same ring of the ylide and the migrating group, would not ensure a higher selectivity, by increasing the probability of encounter of the radicals or by rigidifying the transition state.

However, so far, only *ring-expanded* products have been observed, coming in most cases from a deprotonation of the ring other than the 7-membered one. In fact, in the case of the spirobi[dibenzazepinium] cation **58**, even if the formation of the ylide happened necessarily on the 7-membered ring, the *ring-expanded* amine **59** was obtained (See chapter II-3.1).[9] That's why, to achieve the goal of an endocyclic Stevens rearrangement arising on the 7-membered ring, a careful design was therefore required.

III-2.1.b Choice of the dibenzoazepine-indolinium skeleton

With this established precedent, it occurred to us that the ring other than the 7-membered one was the steering element – readily available indoline rings, in particular. The reasons of this ring choice for the constitution of quaternary ammonium cations of type **86**, made of the 7-membered dibenzo[*c*,*e*]azepinium and the 5-membered indolinium ring joined together at the charged nitrogen atom, are detailed below (*Scheme III-8*).




*Scheme III-8*: Possible enantioselective [1,2]-Stevens rearrangement of the dibenzoazepine-indolinium cations of type **86**.

First, the presence $\alpha$ to the nitrogen atom of homo-benzylic protons on the 5-membered indolinium ring should ensure the deprotonation of the more acidic benzylic protons located on the 7-membered ring (*Scheme III-8*). Second, the presence $\alpha$ to the nitrogen atom of an aryl and a homo-benzylic carbon on the 5-membered ring should disfavour the exocyclic fragmentation/recombination pathway, as the non-deprotonated benzylic carbon of the 7-membered ring ought to be a better migrating group (*Scheme III-8*). *Ring-contracted* tertiary amines of type **87** constituted of non-fused 6- and 5-membered rings should thus result from the [1,2]-Stevens rearrangement of *configurationally labile* dibenzoazepine-indolinium cations of type **86** (*Scheme III-8*).

The association of these cations with enantiopure BINPHAT anion would hopefully lead to high enantiomeric purity. The stereoselectivity would again come from an unbalance in the population of the diastereomeric salts,[14,15] *e.g.* [(*M*)-**86**][BINPHAT] over [(*P*)-**86**][BINPHAT], resulting possibly in the preferential formation of one enantiomer of rearranged product **87** over the other with high level of transfer of chirality.

[14] Yeh, R. M.; Raymond, K. N. *Inorg. Chem.* **2006**, *45*, 1130-1139. Bonnot, C.; Chambron, J.-C.; Espinosa, E. *J. Am. Chem. Soc.* **2004**, *126*, 11412-11413. Green, M. M.; Khatri, C.; Peterson, N. C. *J. Am. Chem. Soc.* **1993**, *115*, 4941-4942. Kirschner, S.; Ahmad, N.; Munir, C.; Pollock, R. J. *Pure Appl. Chem.* **1979**, *51*, 913-923. Pfeiffer, P.; Quehl, K. *Chem. Ber.* **1931**, *64*, 2667-2671

[15] Winkelmann, O.; Linder, D.; Lacour, J.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2007**, 3687-3697. Laleu, B.; Bernardinelli, G.; Chauvin, R.; Lacour, J. *J. Org. Chem.* **2006**, *71*, 7412-7416. Vignon, S. A.; Wong, J.; Tseng, H.-R.; Stoddart, J. F. *Org. Lett.* **2004**, *6*, 1095-1098. Martínez-Viviente, E.; Pregosin, P. S.; Vial, L.; Herse, C.; Lacour, J. *Chem. Eur. J.* **2004**, *10*, 2912-2918. Hiraoka, S.; Harano, K.; Tanaka, T.; Shiro, M.; Shionoya, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5182-5185. Vial, L.; Lacour, J. *Org. Lett.* **2002**, *4*, 3939-3942

### *III-2.2 Studies of the [1,2]-Stevens rearrangement on the cations of dibenzoazepine-indolinium type*

III-2.2.a Synthesis of the bromide salts of the dibenzoazepine-indolinium cations

Our hypothesis was assessed by preparing a series of dibenzoazepine-indolinium cations of type **86** with various substituents at the 5-position of the indolinium ring (*Figure III-5*). Bromide salts [**86a**][Br] to [**86h**][Br] (Z = H, OMe, OBn, F, Cl, Br, I, $NO_2$) were prepared in one-step by condensation of the 2,2'-bis(bromomethyl)biphenyl with the respective commercially available indolines or simply prepared indolinium chlorides, in good yields (**a** = 83%, **b** = 71%, **c** = 73%, **d** = 90%, **e** = 84%, **f** = 69%, **g** = 84%, **h** = 67%). When necessary, the indolinium chloride salts were obtained by reduction of the corresponding indoles with sodium cyanoborohydride[16] followed by a treatment with HCl (1.0 M in $Et_2O$, 43-97% yields).

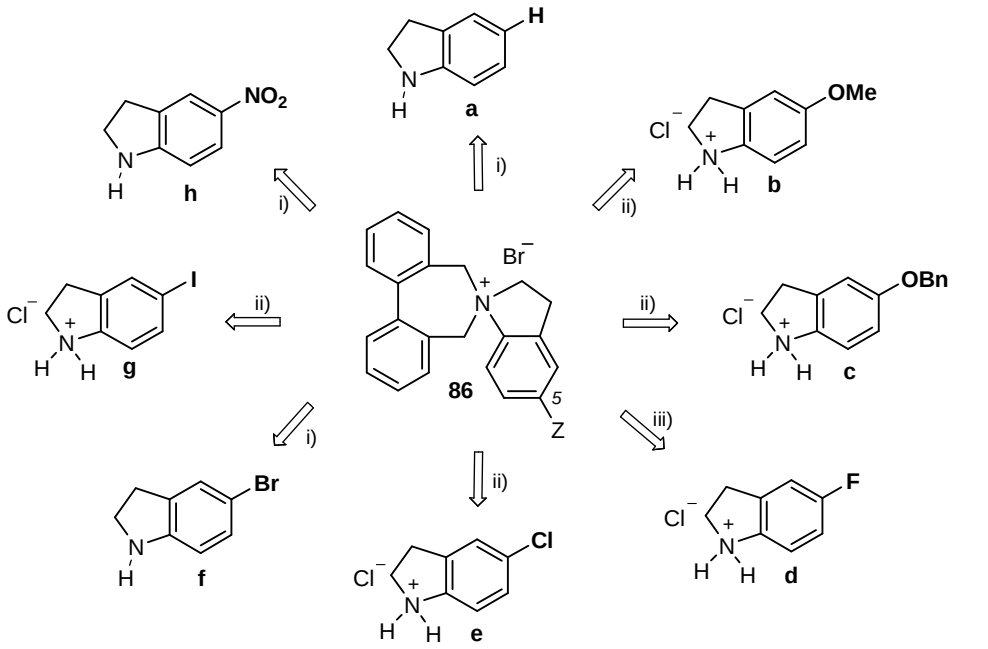



*Figure III-5*: Synthesis of a series of dibenzoazepine-indolinium bromide salts [**86**][Br].

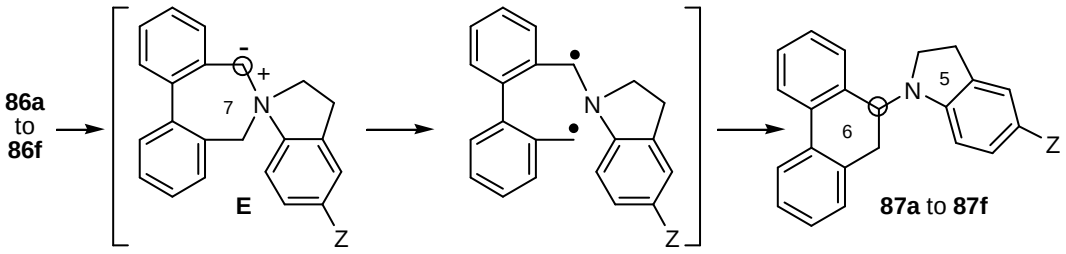
[16] Chandra, T.; Brown, K. L. *Tetrahedron Lett.* **2005**, *46*, 2071-2074. Gangjee, A.; Vasudevan, A.; Queener, S. F. *J. Med.Chem.* **1997**, *40*, 479-485

III-2.2.b Synthesis of the BINPHAT salts of the dibenzoazepine-indolinium cations

The ion pairing with BINPHAT anion was realised by mixing solutions of the bromide salts [**86**][Br] with that of [$Me_2NH_2$][*Δ*-BINPHAT] (or its enantiomer) in $CH_2Cl_2$/acetone. Flash chromatography of the crude mixture on basic alumina with $CH_2Cl_2$ as eluent, afforded the desired pairs [**86a**][*Δ*-BINPHAT] to [**86h**][*Δ*-BINPHAT] as the only eluted salts (70-98% yields).[17] Salt [**86a**][*Λ*-BINPHAT] was similarly prepared (87% yield).

III-2.2.c "Racemic" version of the [1,2]-Stevens rearrangement of the dibenzoazepine-indolinium cations

Like in our previous studies of the Stevens rearrangement, care was taken to select again a neutral base to avoid any trouble with the possible asymmetric ion pairing situation and $P_4$-*t*-Bu was used in particular.[18,19] Treatment of the bromide salts of ammonium cations **86a** to **86f** with $P_4$-*t*-Bu (1.5 equiv, $CH_2Cl_2$, –80 °C, 4h), followed by a quench of the reaction with MeOH (at –80 °C), resulted primarily in the formation of the desired *ring-contracted* amines **87a** to **87f**.




*Scheme III-9*: Pathway for the [1,2]-Stevens rearrangement of dibenzoazepine-indolinium cations of type **86**.

[17] Hexacoordinated phosphate BINPHAT anions confer to their salts a poor affinity for polar chromatographic phases as they elute rapidly over silica gel / alumina, see: Desvergnes-Breuil, V.; Hebbe, V.; Dietrich-Buchecker, C.; Sauvage, J.-P.; Lacour, J. *Inorg. Chem.* **2003**, *42*, 255-257. Monchaud, D.; Jodry, J. J.; Pomeranc, D.; Heitz, V.; Chambron, J.-C.; Sauvage, J.-P.; Lacour, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2317-2319. Lacour, J.; Barchéchath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567-570

[18] Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 1167-1169

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

Indeed, NMR analyses at 25 °C of **87a** to **87f** indicated clearly the formation of these *ring-contracted* 6-membered ring adducts (*Figure III-6*). Other possible regioisomers coming from competing deprotonation/migration pathways were not formed. In fact, these rearranged products resulted from a deprotonation of a benzylic proton localised on the 7-membered dibenzo[*c*,*e*]azepinium ring, these benzylic protons being as stated the most acidic protons on the dibenzoazepine-indolinium derivatives, followed by the generation of the corresponding ylide **E** (*Scheme III-9*). Next, a homolytic fragmentation with a break of the endocyclic N–C bond occurred, providing one biradical intermediate which recombined by migration of the non-deprotonated benzylic carbon to form amines **87a** to **87f**.

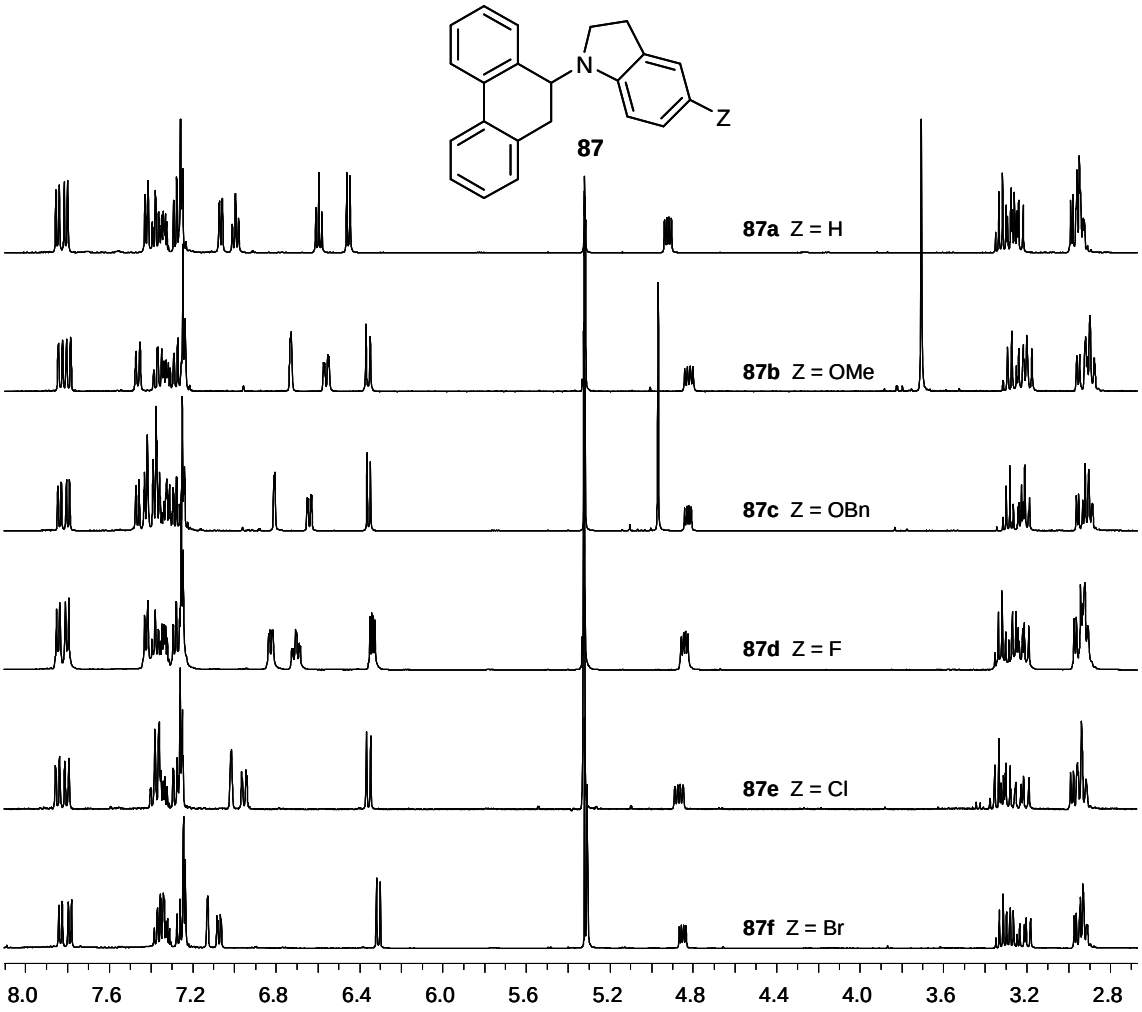



*Figure III-6*: $^{1}$H-NMR (500 MHz, $CD_2Cl_2$, 293 K) spectra of the *ring-contracted* rearrangement products **87a** to **87f**.

The yields of these [1,2]-Stevens rearrangements were excellent for **87a** (92%), moderate with the substituted derivatives **87b** to **87e** (46-53%) and quite low with the bromide tertiary amine **87f** (24%). We believe that the lower yields are due to a competitive Hofmann elimination reaction which occurs under the strong basic conditions used. This Hofmann elimination arised by removal of the acidic (benzylic) hydrogen $\beta$ to the nitrogen, on the 5-membered ring. Indeed, for each [1,2]-shift reaction, the secondary products **88b** to **88e** were isolated and characterised by $^1$H-NMR analysis in particular, as shown in *Figure III-7*.

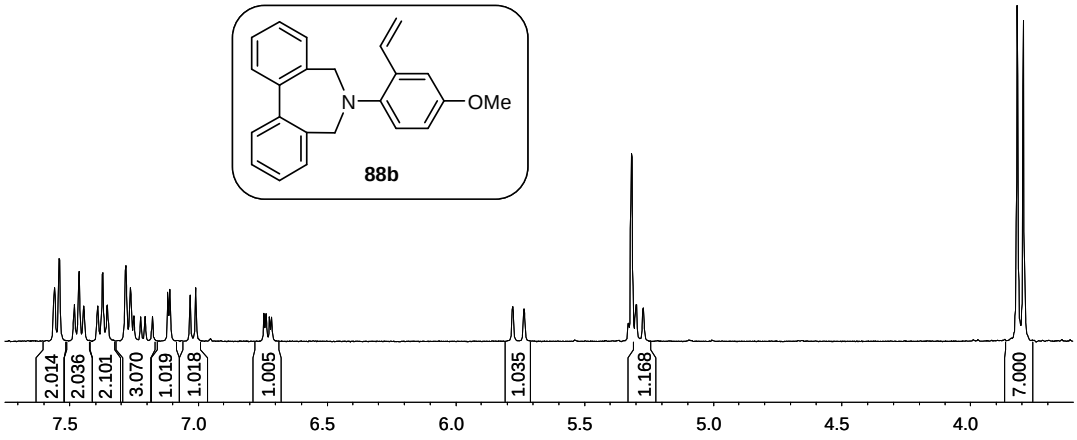


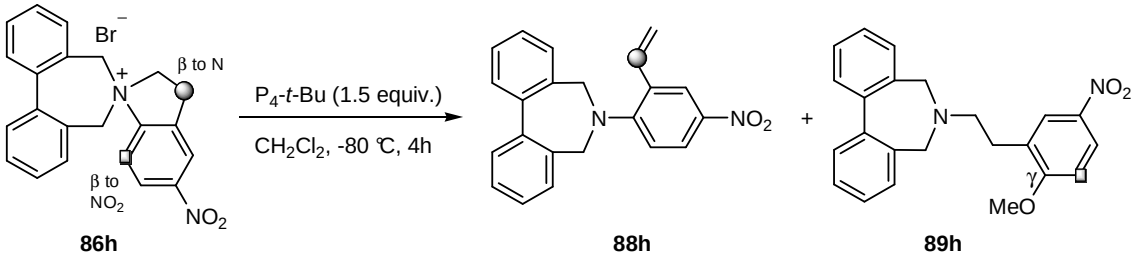

*Figure III-7*: One example of the $^1$H-NMR (400 MHz, $CD_2Cl_2$, 293 K) spectrum of Hofmann elimination product **88b**.

In the particular case of the [1,2]-Stevens rearrangement of salt [**86g**][**Br**] (Z = I), in addition to the Hofmann elimination product **88g**, a mixture of two inseparable racemic *ring-contracted* amines **87g** and **87a**, were obtained containing at the 5-position of the indolinium ring an iodide or a hydrogen atom. These results were deduced from $^1$H-NMR analysis which showed two sets of similar signals in the benzylic region, in a 15:85 ratio for the amines **87g** and **87a** respectively. Chiral Stationary Phase (CSP)-HPLC revealed the presence of two couples of enantiomers, both being in racemic mixtures. The origin of compound **87a** remains at this stage quite mysterious.

Interestingly, treatment of the bromide salt of **86h**, having at the 5-position of the indolinium ring a nitro substituent, with $P_4$-*t*-Bu (1.5 equiv, $CH_2Cl_2$, –80 °C, 4h) gave no traces of rearranged products. In this case, the [**86h**][Br] salt reacted *via* other competitive reactions – Hofmann elimination and benzyne formation in particular. Indeed, the strong electron-withdrawing nitro group increased the acidity of the protons $\beta$ to the nitrogen atom on the 5-membered indolinium ring, compared to the benzylic ones on the 7-membered

dibenzo[*c*,*e*]azepinium ring. Thus, the formation of the Hofmann elimination product **88h** was quite strongly promoted (25% yield, *Scheme III-10*).

Moreover, the aromatic proton $\beta$ to the nitro group being more acidic, the formation of a benzyne intermediate by deprotonation and break of the adjacent C–N bond seemed to be favoured. The product of a nucleophilic addition of the methanol used for quenching on the benzyne intermediate ($\gamma$ to the electron-withdrawing nitro group) **89h**, was formed and isolated (45% yield, *Scheme III-10*). Products **88h** and **89h** were characterised by NMR spectroscopy and Mass measurements.




**86h** **88h** **89h**

*Scheme III-10*: Products obtained from the [**86h**][Br] salt (Z = $NO_2$) treated under strong basic conditions which are commonly used for the [1,2]-Stevens rearrangement.

### *III-2.3 Enantioselective [1,2]-Stevens rearrangement and excellent transfer of chirality*

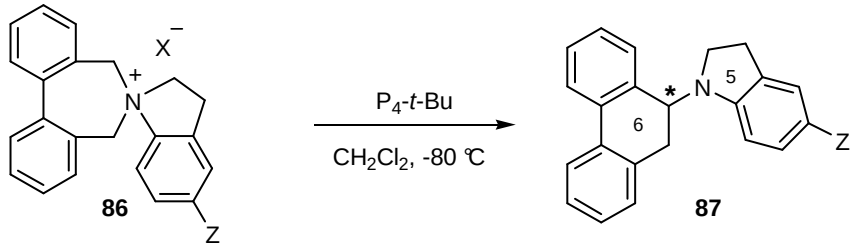
III-2.3.a Enantioselectivity of the reaction of the dibenzoazepine-indolinium cations

With these results in hand, salt [**86a**][$\Delta$-BINPHAT] and its enantiomer [**86a**][$\Lambda$-BINPHAT] were treated with the $P_4$-*t*-Bu base (1.5 equiv, $CH_2Cl_2$, –80 °C, 4h) to yield non-racemic amines (+)-**87a** and (–)-**87a** respectively. Chiral Stationary Phase (CSP)-HPLC revealed an enantiomeric purity of 33% for each (*Table III-4* and *Figure III-8*). The occurrence of an enantioselective reaction was confirmed by the rearrangements of [**86b**][$\Delta$-BINPHAT] to [**86f**][$\Delta$-BINPHAT] that afforded the corresponding dextrorotatory amines (+)-**87b** to (+)-**87f**. The yields were generally in accordance (±4%) with those of the bromide salts.

Whereas electron-donating ether substituents led to poor enantiomeric excess (e.e.) values (20% and 27% for OBn and OMe), the presence of electron-withdrawing halogen atoms (F, Cl and Br) improved significantly the enantioselectivity to 49%, 55% and 42% respectively, values high enough to be clearly considered as “proof of concept”.

Even if the global e.e. seemed low, the values were in line with those of the enantiospecific studies accomplished respectively by West[20] and Tayama.[21,22] The substituent effect, somewhat surprising at first glance,[23] was rationalised in the course of the following study.

*Table III-4*: Enantioselective [1,2]-Stevens rearrangement of the BINPHAT salts of cations **86a** to **86f** and excellent transfer of chirality.[a]




| Z | Salts | Yield % | e.e. %[b] | $[\alpha]_D$[c] | d.e. %[d] | ToC %[e] |
|---|---|---|---|---|---|---|
| H | [**86a**][*Δ*-BINPHAT] | 90 | 33 | (+) | 33 | 100 |
| H | [**86a**][*Λ*-BINPHAT] | 88 | 33 | (–) | 33 | 100 |
| OMe | [**86b**][*Δ*-BINPHAT] | 52 | 27 | (+) | 30 | 90 |
| OBn | [**86c**][*Δ*-BINPHAT] | 50 | 20 | (+) | 20 | 100 |
| F | [**86d**][*Δ*-BINPHAT] | 50 | 49 | (+) | 50 | 98 |
| Cl | [**86e**][*Δ*-BINPHAT] | 48 | 55 | (+) | 60 | 92 |
| Br | [**86f**][*Δ*-BINPHAT] | 28 | 42 | (+) | 54 | 78 |

[a]Conditions: $P_4$-*t*-Bu (1M in Hexane, 1.5 equiv.), $CH_2Cl_2$, -80 °C, 4h; the results being the average of at least two runs; [b]Enantiomeric purity of **87a** to **87f** determined by CSP-HPLC (Chiralpak IB; *n*-Hexane/*i*-PrOH/ethanolamine 95:05:0.1%; 0.5 mL.min$^{-1}$; 23 °C); [c]Sign of the optical rotation of the enantiomers of **87a** to **87f**; [d]Diastereoselectivity of the ion pairing determined by $^1$H and $^{19}$F-NMR spectroscopy at 193 K, in $CD_2Cl_2$, with ±2-3% precision; [e]Transfer of Chirality defined as the ratio of the enantioselectivity (e.e.) over the ionic stereoinduction (d.e.), with ±2-3% precision : ToC = e.e. / d.e. × 100.

[20] Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31-33
[21] Tayama, E.; Nanbara, S.; Nakai, T. *Chem. Lett.* **2006**, *35*, 478-479
[22] In addition, recrystallisations are necessary at the stage of the formation of the stereogenic quaternary ammonium salts to remove minor diastereomeric species. Without this purification prior to the Stevens rearrangement, it is probable that lower levels of enantioselectivity would be obtained.
[23] It is to be noted that substituents Z are not part of the reactive 7-membered ring, but of the rigid indoline ring that remains unchanged during the reaction. In the Tayama study (see ref. 21), substituents were part of the migrating benzyl groups.

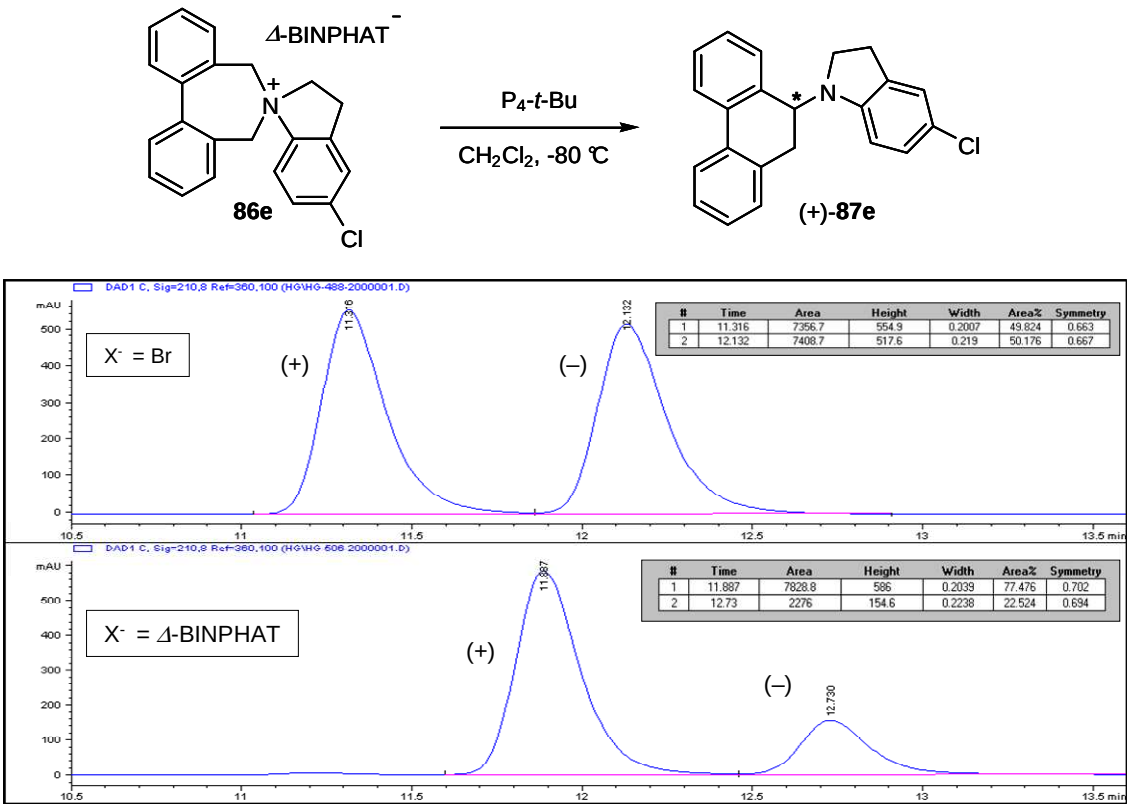



*Figure III-8*: HPLC trace (Chiralpak IB; *n*-Hexane/*i*-PrOH/ethanolamine 95:05:0.1%; 0.5 mL.min$^{-1}$; 23 °C) of amines **86e** from [**86e**][Br] and [**86e**][*Δ*-BINPHAT] salts with 55% e.e.

III-2.3.b Asymmetric induction

To verify that the enantioselectivity of the reaction was, as envisaged, the result of the predominance of one diastereomeric ion pair, a series of variable temperature NMR experiments was performed on the bromide and BINPHAT salts of **86**, under the initial reaction conditions. First, $^{1}$H-NMR at –40 °C (233 K) in $CD_2Cl_2$ clearly showed AB patterns for the benzylic protons of the bromide salts, demonstrating without ambiguity that the exchange between the (*P*) and (*M*) conformers of dibenzoazepine-indolinium cation **86** was slow on the NMR-timescale at this temperature and lower. Then, salts [**86a**][*Δ*-BINPHAT] to [**86f**][*Δ*-BINPHAT] were studied at –40 °C (233 K) and –80 °C (193 K) and, in all cases, enantiopure BINPHAT anion acted as an NMR chiral-solvating agent. NMR signals were clearly split in two sets, one for each of the atropisomers of **86**.

The singlet signals of the OMe substituent of **86b** in $^{1}$H-NMR (*Figure III-9*) or of the fluorine atom of **86d** in $^{19}$F-NMR (*Figure III-10*) were effective probes for asymmetric induction measurement.

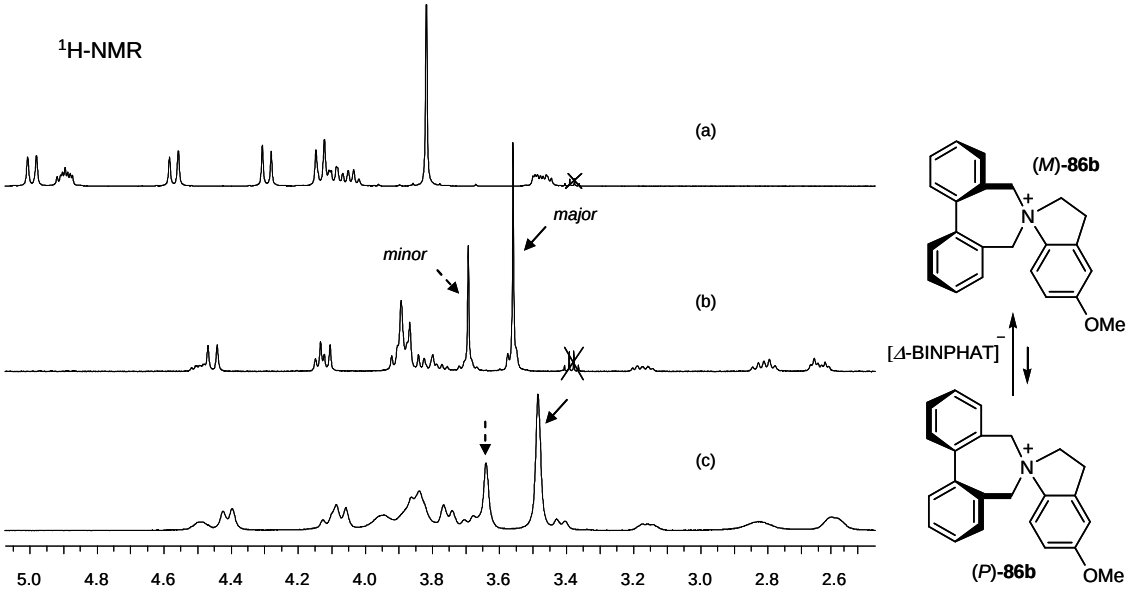



*Figure III-9*: Ion pairing of *Δ*-BINPHAT anion and cation **86b**.

Asymmetric induction as evidenced by $^{1}$H-NMR ($CD_2Cl_2$, 500 MHz): (a) [**86b**][Br], 233 K; (b) [**86b**][*Δ*-BINPHAT], 233 K, 26% d.e.; (c) [**86b**][*Δ*-BINPHAT], 193 K, 32% d.e.

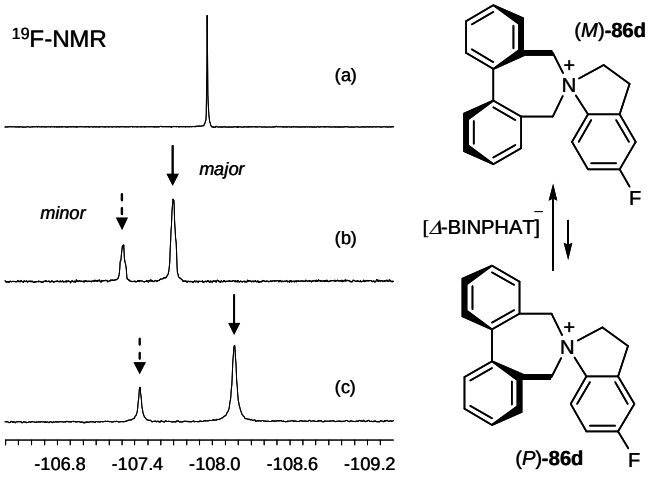



*Figure III-10*: Ion pairing of *Δ*-BINPHAT anion and cation **86d**.

Asymmetric induction as evidenced by $^{19}$F-NMR ($CD_2Cl_2$, 352 MHz): (a) [**86d**][Br], 233 K; (b) [**86d**][*Δ*-BINPHAT], 233 K, 50% d.e.; (c) [**86d**][*Δ*-BINPHAT], 193 K, 52% d.e.

More importantly, these experiments revealed an asymmetric induction of BINPHAT onto the cations. One of the two diastereomeric ion pairs, [(*P*)-**86**][*Δ*-BINPHAT] or [(*M*)-**86**][*Δ*-BINPHAT], is clearly favoured in solution. Integration of the split signals gave ratios from 1.5:1 to 4.0:1 (±2-3%) corresponding to diastereomeric excesses varying from 20% to 60% (±2-3%).

All measurements were carried out at –40 °C (233 K) and –80 °C (193 K, temperature of the reactions). The precision of the measurements at 193 K is slightly limited by some line-broadening effects, compared to those at 233 K (NMR sharper resolution). The diastereomeric excesses measured at 233 K are in close agreement with those observed at 193 K (*Figure III-11* and see appendix, chapter III).[24] In $^1$H-NMR spectra, the differentiation was better followed in the δ 5.8-6.5 ppm region that corresponds to some of the aromatic protons of the cation (*Figure III-11*).

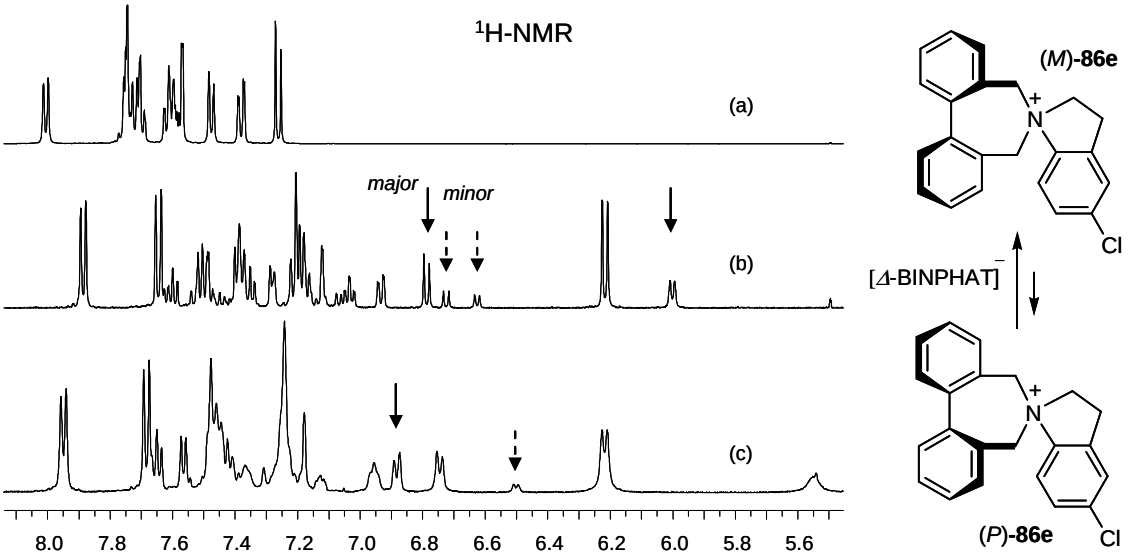



*Figure III-11*: Ion pairing of *Δ*-BINPHAT anion and cation **86e**.
Asymmetric induction as evidenced by $^1$H-NMR ($CD_2Cl_2$, 500 MHz): (a) [**86e**][Br], 233 K; (b) [**86e**][*Δ*-BINPHAT], 233 K, 50% d.e.; (c) [**86e**][*Δ*-BINPHAT], 193 K, 60% d.e.

All the results are reported in *Table III-4*. Better selectivities were obtained for the cations bearing electron-withdrawing halogen atoms.

[24]All calculations of the d.e. were precisely performed from $^1$H-NMR spectra by Gaussian and Lorentzian deconvolutions in the WinNMR program.

III-2.3.c Transfer of chirality

Significantly, the values of the diastereoselectivity within the asymmetric ion pair are essentially identical to those of the enantiomeric purity of the corresponding tertiary amines **87**, to the exception of tertiary amine **87f** (Z = Br). Direct comparison between the two sets of data points (d.e. provided from [**86a**][*Δ*-BINPHAT] to [**86e**][*Δ*-BINPHAT] and e.e. obtained for amines [**87a**] to [**87e**]) shows the existence of an essentially linear correlation (*Figure III-12*), if one does not consider compound **87f**.[25]

This indicates that the transfer of chirality (ToC) from the biaryl axis of the preferred atropisomers of cations **86a** to **86e**, to the new $sp^3$ stereogenic centre of the non-racemic amines **87a** to **87e**, occurs with excellent stereoselectivity (from 90 to 100%, *Table III-4*) – as in the case of Mislow[12] and Závada[13] – and somewhat less selectively for amine **87f** (78% ToC).

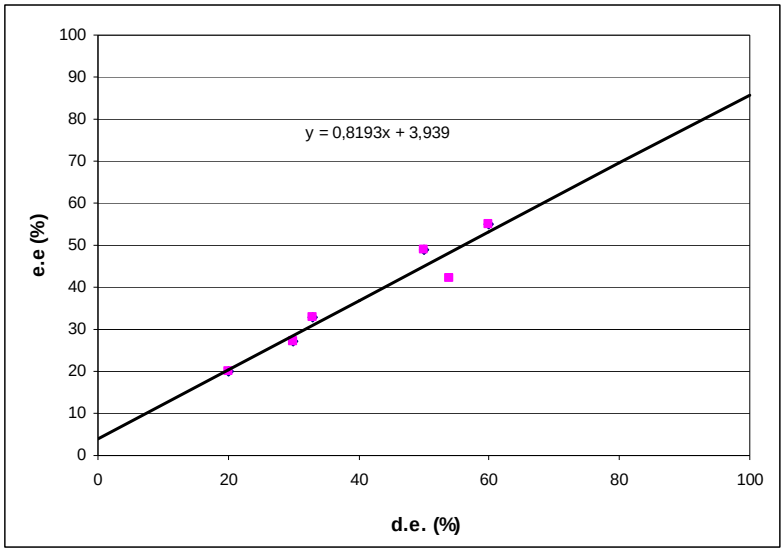
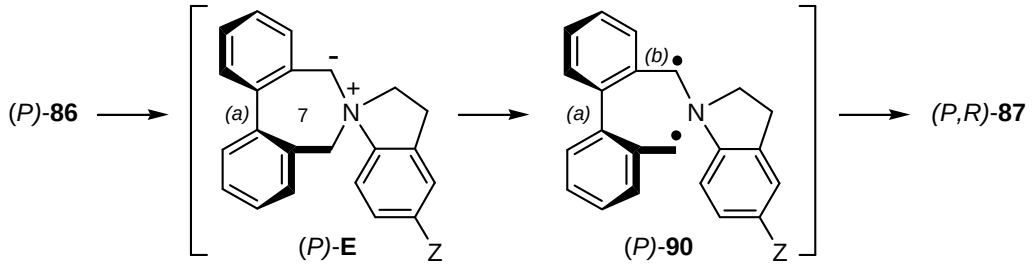



*Figure III-12*: Linear correlation between the d.e. provided from [**86a**][*Δ*-BINPHAT] to [**86f**][*Δ*-BINPHAT] and the e.e. obtained for amines [**87a**] to [**87f**].

[25] Without the inclusion of **87f** in the data series, a linear regression of d.e. = f(e.e.) affords the following trendline ($y = 0.9109x + 1.6395$, $R^2 = 0.9879$).

III-2.3.d Probable mechanism of the enantioselective [1,2]-Stevens rearrangement of the dibenzoazepine-indolinium cations

Interestingly, as we have mentioned earlier, achieving such a high value for the transfer of chirality was not obvious considering the probable mechanism (*Scheme III-11*). The [1,2]-Stevens rearrangement of **86a– f** should involve principally two successive intermediates. The first one is **E**, a zwitterionic ylide generated by deprotonation of one benzylic proton localised on the 7-membered dibenzo[*c*,*e*]azepinium ring. The second intermediate is a radical pair **90** (**a** to **f**) produced by homolytic fragmentation with the break of an endocyclic bond (*Scheme III-11*). Both compounds **E** and **90** are neutral and should enable the BINPHAT anion to diffuse out of the reaction pocket. Loss of enantiomeric purity can then simply occur either by rotation around the biaryl axis of **E** or **90** (*Scheme III-11 (a)*), or by rotation (180°) of the $C_{aryl}$-CHN bond of **90** (*Scheme III-11 (b)*). Although it is difficult at this stage to speculate, the high selectivity of the ToC probably indicates that all the steps leading to amines **87** are extremely fast on the reaction time scale, to the exception of **87f** (Z = Br).[8]




*Scheme III-11*: Possible intermediates **E** and **90** in the rearrangement of **86** to **87**. Loss of chirality may occur by rotation of either *(a)* the biaryl C-C bond or *(b)* the $C_{aryl}$-CHN bond. Configurations are assumed.

### *III-2.4 Pre-conclusion*

In this chapter, we have predicted and shown that a novel *tropos*[26] skeleton, the dibenzoazepine-indolinium favours endocyclic [1,2]-Stevens rearrangement products. The reaction can be tuned with ammonium frameworks, using different substituents at the 5-position of the indolinium ring (Z = H, OMe, OBn, F, Cl, Br).

[26] Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561-1578

Using enantiopure BINPHAT anion as ionic auxiliary, the first decent enantiomeric excesses have been noticed; the e.e. values progressing from 11% for the spirobi-[dibenzazepinium] cation **58** to 55% for the dibenzoazepine-indolinium cation **86e**. Importantly, the transfer of chirality was strongly enhanced from 45-47% for the respective isoindanyl-dibenzoazepinium cation **61** and **58** to 100% for the dibenzoazepine-indolinium cations **86a** and **86c**). So, we managed to reach our goal.

This methodology constitutes an interesting example of double transmission of chirality; first by a supramolecular transfer of the helical chirality of the BINPHAT anion to the axial chirality of cations **86** and by its very effective translation (90 to 100%) to the centred chirality of amines **87**, during the [1,2]-Stevens rearrangement.

As far as we can tell,[20,21] it is also the first enantioselective [1,2]-Stevens rearrangement process that doesn't require the formation of a stereogenic quaternary nitrogen atom.

## III-3 Mechanistic conclusions

Finally, at the end of this study, a global picture starts to take shape for the probable mechanism of the [1,2]-Stevens rearrangement; its exact nature still remaining highly "speculative". Some of the unprecedented observations made during this thesis, like the extremely rapid exchange of deuterium/hydrogen atoms at the ylide formation stage are quite mysterious and unexplained (See chapters II-4.2.d and II-4.3.c).

Yet, if one considers a general 7-membered ring of a diphenylazepinium cation of structure **91** as shown in *Figure III-13*, one can propose a much more concerted mechanism than usually considered (Chapter I-2);[8] allowing us to explain some of the regioselectivity issues in particular. For this, the structure of the ylide is considered. In diarylazepine systems, benzylic protons are known to adopt axial or equatorial positions relative to the plane of the adjacent aromatic rings,[27] and one can assume that the orbital bearing the negative charge of the ylide adopts similar orientations. If so, one should expect that the axial or equatorial geometry of the ylide could influence the stereochemical outcome of the reaction.

The so-called axial $\mathbf{F_{ax}}$ and equatorial $\mathbf{F_{eq}}$ ylides are represented on *Figure III-13* and correspond respectively to the orbital of the negative charge in axial and equatorial orientation.

[27] Tichy, M.; Budesinsky, M.; Gunterova, J.; Zavada, J.; Podlaha, J.; Cisarova, I. *Tetrahedron* **1999**, *55*, 7893-7906

# Chapter IV

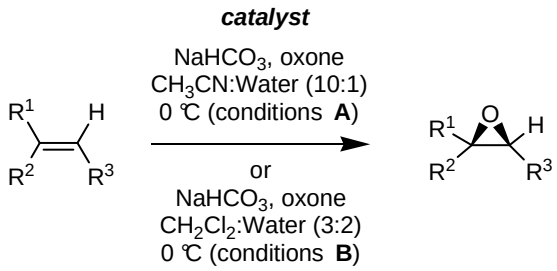
# HOMOLOGOUS AMINE AND IMINIUM CATALYSTS IN ENANTIOSELECTIVE OLEFIN EPOXIDATION

So far, $C_2$-symmetric dibenzo- and dinaphth-[*c*,*e*]azepine have been often used as precursors of our quaternary ammonium cations which were subsequently involved in [1,2]-Stevens rearrangements. It occurred to us that some of these structures could be tested as catalysts in enantioselective epoxidation reactions – such a topic already developed in the group of Prof. Jérôme Lacour. Thus, after a bibliographical introduction and a summary of studies already established in the group, we will present the discussions and the results that we obtained on this different topic of asymmetric organocatalysed epoxidation, concerning particularly the homologous amines and iminium catalysts in enantioselective olefin epoxidation.

## IV-1 Asymmetric organocatalysed epoxidation of olefins in the literature

### *IV-1.1 Introduction*

Chiral non-racemic epoxides are not only useful precursors for organic chemists, for the synthesis of enantiopure molecules,[1] but also frequently-met structures in natural products (*Equation IV-1*).[2]




*Equation IV-1*

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

[2] See for example: Contelles, J. M.; Moilna, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857-2900. Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205. Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543

Indeed, several compounds such as triptolide, epothilones and cryptophycin contain epoxide moities essential for their biological activities (*Figure IV-1*).

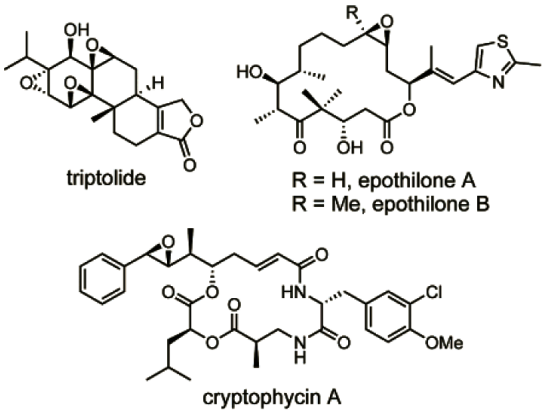



*Figure IV-1*: Examples of natural products containing epoxide groups.

Moreover, epoxides are believed to be key intermediates in the biosynthesis of natural products such as Brevetoxin-B (*Figure IV-2*), monensin and glabrescol.

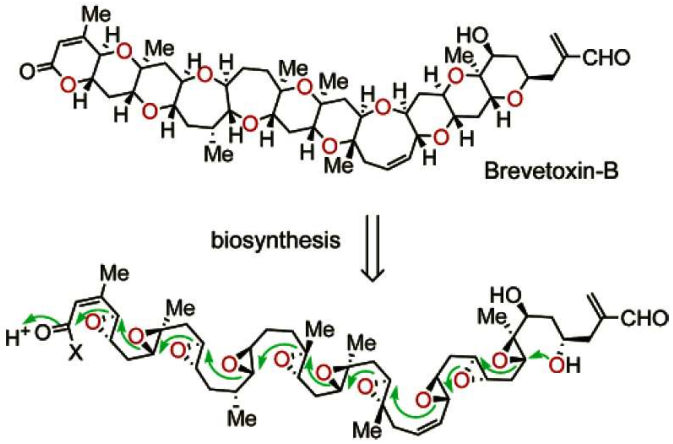



*Figure IV-2*: Biosynthesis of Brevetoxin-B from epoxides.

A number of efficient methods exist for the preparation of epoxides from olefins and many of them use transition metal catalysts.[3] The Sharpless epoxidation is a powerful tool for the

[3] For recent reviews see: Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603-1662. Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457

asymmetric epoxidation of allylic alcohols, the hydroxyl group directing the oxygen transfer to the olefin in an enantioselective fashion.[4]

For non-functionalised olefins, the chiral Mn-salen catalysts developed independently by the groups of Jacobsen[5] and Katsuki[6] are particularly effective for *cis*-olefins. In the recent years, much effort has been devoted to the development of organocatalysed epoxidation which afford metal-free conditions; the catalysts being perhydrates, ketones (dioxiranes), oxaziridine moieties, amines or ammoniums as well as iminium (oxaziridinium) salts.[7] Only the latter class of compounds will be detailed in this chapter.

### *IV-1.2 Oxaziridinium-mediated epoxidation using chiral iminium salts as catalysts*

#### IV-1.2.a Monophasic conditions for epoxidation

Iminium (oxaziridinium) salts are an interesting alternative to the commonly used ketones (dioxiranes).[8] They are easily oxidised *in situ* into oxaziridinium salts which are rather effective oxygen-transfer reagents towards nucleophilic species. Their use as oxidant has been mentionned for the particular transformations of (i) thioethers to sulfoxides, (ii) amines and pyridines to their N-oxide derivatives, (iii) imines to oxaziridines and (iv) electron-rich unfunctionalised olefins to epoxides. Moreover, the propensity of iminium ions to react with Oxone® triple salt, in a slightly acidic medium ($NaHCO_3$) to generate the oxaziridinium species, renders possible the development of catalytic processes (*Figure IV-3*).[9]

[4] 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*; Springer ed.; Jacobsen, E. N.;Pfaltz, A.;Yamamoto, H., Eds.: New York, **1999**; Vol. 2, p 503 pp.

[5] Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123-5126. Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937-6938. Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378-4380. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063-7064. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803

[6] Matsumoto, K.; Katsuki, T. *Asymmetric Synth.* **2007**, 116-120. Katsuki, T. *Chem. Soc. Rev.* **2004**, *33*, 437-444. Katsuki, T. *Transition Met. Org. Synth. (2nd Ed.)* **2004**, *2*, 337-344. Katsuki, T. *Synlett* **2003**, 281-297. Katsuki, T. *Curr. Org. Chem.* **2001**, *5*, 663-678. Katsuki, T. *J. Mol. Catal. A: Chem.* **1996**, *113*, 87-107

[7] Ho, C. Y.; Chen, Y. C.; Wong, M. K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898-906. Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596-7601. Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499-3548

[8] Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715-1717. Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1-9. Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792-8793. Adam, W.; Saha-Moeller, C. R.; Zhao, C.-G. *Org. React. (N. Y.)* **2002**, *61*, 219-516. Barbaro, P.; Bianchini, C. *Chemtracts* **2001**, *14*, 274-277

[9] Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727-13738. Hanquet, G.; Lusinchi, X.; Milliet, P. *C. R. Acad. Sci., Ser. II: Mec., Phys., Chim., Sci. Terre Univers* **1991**, *313*, 625-628

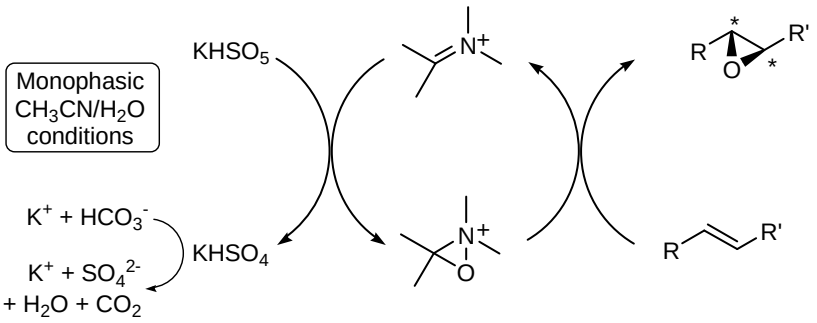
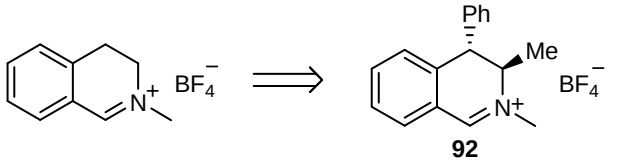



*Figure IV-3*: Monophasic catalytic epoxidation of olefins *via* iminium oxidation by Oxone into oxaziridinium.

The first example of an enantioselective iminium catalysed reaction was reported in 1993 by Hanquet and Lusinchi,[10] with the dihydroisoquinolinium cation **92** as a catalyst; this system was inspired by previous studies done in the Orsay university, in 1976 (*Figure IV-4*).[11]




Milliet, Picot, Lusinchi **1976** Bohé, Hanquet, Lusinchi **1993**

(e.e. up to 35%)

*Figure IV-4*: First reported achiral and chiral dihydroisoquinolinium catalysts.

Since this pioneering work, several successful enantioselective variants of the reaction have been reported as described below (*Figure IV-5* and *Figure IV-6*).

There are essentially two classes of non-racemic iminium catalysts. The first class is composed of exocyclic chiral iminium salts such as compounds [**93**][$ClO_4$],[12] [**94**][$BF_4$][13] and [**95**][X][14] prepared by the condensation of enantiopure pyrrolidine moieties with aldehydes or ketones (*Figure IV-5*). Decent levels of stereoselective induction were obtained using these cations (enantiomeric excess (e.e.) up to 59% with cation **95** on *trans*-stilbene). Rather high catalyst loading is unfortunately required (100 mol% for **93,** 10 mol% for **94**, and between 20 and 50% for **95**), probably due to *in-situ* hydrolysis of the iminium moieties under the aqueous reaction conditions.

[10] Bohe, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 155-166. Bohe, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271-7274

[11] Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1573-1576

[12] Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341-2352

[13] Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810-1812

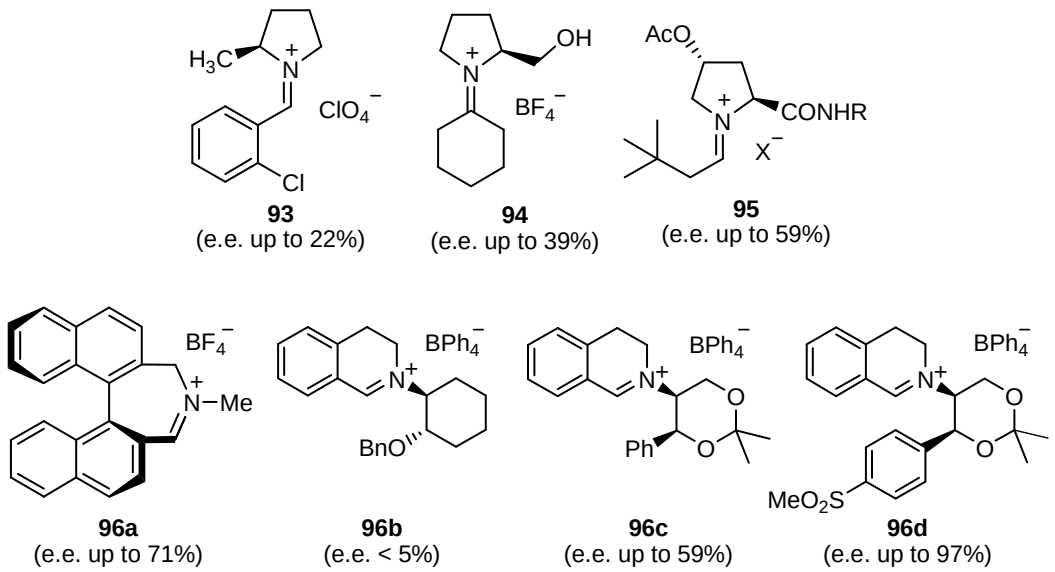



*Figure IV-5*: Known acyclic and cyclic iminium non-racemic catalysts.

The second class is constituted of endocyclic chiral iminium salts (*Figure IV-5*). As mentioned before, the first non-racemic example was salt [**92**][$BF_4$].[10] Using this derivative, modest level of selectivity was achieved (e.e. up to 35%). In 1996, Aggarwal and co-workers reported axially chiral, *configurationally stable*, binaphthyl-based iminium salt [**96a**][$BF_4$]; this catalyst being particularly efficient for the epoxidation of 1-phenyl-cyclohexene (71% e.e.).[15] A mechanistic rationale was proposed by the authors to explain the absolute sense of configuration of the resulting epoxides.[16] In 1998, Page and co-workers modified the core structure of catalyst **92** by introducing stereogenic elements outside rather than inside the 6-membered ring heterocycles.[17] They obtained a quite high selectivity with the iminium salt [**96c**][$BPh_4$] derived from (+)-L-acetonamine[18] than with the [**96b**][$BPh_4$] salt (e.e. 41% and <5% respectively with 1-phenyl-cyclohexene), the chiral appendage (+)-L-acetonamine having thus a strong influence in the enantioselectivity on the epoxidation reaction. Subsequently, Page and co-workers reported a modification of catalyst **96c** carrying a *para*-

[14] Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587-2590
[15] Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191-192
[16] Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 2948-2949
[17] 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*, 6926-6931. Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3325-3334. Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774-2777
[18] (+)-L-Acetonamine is the (+)-(4*S*, 5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane.

methylsulfonyl group (iminium **96d**) that behaves as a very efficient asymmetric catalyst, for benzopyran substrates in particular (e.e. up to 97%).[19]

A second generation of iminium catalysts with exocylic chiral appendages was independently developed by the groups of Page[20] and Lacour.[21] They both used biphenyl **97i**,[20,21] binaphthyl **98i** and **99i** iminium salts;[22] these compounds were derived from the exocyclic chiral auxiliary (+)-L-acetonamine (*Figure IV-6*).

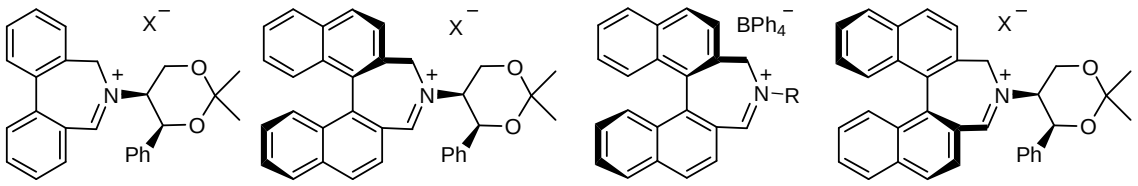



*Figure IV-6*: Non-racemic iminium salts and their absolute configuration; X being a lipophilic non coordinating anion ($BPh_4$ or TRISPHAT).

In the case of **97i**, the twisted 7-membered ring is chiral and *conformationally labile* unlike derivatives **96b–d** and single enantiomers are readily prepared (vide infra). Two different types of salts, differing only by their counterion – namely [**97i**][$BPh_4$] and [**97i**][TRISPHAT] – have been previously utilised in epoxidation reactions – with no major differences observed between the two ion pairing systems.[20,21] Direct comparison of these latter salts of 7-membered **97i** and 6-membered **96b–d** rings showed that most of the reaction rates, conversions and enantioselectivities are enhanced by the use of the larger ring size catalysts.[20] In the case of **98i** and **99i**, the presence of the stereogenic configurationally rigid binaphthyl core creates a diastereomeric relationship. These salts combine Aggarwal's conformationally rigid dinaphthazepinium skeleton (*M* and *P* atropisomers) with Page's (+)-L-acetonamine.[22] Thus, both salts (–)-[**98i**][$BPh_4$] and (+)-[**99i**][$BPh_4$] of (*M*,L) and (*P*,L) respective configurations, were prepared. An interesting matched/mismatched behaviour was detected with salt [**98i**][$BPh_4$] leading to quite higher conversions than its diastereomer. Overall, compound (–)-[**98i**][$BPh_4$] is one of the most effective iminium salt catalysts to date

[19] Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005**, *7*, 375-377
[20] Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, 580-582
[21] Vachon, J.; Perollier, C.; Monchaud, D.; Marsol, C.; Ditrich, K.; Lacour, J. *J. Org. Chem.* **2005**, *70*, 5903-5911. Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8257-8260
[22] Page, P. C. B.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2004**, *6*, 1543-1546

(e.e. up to 95%).[22] Moreover, recently, Page and co-workers[23] have developed new chiral binaphthalene derived-iminium salts [**98j**][$BPh_4$] as organocatalysts, using other exocyclic sterically bulkier appendages than (+)-L-acetonamine, as for example the 2,6 xylidene, *tert*-butylamine (e.e. up to 84%).

IV-1.2.b Biphasic conditions for epoxidation

Traditionally, 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.[15] Previously, it was shown using salt [**97i**][TRISPHAT], strict biphasic $CH_2Cl_2$/water conditions could be employed giving an enhancement of the epoxidation reaction selectivity as well as a good recovery of the products.[21] In fact, the lipophilicity of the 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 presence of the reagents in the two liquid phases occurs: the organic TRISPHAT salts being in the organic layer and Oxone® staying in the aqueous one. Addition of a catalytic amount of 18-crown-6 (18-C-6, 2.5 mol%) establishes a transport mechanism of the couple $KHSO_5/KHSO_4$ between aqueous and organic phases. This allows the oxidation of the iminium cation into the reactive oxaziridinium form in $CH_2Cl_2$ (*Figure IV-7*).

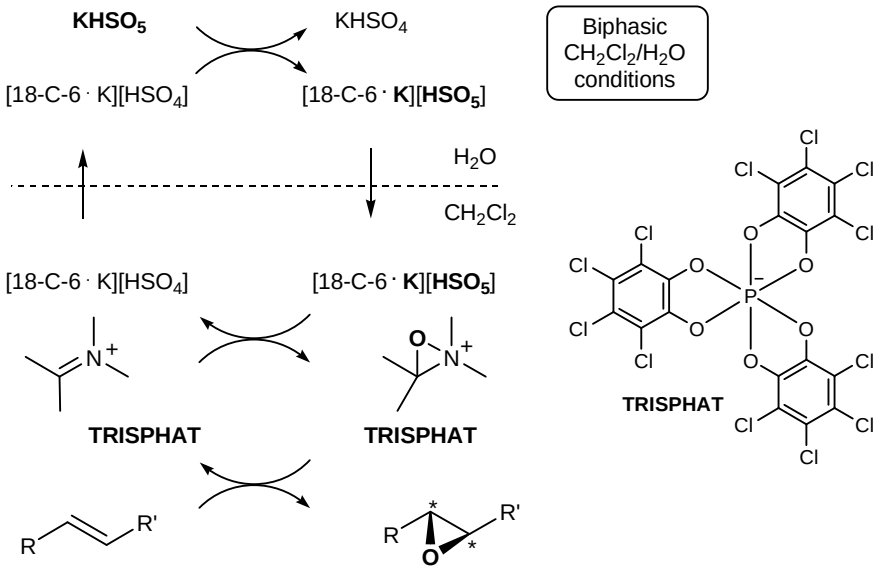



*Figure IV-7*: Proposed catalytic cycle for the biphasic oxaziridinium-catalysed epoxidation.

[23] Page, P. C. B.; Farah, M. M.; Buckley, B. R.; Blacker, A. J. *J. Org. Chem.* **2007**, *72*, 4424-4430

In this context, Lacour and co-workers reported effective enantioselective epoxidation using a series of biphenylazepinium salts,[21,24] binaphthylazepinium[24] salts and finally doubly bridged biphenylazepinium (DBB) salts[25,26] in biphasic $CH_2Cl_2$/water conditions. These epoxidation reactions were also performed in the presence of the TRISPHAT anion (*Figure IV-8*).[27] The results have been reported in the literature and in the Ph.D. thesis of David Monchaud and Jérôme Vachon.

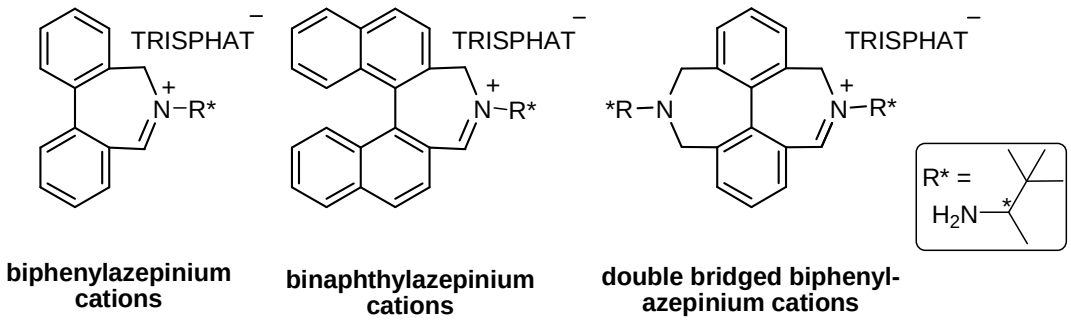



*Figure IV-8*: Various azepinium cations, developed in the Lacour's group, catalysed epoxidation reactions in biphasic conditions in the presence with the TRISPHAT anion.

In summary, it was shown that chiral exocyclic appendages other than (+)-L-acetonamine, the 1,2,2-trimethylpropylamine in particular, can be as efficient for the enantioselective olefin epoxidation. Interestingly, this amine is commercially available in both enantiomeric forms.
Rather high levels of enantiomeric excesses were obtained in the three iminium series. For example, e.e. up to 80%, 86% and 76% were obtained for the epoxidation of 1,2-dihydro-4-phenylnaphthalene catalysed by the biphenyl- binaphthyl- and doubly bridged biphenyl-azepinium (DBB) cations respectively; each containing the 1,2,2-trimethylpropylamine as chiral appendage. In general, the *configurationally stable* binaphthyl- and DBB-skeletons of azepinium cations lead to the highest values. In the binaphthyl series, the sense of stereo-induction in the epoxidation reaction is fully controlled by the configuration of the twisted biaryl. Whereas in the DBB series, it is the exocyclic appendage that is the dominant factor for the sense of the stereo-induction.

[24] Vachon, J.; Lauper, C.; Ditrich, K.; Lacour, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2334-2338
[25] Vachon, J.; Rentsch, S.; Martinez, A.; Marsol, C.; Lacour, J. *Org. Biomol. Chem.* **2007**, *5*, 501-506
[26] Novikov, R.; Vachon, J.; Lacour, J. *Chimia* **2007**, *61*, 236-239
[27] Vachon, J.; Pérollier, C.; Martinez, A.; Lacour, J. In *Regio- and stereo-controlled oxidations and reductions*, Roberts, S. M.; Whittall, J., Eds. VCH-Wiley: Hoboken, N.J., **2007**; Vol. 5, pp 235-239.

### *IV-1.3 Amines or ammonium salts as catalysts for epoxidation*

Whereas the epoxidation of olefins catalysed by iminium salts has been studied for several decades, the mediation of the reaction by amines and/or ammonium salts is still a new topic.[28] It was only in 2000 that the catalysed enantioselective epoxidation of olefins by secondary amines was reported (e.e. up to 66%) by Aggarwal and co-workers.[29] Indeed, a control experiment combining alkene and oxidant in the absence of amine showed that epoxidation reaction could be catalysed by the amine itself, because no epoxide was obtained in this case. They also observed an asymmetric induction when a chiral secondary amine such as 2-substituted pyrrolidine **100** was used (*Figure IV-9*).[29] A first hypothesis proposed by Aggarwal suggested that the amine is oxidised to its radical cation which in turn, oxidises the alkene to the radical cation. In the presence of suitable oxidants, alkene radical cations are converted to epoxides. However, difficulties in reproducing the key comparative control experiments led the authors to look closely to the process mechanism.[30]

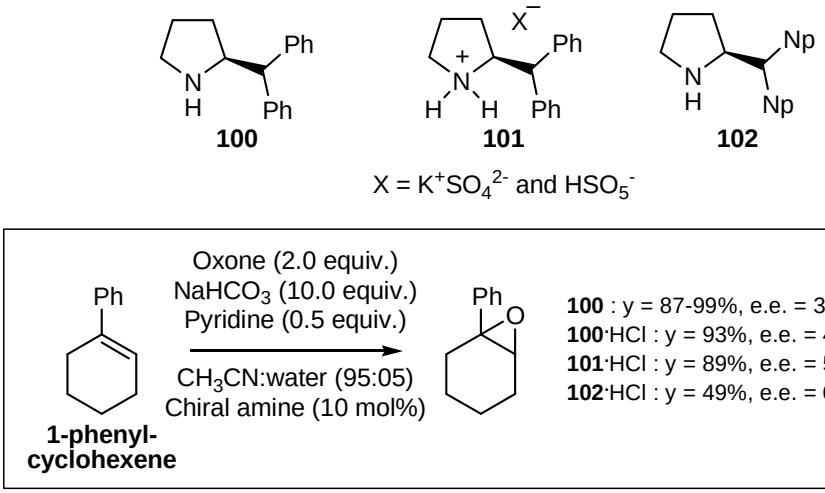


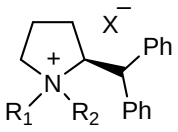

*Figure IV-9*: Asymmetric epoxidation of 1-phenylcyclohexene using chiral amines as catalyst.

They found that more consistent and reproducible results were achieved with the HCl.salt of the amine **100** compared to the amine **100** itself using the epoxidation conditions described in *Figure IV-9*. This modification gave higher enantiomeric excess and shorter reaction times, the pyridine fulfilling its role in acting as a "proton shuttle" during the oxidation process, and

[28] Armstrong, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1460-1462
[29] Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317-8318
[30] Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 11223

limiting epoxide hydrolysis and the subsequent formation of diol.[31] The bulkier catalyst **102** was also tested and led to a better enantioselectivity while performing the reaction at –10 °C (e.e. = 66%). Up to 90% of the chiral amine catalyst could be recovered when reactions were conducted at –10 °C, indicating that the integrity of the amine was maintained during the oxidation process. It was noticed that amine **100** reacted with Oxone, at –10 °C, to give the ammonium salt **101** containing a mixture of potassium sulfate ($K^+SO_4^{2-}$) and peroxymonosulfate ($HSO_5^-$) anions (*Figure IV-9*). When performing the same reaction with the isolated complex **101**, identical enantioselectivity was obtained, indicating that this compound was the active specie for the epoxidation reaction.

*Table IV-1*: Variation of yield and enantioselectivity of the epoxidation of 1-phenylcyclohexene using the corresponding secondary, tertiary and quaternary ammonium salts.




| $R_1$ | $R_2$ | $X^-$ | Yield % | e.e. of epoxide % |
|---|---|---|---|---|
| H | H | Cl | 93 | 46 |
| Me | H | Cl | 58 | 5 |
| Me | Me | $BF_4$ | 13 | 0 |

As highlighted by Armstrong, the reason why complex **101** is more reactive than oxone itself may be that the ammonium couterion acts as a phase-transfer catalyst.[28] Moreover, as shown in *Table IV-1*, the fact that reactivity dropped using the methylated version of catalyst **100** led Aggarwal to propose a novel mode of activation involving hydrogen bonding from $HSO_5^-$ and the ammonium (*Figure IV-10*).[31,32] Therefore, the protonated ammonium salt seems to act as a phase transfer catalyst and helps bring the oxidant into solution through hydrogen bonding, generating a more electrophilic specie.

[31] Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596-7601
[32] Diastereoselective epoxidation reactions of allylic amines with Oxone have also been reported: Aggarwal, V. K.; Fang, G. Y. *Chem. Commun.* **2005**, 3448-3450

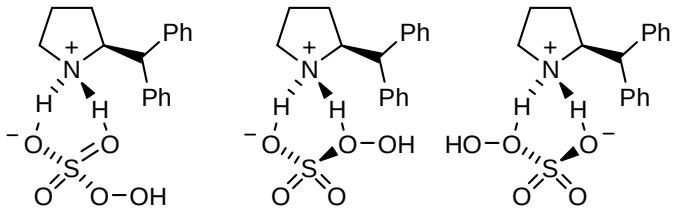


*Figure IV-10*: Possible modes of hydrogen bonding interactions between the secondary ammonium salt and the peroxymonosulfate anion.

Similarly, Yang and co-workers[33] found that amines themselves could promote epoxidation under slightly acidic reaction conditions. A broad range of amines (cyclic, acyclic, primary and secondary) was tested under these conditions (Oxone 4.0 equiv., $NaHCO_3$ 10.0 equiv., amine 1.0 equiv. and *trans*-stilbene 1.0 equiv., in $CH_3CN$:$H_2O$ 10:1, at R.T. for 5h).[33] It was found that cyclic secondary amines are better catalysts than acyclic, primary and secondary amines for the epoxidation of *trans*-stilbene.

Moreover, a systematic investigation of the substituent amine effects on epoxidation demonstrated that cyclic secondary amines (based on the same pyrrolidine moiety as Aggarwal) were efficient catalysts. In fact, an electron-withdrawing atom (O, F) located at the $\beta$-position relative to the amino group is beneficial and can further improve the catalytic efficiency. The highest enantiomeric excess (61%) was obtained for the epoxidation of 1-phenylcyclohexene catalysed by amine **103**, functionalised by a fluorine atom at the $\beta$-position relative to the amino center (*Figure IV-11*). According to the authors,[33] the presence of electronegative fluorine atoms may stabilise the positively charged ammonium salts through favourable charge-dipole interactions or mild hydrogen bond formation with an ammonium proton (*Figure IV-11*).

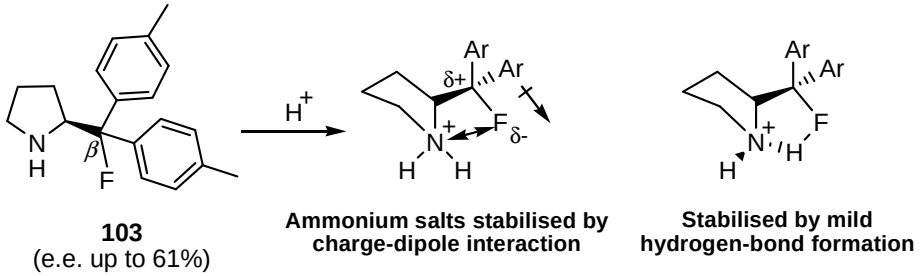



*Figure IV-11*: Stabilisation of the ammonium salts by the fluorine substituent in the $\beta$-position.

[33] Ho, C.-Y.; Chen, Y.-C.; Wong, M.-K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898-906

Under the slightly acidic reaction conditions employed (no pyridine was used) the fluorinated amine can be protonated *in* situ, which obviates the need to perform ammonium salts which are the usual catalysts for the epoxidations. As Aggarwal, Yang supported the notion that the amine plays a dual role in the epoxidation reactions – as a phase transfer catalyst and as an Oxone activator.

## IV-2 Direct comparison of homologous amines and iminium catalysts in enantioselective olefin epoxidation

### *IV-2.1 Scope*

So far, the most selective amine/ammonium catalysts have been based on $\alpha$-substituted pyrrolidine moieties for which no stable iminium analogues can be found. Indeed, most of these species, the most hindered ones in particular, are prone to solvolysis in the reaction conditions.[12,13,14] Consequently, it has been essentially impossible to compare the catalytic activity and selectivity of ammonium moieties with those of the related iminium species. It was therefore debatable as to which of these two classes of related catalysts is the most effective – if either. In this context, we decided to carry out a study in which tertiary amines **97a**, (*M*,L)-**98a** and (*P*,L)-**99a**, directly related to iminium cations **97i**, (*M*,L)-**98i** and (*P*,L)-**99i**, were synthesised (*Figure IV-12*).

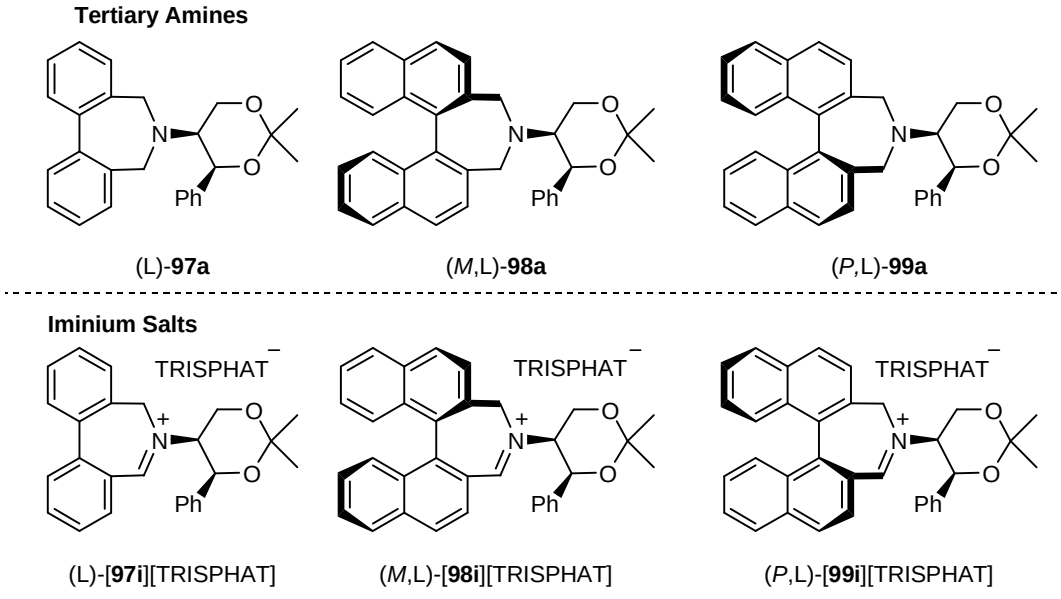



*Figure IV-12*: Non-racemic tertiary amine catalysts and their corresponding iminium salts with their absolute configuration; [TRISPHAT] being [$\Delta$-TRISPHAT] or [*rac*-TRISPHAT].

These six derivatives were tested as catalysts for the enantioselective epoxidation of olefins in two sets of conditions (i) homogeneous $CH_3CN/NaHCO_3/H_2O$ conditions (conditions **A**) and (ii) biphasic $CH_2Cl_2/NaHCO_3$/18-crown-6/$H_2O$ conditions (conditions **B**). The influence of the reaction medium was also examined and different outputs resulted from the reactions that were performed in slightly acidic conditions.[34]

Thus, with each set of compounds **97a** and [**97i**][TRISPHAT], **98a** and [**98i**][TRISPHAT], **99a** and [**99i**][TRISPHAT] available, there was a unique opportunity to perform an amine/ammonium *versus* iminium comparison – tertiary amines of type **97a, 98a** and **99a** being undocumented prior to this study as catalysts in (enantioselective) olefin epoxidation reactions.[34]

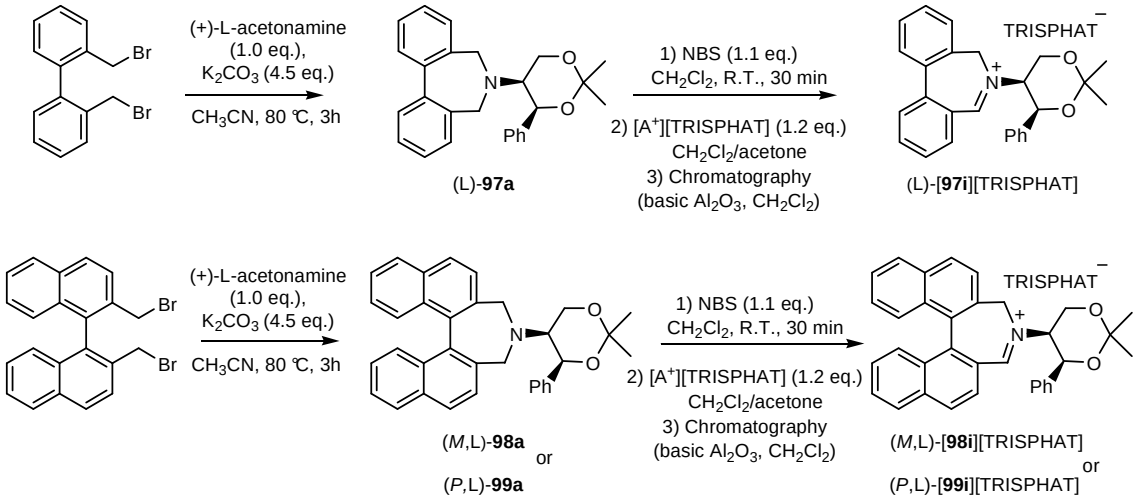
Moreover, the influence of the configuration of the TRISPHAT counterion was tested with the reaction performed in conditions **B**, using salts made from *Δ*-TRISPHAT and *rac*-TRISPHAT respectively.

### *IV-2.2 Preparation of the catalysts: amines and iminiums*

As indicated above, iminium salt [**97i**][TRISPHAT] is an effective catalyst for the asymmetric epoxidation of prochiral alkenes. This compound can be prepared in a three-step protocol from the 2,2'-bis(bromomethyl)biphenyl using standard reactions (*Scheme IV-1*): (i) an alkylation with (+)-L-acetonamine to afford amine **97a** (68%); (ii) a subsequent elimination with *N*-bromosuccinimide to form the iminium salt; and (iii) an ion pair metathesis with an ammonium TRISPHAT salt, the [cinchonidinium][*Δ*-TRISPHAT] salt or the $[Et_2NH_2]$[*rac*-TRISPHAT] salt, to afford the final products [**97i**][*Δ*-TRISPHAT] and [**97i**][*rac*-TRISPHAT] in 58% yield, in two latter steps.

The binaphthyl amines **98a** and **99a** were prepared following the same protocol as **97a** (*Scheme IV-1*). Better yields were obtained (76% and 88% respectively), with (*M*)- and (*P*)-2,2'-bis-(bromomethyl)-1,1'-binaphthyl as starting substrates. These compounds were further derivatised into the diastereomeric iminium salts (*M*,L)-[**98i**][TRISPHAT] and (*P*,L)-[**99i**][TRISPHAT]. In fact, the iminium salts [**98i**][*Δ*-TRISPHAT] and [**99i**][*Δ*-TRISPHAT] were obtained in 60-57% respective yields, whereas [**98i**][*rac*-TRISPHAT] and [**99i**][*rac*-TRISPHAT] were isolated in 68-64% respective yields, after elimination and ion pair exchange metathesis.

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




*Scheme IV-1*: Synthesis of the catalysts: amines and corresponding iminium salts; [A]=[cinchonidinium] or [$Et_2NH_2$] and [TRISPHAT]=[$\Delta$-TRISPHAT] or [*rac*-TRISPHAT].

### *IV-2.3 Results and discussion of the epoxidation reaction*

Two different sets of epoxidation conditions (**A**: $CH_3CN$:$H_2O$ (10:1) and **B**: $CH_2Cl_2$:$H_2O$ (3:2) with 18-crown-6) and three different prochiral tri-substituted unfunctionalised alkenes (**104**–**106**) were selected for the study (*Figure IV-13*).

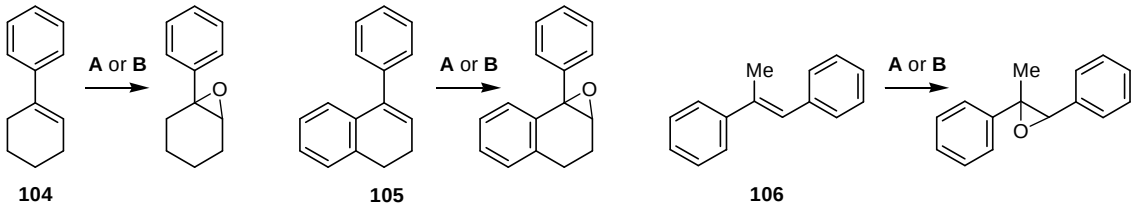



*Figure IV-13*

IV-2.3.a Comparison between the biphenylazepine **97a** and the biphenyl-azepinium **97i** catalysts

The results for the biphenyl (**97a** and **97i**) catalysts are reported in *Table IV-2*. Significantly, both reagents **97a** and [**97i**][TRISPHAT] behaved as effective catalysts under the two sets of experimental conditions. In view of the previous results by the group of Yang,[33] one can reason that the presence of two electron-withdrawing oxygen atoms at the $\beta$-position relative to the amino group in L-acetonamine, activates the catalytic activity of the amine/ammonium salt.

Non-racemic epoxides of analogous absolute configurations were isolated from the reactions with **97a** and [**97i**][TRISPHAT]. Whereas amine **97a** performed better in terms of conversions and enantiomeric excesses in homogeneous $CH_3CN/H_2O$ medium (conditions **A**), iminium salt [**97i**][TRISPHAT] gave better (overall) results in biphasic $CH_2Cl_2/H_2O$ medium (conditions **B**). Enantiomeric excesses from 51% to 68-69% (alkene **105**) were respectively obtained with **97a** and [**97i**][TRISPHAT], the 51% value being in fair comparison with that previously obtained with secondary amine/ammonium salts.[29,30,31,33] For the epoxidation reactions involving the iminium cation **97i** in conditions **B**, the configuration of the counterion played a little effect. In fact, the same e.e. values were obtained with both counterions: *Δ*-TRISPHAT and *rac*-TRISPHAT; conversions being slightly better with the racemic TRISPHAT salt.[35]

*Table IV-2*: Asymmetric epoxidation of olefins **104–106** using **97a** and [**97i**][TRISPHAT] as catalysts

| | Amine **97a** | | | | | |
|---|---|---|---|---|---|---|
| | Conditions **A**[a] | | | Conditions **B**[b] | | |
| Alkene[c] | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. |
| **104** | 90[e,f] | 53 | (–)-(*S*,*S*) | 78[d] | 26 | (–)-(*S*,*S*) |
| **105** | 50[e,f] | 51 | (+)-(1*R*,2*S*) | 66[d] | 23 | (+)-(1*R*,2*S*) |
| **106** | 97[d] | 36 | (–)-(*S*,*S*) | 73[d] | 21 | (–)-(*S*,*S*) |

| | Iminium [**97i**][TRISPHAT] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | [**97i**][*Δ*-TRISPHAT] | | | | | | [**97i**][*rac*-TRISPHAT] | | |
| | Conditions **A**[a] | | | Conditions **B**[b] | | | Conditions **B**[b] | | |
| Alkene[c] | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. |
| **104** | 75[e,f] | 54 | (–)-(*S*,*S*) | 81[d] | 54 | (–)-(*S*,*S*) | 97[d] | 54 | (–)-(*S*,*S*) |
| **105** | 36[e,f] | 57 | (+)-(1*R*,2*S*) | 85[d] | 68 | (+)-(1*R*,2*S*) | 99[d] | 69 | (+)-(1*R*,2*S*) |
| **106** | 95[d] | 33 | (–)-(*S*,*S*) | 88[d] | 36 | (–)-(*S*,*S*) | 95[d] | 37 | (–)-(*S*,*S*) |

[a]Conditions **A**: 5 mol % of catalyst, 2.0 equiv. Oxone®, 5.0 equiv. $NaHCO_3$, $CH_3CN:H_2O$ (10:1), 0 °C; average of at least two runs. [b]Conditions **B**: 5 mol % of catalyst, 2.5 mol % 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, $CH_2Cl_2:H_2O$ (3:2), 0 °C; average of at least two runs. [c]The enantiomeric excesses were determined by CSP-GC (**104**, Chiraldex Hydrodex *β*-3P) or CSP-HPLC (**105** and **106**, Chiralcel OD-H); the conversions were obtained using an internal standard (naphthalene). [d]2h reaction time. [e]15 min reaction time; [f]Complete conversion was observed in 2h along with some product decomposition. Care was thus taken to select a shorter reaction time.

[35] In $CH_3CN/H_2O$ conditions (**A**), we used only the iminium [**97i**][*Δ*-TRISPHAT] salt due to a better solubility of this salt compared to the ones formed with racemic TRISPHAT anion reactions. In the monophasic medium reactions, the counterion does not play any role.

IV-2.3.b Comparison between the binaphthylazepine **98a**/**99a** and the biphenylazepinium **98i**/**99i** catalysts

To extend the scope of the study and to increase the selectivity of the amine/ammonium catalysed reactions, two diastereomeric conformationally rigid dinaphthazepines (*M*,L)-**98a** and (*P*,L)-**99a** were tested in the same fashion[36] for the enantioselective olefin epoxidation. Direct comparison was also realised with their homologous iminium salts (*M*,L)-[**98i**][TRISPHAT] and (*P*,L)-[**99i**][TRISPHAT] under the same epoxidation conditions.[34] The results are reported in *Table IV-3* for the binaphthyl catalysts (**98a** and **98i**) and in *Table IV-4* for their diastereomers (**99a** and **99i**).

All four derivatives behave as catalysts. Careful analysis of the data reveals a number of subtleties, but some general trends can be noted.

As far as solvent effects are concerned, $CH_3CN/H_2O$ conditions (**A**) were found better than biphasic $CH_2Cl_2/H_2O$ (**B**), in an overall manner. In fact, better conversions occurred in the more polar conditions. In several cases, the reactions were complete in 15min using conditions **A**, whereas a time of 2h was necessary with the halogenated solvent mixture. This is true for all catalysts and compound **98a** in particular (*e.g.*, olefin **104**, **A**: 15min, 100% *vs* **B**: 2h, 90%). This trend is also valid for the enantiomeric excesses, which were higher in more polar conditions (olefin **105**, catalyst **98a**, **A**: e.e. 80% *vs* **B**: e.e. 45%). These results confirm the previous observations that higher values are obtained for both conversions and enantiomeric excesses using more polar solvent conditions and amines as catalysts.[29,30,31,33]

If one compares the selectivity of the diastereomeric catalysts together – that is **98a** with **99a** and **98i** with **99i** – analogous levels of stereoinduction in the (*M*,L) and (*P*,L) series are observed. The single difference is the reversal of the chiral induction sense for the non-racemic epoxides. This indicates that the binaphthyl framework is a more effective chiral auxiliary than (+)-L-acetonamine, since the configuration of the epoxides changes with the inversion of the absolute configuration of the biaryl moiety.

This general lack of 'matched'/'mismatched' distinction, as far as enantiomeric excesses are concerned, does not apply to conversions. Catalyst **98i** performed better than **99i** essentially in terms of conversions – as previously reported.[22] Amine **98a** also catalysed the reaction better than **99a**, in biphasic $CH_2Cl_2/H_2O$ conditions in particular (*e.g.* olefin **105**, conditions **B**, **98a**: 87% *vs* **99a**: <5%).

[36] Olefins **104**–**106** were treated under conditions **A** and **B** with substoichiometric amounts (5 mol %) of **98a**, **99a**, [**98i**][TRISPHAT] and [**99i**][TRISPHAT].

*Table IV-3*: Asymmetric epoxidation of olefins **104–106** using **98a** and [**98i**][TRISPHAT] as catalyst

| | Amine **98a** | | | | | |
|---|---|---|---|---|---|---|
| | Conditions **A**[a] | | | Conditions **B**[b] | | |
| Alkene[c] | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. |
| **104** | 100[e,f] | 78 | (–)-(*S*,*S*) | 90[d] | 65 | (–)-(*S*,*S*) |
| **105** | 99[e,f] | 80 | (+)-(1*R*,2*S*) | 87[d] | 45 | (+)-(1*R*,2*S*) |
| **106** | 94[d] | 48 | (–)-(*S*,*S*) | 58[d] | 48 | (–)-(*S*,*S*) |

| | Iminium [**98i**][TRISPHAT] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | [**98i**][*Δ*-TRISPHAT] | | | | | | [**98i**][*rac*-TRISPHAT] | | |
| | Conditions **A**[a] | | | Conditions **B**[b] | | | Conditions **B**[b] | | |
| Alkene[c] | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. |
| **104** | 64[e,f] | 79 | (–)-(*S*,*S*) | 99[d] | 77 | (–)-(*S*,*S*) | 98[d] | 78 | (–)-(*S*,*S*) |
| **105** | 34[e,f] | 71 | (+)-(1*R*,2*S*) | 90[d] | 78 | (+)-(1*R*,2*S*) | 98[d] | 77 | (+)-(1*R*,2*S*) |
| **106** | 88[d] | 47 | (–)-(*S*,*S*) | 80[d] | 46 | (–)-(*S*,*S*) | 87[d] | 46 | (–)-(*S*,*S*) |

*Table IV-4*: Asymmetric epoxidation of olefins **104–106** using **99a** and [**99i**][TRISPHAT] as catalysts

| | Amine **99a** | | | | | |
|---|---|---|---|---|---|---|
| | Conditions **A**[a] | | | Conditions **B**[b] | | |
| Alkene[c] | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. |
| **104** | 99[d] | 76 | (+)-(*R*,*R*) | 70[d] | 77 | (+)-(*R*,*R*) |
| **105** | 97[d] | 78 | (–)-(1*S*,2*R*) | <5[d] | 57 | (–)-(1*S*,2*R*) |
| **106** | 97[d] | 52 | (+)-(*R*,*R*) | 23[d] | 53 | (+)-(*R*,*R*) |

| | Iminium [**99i**][TRISPHAT] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | [**99i**][*Δ*-TRISPHAT] | | | | | | [**99i**][*rac*-TRISPHAT] | | |
| | Conditions **A**[a] | | | Conditions **B**[b] | | | Conditions **B**[b] | | |
| Alkene[c] | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. | Conv. % | e.e. % | Conf. |
| **104** | 98[d] | 81 | (+)-(*R*,*R*) | 54[d] | 78 | (–)-(*S*,*S*) | 50[d] | 76 | (+)-(*R*,*R*) |
| **105** | 99[d] | 83 | (–)-(1*S*,2*R*) | 33[d] | 69 | (–)-(1*S*,2*R*) | 42[d] | 71 | (–)-(1*S*,2*R*) |
| **106** | 85[d] | 52 | (+)-(*R*,*R*) | 15[d] | 54 | (–)-(*S*,*S*) | 15[d] | 50 | (+)-(*R*,*R*) |

*Tables IV-3 and IV-4*: [a]Conditions **A**: 5 mol % of catalyst, 2.0 equiv. Oxone®, 5.0 equiv. $NaHCO_3$, $CH_3CN$:$H_2O$ (10:1), 0 °C; average of at least two runs. [b]Conditions **B**: 5 mol % of catalyst, 2.5 mol % 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, $CH_2Cl_2$:$H_2O$ (3:2), 0 °C; average of at least two runs. [c]The enantiomeric excesses were determined by CSP-GC (**104**, Chiraldex Hydrodex *β*-3P) or CSP-HPLC (**105** and **106**, Chiralcel OD-H); the conversions were obtained using an internal standard (naphthalene). [d]2h reaction time. [e]15min reaction time; [f]Complete conversion was observed in 2h along with some product decomposition. Care was thus taken to select a shorter reaction time.

If one now compares the selectivity of the homologous amine and the iminium salts – that is, **98a** with **98i** and **99a** with **99i** – one notices that the amines and iminium salts induce the same sense of stereoselective induction onto the non-racemic epoxides and lead to comparable levels of enantiomeric excesses (with the "exception" of olefin **105**).
A subtle solvent effect is observed for compounds **98a** and **98i**, the amine performing slightly better in homogeneous conditions **A** (olefin **105**, catalyst **98a**, **A**: e.e. 80% *vs* **B**: e.e. 45%) and the iminium in biphasic conditions **B** (olefin **105**, catalyst **98i**, **A**: e.e. 71% *vs* **B**: e.e. 78%). For derivatives **99a** and **99i**, the best results are obtained in conditions **A** (olefin **105**, catalyst **99a**, **A**: e.e. 78% *vs* **B**: e.e. 57% and catalyst **99i**, **A**: e.e. 83% *vs* **B**: e.e. 69%).

As in the case of the biphenyl iminium cation **97i**, the configuration of the TRISPHAT anion has no influence on the enantioselectivity of the epoxidation reactions when the binaphthyl iminium cations **98i** and **99i** are used as catalysts in conditions **B**. Indeed, the same e.e. values were obtained in both cases with the iminium salts [**98i**][*Δ*-TRISPHAT] and [**98i**][*rac*-TRISPHAT] or [**99i**][*Δ*-TRISPHAT] and [**99i**][*rac*-TRISPHAT]. Moreover, quite higher conversions are found when the counterion of the iminium cations was the racemic TRISPHAT salt.[37]

### *IV-2.4 Conclusion*

As catalysts for the enantioselective epoxidation of some prochiral olefins, the tertiary amines **97a–99a** act essentially as good as their corresponding iminium salts **97i–99i**, in the $CH_3CN$/water conditions in particular (e.e. up to 80% for olefin **105** with amine catalyst (*M*,L)-**98a**). The 95% e.e. obtained by Page with the iminium catalyst [(*M*,L)-**98i**][$BF_4$] have not been exceeded but amine catalyst **98a** showed promising results.
Preparation of the amines requiring less synthetic steps than the preparation of the iminium salts, it is advantageous to use these "simpler" reagents for synthetic applications. Moreover, it was interesting to study other types of azepine catalysts – in the context of the enantioselective epoxidation.

[37] In $CH_3CN/H_2O$ conditions (**A**), we used only the iminium [**98i**] or [**99i**][*Δ*-TRISPHAT] salts due to better solubility of these salts compared to the ones formed with the racemic TRISPHAT anion. In, the monophasic medium reactions, the counterion does not play any role.

After the observations of these interesting catalyses by the amine derivatives (**97a, 98a** and **99a**), further studies were then performed in the group of Prof. Jérôme Lacour. In recent works, it was shown that biphenyl/binaphthyl-azepines[24] and doubly bridged biphenyl-azepines[26] with various chiral such appendages as the 1,2,2-trimethylpropylamine in particular, were effective catalysts in enantioselective olefin epoxidation.

In most cases, the amines and iminium ions lead to similar reactivity patterns and enantiomeric excesses. It is therefore reasonable to consider a single mechanistic pathway for the two processes,[38] although subtleties indicate that sharp differences can sometimes arise.

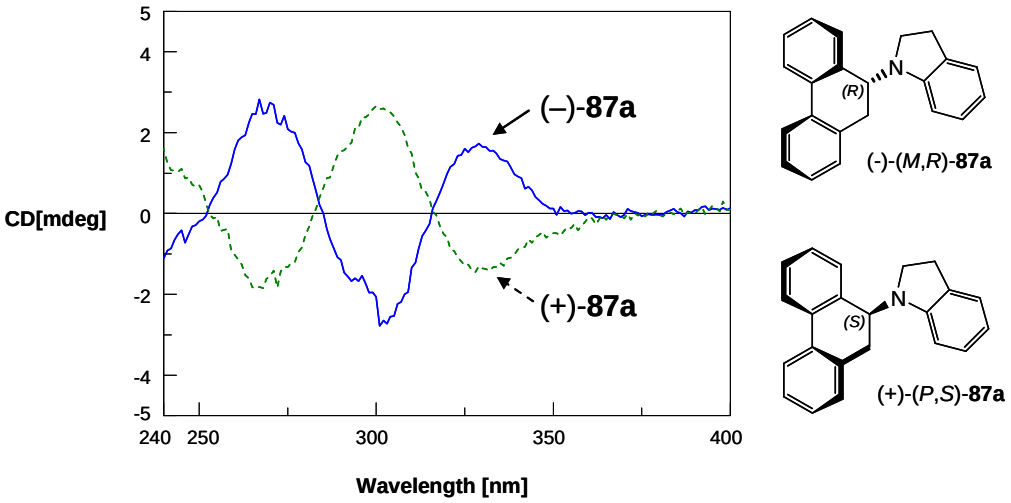
[38] It is in that sense, very different from the recent studies of Aggarwal and Yang on the epoxidation of olefins mediated by catalytic aliphatic secondary ammonium salts.

# PERSPECTIVES

So, to the exception of chapter IV that has concerned a somewhat different project on the enantioselective epoxidation of prochiral olefins, much of the content of this thesis has concerned (mechanistic) studies on the [1,2]-Stevens rearrangement – and the development of an enantioselective variant of it in particular. What can be noticed is that, actually and unfortunately, some bits of information are missing concerning some of the products of the enantioselective [1,2]-Stevens rearrangements, and dibenzoazepine-indolinium cations **86** in particular. For instance, the relative configuration of the *tropos* ammonium cations remains to be determined in solution when associated with BINPHAT anions (See chapter II-4.1.d) – despite continuous efforts on our side. So is the absolute configuration of the rearranged products **87**. It is indeed unfortunate as, without this stereochemical information, it is difficult to establish a more precise mechanism for the transformation of the quaternary ammonium ions to the non-racemic tertiary amines.

As far as products **87** are concerned, we never succeeded in obtaining monocrystals of enantiopure hydrochloride salts of these derivatives which could have led to the determination of the absolute configuration of the adducts by X-ray structural analysis. However, we think that the combined application of NMR spectroscopy and CD can be used to approach a solution to this configuration issue. In the $^{1}$H-NMR spectra of compounds **87a** to **87f**, obtained from the rearrangement of **86a** to **86f**, an AMX proton system is clearly identified for the benzylic protons on the 6-membered ring. Experimentally, the coupling constants between the proton $\alpha$ to the nitrogen atom and the two adjacent benzylic $\beta$ protons are $^{3}J$ ($H_{\alpha}$,$H_{\beta}$) = 10.4 and 5.3 Hz. These large and small values of the coupling constants correspond, according to the Karplus' rules, to diaxial and axial-equatorial relationships for the protons respectively. The amino group (indolinium ring) must thus adopt an equatorial-like position on the 6-membered ring and the adjacent $\alpha$ proton an axial-like one.

Moreover, CD analysis of compounds **87** in $CH_2Cl_2$, and (+)-**87a** and (–)-**87a** in particular, shows negative or positive *Cotton* effects at ~ 260 nm (See *CD spectra* below) which are most probably indicative of preferred *P* or *M* torsion of the biphenyl chromophore of **87** respectively (See chapter II-4.1.d, reference 42). The combination of these two spectral measurements is then indicative of the absolute configuration of products **87**. Compounds (+)-**87a** and (–)-**87a** ought to be the (*S*)-**87a** and (*R*)-**87a** enantiomers respectively.




<u>*CD spectra*</u>: of (+)-**87a** (dashed) and (–)-**87a** (plain), $CH_2Cl_2$, 20 °C.

Finally, at the end of this thesis and reflecting on what would be the ideal system for further studies, it is quite clear that better results should occur if the good diastereoselectivity observed during the asymmetric ion pairing of cations of type **61** and BINPHAT (d.e. 76% in $CD_2Cl_2$) could be retained while engineering a Stevens rearrangement with the same level of transfer of chirality as that observed in the endocyclic [1,2]-Stevens rearrangement of cations **86** (ToC up to 100%). To do so, we believe that the "simplest" way would be to modify the skeleton of cation **61** to force a deprotonation of the 7-membered ring and an endocyclic migration of the other benzylic carbon altogether.

We propose to achieve this goal by introducing electron-withdrawing substituents at the para positions of the biphenyl skeleton that would increase both the acidity of the benzylic protons of the 7-membered ring and the migratory aptitude of the endocyclic carbon (See *Figure* below). What remains also to be seen is the influence of these electron-withdrawing groups on the diastereoselectivity of the asymmetric ion pairing; the good precedents of cations **86d** and **86e** (with the fluorine and chlorine substituents) leaving quite a bit of hope.

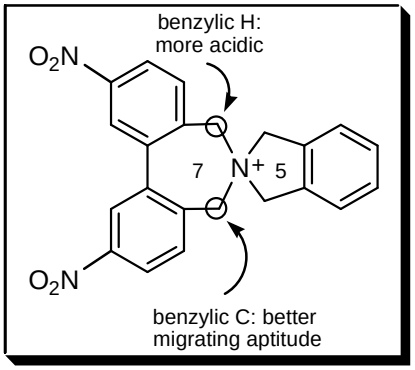



*Figure*: Proposed modified structure.

# EXPERIMENTAL PART

## General Remarks

All reactions were carried out under dry nitrogen or argon 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. Column chromatography was performed in air and under pressure (0.1-0.3 bar) , using silicagel 60, 40 μm or Fluka basic alumina type 5016A.

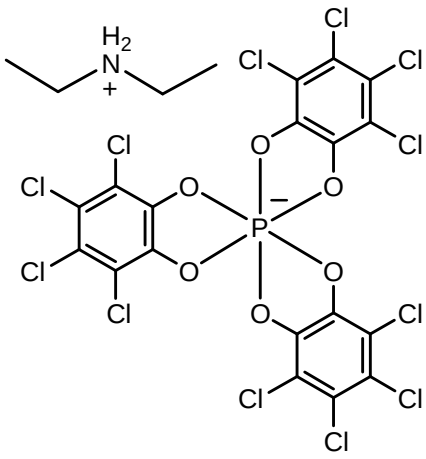
NMR spectra were recorded on Bruker AMX-400 or AMX-500 at 22 °C (298 K) unless otherwise specified. $^{1}$H-NMR chemical shifts are given in ppm relative to $Me_4Si$ with the solvent resonance used as the internal standard. $^{13}$C-NMR chemical shifts were given in ppm relative to $Me_4Si$, with the solvent resonance used as the internal standard. $^{31}$P-NMR chemical shifts were reported in ppm relative to $H_3PO_4$. $^{19}$F-NMR chemical shifts are given in ppm relative to $CFCl_3$. When necessary, assignment of the signals was achieved using COSY, HSQC, HMBC and NOESY experiments. Data were reported as follows: chemical shift (δ) in ppm on the δ scale, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, td = triplet of doublet, t = triplet, q = quartet and m = multiplet), coupling constant *J* (Hz), and integration (br = broad signal). Unless otherwise noted, the coupling constants concern proton-proton coupling.

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. The absorption is indicated in wave numbers ($cm^{-1}$). 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; $\lambda_{max}$ are given in nm and molar adsorption coefficient $\varepsilon$ 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; $\lambda$ are given in nm and molar circular dichroic absorptions ($\Delta\varepsilon$ in $cm^2 \cdot mmol^{-1}$). Optical rotations were measured on a Perkin-Elmer 241 or 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 UV-visible diode-array detector using Chiralpak AD-H (0.46 x 25 cm), Chiralpak IB (0.46 x 25 cm) and Chiralcel OD-H (0.46 x 25 cm) columns. Chiral Stationary Phase (CSP) chromatography was performed on a *Hewlett Packard 6890* GC chromatograph using a Hydrodex-$\beta$ column (25m x 0.25 m, $H_2$, 40 Psi). Retention times ($t_R$) are given in minutes (min).

# CHAPTER II – TOWARDS AN ENANTIOSELECTIVE [1,2]-STEVENS REARRANGEMENT

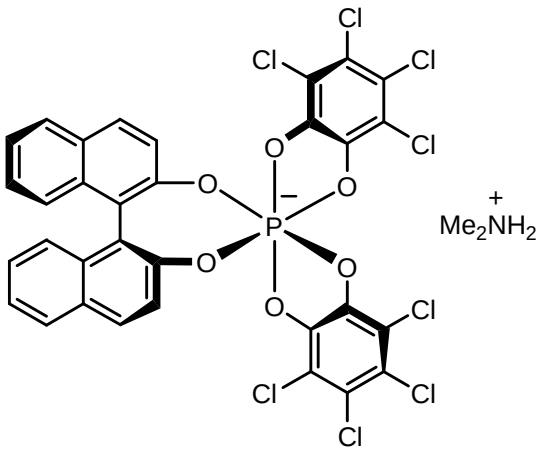
**diethylammonium [*rac*-tris(tetrachlorobenzenediolato)phosphate(V)] or [$Et_2NH_2$] [*rac*-TRISPHAT]:**



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 (crystallised and sublimed) (24.2 mmol, 3 equiv.) 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, 1.0 equiv.) 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, 1.0 equiv.) 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 Buchner 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 s, $NH_2$, 2H), 2.92 (q, $NCH_2$, 4H, $J$ = 7.1 Hz), 1.16 (t, Me, 6H, $J$ = 7.1 Hz); **$^{13}$C-NMR** (100 MHz, DMSO-$d_6$) δ 141.6 ($C^{IV}$, $J_{C\text{-}P}$ = 6.6 Hz), 122.6 ($C^{IV}$), 113.6 ($C^{IV}$, $J_{C\text{-}P}$ = 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* (rel intensity) 768.5 (100% $[M]^-$, TRISPHAT); Anal. Calculated 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.

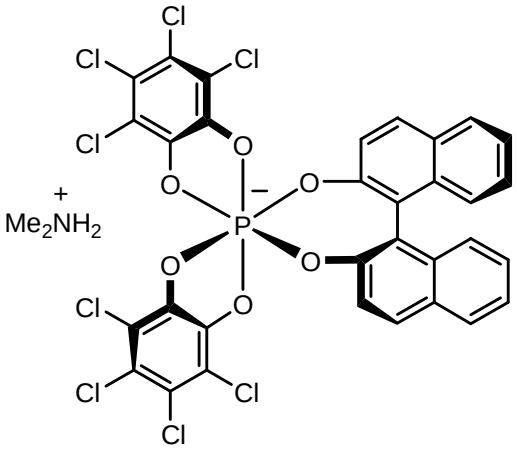
**dimethylammonium [*Δ*-bis(tetrachlorobenzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [$Me_2NH_2$][*Δ*-BINPHAT]:**



To a solution of 3.43 g (13.97 mmol, 1.0 equiv.) of tetrachlorocatechol (crystallised and sublimed) in 45 mL of dry toluene under a nitrogen atmosphere in a flame-dried 250 mL two-necked round-bottomed flask, equipped with a magnetic stirring bar, a reflux condenser, was slowly added 2.54 mL (13.97 mmol, 1.0 equiv.) of tris-(dimethylamino)phosphine (HMPA), freshly distilled. The mixture was refluxed for 15 min and the solvent was removed under reduced pressure. The white residue was carefully dried in vacuo. 40 mL of $Et_2O$ and 3.46 g (13.97 mmol, 1.0 equiv.) of *o*-chloranil were added following by 36 mL of $Et_2O$ to rinse all. The mixture was stirred at room temperature for 3 hours until a precipitate was formed and the colour of the solution turned to orange. Then 4.0 g of (*S*)-BINOL (13.97 mmol, 1.0 equiv.) was added following by 38 mL of $Et_2O$. After 18 hours the white precipitate formed was filtered over a Buchner funnel, washed rapidly with $Et_2O$ and $CH_2Cl_2$ distilled and then with Pentane. The pure titled compound was obtained as a white solid after drying under high vacuum (8.3 g, 70%).

**M.p.** > 215-216°C (decomposition); **$[\alpha]_D^{20}$** –42 (*c* 0.16; MeOH); **IR** (KBr): 3642, 3176, 3056, 2809, 2458, 1592, 1450, 1390, 1332, 1301, 1235, 1075, 992, 952, 828, 783, 753, 674, 618; **$^1$H-NMR** (400 MHz, DMSO-$d_6$, 293 K) δ 2.53 (s, 6H); 6.56 (d, 2H, *J* = 8.8 Hz); 7.26 (d, 4H, *J* = 3.6 Hz); 7.38 (m, 2H); 7.82 (d, 2H, *J* = 8.8 Hz); 7.94 (d, 2H, *J* = 8.0 Hz); 8.15 (br s, 2H); **$^{13}$C-NMR** (100 MHz, MeOH-$d_6$, 293 K) δ 153.2 (d, *J* = 12 Hz), 144.1 (d, *J* = 5.3 Hz), 143.5 (d, *J* = 9.1 Hz), 133.7, 132.1, 130.4, 129.3, 128.0, 126.5, 125.2, 124.3 (d, *J* = 3.0 Hz), 123.6 (d, *J* = 3.0 Hz), 123.6, 122.2, 115.1 (d, *J* = 20 Hz), 115.0 (d, *J* = 18 Hz), 35.5; **$^{31}$P-NMR** (162 MHz, DMSO-$d_6$, 293 K): δ –81.8; **MS-ES** (-) *m/z* (rel intensity) 807.0 (100% $[M]^-$, BINPHAT); **UV** (MeOH, $1.25\cdot10^{-5}$ M): $\lambda_{max}$ (ε) 329 ($8.9\cdot10^3$), 301 ($2.1\cdot10^4$), 220 ($2.1\cdot10^5$); **CD** (MeOH, $7.70\cdot10^{-6}$ M, 20°C): λ (Δε) 300 (-19), 262 (29), 243 (-107), 229 (248).

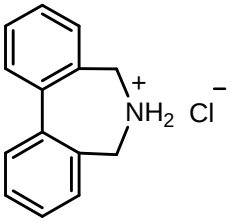
**dimethylammonium [*Λ*-bis(tetrachlorobenzenediolato)mono((*R*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [$Me_2NH_2$][*Λ*-BINPHAT]:**



Prepared following the above procedure starting from (*R*)-BINOL (67%). The characterisation data are the same for those reported for [$Me_2NH_2$][*Δ*-BINPHAT], except:

**$[\alpha]_D^{20}$** +41 (*c* 0.16, MeOH); **CD** (MeOH, $1.25 \cdot 10^{-5}$ M, 20°C): λ (Δε) 295 (23); 262 (-21); 243 (122); 229 (-250).

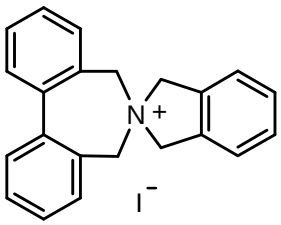
**6,7-dihydro-5H-dibenzo[*c*,*e*]azepinium chloride:**



To a suspension of biphenyl-2,2'-dicarbaldehyde (1.0 g, 4.756 mmol, 1.0 equiv.) in MeOH (35 mL) was added ammonium acetate (7.3 g, 95.120 mmol, 20 equiv.) and then sodium cyanoborohydride (837 mg, 13.320 mmol, 2.8 equiv.). After 24 h of reaction at room temperature, HCl (~36% *aq*.) was added dropwise till p*H* ~ 1-2. The solvents were evaporated and the wet residue was dissolved in water. The aqueous phase was washed with $Et_2O$ (3 x 50 mL) and basified with KOH pellets until p*H* > 7. The basic aqueous phase was saturated with NaCl and extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic phases were dried with $Na_2SO_4$ and concentrated under reduced pressure. The oil was dissolved in a minimum amount of $CH_2Cl_2$ and dropwise addition of HCl (1.0 M in $Et_2O$) provided a white precipitate, which was collected by filtration over a Buchner funnel to afford the desired salt as a white solid (795 mg, 72%).

**M.p.** 287 °C; **IR** (neat): 3019, 2905, 2696, 2569, 2448, 1593, 1485, 1439, 1393, 1331, 1196, 1124, 1015, 959, 867, 747 $cm^{-1}$; **$^1$H-NMR** (400 MHz, DMSO-$d_6$, 293 K) δ 9.81 (br s, 2H), 7.71-7.53 (m, 8H), 3.88 (br s, 4H); **$^{13}$C-NMR** (100 MHz, DMSO-$d_6$, 293 K) δ 141.1 ($2C^{IV}$), 131.9 (2CH), 131.1 (2CH), 130.5 ($2C^{IV}$), 129.5 (2CH), 129.3 (2CH), 45.7 ($2CH_2$); **MS-ES** (+) *m/z* (rel intensity) 427.3 (57%), 196.5 (100% $[M]^+$).

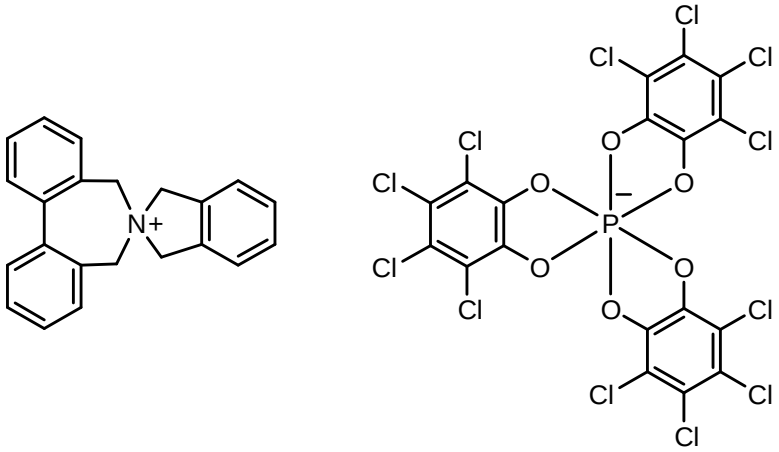
**6,6-isoindanyl-6,7-dihydro-5H-dibenzo[*c,e*]azepinium iodide or [61][I]:**



To a suspension of 6,7-dihydro-5H-dibenzo[*c,e*]azepinium chloride (400 mg, 1.726 mmol, 1.0 equiv.) in $CH_3CN$ (20 mL) was added $K_2CO_3$ (1.07 g, 7.767 mmol, 4.5 equiv.) and 1,2-bis(iodomethyl)benzene (742 mg, 2.071 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 3 h, under a nitrogen atmosphere and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$ and the inorganic salts filtered. To the mother liquor was added an excess of KI (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over basic alumina using $CH_3CN$ as eluent. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$, and dropwise addition of $Et_2O$ provided a yellow precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a yellow solid (651 mg, 89%).

**M.p.** 252 °C (decomposition); **IR** (neat): 3423, 2957, 1604, 1483, 1445, 1356, 1203, 1025, 1013, 906, 869, 753, 670 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 7.75 (d, 2H, *J* = 7.2 Hz), 7.73-7.69 (m, 4H), 7.60-7.55 (m, 2H), 7.49-7.45 (m, 4H), 5.61 (d, 2H, *J* = 13.9 Hz), 5.10 (d, 2H, *J* = 13.2 Hz), 4.93 (d, 2H, *J* = 13.9 Hz), 3.87 (d, 2H, *J* = 13.2 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 140.7 ($2C^{IV}$), 132.2 ($2C^{IV}$), 131.5 (2CH), 131.2 (2CH), 129.5 (2CH), 129.3 (2CH), 128.9 (2CH), 127.3 ($2C^{IV}$), 123.9 (2CH), 66.8 ($2CH_2$), 62.3 ($2CH_2$); **MS-ES** (+) *m/z* (rel intensity) 299.3 (25%), 298.1 (75% $[M]^+$), 181.3 (100%), 166.3 (100%); **HRMS**: Calculated for $C_{22}H_{20}N$ 298.1590, found 298.1592.

**6,6-isoindanyl-6,7-dihydro-5H-dibenzo[*c,e*]azepinium [*rac*-tris(tetrachlorobenzenediolato)-phosphate(V)] or [61][*rac*-TRISPHAT]:**



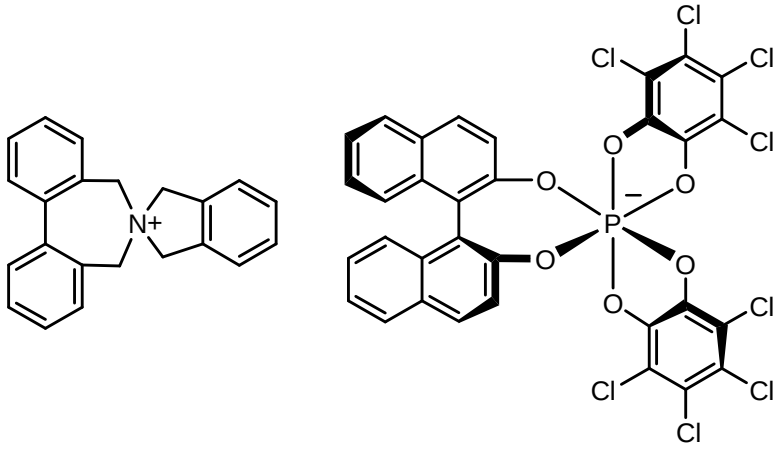
To a solution of diphenylazepinium salt [**61**][I] (130 mg, 0.306 mmol, 1.0 equiv.) in $CH_2Cl_2$ (10 mL) was added a solution of salt $[Et_2NH_2]$[*rac*-TRISPHAT] (299 mg, 0.367 mmol, 1.2 equiv.) in acetone (16 mL). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent to afford the title compound as a white solid (292 mg, 89%).

**M.p.** 236 °C (decomposition); **IR** (neat): 1445, 1388, 1300, 1235, 989, 821, 766, 669 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 7.73-7.69 (m, 4H), 7.55-7.50 (m, 4H), 7.48-7.44 (m, 4H), 5.08 (d, 2H, *J* = 14.2 Hz), 4.73 (d, 2H, *J* = 14.2 Hz), 4.36 (d, 2H, *J* = 13.2 Hz), 4.02 (d, 2H, *J* = 13.2 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –81.7; **MS-ES** (+) *m/z* (rel intensity) 299.5 (30%), 298.5 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 769.1 (100% $[M]^-$, TRISPHAT); **HRMS**: Calculated for $C_{22}H_{20}N$ 298.1590, found 298.1601 and calculated for $C_{18}O_6P^{35}Cl_{11}{}^{37}Cl$ 764.5672, found 764.5693.

**General procedure for the synthesis of the isoindanyl-diphenylazepinium BINPHAT salts [61][*Δ*-BINPHAT] and [61][*Λ*-BINPHAT]:**

To a solution of diphenylazepinium salt [**61**][I] (1.0 equiv.) in $CH_2Cl_2$ (3.4 mL per 0.1 mmol of substrate) was added a solution of salt [$Me_2NH_2$][*Δ*-BINPHAT] (or its enantiomer, 1.2 equiv.) in acetone (5.1 mL per 0.1 mmol of substrate). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent.

**6,6-isoindanyl-6,7-dihydro-5H-dibenzo[*c*,*e*]azepinium [*Δ*-bis(tetrachlorobenzenediolato)-mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [61][*Δ*-BINPHAT]:**

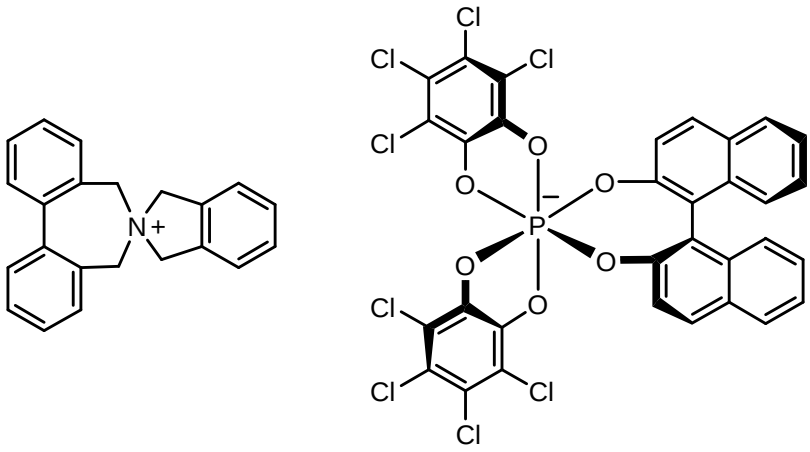


Starting from 100 mg (0.235 mmol, 1.0 equiv.) of [**61**][I], [**61**][*Δ*-BINPHAT] salt was obtained as a white solid after purification by column chromatography (233 mg, 90%).

**M.p.** 227 °C (decomposition); **$[\alpha]_D^{20}$** –77.2 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 1592, 1450, 1388, 1230, 992, 952, 817, 780, 750, 668 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.92 (d, 2H, BT, *J* = 8.0 Hz), 7.53 (d, 2H, BT, *J* = 8.8 Hz), 7.47-7.13 (m, 6H, BT + 6H, *Maj* + 12H, *min*), 7.03 (t, 2H, *Maj*, *J* = 7.2 Hz), 6.67 (br s, 2H, *Maj*), 6.44 (d, 2H, *Maj*, *J* = 7.2 Hz), 5.90 (d, 2H, BT, *J* = 8.8 Hz), 4.90 (d, 2H, *min*, *J* = 14.2 Hz), 4.56 (d, 2H, *Maj*, *J* = 14.2 Hz), 4.42-4.39 (m, 2H, *Maj* + 2H, *min*), 4.21 (d, 2H, *min*, *J* = 13.2 Hz), 4.14 (d, 2H, *Maj*, *J* = 13.2 Hz), 3.66 (d, 2H, *Maj*, *J* = 13.2 Hz), 3.58 (d, 2H, *min*, *J* = 13.2 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.3; **MS-ES** (+) *m/z* (rel intensity) 299.5 (27%), 298.5 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 807.5 (100% $[M]^-$, BINPHAT);

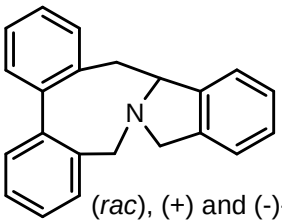
**HRMS**: Calculated for $C_{22}H_{20}N$ 298.1590, found 298.1598 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7894.

**6,6-isoindanyl-6,7-dihydro-5H-dibenzo[*c,e*]azepinium [*Λ*-bis(tetrachlorobenzenediolato)-mono((*R*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [61][*Λ*-BINPHAT]:**



Starting from 60 mg (0.141 mmol, 1.0 equiv.) of [**61**][I], [**61**][*Λ*-BINPHAT] salt was obtained as a white solid after purification by column chromatography (136 mg, 87%).
$[\alpha]_D^{20}$ +77.6 (*c* 0.1, $CH_2Cl_2$).

**Tertiary amine 62:**



(*rac*), (+) and (-)-**62**

To a solution of the required ammonium [**61**][*rac*-TRISPHAT] salt (48 mg, 0.045 mmol, 1.0 equiv.) or [**61**][*Δ*-BINPHAT] salt (50 mg 0.045 mmol, 1.0 equiv.) or [**61**][*Λ*-BINPHAT] salt (50 mg 0.045 mmol, 1.0 equiv.) in dry $CH_2Cl_2$ (2.2 mL) at –80 °C was added the $P_4$-*t*-Bu base (1 M in Hexane, 68 µL, 0.068 mmol, 1.5 equiv.). After stirring 4 h at –80 °C, under a nitrogen atmosphere, the reaction was quenched by addition of MeOH (2.2 mL), by cannulation at –80 °C. The mixture was concentrated under reduced pressure. The residue was dissolved in a minimum amount of $CH_2Cl_2$ and the precipitate upon addition of $Et_2O$ filtered. The mother liquor was concentrated in vacuo and the resulting compound was purified by column chromatography using $Et_2O$ as eluent. The desired compound **62** was obtained as a pink oil, as (*rac*)-**62** (2.0 mg, 15%), (+)-**62** (3.8 mg, 28%) and (–)-**62**

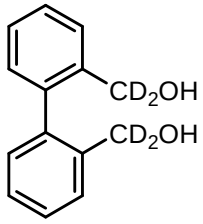
(3.8 mg, 28%) respectively. The enantiomeric excess was measured using a CSP-HPLC (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C).

**IR** (neat): 3056, 2923, 2853, 1694, 1481, 1462, 1436, 1140, 1119, 1071, 752, 735, 721, 668 cm$^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.44-7.30 (m, 9H), 7.25-7.16 (m, 3H), 4.39 (dd, 1H, *J* = 10.1 Hz, *J* = 2.3 Hz), 4.21 (dd, 1H, *J* = 12.6 Hz, *J* = 2.3 Hz), 4.05 (d, 1H, *J* = 12.6 Hz), 3.99 (d, 1H, *J* = 14.6 Hz), 3.74 (d, 1H, *J* = 14.6 Hz), 2.69 (dd, 1H, *J* = 13.6 Hz, *J* = 1.0 Hz), 2.41 (dd, 1H, *J* = 13.6 Hz, *J* = 10.1 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 144.8 ($C^{IV}$), 141.5 ($C^{IV}$), 141.3 ($C^{IV}$), 140.1 ($C^{IV}$), 139.8 ($C^{IV}$), 136.3 ($C^{IV}$), 131.4 (CH), 129.9 (2CH), 129.8 (CH), 128.5 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 126.4 (CH), 122.5 (CH), 122.4 (CH), 68.6 (CH), 53.6 ($CH_2$), 51.8 ($CH_2$), 40.3 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 299.1 (25%), 298.1 (100% [M+1]), 181.3 (80%), 166.1 (52%); **HRMS**: Calculated for $C_{22}H_{20}N$ 298.1590, found 298.1596.

(+)-**62**: **$[\alpha]_D^{20}$** +21.7 (*c* 0.1, $CH_2Cl_2$).

(–)-**62**: **$[\alpha]_D^{20}$** –21.5 (*c* 0.1, $CH_2Cl_2$).

**(2'-hydroxy-dideuterio-methyl-biphenyl-2-yl)-methanol:**

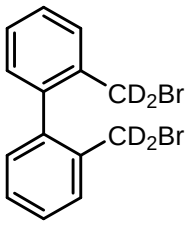



To a suspension of diphenic anhydride (2.5 g, 11.15 mmol, 1.0 equiv.) in dry $Et_2O$ (24 mL) and dry toluene (16 mL), at 0 °C, under argon atmosphere was added dropwise $LiAlD_4$ (950 mg, 23.08 mmol, 2.07 equiv.). The mixture was heated at 50 °C under argon over 2 h. The reaction was left to cool down to room temperature. Excess hydride was decomposed by slow addition of water and $Et_2O$ was added. After filtration over a Buchner funnel, the organic layer was separated and the aqueous phase extracted twice with $Et_2O$. The organic phases were combined, washed with brine and dried with $Na_2SO_4$. After evaporation of the solvents, the desired compound was obtained as a white solid (1.34 g, 55%).

**M.p.** 111 °C; **IR** (neat): 3330, 3230, 3062, 2877, 1476, 1439, 1372, 1212, 1121, 1093, 1049, 1038, 1005, 975, 957, 754 cm$^{-1}$; **$^{1}$H-NMR** (500 MHz, $CDCl_3$, 293 K) δ 7.47 (dd, 2H, *J* = 7.4 Hz, *J* = 1.2 Hz), 7.39 (dt, 2H, *J* = 7.4 Hz, *J* = 1.4 Hz), 7.34 (dt, 2H, *J* = 7.4 Hz, *J* = 1.4 Hz), 7.14 (dd, 2H, *J* = 7.4H z, *J* = 1.1 Hz), 3.23 (br s, 2H); **$^{13}$C-NMR** (126 MHz, $CDCl_3$, 293 K) δ 139.6 ($2C^{IV}$),

138.1 ($2C^{IV}$ ), 129.2 (2CH), 129.1 (2CH), 127.6 (2CH), 127.2 (2CH), 61.6 (multiplet by coupling to $^{2}H$ (I=1)); **LR-MS** (EI) *m/e* 199 (100% [M]-$H_2O$).

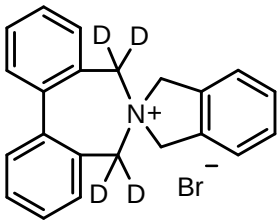
**2,2'-bis(bromo-dideuterio-methyl)biphenyl:**




A mixture of (2'-hydroxy-dideutero-methyl-biphenyl-2-yl)-methanol (1.34 g, 6.139 mmol, 1.0 equiv.) and HBr (~48% *aq.*, 27 mL) was heated at reflux during 1 h. The reaction mixture was diluted with water and then extracted with $CHCl_3$. The combined organic phases were washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo to give the pure titled compound without purification as a brown solid (2.06 g, 97%).

**M.p.** 91 °C; **IR** (neat): 3061, 3017, 1474, 1439, 1272, 1219, 1063, 1007, 935, 882, 791, 763 $cm^{-1}$; **$^{1}$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 7.29 (dd, 2H, *J* = 7.3 Hz, *J* = 1.5 Hz), 7.39 (dt, 2H, *J* = 7.5 Hz, *J* = 1.5 Hz), 7.43 (dt, 2H, *J* = 7.3 Hz, *J* = 1.5 Hz), 7.56 (dd, 2H, *J* = 7.5 Hz, *J* = 1.5 Hz); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 139.4 ($2C^{IV}$), 135.8 ($2C^{IV}$), 130.7 (2CH), 130.1 (2CH), 128.7 (2CH), 128.3 (2CH), 31.5 (multiplet by coupling to $^{2}H$ (I=1)); **HRMS**: Calculated for $C_{14}H_8D_4Br_2$ 343.95363, found 343.95794.

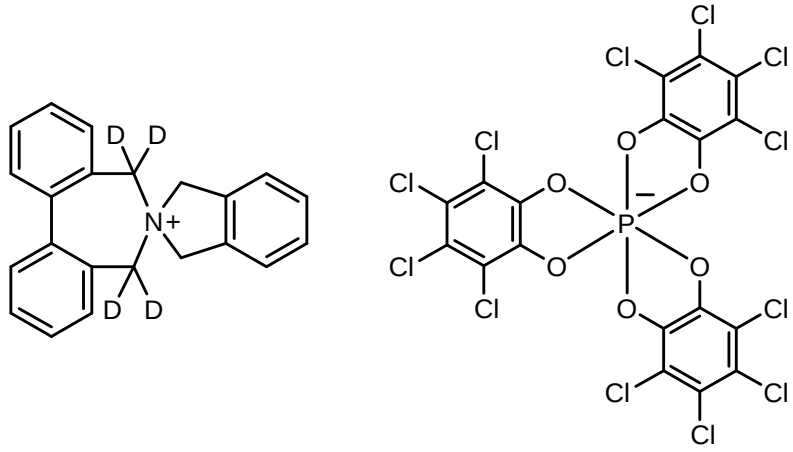
**6,6-isoindanyl-6,7-dideuterio-5H-dibenzo[*c,e*]azepinium bromide or [67][Br]:**




To a suspension of 1,3-dihydroisoindolium chloride (100 mg, 0.642 mmol, 1.0 equiv.) in $CH_3CN$ (10 mL) was added $K_2CO_3$ (400 mg, 2.891 mmol, 4.5 equiv.) and 2,2'-bis(bromo-dideuterio-methyl)biphenyl (265 mg, 0.770 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 3 h, under a nitrogen atmosphere and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$ and the inorganic salts filtered. To the mother liquor was added an excess of KBr (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over basic alumina using $CH_3CN$ as eluent. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$, and dropwise addition of $Et_2O$ provided a white precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a white solid (131 mg, 53%).

**M.p.** 248 °C (decomposition); **IR** (neat): 3058, 2957, 1484, 1448, 1334, 1071, 1062, 955, 860, 832, 745, 656 $cm^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 7.77 (d, 2H, *J* = 7.4 Hz), 7.72-7.68 (m, 4H), 7.59-7.54 (m, 2H), 7.47-7.43 (m, 4H), 5.68 (d, 2H, *J* = 13.9 Hz), 4.91 (d, 2H, *J* = 13.9 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 140.7 ($2C^{IV}$), 132.4 ($2C^{IV}$), 131.4 (2CH), 131.3 (2CH), 129.4 (2CH), 129.2 (2CH), 128.8 (2CH), 127.3 ($2C^{IV}$), 123.8 (2CH), 66.4 ($2CH_2$); **MS-ES** (+) *m/z* (rel intensity) 303.3 (25%), 302.3 (100% $[M]^+$), 185.3 (97%), 168.3 (72%); **HRMS**: Calculated for $C_{22}H_{16}D_4N$ 302.1841, found 302.1852.

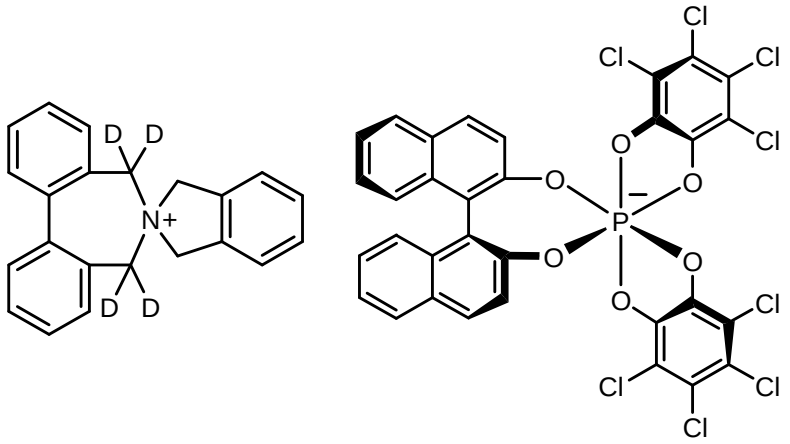
**6,6-isoindanyl-6,7-dideuterio-5H-dibenzo[*c,e*]azepinium [*rac*-tris(tetrachlorobenzene-diolato)phosphate(V)] or [67][*rac*-TRISPHAT]:**




To a solution of diphenylazepinium salt [**67**][Br] (70 mg, 0.183 mmol, 1.0 equiv.) in $CH_2Cl_2$ (6 mL) was added a solution of salt [$Et_2NH_2$][*rac*-TRISPHAT] (179 mg, 0.219 mmol, 1.2 equiv.) in acetone (10 mL). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent to afford the title compound as a white solid (190 mg, 97%).

**$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 7.73-7.71 (m, 4H), 7.54-7.51 (m, 4H), 7.49-7.45 (m, 4H), 5.07 (d, 2H, *J* = 14.2 Hz), 4.73 (d, 2H, *J* = 14.2 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –81.4.

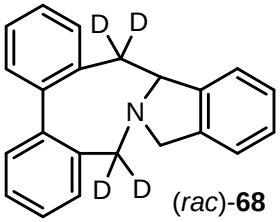
**6,6-isoindanyl-6,7-dideuterio-5H-dibenzo[*c*,*e*]azepinium [*Δ*-bis(tetrachlorobenzenediolato)-mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [67][*Δ*-BINPHAT]:**




To a solution of diphenylazepinium salt [**67**][Br] (40 mg, 0.105 mmol, 1.0 equiv.) in $CH_2Cl_2$ (4 mL) was added a solution of salt [$Me_2NH_2$][*Δ*-BINPHAT] (107 mg, 0.126 mmol, 1.2 equiv.) in acetone (5 mL). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent to afford the title compound as a white solid (116 mg, 99%).

**M.p.** 199 °C (decomposition); **$[\alpha]_D^{20}$** –75.8 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 1712, 1592, 1450, 1389, 1237, 991, 953, 818, 748, 671 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.93 (d, 2H, BT, *J* = 8.0 Hz), 7.58-7.24 (m, 8H, BT + 6H, *Maj* + 12H, *min*), 7.13 (br s, 2H, *Maj*), 6.98 (br s, 2H, *Maj*), 6.48 (br s, 2H, *Maj*), 6.0 (d, 2H, BT, *J* = 8.8 Hz), 4.95 (d, 2H, *min*, *J* = 14.2 Hz), 4.67 (d, 2H, *Maj*, *J* = 14.2 Hz), 4.55-4.52 (m, 2H, *Maj* + 2H, *min*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.3; **MS-ES** (+) *m/z* (rel intensity) 303.3 (26%), 302.1 (100% $[M]^+$), 149.1 (25%), **MS-ES** (-) *m/z* (rel intensity) 807.5 (100% $[M]^-$, BINPHAT.

**"Half-deuterated" tertiary amine 67:**

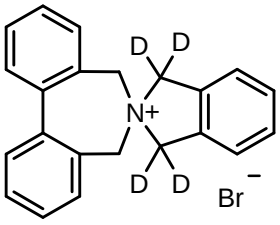


(*rac*)-**68**

To a solution of the required ammonium [**67**][*rac*-TRISPHAT] salt (60 mg, 0.056, 1.0 equiv.) or [**67**][*Δ*-BINPHAT] salt (60 mg, 0.054 mmol, 1.0 equiv.) in dry $CH_2Cl_2$ (2.7 mL) at –80 °C was added the $P_4$-*t*-Bu base (1 M in Hexane, 84 µL, 0.084 mmol or 81 µL, 0.081 mmol, 1.5 equiv.). After stirring 4 h at –80 °C, under a nitrogen atmosphere, the reaction was quenched by addition of MeOH (2.7 mL), by cannulation at –80 °C. The mixture was concentrated under reduced pressure. The residue was dissolved in a minimum amount of $CH_2Cl_2$ and the precipitate upon addition of $Et_2O$ filtered. The mother liquor was concentrated in vacuo and the resulting compound was purified by column chromatography using $Et_2O$ as eluent. The desired compound **68** was obtained as a pink oil, as (*rac*)-**68** (3.0 mg, 18%) and (*rac*)-**68** (3.0 mg, 18%) respectively. The lacks of enantiomeric excesses were measured using a CSP-HPLC (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C).

**IR** (neat): 3331, 2923, 2854, 1726, 1644, 1480, 1457, 1264, 1124, 1092, 751 cm$^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.44-7.42 (m, 2H), 7.37-7.29 (m, 7H), 7.25-7.16 (m, 3H), 4.37 (d, 1H, *J* = 2.3 Hz), 4.21 (dd, 1H, *J* = 12.6 Hz, *J* = 2.3 Hz), 4.05 (d, 1H, *J* = 12.6 Hz); **MS-ES** (+) *m/z* (rel intensity) 303.5 (20%), 302.5 (100% [M+1]); **HRMS**: Calculated for $C_{22}H_{16}D_4N$ 302.1841, found 302.1844.

**6,6-dideuterio-isoindanyl-6,7-dihydro-5H-dibenzo[*c,e*]azepinium bromide or [70][Br]:**

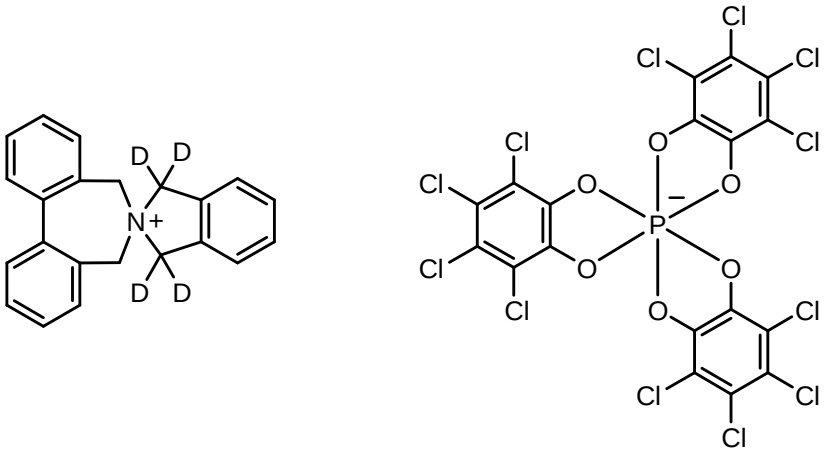



To a suspension of 6,7-dihydro-5H-dibenzo[*c,e*]azepinium chloride (150 mg, 0.647 mmol, 1.0 equiv.) in $CH_3CN$ (10 mL) was added $K_2CO_3$ (402 mg, 2.913 mmol, 4.5 equiv.) and 1,2- bis(bromo-dideuterio-methyl)benzene (208 mg, 0.776 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 3 h, under a nitrogen atmosphere and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$ and the inorganic salts filtered. To the mother liquor was added an excess of KBr (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over basic alumina using $CH_3CN$ as eluent. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$, and

dropwise addition of $Et_2O$ provided a white precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a white solid (651 mg, 94%).

**M.p.** 247 °C (decomposition); **IR** (neat): 2954, 1479, 1460, 1386, 1206, 1073, 955, 887, 748, 738, 663 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 7.77 (d, 2H, *J* = 7.5 Hz), 7.71-7.68 (m, 4H), 7.59-7.55 (m, 2H), 7.47-7.41 (m, 4H), 5.18 (d, 2H, *J* = 13.2 Hz), 3.82 (d, 2H, *J* = 13.2 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 140.7 ($2C^{IV}$), 132.3 ($2C^{IV}$), 131.4 (2CH), 131.3 (2CH), 129.4 (2CH), 129.2 (2CH), 128.8 (2CH), 127.4 ($2C^{IV}$), 123.8 (2CH), 61.9 ($2CH_2$); **MS-ES** (+) *m/z* (rel intensity) 303.4 (26%), 302.3 (100% $[M]^+$), 182.3 (90%), 167.1 (48%), 166.4 (66%); **HRMS**: Calculated for $C_{22}H_{16}D_4N$ 302.1841, found 302.1841.

**6,6-dideuterio-isoindanyl-6,7-dihydro-5H-dibenzo[*c,e*]azepinium [*rac*-tris(tetrachloro-benzenediolato)phosphate(V)] or [70][*rac*-TRISPHAT]:**

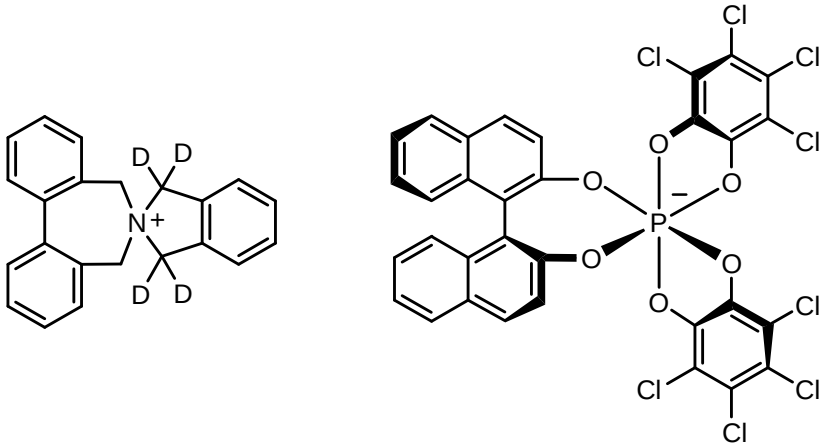



To a solution of diphenylazepinium salt [**70**][Br] (80 mg, 0.209 mmol, 1.0 equiv.) in $CH_2Cl_2$ (7 mL) was added a solution of salt $[Et_2NH_2]$[*rac*-TRISPHAT] (205 mg, 0.251 mmol, 1.2 equiv.) in acetone (11 mL). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent to afford the title compound as a white solid (202 mg, 90%).

**M.p.** 288 °C (decomposition); **IR** (neat): 1446, 1389, 1235, 989, 822, 733, 717, 669 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 7.73-7.70 (m, 4H), 7.55-7.51 (m, 4H), 7.49-7.44 (m, 4H), 4.35 (d, 2H, *J* = 13.2 Hz), 4.03 (d, 2H, *J* = 13.2 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –81.4; **MS-ES** (+) *m/z* (rel intensity) 303.4 (30%), 302.6 (100% $[M]^+$), **MS-ES** (-) *m/z*

(rel intensity) 769.1 (100% $[M]^-$, TRISPHAT); **HRMS**: Calculated for $C_{22}H_{16}D_4N$ 302.1841, found 302.1830 and calculated for $C_{18}O_6P^{35}Cl_{11}{}^{37}Cl$ 764.5672, found 764.5665.

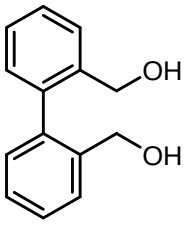
**6,6-dideuterio-isoindanyl-6,7-dihydro-5H-dibenzo[*c,e*]azepinium [*Δ*-bis(tetrachlorobenzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [70][*Δ*-BINPHAT]:**




To a solution of diphenylazepinium salt [**70**][Br] (70 mg, 0.183 mmol, 1.0 equiv.) in $CH_2Cl_2$ (6 mL) was added a solution of salt $[Me_2NH_2]$[*Δ*-BINPHAT] (187 mg, 0.220 mmol, 1.2 equiv.) in acetone (9 mL). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent to afford the title compound as a white solid (178 mg, 88%).

**M.p.** 219 °C (decomposition); $[\alpha]_D^{20}$ –86.8 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 1592, 1450, 1389, 1237, 992, 952, 817, 780, 749, 732, 668 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.93 (d, 2H, BT, *J* = 8.0 Hz), 7.55-7.18 (m, 8H, BT + 6H, *Maj* + 12H, *min*), 7.05 (br s, 2H, *Maj*), 6.77 (br s, 2H, *Maj*), 6.41 (br s, 2H, *Maj*), 5.93 (d, 2H, BT, *J* = 8.8 Hz), 4.24-4.15 (m, 2H, *min* + 2H, *Maj*), 3.67 (d, 2H, *Maj*, *J* = 13.2 Hz), 3.58 (d, 2H, *min*, *J* = 13.2 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.3; **MS-ES** (+) *m/z* (rel intensity) 303.4 (23%), 302.3 (100% $[M]^+$), 241.6 (25%), 149.1 (46%), **MS-ES** (-) *m/z* (rel intensity) 807.3 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{22}H_{16}D_4N$ 302.1841, found 302.1845 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7857.

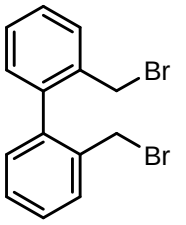
**(2'-hydroxy-methyl-biphenyl-2-yl)-methanol:**




To a suspension of diphenic anhydride (2.0 g, 8.92 mmol, 1.0 equiv.) in dry $Et_2O$ (20 mL), at 0 °C, under argon atmosphere was added dropwise $LiAlH_4$ (19.18 mmol, 2.15 equiv.). The mixture was heated at reflux for 4h. The reaction was left to cool down to room temperature. After dilution with $Et_2O$, the reaction mixture was acidified with HCl (1 N) to dropwise till p*H* ~ 1-2 and extracted with $Et_2O$. The combined organic phases were washed with brine and dried with $Na_2SO_4$. After evaporation of the solvents, the desired pure compound was obtained without purification as a white solid (1.7 g, 89%).

**M.p.** 110 °C; **IR** (neat): 3328, 3230, 3062, 2877, 1478, 1442, 1424, 1340, 1250, 1193, 1100, 1031, 1001, 957, 752 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 7.50 (dd, 2H, *J* = 7.6 Hz, *J* = 1.5 Hz), 7.41 (dt, 2H, *J* = 7.3 Hz, *J* = 1.5 Hz), 7.35 (dt, 2H, *J* = 7.3 Hz, *J* = 1.5 Hz), 7.17 (dd, 2H, *J* = 7.3 Hz, *J* = 1.2 Hz), 4.37 (d, 2H, *J* = 11.6 Hz), 4.22 (d, 2H, *J* = 10.4 Hz), 2.45 (br s, 2H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 140.0 ($2C^{IV}$), 138.6 ($2C^{IV}$), 129.7 (2CH), 129.6 (2CH), 128.1 (2CH), 127.7 (2CH), 62.9 ($2CH_2$); **LR-MS** (EI) *m/e* 196 (100% [M]-$H_2O$).

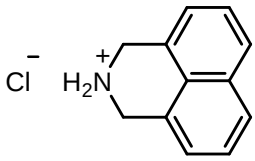
**2,2'-bis(bromo-dideuterio-methyl)biphenyl:**




A mixture of (2'-Hydroxymethyl-biphenyl-2-yl)-methanol (1.026 g, 4.77 mmol, 1.0 equiv.) and HBr (48% aqueous, 22 mL) was heated at reflux during 1h. After adding water, the compound was extracted with $CHCl_3$. The combined organic phases were washed with brine, dried with $Na_2SO_4$ and concentrated under vacuum. The desired compound was obtained pure without purification as a pale brown solid (1.5 g, 92%).

**M.p.** 89 °C; **IR** (neat): 3061, 2923, 2853, 1474, 1434, 1270, 1218, 1081, 1007, 810, 768, 755 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 7.57 (dd, 2H, *J* = 7.6 Hz, *J* = 1.5 Hz), 7.44 (dt, 2H, *J* = 7.3 Hz, *J* = 1.5 Hz), 7.39 (dt, 2H, *J* = 7.3 Hz, *J* = 1.5 Hz), 7.29 (dd, 2H, *J* = 7.3 Hz, *J* = 1.2 Hz), 4.35 (d, 2H, *J* = 10.4 Hz), 4.20 (d, 2H, *J* = 10.4 Hz); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 139.5 ($2C^{IV}$), 135.9 ($2C^{IV}$), 130.8 (2CH), 130.3 (2CH), 128.8 (2CH), 128.5 (2CH), 32.1 ($2CH_2$); **HRMS:** Calculated for $C_{22}H_{19}N$ 339.92853, found 339.92725.

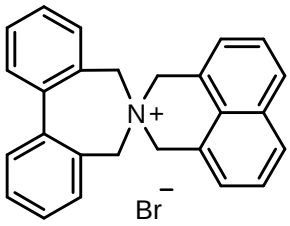
**2,3-dihydro-1H-benz[*de*]isoquinolinium chloride or IV:**



The 2,3-dihydro-1H-benz[*de*]isoquinoline (361 mg, 2.133 mmol) was synthesized according to the literature[1] was dissolved in a minimum amount of $CH_2Cl_2$. Dropwise addition of HCl (1.0 M in $Et_2O$) provided a pale brown precipitate, which was collected by filtration over a Buchner funnel to afford the desired corresponding salt as a pale brown solid (435 mg, 99%).

**M.p.** 278 °C (decomposition); **IR** (neat): 2969, 2944, 2742, 2714, 2690, 2589, 2467, 1739, 1582, 1515, 1457, 1404, 1379, 1235, 820, 795, 770 $cm^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$ + MeOH-$d_4$, 293 K) δ 7.87 (d, 2H, *J* = 8.2 Hz), 7.53 (t, 2H, *J* = 6.9 Hz), 7.41 (d, 2H, *J* = 6.9 Hz), 4.6 (s, 4H), 2.48 (br s, 2H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$ + MeOH-$d_4$, 293 K) δ 133.4 ($C^{IV}$), 128.7 (2CH), 126.6 (2CH), 126.4 ($C^{IV}$), 125.9 ($2C^{IV}$), 124.3 (2CH), 46.8 ($2CH_2$); **MS-ES** (+) *m/z* (rel intensity) 170.3 (100% $[M]^+$), 153.4 (36%), 128.3 (25%); **HRMS**: Calculated for $C_{12}H_{12}N$ 170.0964, found 170.0971.

**6,6-isoquinoline-6,7-dihydro-5H-dibenzo[*c,e*]azepinium bromide [73][Br]:**

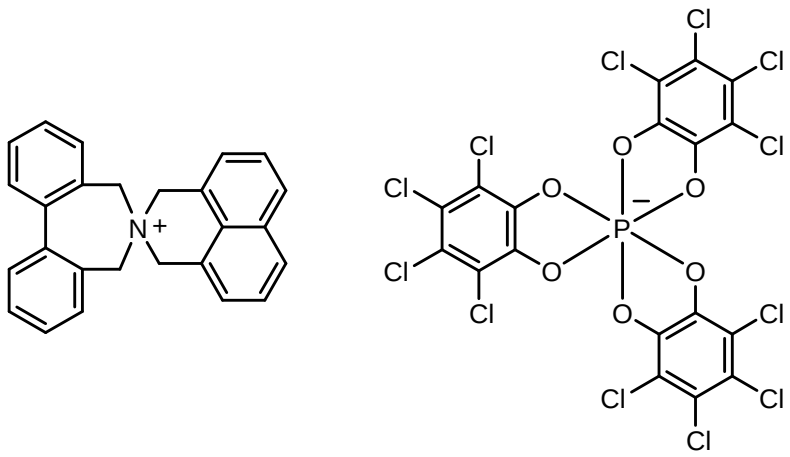


To a suspension of 2,3-dihydro-1H-benz[*de*]isoquinolinium chloride (140 mg, 0.680 mmol, 1.0 equiv.) in $CH_3CN$ (5 mL) was added $K_2CO_3$ (423 mg, 3.060 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (277 mg, 0.816 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 3 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$ and the inorganic salts filtered. To the mother liquor was added an excess of KBr (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated to 1 mL. Dropwise addition of $Et_2O$ provided a pale brown precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a pale brown solid (190 mg, 65%).

[1] Zheng, S.; Lan, J.; Khan, S. I.; Rubin, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5786-5791. Beetz, T.; Meuleman, D. G.; Wieringa, J. H. *J. Med. Chem.* **1982**, *25*, 714-719

**M.p.** 325°C (decomposition); **IR** (neat): 3042, 2949, 1461, 1445, 1406, 885, 822, 785, 758, 750 $cm^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 8.03 (d, 1H, *J* = 7.2 Hz), 7.95 (d, 1H, *J* = 8.3 Hz), 7.90 (d, 1H, *J* = 8.2 Hz), 7.72-7.60 (m, 6H), 7.52-7.44 (m, 3H), 7.35 (d, 1H, *J* = 7.1 Hz), 7.03 (d, 1H, *J* = 7.5 Hz), 6.66 (d, 1H, *J* = 13.7 Hz), 6.04 (d, 1H, *J* = 12.9 Hz), 5.91 (d, 1H, *J* = 15.0 Hz), 4.66 (d, 1H, *J* = 13.7 Hz), 4.52 (d, 1H, *J* = 15.0 Hz), 3.97 (d, 1H, *J* = 13.3 Hz), 3.75 (d, 1H, *J* = 12.9 Hz), 3.41 (d, 1H, *J* = 13.3 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 141.0 ($C^{IV}$), 140.5 ($C^{IV}$), 132.4 (CH), 132.3 ($C^{IV}$), 131.4 (CH), 131.2 (CH), 131.1 (CH), 129.2 (CH), 129.0 (3CH), 128.6 (CH), 128.5 (CH), 126.8 ($C^{IV}$), 126.7 (CH), 126.5 (CH), 126.4 ($C^{IV}$), 125.3 ($C^{IV}$), 125.2 (CH), 125.1 (CH), 123.7 ($C^{IV}$), 123.2 ($C^{IV}$), 63.5 ($CH_2$), 61.6 ($CH_2$), 59.3 ($CH_2$), 58.5 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 349.3 (33%), 348.1 (66% $[M]^+$), 181.3 (100%), 166.1 (75%); **HRMS**: Calculated for $C_{26}H_{22}N$ 348.1746, found 348.1739.

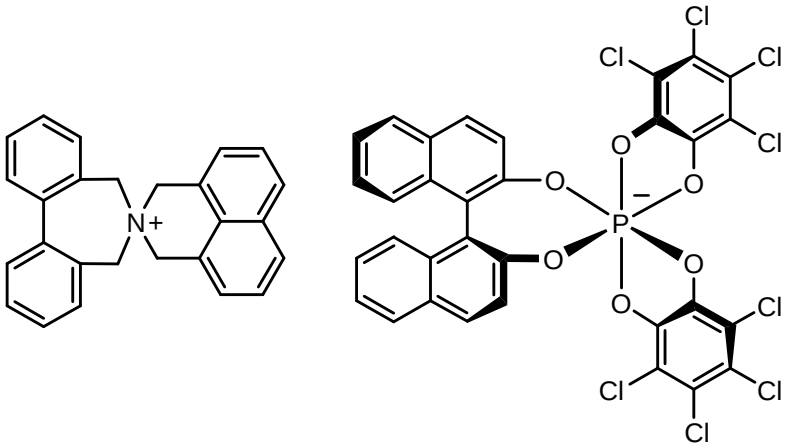
**6,6-isoquinoline-6,7-dihydro-5H-dibenzo[*c,e*]azepinium [*rac*-tris(tetrachlorobenzene-diolato)phosphate(V)] or [73][*rac*-TRISPHAT]:**




To a solution of diphenylazepinium salt [**73**][Br] (100 mg, 0.233 mmol, 1.0 equiv.) in $CH_2Cl_2$ (8 mL) was added a solution of salt [$Et_2NH_2$][*rac*-TRISPHAT] (228 mg, 0.280 mmol, 1.2 equiv.) in acetone (12 mL). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent to afford the title compound as a white solid (256 mg, 98%).

**M.p.** 269 °C (decomposition); **IR** (neat): 2923, 1446, 1390, 1238, 990, 819, 720, 669 $cm^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 8.00-7.95 (m, 2H), 7.90-7.88 (m, 1H), 7.72-7.61 (m, 5H), 7.54 (d, 1H, *J* = 7.0 Hz), 7.46 (t, 1H, *J* = 7.3 Hz), 7.28-7.21 (m, 2H), 7.18 (t, 1H, *J* = 7.3 Hz), 7.06 (d, 1H, *J* = 7.0 Hz), 5.20 (d, 1H, *J* = 14.6 Hz), 4.97 (d, 1H, *J* = 14.9 Hz), 4.80 (d, 1H, *J* = 14.9 Hz), 4.49 (d, 1H, *J* = 12.9 Hz), 4.16 (d, 1H, *J* = 12.9 Hz), 4.03 (d, 1H, *J* = 13.2 Hz), 3.48 (d, 1H, *J* = 13.2 Hz), 3.29-3.21 (m, 1H); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –81.7; **MS-ES** (+) *m/z* (rel intensity) 349.4 (32%), 348.5 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 769.1 (100% $[M]^-$), TRISPHAT); **HRMS**: Calculated for $C_{26}H_{22}N$ 348.1746, found 348.1445 and calculated for $C_{18}O_6P^{35}Cl_{11}{}^{37}Cl$ 764.5672, found 764.5691.

**6,6-isoquinoline-6,7-dihydro-5H-dibenzo[*c*,*e*]azepinium [*Δ*-bis(tetrachlorobenzenediolato)-mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [73][*Δ*-BINPHAT]:**

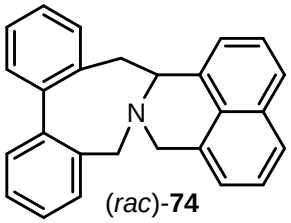



To a solution of diphenylazepinium salt [**73**][Br] (100 mg, 0.233 mmol, 1.0 equiv.) in $CH_2Cl_2$ (8 mL) was added a solution of salt $[Me_2NH_2]$[*Δ*-BINPHAT] (239 mg, 0.280 mmol, 1.2 equiv.) in acetone (12 mL). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent to afford the title compound as a white solid (221 mg, 82%).

**M.p.** 231 °C (decomposition); **$[\alpha]_D^{20}$** –91.1 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2971, 1738, 1450, 1387, 1230, 992, 952, 817, 780, 746 $cm^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.95-7.82 (m, 2H, BT + 2H, *Maj* + 2H, *min*), 7.59-7. 32 (m, 6H, BT + 4H, *Maj* + 12H, *min*), 7.27-6.89 (m, 2H, BT + 6H, *Maj*), 6.70 (br s, 1H, *Maj*), 6.13 (br s, 1H, *Maj*), 6.01 (d, 2H, BT, *J* = 8.8 Hz), 5.65 (d, 1H, *min*, *J* = 13.8 Hz), 5.20 (d, 1H, *Maj*),

4.78 (d, 1H, *min*, *J* = 14.5 Hz), 4.69-4.57 (m, 2H, *Maj*), 4.32-4.24 (m, 2H, *Maj* + 1H, *min*), 4.12 (d, 2H, *min*, *J* = 12.6 Hz), 3.84 (d, 1H, *min*, *J* = 12.9 Hz), 3.73 (d, 2H, *Maj*, *J* = 11.0 Hz), 3.58 (d, 1H, *min*, *J* = 12.9 Hz), 3.28 (d, 1H, *min*, *J* = 12.9 Hz), 3.11 (d, 1H, *Maj*, *J* = 11.0 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ – 83.0; **MS-ES** (+) *m/z* (rel intensity) 349.5 (34%), 348.5 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 807.3 (100% $[M]^-$), BINPHAT); **HRMS**: Calculated for $C_{26}H_{22}N$ 348.1746, found 348.1747 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7870.

**Tertiary amine 74:**



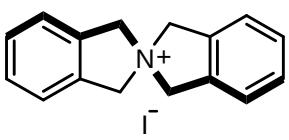
(*rac*)-**74**

To a solution of the required ammonium [**73**][*rac*-TRISPHAT] salt (48 mg, 0.043, 1.0 equiv.) or [**73**][*Δ*-BINPHAT] salt (50 mg, 0.043 mmol, 1.0 equiv.) in dry $CH_2Cl_2$ (2.2 mL) at –80 °C was added the $P_4$-*t*-Bu base (1 M in Hexane, 47 µL, 0.0473 mmol, 1.1 equiv.). After stirring 4 h at –80 °C, under a nitrogen atmosphere, the reaction was quenched by addition of MeOH (2.2 mL), by cannulation at –80 °C. The mixture was concentrated under reduced pressure. The residue was dissolved in a minimum amount of $CH_2Cl_2$ and the precipitate upon addition of $Et_2O$ filtered. The mother liquor was concentrated in vacuo and the resulting compound was purified by column chromatography using $Et_2O$:$CH_2Cl_2$ 99:01 as eluent. The desired compound **74** was obtained as a yellow solid, as (*rac*)-**74** (13.8 mg, 92%) and (*rac*)-**74** (14.5 mg, 96%) respectively. The lacks of enantiomeric excesses were measured using a CSP-HPLC (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C).

**M.p.** 82 °C; **IR** (neat): 3054, 2923, 1599, 1481, 1437, 1342, 1263, 1118, 1107, 1029, 810, 798, 772, 754, 739, 724, 702 cm$^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.76-7.71 (m, 2H), 7.58-7.51 (m, 4H), 7.49-7.35 (m, 7H), 7.28 (d, 1H, *J* = 6.9 Hz), 4.43 (d, 1H, *J* = 8.3 Hz), 4.25 (d, 1H, *J* = 14.3 Hz), 4.15 (d, 1H, *J* = 15.1 Hz), 3.93 (d, 1H, *J* = 15.1 Hz), 3.84 (d, 1H, *J* = 14.3 Hz), 2.90 (dd 1H, *J* = 14.0 Hz, *J* = 8.3 Hz), 2.73 (d, 1H, *J* = 14.0 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 141.9 ($C^{IV}$), 141.6 ($C^{IV}$), 140.9 ($C^{IV}$), 139.9 ($C^{IV}$), 135.4 ($C^{IV}$), 134.1 ($C^{IV}$), 133.4 ($C^{IV}$), 132.3 (CH), 130.4 (2CH), 129.9 (CH), 128.7 (CH), 128.0 (CH), 127.4 (CH), 127.0 ($C^{IV}$), 126.4 (CH), 126.3 (CH), 126.2 (CH), 126.1 (CH), 125.8 (CH), 122.8 (CH), 121.9 (CH), 66.4 (CH), 58.3 ($CH_2$), 49.0 ($CH_2$), 38.7 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 349.1 (37%), 348.1 (100% [M+1]), 167.3 (46%); **HRMS**: Calculated for $C_{26}H_{22}N$ 348.1746, found 348.1740.

# CHAPTER III – ENANTIOSELECTIVE [1,2]-STEVENS REARRANGEMENT AND EXCELLENT TRANFER OF CHIRALITY

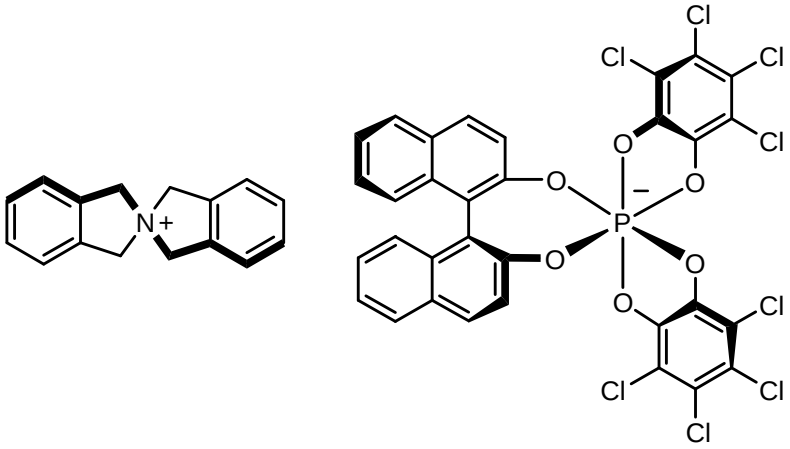
**1,1',3,3'-tetrahydrospiro[isoindole-2,2'-isoindolium] iodide or [81][I]:**



To a suspension of 1,2-bis(iodomethyl)benzene (765 mg, 2.137 mmol, 1.0 equiv.) in methanol (15 mL) was added $NH_4OH$ (5.0 equiv., ~ 25% in water, 0.9 mL). The reaction mixture was heated to reflux for 1 h 30 min and let cool down. 20 mL of water were added and the product precipitated. The resulting white solid was collected by filtration after washing with a minimum amount of water, to afford the pure titled compound (272 mg, 36%).

**M.p.** 314 °C (decomposition); **IR** (neat): 2865, 1467, 1447, 1340, 1042, 893, 759, 685 $cm^{-1}$; **$^{1}$H-NMR** (400 MHz, DMSO-$d_6$, 293 K) δ 7.49-7.43 (m, 8H), 5.06 (s, 8H); **$^{13}$C-NMR** (100 MHz, DMSO-$d_6$, 293 K) δ 133.8 ($4C^{IV}$), 128.8 (4CH), 123.6 (4CH), 67.8 ($4CH_2$); **MS-ES** (+) *m/z* (rel intensity) 223.4 (19%), 222.3 (100% $[M]^+$); **HRMS**: Calculated for $C_{16}H_{16}N$ 222.1277, found 222.1279.

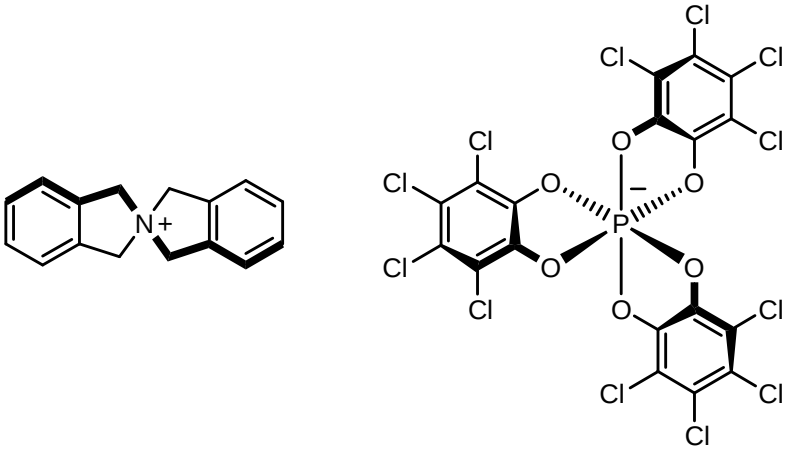
**1,1',3,3'-tetrahydrospiro[isoindole-2,2'-isoindolium] [*Δ*-bis(tetrachlorobenzenediolato)-mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [81][*Δ*-BINPHAT]:**



In a round bottom flask equipped with a magnetic stirring bar, the tetrahydro-spiro[isoindole-isoindolium] iodide salt [**81**][I] (200 mg, 0.573 mmol, 1.0 equiv.) and [$Me_2NH_2$][*Δ*-BINPHAT] (586 mg, 0.687 mmol, 1.2 equiv.) was dissolved in ~ 30 mL of MeOH. Dropwise addition of water and cooling at 0 °C during 30 min provided a white solid, which was collected by filtration to afford the desired compound as a white solid (332 mg, 56%).

**M.p.** 217 °C (decomposition); **$[\alpha]_D^{20}$** –27.2 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2971, 1739, 1448, 1373, 1229, 1218, 991, 952, 817, 781, 747 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CD_2Cl_2$, 293 K) δ 7.87 (d, 2H, BT, *J* = 8.0 Hz), 7.62 (d, 2H, BT, *J* = 8.8 Hz), 7.37 (t, 2H, BT, *J* = 7.5 Hz), 7.30 (d, 2H, BT, *J* = 8.5 Hz), 7.12-7.06 (m, 2H, BT + 4H), 6.70-6.68 (m, 4H), 6.28 (d, 2H, BT, *J* = 8.8 Hz), 4.55 (d, 4H, *J* = 13.8 Hz), 4.25 (d, 4H, *J* = 13.8 Hz); **$^{31}$P-NMR** (162 MHz, $CD_2Cl_2$, 293 K) δ –83.1; **MS-ES** (+) *m/z* (rel intensity) 223.3 (23%), 222.6 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 807.5 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{16}H_{16}N$ 222.1277, found 222.1284 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7907.

**1,1',3,3'-tetrahydrospiro[isoindole-2,2'-isoindolium] [*Δ*-tris(tetrachlorobenzenediolato)-phosphate(v)] or [81][*Δ*-TRISPHAT]:**

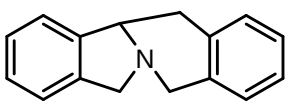



To a solution of the tetrahydro-spiro[isoindole-isoindolium] iodide salt [**81**][I] (50 mg, 0.143 mmol, 1.0 equiv.) in a mixture $CH_2Cl_2$:MeOH 90:10 (3.4 mL per 0.1 mmol of substrate), was added a solution of salt [cinchonidinium][*Δ*-TRISPHAT] (1.2 equiv.) in a mixture water:acetone 90:10 (5.1 mL per 0.1 mmol of substrate). After stirring for 30 min, the solvents were removed under reduced pressure. The desired ammonium [**81**][*Δ*-TRISPHAT] salt was recovered as a

white solid (107 mg, 75%) after purification by column chromatography over basic alumina using $CH_2Cl_2$ as eluent.

**M.p.** 224 °C; **$[\alpha]_D^{20}$** –371.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2971, 1739, 1443, 1388, 1235, 988, 816, 717, 668 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CD_2Cl_2$, 293 K) δ 7.49-7.46 (m, 4H), 7.41-7.38 (m, 4H), 5.07 (s, 0.4H), 5.03 (d, 7.2H, *J* = 3.8 Hz), 4.99 (s, 0.4H); **$^{31}$P-NMR** (162 MHz, $CD_2Cl_2$, 293 K) δ –81.0; **MS-ES** (+) *m/z* (rel intensity) 223.6 (22%), 222.6 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 769.3 (100% $[M]^-$), TRISPHAT); **HRMS**: Calculated for $C_{16}H_{16}N$ 222.1277, found 222.1271 and calculated for $C_{18}O_6P^{35}Cl_{11}{}^{37}Cl$ 764.5672, found 764.5672.

**Tertiary amine 82:**




(*rac*)-**82**

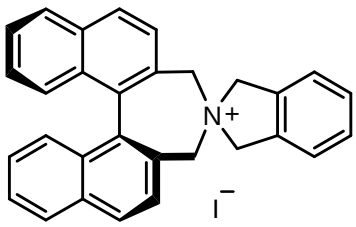
To a solution of the required ammonium [**81**][*Δ*-BINPHAT] salt (45 mg, 0.044 mmol, 1.0 equiv.) in dry $CH_2Cl_2$ (2.2 mL) at –80 °C was added the $P_4$-*t*-Bu base (1 M in Hexane, 66 μL, 0.066 mmol, 1.5 equiv.). After stirring 4 h at –80 °C, under a nitrogen atmosphere, the reaction was quenched by addition of MeOH (2.2 mL), by cannulation at –80 °C. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography using $Et_2O$ as eluent. The desired compound **82** was obtained as a yellow oil, as (*rac*)-**82** (1.2 mg, 12%). The lack of enantiomeric excess was measured using a CSP-HPLC (Chiralpak AD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 $mL.min^{-1}$; 23 °C).

**IR** (neat): 3026, 2924, 2771, 2721, 1475, 1452, 1378, 1369, 1300, 1146, 1081, 1065, 1018, 983, 751, 735 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.31-7.12 (m, 8H), 4.30 (d, 1H, *J* = 11.6 Hz), 4.17 (d, 1H, *J* = 14.6 Hz), 3.88 (d, 1H, *J* = 14.6 Hz), 3.77-3.72 (m, 2H), 3.34 (dd, 1H, *J* = 15.1 Hz, *J* = 3.3 Hz), 2.93 (dd, 1H, *J* = 15.1 Hz, *J* = 10.3 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 144.0 ($C^{IV}$), 140.8 ($C^{IV}$), 136.3 ($C^{IV}$), 134.9 ($C^{IV}$), 130.0 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 126.3 (CH), 122.8 (CH), 121.6 (CH), 64.7 (CH), 58.5 ($CH_2$), 54.8 ($CH_2$), 34.5 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 223.3 (21%), 222.3 (100 % [M+1]); **HRMS**: Calculated for $C_{16}H_{16}N$ 222.1277, found 222.1267.

**General procedure for the synthesis of isoindanyl-dinaphthazepinium iodide salts [(*P*)-84][I] and [(*M*)-84][I]:**

To a suspension of (*P*) or (*M*)-3,5-dihydro-4H-dinaphth[2,1-*c*:1'2'-*e*]-azepine[2] (1.0 equiv.) in $CH_3CN$ (1.4 mL per 0.1 mmol of substrate) was added $K_2CO_3$ (4.5 equiv.) and 1,2-bis(iodomethyl)benzene (1.2 equiv.). The mixture was heated at 80 °C for 15 h, under a nitrogen atmosphere and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$ and the inorganic salts filtered. The resulting compound was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 98:02. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$, and dropwise addition of $Et_2O$ provided a yellow precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a yellow solid.

**(*P*)-6,6-isoindanyl-3,5-dihydro-4H-dinaphth[2,1-*c*;1',2'-*e*]azepinium iodide or [(*P*)-84][I]:**

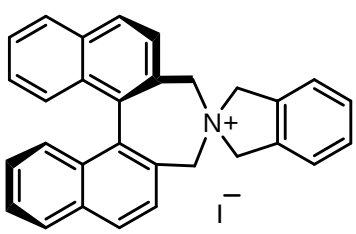


Starting from 325 mg (1.100 mmol) of (*P*)-3,5-dihydro-4H-dinaphth[2,1-*c*:1'2'-*e*]-azepine, [(*P*)-**84**][I] was obtained as a yellow solid after purification by column chromatography (435 mg, 75%).

**M.p.** 221 °C (decomposition); $[\alpha]_D^{20}$ +206.6 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 3446, 2971, 1738, 1595, 1510, 1464, 1435, 1366, 1229, 1217, 1029, 866, 823, 751, 705 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 8.20 (d, 2H, *J* = 8.5 Hz), 8.08 (d, 2H, *J* = 8.2 Hz), 7.93 (d, 2H, *J* = 8.5 Hz), 7.65-7.61 (m, 2H), 7.50-7.47 (m, 6H), 7.41-7.37 (m, 2H), 5.64 (d, 2H, *J* = 13.8 Hz), 5.33 (d, 2H, *J* = 13.2 Hz), 4.86 (d, 2H, *J* = 13.8 Hz), 3.95 (d, 2H, *J* = 13.2 Hz); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 137.1 ($2C^{IV}$), 135.1 ($2C^{IV}$), 132.8 ($2C^{IV}$), 131.7 ($2C^{IV}$), 130.9 (2CH), 130.1 (2CH), 129.0 (2CH), 128.0 (2CH), 127.9 (2CH), 127.6 (2CH), 127.4 (2CH), 127.2 ($2C^{IV}$), 124.2 (2CH), 67.6 ($2CH_2$), 63.7 ($2CH_2$); **MS-ES** (+) *m/z* (rel intensity) 398.1 (34% $[M]^+$), 281.1 (98%), 266.1 (100%); **HRMS**: Calculated for $C_{30}H_{24}N$ 398.1903, found 398.1899.

[2] This compound was synthesised according to the following literature: Zheng, S.; Lan, J.; Khan, S. I.; Rubin, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5786-5791. Beetz, T.; Meuleman, D. G.; Wieringa, J. H. *J. Med. Chem.* **1982**, *25*, 714-719

**(*M*)-6,6-isoindanyl-3,5-dihydro-4H-dinaphth[2,1-*c*;1',2'-*e*]azepinium iodide or [(*M*)-84][I]:**



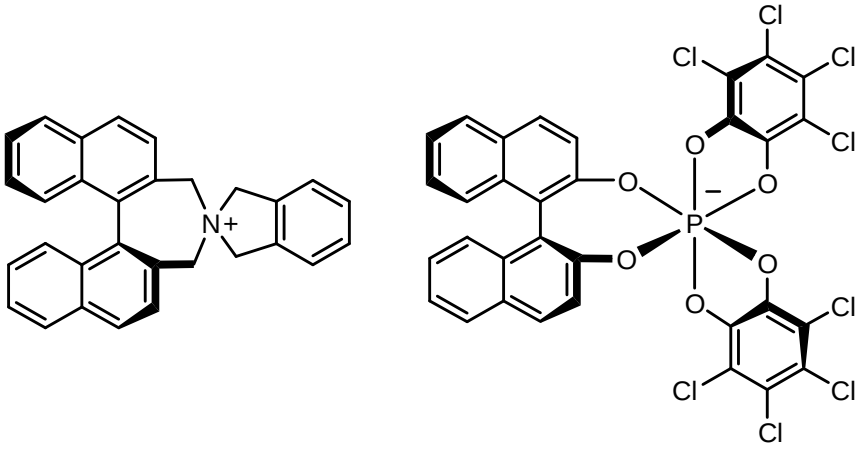
Starting from 220 mg (0.745 mmol) of (*M*)-3,5-dihydro-4H-dinaphth[2,1-*c*:1'2'-*e*]-azepine, [(*M*)-**84**][I] was obtained as a yellow solid after purification by column chromatography (310 mg, 79%).

$[\alpha]_D^{20}$ –206.5 (*c* 0.1, $CH_2Cl_2$).

**General procedure for the synthesis of the isoindanyl-dinaphthazepinium BINPHAT salts [(*P*)-84][*Δ*-BINPHAT] and [(*M*)-84][*Δ*-BINPHAT]:**

To a solution of diarylazepinium salt [**84**][I] (1.0 equiv.) in $CH_2Cl_2$ (3.4 mL per 0.1 mmol of substrate) was added a solution of salt $[Me_2NH_2]$[*Δ*-BINPHAT] (or its enantiomer, 1.2 equiv.) in acetone (5.1 mL per 0.1 mmol of substrate). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent.

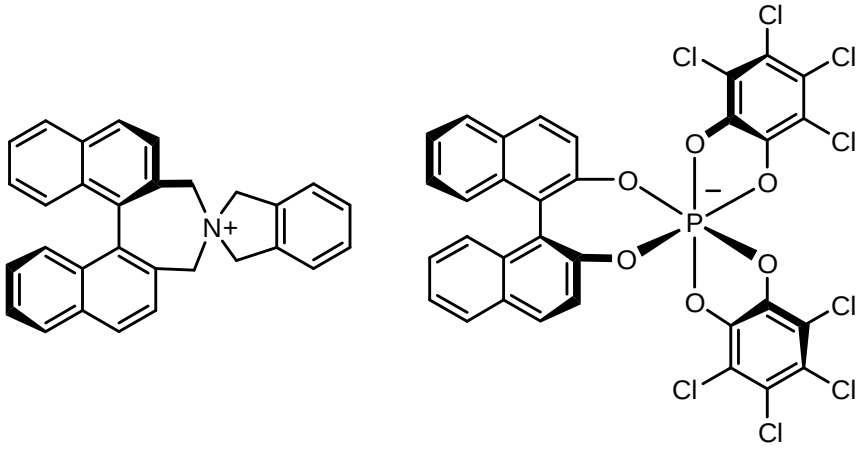
**(*P*)-6,6-isoindanyl-3,5-dihydro-4H-dinaphth[2,1-*c*;1',2'-*e*]azepinium [*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [(*P*)-84][*Δ*-BINPHAT]:**



Starting from 80 mg (0.152 mmol) of [(*P*)-**84**][I], [(*P*)-**84**][*Δ*-BINPHAT] salt was obtained as a white solid after purification by column chromatography (168 mg, 92%).

**M.p.** 181 °C (decomposition); **$[\alpha]_D^{20}$** +92.2 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 1593, 1450, 1388, 1229, 992, 952, 816, 781, 749, 668 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.95 (d, 2H, *J* = 8.3 Hz), 7.84 (d, 2H, BT, *J* = 8.2 Hz), 7.78 (d, 2H, BT, *J* = 8.0 Hz), 7.59-7.53 (m, 4H), 7.38-7.22 (m, 6H, BT + 6H), 7.14 (d, 2H, *J* = 8.5 Hz), 7.00-6.97 (m, 2H), 6.40 (d, 2H, BT, *J* = 8.6 Hz), 4.92 (d, 2H, *J* = 14.0 Hz), 4.38-4.34 (m, 4H), 3.68 (d, 2H, *J* = 13.0 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 293 K) δ –83.0; **MS-ES** (+) *m/z* (rel intensity) 399.3 (35%), 398.5 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 807.5 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{30}H_{24}N$ 398.1903, found 398.1904 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7894.

**((*M*)-6,6-isoindanyl-3,5-dihydro-4H-dinaphth[2,1-*c*;1',2'-*e*]azepinium [*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [(*M*)-84] [*Δ*-BINPHAT]:**



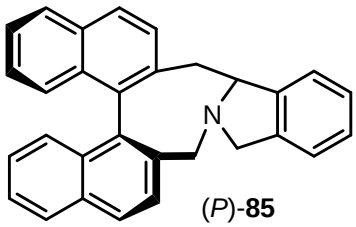

Starting from 80 mg (0.152 mmol) of [(*M*)-**84**][I], [(*M*)-**84**][*Δ*-BINPHAT] salt was obtained as a white solid after purification by column chromatography (180 mg, 99 %).

**M.p.** 243 °C (decomposition); **$[\alpha]_D^{20}$** –194.3 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 1593, 1451, 1390, 1303, 1238, 1009, 991, 953, 819, 782, 749, 668 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.95 (t, 2H, BT + 2H, *J* = 8.3 Hz), 7.73 (d, 2H, BT, *J* = 8.3 Hz), 7.60-7.47 (m, 4H, BT + 2H), 7.33-7.19 (m, 2H, BT + 8H), 6.97 (d, 2H, *J* = 8.3 Hz), 6.74 (br s, 2H), 5.92 (d, 2H, BT, *J* = 8.6 Hz), 4.52-4.41 (m, 6H), 3.85 (d, 2H, *J* = 13.1 Hz); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 293 K) δ –83.3; **MS-ES** (+) *m/z* (rel intensity) 399.5 (40%), 398.1 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 807.5 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{30}H_{24}N$ 398.1903, found 398.1896 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7839.

**Typical procedure for the Stevens rearrangement of the isoindanyl-dinaphthazepinium cations:**

To a solution of the required ammonium salt [**84**][I] (1.0 equiv.) or [**84**][*Δ*-BINPHAT] salt (1.0 equiv.) in dry $CH_2Cl_2$ (0.5 mL per 0.01 mmol of substrate) at –80 °C was added the $P_4$-*t*-Bu base (1 M in Hexane, 1.5 equiv.). After stirring 4 h at –80 °C, under a nitrogen atmosphere, the reaction was quenched by addition of MeOH (0.5 mL per 0.01 mmol of substrate), by cannulation at –80 °C. The mixture was concentrated under reduced pressure. The residue was dissolved in a minimum amount of $CH_2Cl_2$ and the precipitate upon addition of $Et_2O$ filtered. The mother liquor was concentrated in vacuo and the resulting compound was purified by column chromatography.

**Tertiary amine (*P*)-85:**

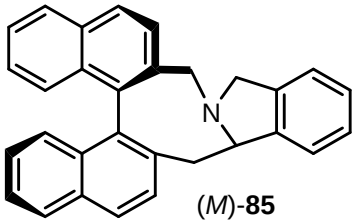


(*P*)-**85**

Starting from 25 mg (0.047 mmol) of [(*P*)-**84**][I] or 60 mg (0.049 mmol) of [(*P*)-**84**][*Δ*-BINPHAT], the desired compound **85** was obtained after purification by column chromatography (basic alumina, $Et_2O$) as a pale pink oil, as a single diastereomer (*P*)-**85** (7.8 mg, 42%) and (*P*)-**85** (6.2 mg, 32%) respectively. The diastereomeric excess was determined by $^1$H-NMR analysis at 293 K.

**$[\alpha]_D^{20}$** +80.8 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2922, 2853, 1596, 1506, 1462, 1329, 1259, 1133, 1085, 1026, 952, 827, 812, 747, 735, 703 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 8.04 (d, 1H, *J* = 8.2 Hz), 7.97-7.91 (m, 3H), 7.67 (d, 1H, *J* = 8.5 Hz), 7.62 (d, 1H, *J* = 8.2 Hz), 7.43-7.36 (m, 3H), 7.24-7.12 (m, 6H), 7.04 (d, 1H, *J* = 8.5 Hz), 4.38 (d, 1H, *J* = 10.1 Hz), 4.17 (dd, 1H, *J* = 12.4 Hz, *J* = 2.3 Hz), 4.11-4.07 (m, 2H), 3.83 (d, 1H, *J* = 14.5 Hz), 2.79 (d, 1H, *J* = 13.2 Hz), 2.55 (dd, 1H, *J* = 13.2 Hz, *J* = 10.1 Hz ); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 144.5 ($C^{IV}$), 139.9 ($C^{IV}$), 138.4 ($C^{IV}$), 135.6 ($C^{IV}$), 134.9 ($C^{IV}$), 134.8 ($C^{IV}$), 133.3 ($C^{IV}$), 133.1 ($C^{IV}$), 133.0 ($C^{IV}$), 132.4 ($C^{IV}$), 129.6 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.0 (2CH), 126.3 (CH), 126.2 (CH), 125.7 (CH), 125.4 (CH), 122.5 (CH), 122.4 (CH), 68.1 (CH), 53.9 ($CH_2$), 52.1 ($CH_2$), 40.6 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 399.5 (39%), 398.5 (100 % [M+1]), 281.0 (80%), 266.0 (84%); **HRMS**: Calculated for $C_{30}H_{24}N$ 398.1903, found 398.1898.

**Tertiary amine (*M*)-85:**

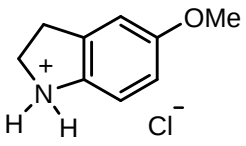


(*M*)-**85**

Starting from 25 mg (0,047 mmol) of [(*M*)-**84**][I] or 60 mg (0.049 mmol) of [(*M*)-**84**][*Δ*-BINPHAT], the desired compound **85** was obtained after purification by column chromatography (basic alumina, $Et_2O$) as a pale pink oil, as a single diastereomer (*M*)-**85** (7.8 mg, 42%) and (*M*)-**85** (6.4 mg, 33%) respectively. The diastereomeric excess was determined by $^1$H-NMR analysis at 293 K.

**$[\alpha]_D^{20}$** –80.4 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2922, 2853, 1596, 1506, 1462, 1329, 1259, 1133, 1085, 1026, 952, 827, 812, 747, 735, 703 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 8.04 (d, 1H, *J* = 8.2 Hz), 7.97-7.91 (m, 3H), 7.67 (d, 1H, *J* = 8.5 Hz), 7.62 (d, 1H, *J* = 8.2 Hz), 7.43-7.36 (m, 3H), 7.24-7.12 (m, 6H), 7.04 (d, 1H, *J* = 8.5 Hz), 4.38 (d, 1H, *J* = 10.1 Hz), 4.17 (dd, 1H, *J* = 12.4 Hz, *J* = 2.3 Hz), 4.11-4.07 (m, 2H), 3.83 (d, 1H, *J* = 14.5 Hz), 2.79 (d, 1H, *J* = 13.2 Hz), 2.55 (dd, 1H, *J* = 13.2 Hz, *J* = 10.1 Hz ); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 144.5 ($C^{IV}$), 139.9 ($C^{IV}$), 138.4 ($C^{IV}$), 135.6 ($C^{IV}$), 134.9 ($C^{IV}$), 134.8 ($C^{IV}$), 133.3 ($C^{IV}$), 133.1 ($C^{IV}$), 133.0 ($C^{IV}$), 132.4 ($C^{IV}$), 129.6 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.0 (2CH), 126.3 (CH), 126.2 (CH), 125.7 (CH), 125.4 (CH), 122.5 (CH), 122.4 (CH), 68.1 (CH), 53.9 ($CH_2$), 52.1 ($CH_2$), 40.6 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 399.5 (35%), 398.5 ([M+1] 100 %), 281.3 (41%), 279.4 (23%), 266.0 (31%); **HRMS**: Calculated for $C_{30}H_{24}N$ 398.1903, found 398.1913.

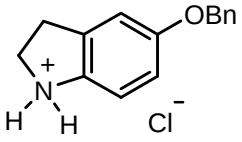
**5-methoxyindolinium chloride:**




To a solution of 5-methoxyindole (500 mg, 3.40 mmol, 1.0 equiv.) in acetic acid (35 mL) was added $NaBH_3CN$ (640 mg, 10.19 mmol, 3.0 equiv.) portion wise (0.5 equiv. each time) over 10 min period, at 0 °C. The reaction mixture was further stirred for 2 h at room temperature after the last addition and was monitored by TLC. After completion of the reaction, a small amount of water (~2-3 mL) was added to the reaction and acetic acid was evaporated under reduced pressure. After dilution with AcOEt, the reaction mixture was neutralised with $Na_2CO_3$ (saturated aqueous solution) to dropwise till p*H* ~ 7-8 and extracted with AcOEt. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to afford viscous oil. The oil was finally purified by column

chromatography over silica gel using Cyclohexane:AcOEt as eluent from 90:10 to 50:50. After evaporation of the solvent, the product was dissolved in a minimum amount of AcOEt and dropwise addition of HCl (1.0 M in $Et_2O$) provided a pale purple precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired salt as a pale purple solid (319 mg, 51%).
**M.p.** 170 °C (decomposition); **IR** (neat): 3076, 2824, 2586, 2487, 1937, 1604, 1497, 1468, 1438, 1317, 1271, 1199, 1186, 1091, 1022, 927, 873, 835 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 8.67 (s, 1H), 8.48 (d, 2H, *J* = 1.0 Hz), 5.64 (s, 3H), 5.43 (t, 2H, *J* = 8.3 Hz), 4.90 (t, 2H, *J* = 8.3 Hz); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 161.0 ($C^{IV}$), 136.6 ($C^{IV}$), 128.4 (CH), 120.8 (CH), 114.3 (CH), 111.0 (CH), 55.9 ($CH_3$), 46.0 ($CH_2$), 29.5 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 487.5 (29%), 150.1 (100% $[M]^+$), 151.4 (55%), 135.4 (24%); **HRMS**: Calculated for $C_9H_{12}NO$ 150.0913, found 150.0918.

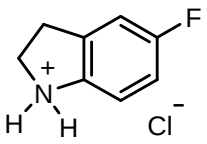
**5-benzyloxyindolinium chloride:**




A solution of 5-benzyloxyindole (350 mg, 1.57 mmol, 1.0 equiv.) in acetic acid (4.2 mL) was stirred for 10 min at 12-14 °C and $NaBH_3CN$ (325 mg, 5.18 mmol, 3.3 equiv.) was added portion wise under a nitrogen atmosphere at the same temperature. The reaction mixture was further stirred for 2 h at 12-14 °C and was monitored by TLC. After completion of the reaction, the mixture was neutralised with NaOH (50% aqueous) to dropwise till p*H* ~ 7-8. Finally $Et_2O$ and water were added and the mixture was stirred for 30 min. The $Et_2O$ layer was separated, the extraction was repeated two more times, and the combined $Et_2O$ layers were washed with brine. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to afford viscous oil. The oil was finally purified by column chromatography over silica gel using Cyclohexane:AcOEt as eluent from 70:30 to 60:40. After evaporation of the solvent, the product was dissolved in a minimum amount of AcOEt and dropwise addition of cold HCl (1.0 M in $Et_2O$) at 0 °C provided a pale white precipitate, which was collected by filtration and washed with cold $Et_2O$ to afford the desired salt as a white solid (328 mg, 80%).
**M.p.** 182 °C; **IR** (neat): 3390, 2614, 2457, 1716, 1603, 1493, 1451, 1389, 1264, 1226, 1176, 1015, 940, 852, 806, 747, 702 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 7.48 (d, 1H, *J* = 9.0 Hz), 7.40-7.31 (m, 5H), 6.90 (m, 2H), 5.0 (s, 2H), 3.91 (t, 2H, *J* = 7.1 Hz), 3.24 (t, 2H,

*J* = 7.1 Hz); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 160.0 ($C^{IV}$), 136.5 ($C^{IV}$), 136.4 ($C^{IV}$), 129.0 ($C^{IV}$), 128.8 (2CH), 128.3 (CH), 127.5 (2CH), 120.7 (CH), 115.2 (CH), 112.0 (CH), 70.6 ($CH_2$), 46.2 ($CH_2$), 29.6 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 228.6 (14%), 227.6 (84%), 226.4 (100% $[M]^+$); **HRMS**: Calculated for $C_{15}H_{16}NO$ 226.1226, found 226.1223.

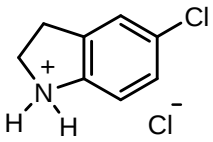
**5-fluroindolinium chloride:**




A solution of 5-fluoroindole (350 mg, 2.59 mmol, 1.0 equiv.) in acetic acid (7.0 mL) was stirred for 10 min at 12-14 °C and $NaBH_3CN$ (537 mg, 8.55 mmol, 3.3 equiv.) was added portion wise under a nitrogen atmosphere at the same temperature. The reaction mixture was further stirred for 2 h at 12-14 °C and was monitored by TLC. After completion of the reaction, the mixture was neutralised with NaOH (50% aqueous) to dropwise till p*H* ~ 7-8. Finally $Et_2O$ and water were added and the mixture was stirred for 30 min. The $Et_2O$ layer was separated, the extraction was repeated two more times, and the combined $Et_2O$ layers were washed with brine. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to afford viscous oil. The oil was finally purified by column chromatography over silica gel using Cyclohexane:AcOEt 80:20 as eluent. After evaporation of the solvent, the product was dissolved in a minimum amount of AcOEt, under a nitrogen atmosphere, at 0 °C and cold HCl (1.0 M in $Et_2O$) was added dropwise until complete formation of a white precipitate. The solvent was removed by cannulation under a nitrogen atmosphere. After drying under vacuum, the desired salt was obtained as a white solid (189 mg, 43%).

**M.p.** 131 °C (decomposition); **IR** (neat): 3482, 2823, 2574, 2449, 1633, 1591, 1490, 1451, 1403, 1263, 1163, 1132, 939, 861, 813, 749 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 11.76 (br s, 2H), 7.65 (s, 1H), 7.07 (d, 2H, *J* = 7.3 Hz), 4.0 (br s, 2H), 3.34 (br s, 2H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 164.8-162.3 (d, $C^{IV}$, $J_{C-F}$ = 249.0 Hz), 137.6 ($C^{IV}$), 137.5 ($C^{IV}$), 131.6 ($C^{IV}$), 121.7 (d, CH, $J_{C-F}$ = 9.2 Hz), 116.0-115.8 (d, CH, $J_{C-F}$ = 24.3 Hz), 113.4-113.1 (d, CH, $J_{C-F}$ = 24.3 Hz), 46.4 ($CH_2$), 29.5 ($CH_2$); **$^{19}$F-NMR** (212 MHz, $CD_2Cl_2$, 293 K) δ –111.0; **MS-ES** (+) *m/z* (rel intensity) 475.6 (41%), 338.3 (39%), 277.5 (26%), 253.6 (31%), 139.4 (72%), 138.4 (100% $[M]^+$); **HRMS**: Calculated for $C_8H_9NF$ 138.0713, found 138.0720.

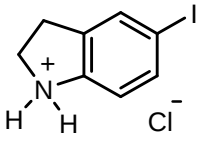
**5-choroindolinium chloride:**



A solution of 5-chloroindole (400 mg, 2.65 mmol, 1.0 equiv.) in acetic acid (7.0 mL) was stirred for 10 min at 12-14 °C and $NaBH_3CN$ (550 mg, 8.74 mmol, 3.3 equiv.) was added portion wise under a nitrogen atmosphere at the same temperature. The reaction mixture was further stirred for 2 h at 12-14 °C and was monitored by TLC. After completion of the reaction, the mixture was neutralised with NaOH (50% aqueous) to dropwise till p*H* ~ 7-8. Finally $Et_2O$ and water were added and the mixture was stirred for 30 min. The $Et_2O$ layer was separated, the extraction was repeated two more times, and the combined $Et_2O$ layers were washed with brine. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to afford viscous oil. The oil was finally purified by column chromatography over silica gel using Cyclohexane:AcOEt 80:20 as eluent. After evaporation of the solvent, the product was dissolved in a minimum amount of AcOEt and dropwise addition of cold HCl (1.0 M in $Et_2O$) at 0 °C provided a pale white precipitate, which was collected by filtration and washed with cold $Et_2O$ to afford the desired salt as a white solid (374 mg, 75%).

**M.p.** 180 °C; **IR** (neat): 3033, 2789, 2601, 2465, 1595, 1568, 1483, 1463, 1422, 1386, 1160, 1104, 898, 879, 803 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 11.8 (br s, 2H), 7.59 (d, 1H, *J* = 8.0 Hz), 7.36-7.33 (m, 2H), 3.96 (t, 2H, *J* = 6.3 Hz), 3.31 (t, 2H, *J* = 6.3 Hz); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 137.0 ($C^{IV}$), 136.0 ($C^{IV}$), 134.4 ($C^{IV}$), 129.0 (CH), 126.3 (CH), 121.3 (CH), 45.9 ($CH_2$), 29.3 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 491.8 (33%), 338.5 (29%), 157.1 (11%), 156.1 (83%), 155.1 (33%), 154.1 (100% $[M]^+$); **HRMS**: Calculated for $C_8H_9NCl$ 154.0418, found 154.0412.

**5-iodoindolinium chloride:**

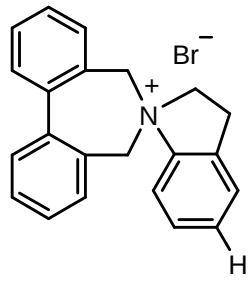


A solution of 5-iodooindole (500 mg, 2.06 mmol, 1.0 equiv.) in acetic acid (5.5 mL) was stirred for 10 min at 12-14 °C and $NaBH_3CN$ (427 mg, 6.79 mmol, 3.3 equiv.) was added portion wise under a nitrogen atmosphere at the same temperature. The reaction mixture was further stirred for 2 h at 12-14 °C and was monitored by TLC. After completion of the reaction, the mixture was neutralised with NaOH (50% aqueous) to dropwise till p*H* ~ 7-8. Finally $Et_2O$ and water were added and the mixture was stirred for 30 min. The $Et_2O$ layer was separated, the extraction was repeated two more times, and the

combined $Et_2O$ layers were washed with brine. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to afford viscous oil. The oil was finally purified by column chromatography over silica gel using Cyclohexane:AcOEt 80:20 as eluent. After evaporation of the solvent, the product was dissolved in a minimum amount of AcOEt and dropwise addition of cold HCl (1.0 M in $Et_2O$) at 0 °C provided a pale yellow precipitate, which was collected by filtration and washed with cold $Et_2O$ to afford the desired salt as a pale yellow solid (387 mg, 97%).

**M.p.** 136 °C (decomposition); **IR** (neat): 2572, 2448, 1886, 1583, 1553, 1475, 1391, 1160, 1061, 879, 856, 807 $cm^{-1}$; **$^1$H-NMR** (400 MHz, $CDCl_3$, 293 K) δ 7.68 (s, 1H), 7.63 (d, 1H, *J* = 8.3 Hz), 7.24 (d, 1H, *J* = 8.3 Hz), 3.87 (t, 2H, *J* = 7.8 Hz), 3.26 (t, 2H, *J* = 7.8 Hz); **$^{13}$C-NMR** (100 MHz, $CDCl_3$, 293 K) δ 137.7 (CH), 137.6 ($2C^{IV}$), 137.0 ($C^{IV}$), 120.8 (CH), 46.0 ($CH_2$), 29.2 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 338.5 (29%), 247.1 (33%), 246.3 (100% $[M]^+$), 120.3 (34%); **HRMS**: Calculated for $C_8H_9NI$ 245.9774, found 245.9779.

**5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86a][Br]:**

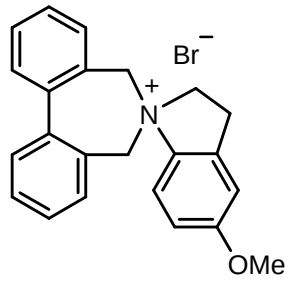



To a suspension of indoline (150 mg, 1.253 mmol, 1.0 equiv.) in $CH_3CN$ (21 mL) was added $K_2CO_3$ (780 mg, 5.637 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (511 mg, 1.504 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 6 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$ and the inorganic salts filtered. The mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 95:05. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$, and dropwise addition of $Et_2O$ provided a white precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a white solid (390 mg, 83%).

**M.p.** 250 °C (decomposition); **IR** (neat): 2999, 2940, 1606, 1485, 1455, 1380, 1201, 1090, 1013, 917, 789, 775, 731, 711 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 8.28 (d, 1H, *J* = 7.5 Hz), 7.75-7.68 (m, 4H), 7.63-7.54 (m, 4H), 7.47 (d, 1H, *J* = 7.5 Hz), 7.41- 7.37 (m, 1H), 7.30 (d, 1H, *J* = 8.4 Hz), 5.00 (d, 1H, *J* = 13.0 Hz), 4.92-4.88 (m, 1H), 4.64 (d, 1H, *J* = 13.3 Hz), 4.32 (d, 1H, *J* = 13.3 Hz), 4.20-4.03 (m, 3H), 3.55-3.49 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 145.4 ($C^{IV}$), 140.8 ($C^{IV}$), 140.3 ($C^{IV}$), 134.4 ($C^{IV}$), 132.4 (CH), 131.7 (CH), 131.6 (2CH),

131.5 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 127.3 (CH), 127.2 ($C^{IV}$), 127.0 ($C^{IV}$), 118.2 (CH), 67.3 ($CH_2$), 64.5 ($CH_2$), 64.2 ($CH_2$), 27.2 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 338.3 (23%) 323.3 (36%), 299.5 (30%), 298.5 (100% $[M]^+$); **HRMS**: Calculated for $C_{22}H_{20}N$ 298.1590, found 298.1597.

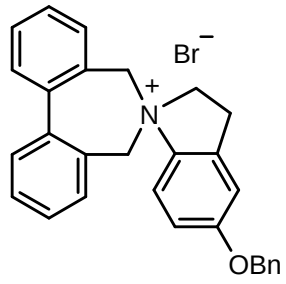
**5'-methoxy-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86b][Br]:**




To a suspension of 5-methoxyindolinium chloride (250 mg, 1.351 mmol, 1.0 equiv.) in $CH_3CN$ (22 mL) was added $K_2CO_3$ (840 mg, 6.079 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (551 mg, 1.621 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 6 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$:MeOH 1:1 and the inorganic salts filtered. To the mother liquor was added an excess of KBr (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 95:05. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$:MeOH 1:1, and dropwise addition of $Et_2O$ provided a white precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a white solid (404 mg, 71%).

**M.p.** 258 °C (decomposition); **IR** (neat): 3001, 2957, 1602, 1481, 1447, 1259, 1169, 1147, 1026, 876, 858, 796, 771 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 8.27 (d, 1H, *J* = 7.5 Hz), 7.74-7.67 (m, 4H), 7.63-7.56 (m, 2H), 7.46 (d, 1H, *J* = 7.5 Hz), 7.17 (d, 1H, *J* = 8.8 Hz), 7.00 (d, 1H, *J* = 2.5 Hz), 6.84 (dd, 1H, *J* = 8.8 Hz, *J* = 2.5 Hz), 4.99 (d, 1H, *J* = 13.0 Hz), 4.92-4.87 (m, 1H), 4.57 (d, 1H, *J* = 13.2 Hz), 4.29 (d, 1H, *J* = 13.2 Hz), 4.15-4.02 (m, 3H), 3.82 (s, 3H), 3.50-3.44 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 161.5 ($C^{IV}$), 140.8 ($C^{IV}$), 140.3 ($C^{IV}$), 138.2 ($C^{IV}$), 136.3 ($C^{IV}$), 132.3 (CH), 131.6 (2CH), 131.4 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 127.3 ($C^{IV}$), 127.2 ($C^{IV}$), 119.0 (CH), 115.0 (CH), 110.0 (CH), 67.6 ($CH_2$), 64.9 ($CH_2$), 64.6 ($CH_2$), 55.9 ($CH_3$), 27.4 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 391.5 (25%), 329.5 (29%), 328.5 (100% $[M]^+$), 323.3 (21%); **HRMS**: Calculated for $C_{23}H_{22}NO$ 328.1695, found 328.1685.

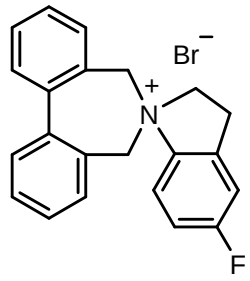
**5'-(benzyloxy)-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86c][Br]:**




To a suspension of 5-benzyloxyindolinium chloride (125 mg, 0.479 mmol, 1.0 equiv.) in $CH_3CN$ (8 mL) was added $K_2CO_3$ (298 mg, 2.154 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (195 mg, 0.574 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 6 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$:MeOH 1:1 and the inorganic salts filtered. To the mother liquor was added an excess of KBr (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 90:10. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$:MeOH 1:1, and dropwise addition of $Et_2O$ provided a white precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a white solid (170 mg, 73%).

**M.p.** 180 °C; **IR** (neat): 3376, 2924, 1599, 1485, 1454, 1266, 1166, 1013, 758 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 8.26 (d, 1H, *J* = 7.6 Hz), 7.74-7.66 (m, 4H), 7.62-7.56 (m, 2H), 7.48-7.33 (m, 6H), 7.19 (d, 1H, *J* = 8.8 Hz), 7.07 (d, 1H, *J* = 2.5 Hz), 6.90 (dd, 1H, *J* = 8.8 Hz, *J* = 2.5 Hz), 5.07 (s, 2H), 5.00 (d, 1H, *J* = 13.0 Hz), 4.90-4.86 (m, 1H), 4.59(d, 1H, *J* = 13.2 Hz), 4.28 (d, 1H, *J* = 13.2 Hz), 4.14-4.02 (m, 3H), 3.49-3.44 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 160.6 ($C^{IV}$), 140.8 ($C^{IV}$), 140.4 ($C^{IV}$), 138.4 ($C^{IV}$), 136.4 ($C^{IV}$), 135.7 ($C^{IV}$), 132.4 (CH),131.7 (CH), 131.6 (CH), 131.4 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.6 (2CH), 128.3 (CH), 127.7 (2 CH), 127.3 ($C^{IV}$), 127.2 ($C^{IV}$), 119.1 (CH), 115.6 (CH), 111.5 (CH), 70.2 ($CH_2$), 67.6 ($CH_2$), 64.9 ($CH_2$), 64.6 ($CH_2$), 27.4 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 405.5 (38%), 404.6 (100% $[M]^+$), 323.5 (28%); **HRMS**: Calculated for $C_{29}H_{26}NO$ 404.2008, found 404.2007.

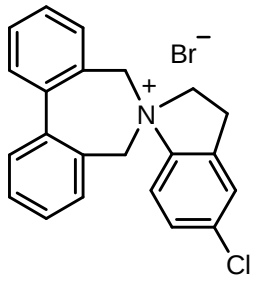
**5'-fluoro-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86d][Br]:**




To a suspension of 5-fluoroindolinium chloride (59 mg, 0.341 mmol, 1.0 equiv.) in MeOH (6 mL) was added $NaHCO_3$ (58 mg, 0.682 mmol, 2.0 equiv.) and 2,2'-bis(bromomethyl)biphenyl (140 mg, 0.409 mmol, 1.2 equiv.). The mixture was heated at 65 °C for 6 h and let cool down. After adding an excess of KBr (20 equiv.), the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 90:10. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$:MeOH 1:1, and dropwise addition of $Et_2O$ provided a pale grey precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a pale grey solid (121 mg, 90%).

**M.p.** 260 °C (decomposition); **IR** (neat): 3000, 2956, 2924, 1728, 1601, 1480, 1447, 1367, 1259, 1202, 1146, 1121, 1013, 929, 874, 863, 816, 798, 768, 749 $cm^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K) δ 8.33 (d, 1H, *J* = 7.5 Hz), 7.75-7.67 (m, 4H), 7.61-7.57 (m, 2H), 7.46 (d, 1H, *J* = 7.5 Hz), 7.28-7.24 (m, 2H), 7.08 (td, 1H, *J* = 8.8 Hz, *J* = 2.5 Hz), 5.13 (d, 1H, *J* = 13.0 Hz), 5.00-4.96 (m, 1H), 4.67 (d, 1H, *J* = 13.2 Hz), 4.30 (d, 1H, *J* = 13.2 Hz), 4.24-4.12 (m, 3H), 3.55-3.50 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 233 K) δ 164.7-162.7 (d, $C^{IV}$, $J_{C-F}$ = 251.8 Hz), 141.4 ($C^{IV}$), 140.9 ($C^{IV}$), 140.4 ($C^{IV}$), 137.6 (d, $C^{IV}$, $J_{C-F}$ = 9.7 Hz), 132.5 (CH), 131.7 (CH), 131.6 (CH), 131.5 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 127.1 ($C^{IV}$), 127.0 ($C^{IV}$), 120.0 (d, CH, $J_{C-F}$ = 9.7 Hz), 116.2 (d, CH, $J_{C-F}$ = 24.3 Hz), 114.3 (d, CH, $J_{C-F}$ = 24.3 Hz), 67.7 ($CH_2$), 65.1 ($CH_2$), 64.7 ($CH_2$), 27.5 ($CH_2$); **$^{19}$F-NMR** (352 MHz, $CD_2Cl_2$, 233 K) δ –108.06; **MS-ES** (+) *m/z* (rel intensity) 323.3 (39%), 317.5 (28%), 316.1 (100% $[M]^+$), 122.2 (33%); **HRMS**: Calculated for $C_{22}H_{19}NF$ 316.1496, found 316.1504.

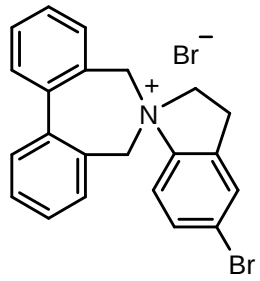
**5'-chloro-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86e][Br]:**




To a suspension of 5-chloroindolinium chloride (61 mg, 0.323 mmol, 1.0 equiv.) in $CH_3CN$ (6 mL) was added $K_2CO_3$ (200 mg, 1.452 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (132 mg, 0.387 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 6 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$:MeOH 1:1 and the inorganic salts filtered. To the mother liquor was added an excess of KBr (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 90:10. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$:MeOH 1:1, and dropwise addition of $Et_2O$ provided a pale grey precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a pale grey solid (111 mg, 84%).

**M.p.** 269 °C (decomposition); **IR** (neat): 3412, 2962, 2923, 1732, 1602, 1533, 1470, 1451, 1426, 1350, 1144, 1100, 1066, 1011, 899, 885, 796, 775, 723 cm-1; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 8.0 (d, 1H, *J* = 7.5 Hz), 7.77-7.69 (m, 4H), 7.63-7.57 (m, 3H), 7.47 (d, 1H, *J* = 7.5 Hz), 7.38 (dd, 1H, *J* = 8.8 Hz, *J* = 2.2 Hz), 7.26 (d, 1H, *J* = 8.8 Hz), 4.76-4.65 (m, 3H), 4.32 (d, 1H, *J* = 13.2 Hz), 4.22-4.14 (m, 2H), 3.87-3.81 (m, 1H), 3.56-3.50 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 144.0 ($C^{IV}$), 140.8 ($C^{IV}$), 140.4 ($C^{IV}$), 137.3 ($C^{IV}$), 136.5 ($C^{IV}$), 132.0 (CH),131.8 (CH), 131.7 (CH), 131.6 (CH), 129.6 (CH), 129.3 (2CH), 129.2 (CH), 129.1 (CH), 127.4 (CH), 127.0 ($C^{IV}$), 126.5 ($C^{IV}$), 119.4 (CH), 67.2 ($CH_2$), 64.8 ($CH_2$), 64.7 ($CH_2$), 27.0 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 335.5 (10%), 334.4 (37%), 333.5 (27%), 332.5 (100% $[M]^+$), 323.5 (57%), 279.5 (39%), 122.3 (37%); **HRMS**: Calculated for $C_{22}H_{19}N^{35}Cl$ 332.1200, found 332.1207.

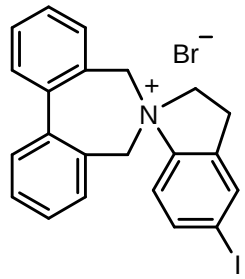
**5'-bromo-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86f][Br]:**




To a suspension of 5-bromoindoline (200 mg, 1.007 mmol, 1.0 equiv.) in $CH_3CN$ (17 mL) was added $K_2CO_3$ (626 mg, 4.531 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (411 mg, 1.208 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 6 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$:MeOH 1:1 and the inorganic salts filtered. The mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 90:10. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$:MeOH 1:1, and dropwise addition of $Et_2O$ provided a pale brown precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a pale brown solid (317 mg, 69%).

**M.p.** 259 °C (decomposition); **IR** (neat): 2962, 1730, 1582, 1469, 1442, 1428, 1377, 1147, 1096, 1065, 897, 885, 819, 796, 775, 721 $cm^{-1}$; **$^{1}$H-NMR** (500 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 7.91 (d, 1H, *J* = 7.5 Hz), 7.77-7.70 (m, 5H), 7.63-7.58 (m, 2H), 7.54 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.47 (d, 1H, *J* = 7.5 Hz), 7.21 (d, 1H, *J* = 8.8 Hz), 4.69-4.61 (m, 3H), 4.31 (d, 1H, *J* = 13.2 Hz), 4.23 (d, 1H, *J* = 13.2 Hz), 4.15-4.10 (m, 1H), 3.55-3.49 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 144.5 ($C^{IV}$), 140.8 ($C^{IV}$), 140.4 ($C^{IV}$), 136.6 ($C^{IV}$), 132.2 (CH), 131.9 (3 CH), 131.7 (CH), 130.4 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 127.0 ($C^{IV}$), 126.4 ($C^{IV}$), 125.5 ($C^{IV}$), 119.7 (CH), 67.2 ($CH_2$), 64.8 ($CH_2$), 64.7 ($CH_2$), 26.8 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 379.1 (30%), 378.4 (10%), 377.5 (35%), 376.4 (100% $[M]^+$), 323.3 (66%), 279.5 (30%); **HRMS**: Calculated for $C_{22}H_{19}N^{79}Br$ 376.0695, found 376.0695.

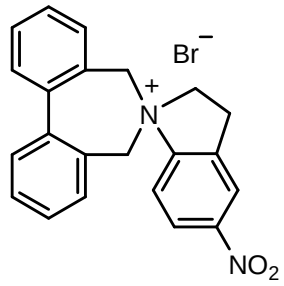
**5'-iodo-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86g][Br]:**




To a suspension of 5-iodoindoline chloride (135 mg, 0.480 mmol, 1.0 equiv.) in $CH_3CN$ (8 mL) was added $K_2CO_3$ (299 mg, 2.162 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (196 mg, 0.576 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 6 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$:MeOH 1:1 and the inorganic salts filtered. To the mother liquor was added an excess of KBr (20 equiv.) and the mixture was stirred for 30 min. The resulting KCl salts filtered and the mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 90:10. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$:MeOH 1:1, and dropwise addition of $Et_2O$ provided a pale yellow precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a pale yellow solid (202 mg, 84%).

**M.p.** 248 °C (decomposition); **IR** (neat): 2962, 2922, 1733, 1580, 1471, 1450, 1429, 1375, 1152, 1093, 896, 885, 795, 771, 720 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 7.95 (s, 0.6H), 7.86 (d, 0.6H, $J$ = 7.5 Hz), 7.81-7.71 (m, 4.8H), 7.64-7.37 (m, 4.4H), 7.09 (d, 0.6H, $J$ = 8.8 Hz), 4.63-4.23 (m, 5H), 4.05 (m, 1H), 3.75-3.64 (m, 1H), 3.53-3.47 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 145.5 ($C^{IV}$), 140.7 ($C^{IV}$), 140.5 ($C^{IV}$), 138.1 (CH), 136.4 (CH), 133.9 ($C^{IV}$), 131.7 (2 CH), 131.6 (CH), 129.6 (CH), 129.3 (2CH), 128.4 ($C^{IV}$), 127.4 (CH), 127.2 ($C^{IV}$), 126.4 ($C^{IV}$), 119.8 (CH), 118.2 (CH), 67.1 ($CH_2$), 64.7 ($CH_2$), 64.4 ($CH_2$), 26.8 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 425.5 (30%), 424.4 (100% $[M]^+$), 298.6 (21%), 279.5 (24%), 122.3 (21%); **HRMS**: Calculated for $C_{22}H_{19}NI$ 424.0556, found 424.0537.

**5'-nitro-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium bromide or [86h][Br]:**



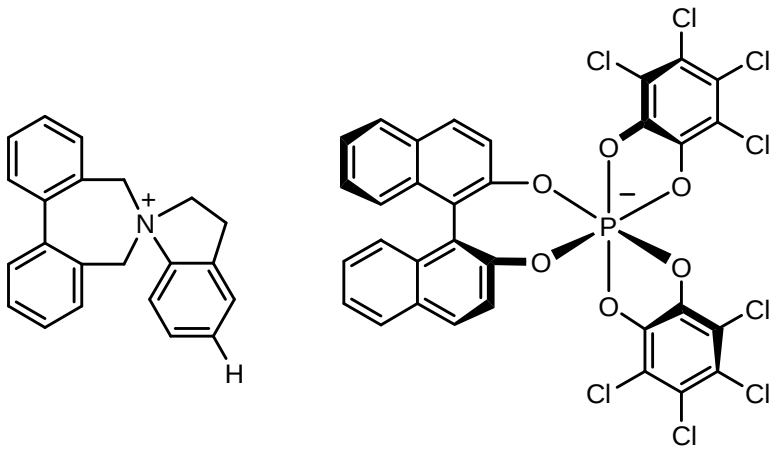

To a suspension of 5-iodoindoline (150 mg, 0.914 mmol, 1.0 equiv.) in $CH_3CN$ (16 mL) was added $K_2CO_3$ (528 mg, 4.112 mmol, 4.5 equiv.) and 2,2'-bis(bromomethyl)biphenyl (373 mg, 1.097 mmol, 1.2 equiv.). The mixture was heated at 80 °C for 6 h and then concentrated under reduced pressure. The residue was triturated in $CH_2Cl_2$:MeOH 1:1 and the inorganic salts filtered. The mother liquor was concentrated in vacuo. The compound was purified by column chromatography over silica gel using $CH_2Cl_2$ as eluent and then $CH_2Cl_2$:MeOH from 99:01 to 90:10. After evaporation of the solvent, the product was dissolved in a minimum amount of $CH_2Cl_2$:MeOH 1:1, and dropwise addition of $Et_2O$ provided a pale orange precipitate, which was collected by filtration and washed with $Et_2O$ to afford the desired compound as a pale orange solid (258 mg, 67%).

**M.p.** 215 °C (decomposition); **IR** (neat): 3488, 3417, 2964, 1601, 1533, 1476, 1449, 1385, 1349, 1205, 1071, 923, 795, 767, 747 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 8.43 (d, 1H, *J* = 2.2 Hz), 8.26 (dd, 1H, *J* = 8.8 Hz, *J* = 2.2 Hz), 7.98 (d, 1H, *J* = 7.5 Hz), 7.79-7.71 (m, 4H), 7.63-7.60 (m, 2H), 7.54-7.50 (m, 2H), 4.86-4.79 (m, 3H), 4.35 (d, 1H, *J* = 13.2 Hz), 4.31-4.19 (m, 2H), 3.97-3.91 (m, 1H), 3.68-3.63 (m, 1H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$+MeOH-$d_4$, 233 K) δ 149.7 ($C^{IV}$), 149.3 ($C^{IV}$), 140.8 ($C^{IV}$), 140.5 ($C^{IV}$), 137.2 ($C^{IV}$), 132.0 (3CH), 131.7 (CH), 129.7 (CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 126.8 ($C^{IV}$), 126.1($C^{IV}$), 124.8 (CH), 122.8 (CH), 119.6 (CH), 67.1 ($CH_2$), 65.1 ($CH_2$), 64.8 ($CH_2$), 27.1 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 344.5 (30%), 343.3 (100% $[M]^+$), 342.4 (22%), 338.3 (24%), 323.4 (58%), 279.5 (49%), 122.1 (31%); **HRMS**: Calculated for $C_{22}H_{19}N_2O_2$ 343.1441, found 343.1444.

**General procedure for the synthesis of the dibenzoazepine-indolinium BINPHAT salts [87a][*Δ*-BINPHAT] to [87h][*Δ*-BINPHAT] and [87a][*Λ*-BINPHAT]:**

To a solution of diphenylazepinium (1.0 equiv.) in $CH_2Cl_2$ or in $CH_2Cl_2$:MeOH 1:1 (3.4 mL per 0.1 mmol of substrate) was added a solution of salt [$Me_2NH_2$][*Δ*-BINPHAT] (or its enantiomer, 1.2 equiv.) in acetone (5.1 mL per 0.1 mmol of substrate). After stirring for 10 min, the mixture was concentrated under reduced pressure. The resulting salt was purified by column chromatography over basic alumina using $CH_2Cl_2$ as eluent.

**5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis(tetrachlorobenzene-diolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86a][*Δ*-BINPHAT]:**

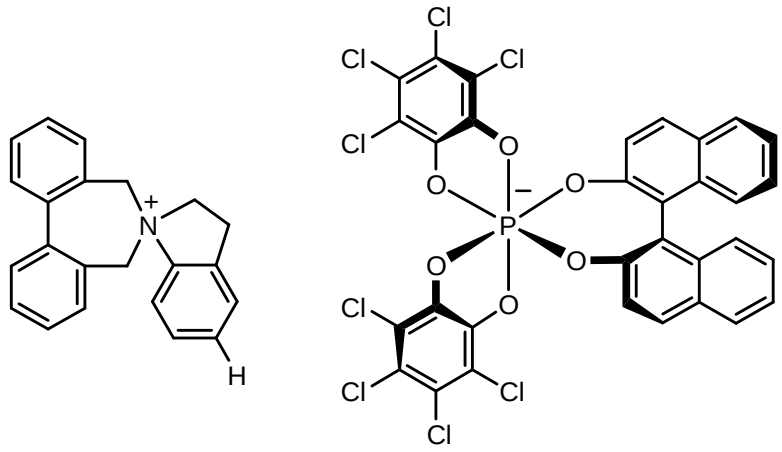


Starting from 80 mg (0.212 mmol) of [**86a**][Br], salt [**86a**][*Δ*-BINPHAT] was obtained as a white solid after purification by column chromatography (226 mg, 97%).

**M.p.**243 °C (decomposition); **$[\alpha]_D^{20}$** –123.4 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 1593, 1453, 1389, 1236, 993, 953, 820, 783, 752, 730, 698, 671 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.83 (d, 2H, BT, *J* = 8.2 Hz), 7.58 (d, 2H, BT, *J* = 8.8 Hz), 7.50-7.03 (m, 6H, BT + 10H, *Maj* + 10H, *min*), 6.85 (d, 1H, *Maj*, *J* = 8.2 Hz), 6.75 (d, 1H, *min*, *J* = 8.2 Hz), 6.54 (d, 1H, *min*, *J* = 7.2 Hz), 6.47 (d, 1H, *Maj*, *J* = 7.2 Hz), 6.14 (d, 2H, BT, *J* = 8.8 Hz), 4.53-4.49 (m, 1H, *min*), 4.39 (d, 1H, *Maj*, *J* = 14.0 Hz), 4.11-4.07 (m, 1H, *Maj* + 1H, *min*), 3.85-3.69 (m, 4H, *Maj* + 5H, *min*), 3.20-3.15 (m, 1H, *min*), 2.65-2.59 (m, 1H, *Maj*), 2.51-2.44 (m, 1H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.3; **MS-ES** (+) *m/z* (rel intensity) 338.5 (38%), 299.5 (67%), 298.4 (100% $[M]^+$), 181.4 (34%), 122.3 (31%), **MS-ES** (-) *m/z*

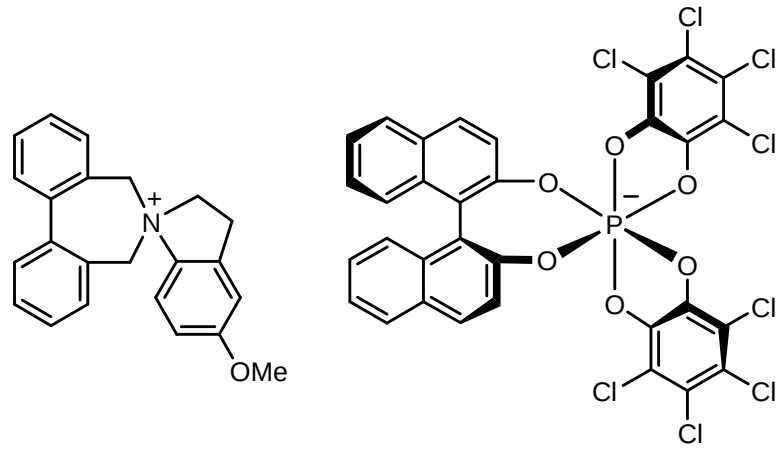
(rel intensity) 807.3 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{22}H_{20}N$ 298.1590, found 298.1589 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7901.

**5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Λ*-bis(tetrachlorobenzene-diolato)mono((*R*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86a][*Λ*-BINPHAT]:**



Starting from 40 mg (0.0.106 mmol) of [**86a**][Br], salt [**86a**][*Λ*-BINPHAT] was obtained as a white solid after purification by column chromatography (136 mg, 87%).
$[\alpha]_D^{20}$ +123.6 (*c* 0.1, $CH_2Cl_2$).

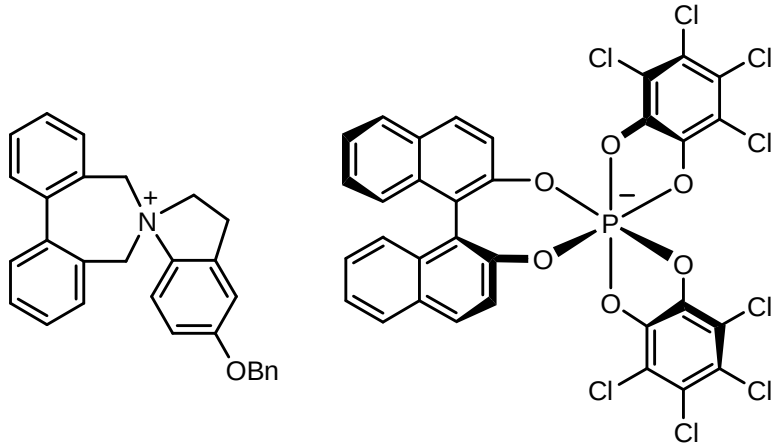
**5'-methoxy-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86b][*Δ*-BINPHAT]:**



Starting from 80 mg (0.196 mmol) of [**86b**][Br], salt [**86b**][*Δ*-BINPHAT] was obtained as a white solid after purification by column chromatography (218 mg, 98%).

**M.p.** 218 °C (decomposition); **$[\alpha]_D^{20}$** –128.7 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2926, 1723, 1594, 1488, 1451, 1388, 1269, 1230, 992, 953, 817, 781, 752, 731 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.84 (d, 2H, BT, *J* = 8.2 Hz), 7.63-7.06 (m, 8H, BT + 8H, *Maj* + 8H, *min*), 6.80 (m, 1H, *Maj* + 1H, *min*), 6.72-6.67 (m, 2H, *min*), 6.60 (m, 1H, *Maj* + 1H, *min*) 6.44 (dd, 1H, *Maj*, *J* = 9.1 Hz, *J* = 2.5 Hz), 6.28-6.25 (m, 2H, BT + 1H, *Maj*), 4.52-4.44 (m, 1H, *Maj* + 1H, *min*), 4.15-4.10 (m, 1H, *Maj* + 1H, *min*), 3.92-3.75 (m, 4H, *Maj* + 5H, *min*), 3.69 (s, 3H, *min*), 3.56 (s, 3H, *Maj*), 3.20-3.14 (m, 1H, *min*), 2.84-2.78 (m, 1H, *Maj*), 2.66-2.62 (m, 1H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.4; **MS-ES** (+) *m/z* (rel intensity) 329.5 (38%), 328.5 (100% $[M]^+$), 338.5 (31%), 122.2 (28%), **MS-ES** (-) *m/z* (rel intensity) 807.3 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{23}H_{22}NO$ 328.1695, found 328.1680 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7918.

**5'-(benzyloxy)-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis-(tetrachlorobenzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86c] [*Δ*-BINPHAT]:**

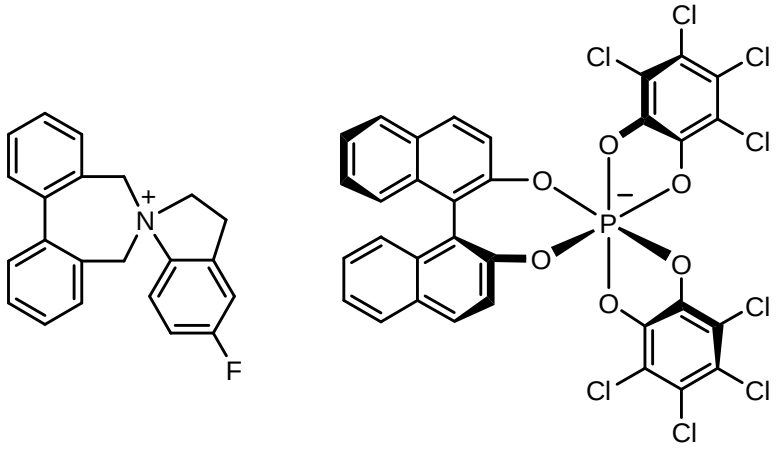



Starting from 90 mg (0.186 mmol) of [**86c**][Br], salt [**86c**][*Δ*-BINPHAT] was obtained as a white solid after purification by column chromatography (195 mg, 87%).

**M.p.** 202 °C (decomposition); **$[\alpha]_D^{20}$** –105.9 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2925, 1739, 1594, 1485, 1451, 1388, 1236, 992, 953, 819, 782, 752, 732 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.78 (d, 2H, BT, *J* = 8.2 Hz), 7.61-7.28 (m, 8H, BT + 8H, *Maj* + 8H, *min*), 7.22 (d, 1H, *Maj*, *J* = 7.2 Hz), 7.15-7.12 (m, 3H, *Maj* + 4H, *min*), 6.89 (sd, 1H, *min*, *J* = 1.9 Hz), 6.77 (d, 1H, *Maj*, *J* = 8.8 Hz), 6.72-6.69 (m, 1H, *min*), 6.65-6.63

(m, 1H, *Maj* + 1H, *min*), 6.49 (dd, 1H, *Maj*, *J* = 8.8 Hz, *J* = 2.2 Hz), 6.46 (d, 1H, *min*, *J* = 7.7 Hz), 6.27 (d, 1H, *Maj*, *J* = 7.5 Hz), 6.17 (d, 2H, BT, *J* = 8.8 Hz), 4.97 (d, 1H, *min*, *J* = 11.3 Hz), 4.81-4.77 (m, 1H, *Maj* + 1H, *min*), 4.70 (d, 1H, *Maj*, *J* = 11.0 Hz), 4.54-4.49 (m, 1H, *min*), 4.40 (d, 1H, *Maj*, *J* = 13.9 Hz), 4.14-4.08 (m, 1H, *Maj* + 1H, *min*), 3.94-3.82 (m, 4H, *Maj* + 2H, *min*), 3.76 (d, 1H, *min*, *J* = 12.9 Hz), 3.71-3.66 (m, 1H, *min*), 3.46 (d, 1H *min*, *J* = 12.9 Hz), 3.2-3.14 (m, 1H, *min*), 2.82-2.72 (m, 1H, *Maj*), 2.67-2.60 (m, 1H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.2; **MS-ES** (+) *m/z* (rel intensity) 405.5 (42%), 404.6 (100% $[M]^+$), 122.3 (22%), **MS-ES** (-) *m/z* (rel intensity) 807.3 (100% $[M]^-$, BINPHAT), 769.1 (20%); **HRMS**: Calculated for $C_{29}H_{26}NO$ 404.2008, found 404.2010 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7884.

**5'-fluoro-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86d][*Δ*-BINPHAT]:**

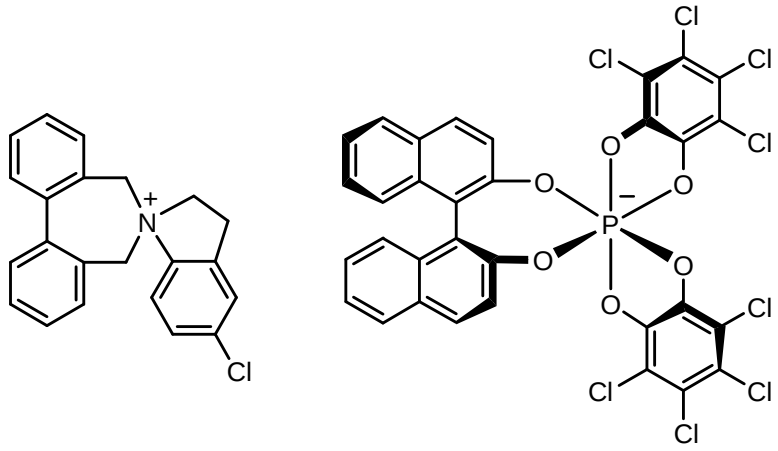



Starting from 80 mg (0.202 mmol) of [**86d**][Br], salt [**86d**][*Δ*-BINPHAT] was obtained as a pale brown solid after purification by column chromatography (157 mg, 70%).

**M.p.** 196 °C (decomposition); **$[\alpha]_D^{20}$** –122.7 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2925, 1738, 1593, 1483, 1452, 1389, 1236, 992, 953, 818, 782, 751, 731 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.86 (d, 2H, BT, *J* = 8.5 Hz), 7.63 (d, 2H, BT, *J* = 8.8 Hz), 7.60-6.83 (m, 6H, BT + 9H, *Maj* + 9H, *min*), 6.76 (dd, 1H, *min*, *J* = 9.1 Hz, *J* = 4.1 Hz), 6.71 (td, 1H, *Maj*, *J* = 8.5 Hz, *J* = 2.5 Hz), 6.65 (d, 1H, *min*, *J* = 7.2 Hz), 6.30 (d, 1H, *Maj*, *J* = 7.6 Hz), 6.21 (d, 2H, BT, *J* = 8.8 Hz), 4.54-4.49 (m,1H, *min*), 4.42 (d, 1H, *Maj*, *J* = 14.0 Hz), 4.15 (d, 1H, *Maj*, *J* = 14.0 Hz), 4.08 (d, 1H, *min*, *J* = 12.9 Hz), 3.94-3.76 (m, 4H,

*Maj* + 3H, *min*), 3.71-3.65 (m, 1H, *min*), 3.61 (d, 1H, *min*, *J* = 12.9 Hz), 3.19-3.13 (m, 1H, *min*), 2.78-2.71 (m, 1H, *Maj*), 2.60-2.56 (m, 1H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ–83.8; **$^{19}$F-NMR** (352 MHz, $CD_2Cl_2$, 233 K) δ –107.41 (s, *min*), –107.79 (s, *Maj*); **MS-ES** (+) *m/z* (rel intensity) 338.3 (23%), 317.5 (31%), 316.4 (100% $[M]^+$), **MS-ES** (-) *m/z* (rel intensity) 807.3 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{22}H_{19}NF$ 316.1496, found 316.1500 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7909.

**5'-chloro-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86e][*Δ*-BINPHAT]:**

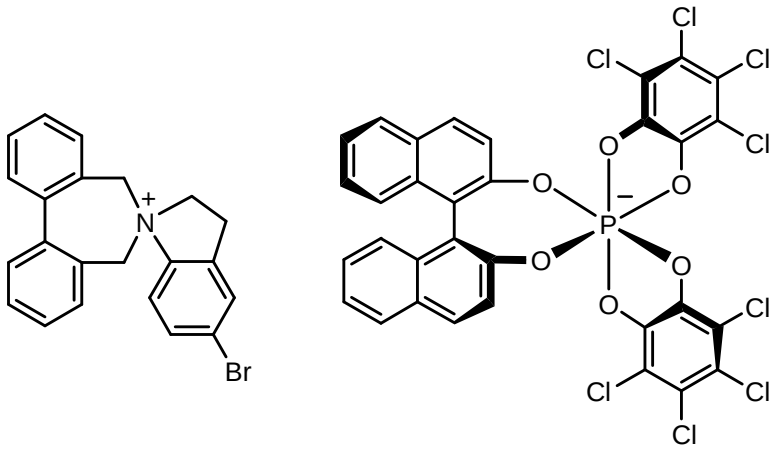


Starting from 100 mg (0.243 mmol) of [**86e**][Br], salt [**86e**][*Δ*-BINPHAT] was obtained as a pale brown solid after purification by column chromatography (214 mg, 77%).

**M.p.** 208 °C (decomposition); **$[\alpha]_D^{20}$** –144.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 3052, 1591, 1450, 1388, 1236, 992, 952, 817, 781, 751, 726 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.88 (d, 2H, BT, *J* = 8.2 Hz), 7.63-7.02 (m, 8H, BT + 8H, *Maj* + 9H, *min*), 6.93 (dd, 1H, *Maj*, *J* = 8.5 Hz, *J* = 1.9 Hz), 6.78 (d, 1H, *Maj*, *J* = 8.8 Hz), 6.72 (d, 1H, *min*, *J* = 8.8 Hz), 6.62 (d, 1H, *min*, *J* = 7.6 Hz), 6.21 (d, 2H, BT, *J* = 8.8 Hz), 6.00 (d, 1H, *Maj*, *J* = 7.6 Hz), 4.47-4.45 (m,1H, *Maj* + 1H, *min*), 4.15 (d, 1H, *Maj*, *J* = 14.1 Hz), 4.10-3.67 (m, 4H, *Maj* + 5H, *min*), 3.57 (d, 1H, *min*, *J* = 12.6 Hz), 3.17-3.11 (m, 1H, *min*), 2.88-2.81 (m, 1H, *Maj*), 2.70-2.65 (m, 1H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.5; **MS-ES** (+) *m/z* (rel intensity) 339.5 (15%), 338.3 (46%), 335.4 (12%), 334.5 (43%), 333.6 (30%), 332.5 (100% $[M]^+$), 122.1 (26%), **MS-ES** (-) *m/z* (rel intensity) 807.5 (100% $[M]^-$, BINPHAT);

**HRMS**: Calculated for $C_{22}H_{19}N^{35}Cl$ 332.1200, found 332.1207 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7883.

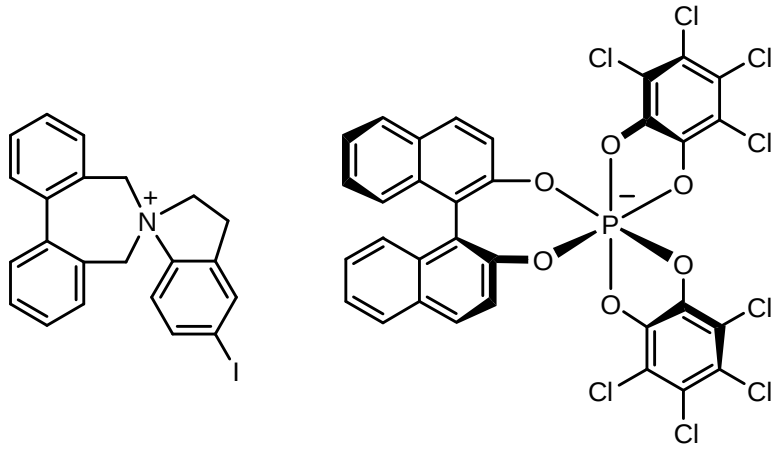
**5'-bromo-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86f][*Δ*-BINPHAT]:**




Starting from 90 mg (0.198 mmol) of [**86f**][Br], salt [**86f**][*Δ*-BINPHAT] was obtained as a pale grey solid after purification by column chromatography (206 mg, 88%).

**M.p.** 228 °C (decomposition); $[\alpha]_D^{20}$ –136.7 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2924, 1723, 1592, 1450, 1388, 1235, 992, 952, 818, 781, 752, 731 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.88 (d, 2H, BT, *J* = 8.2 Hz), 7.66-7.05 (m, 8H, BT + 8H, *Maj* + 9H, *min*), 7.00 (td, 1H, *Maj*, *J* = 7.2 Hz, *J* = 1.6 Hz), 6.70 (d, 1H, *Maj*, *J* = 8.8 Hz), 6.61 (d, 1H, *min*, *J* = 8.8 Hz), 6.50 (d, 1H, *min*, *J* = 7.6 Hz), 6.19 (d, 2H, BT, *J* = 8.8 Hz), 5.89 (d, 1H, *Maj*, *J* = 7.2 Hz), 4.51-4.44 (m, 1H, *Maj* + 1H, *min*), 4.16-4.07 (m, 2H, *Maj* + 1H, *min*), 4.01-3.94 (m, 2H, *Maj*), 3.86-3.71 (m, 1H, *Maj* + 4H, *min*), 3.48 (d, 1H, *min*, *J* = 12.9 Hz), 3.17-3.11 (m, 1H, *min*), 2.88-2.81 (m, 1H, *Maj*), 2.71-2.66 (m, 1H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.4; **MS-ES** (+) *m/z* (rel intensity) 419.5 (34%), 379.1 (21%), 378.4 (9%), 377.5 (27%), 376.4 (100% $[M]^+$), 149.3 (44%), 122.1 (65%), **MS-ES** (-) *m/z* (rel intensity) 807.5 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{22}H_{19}N^{79}Br$ 376.0695, found 376.0698 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7891.

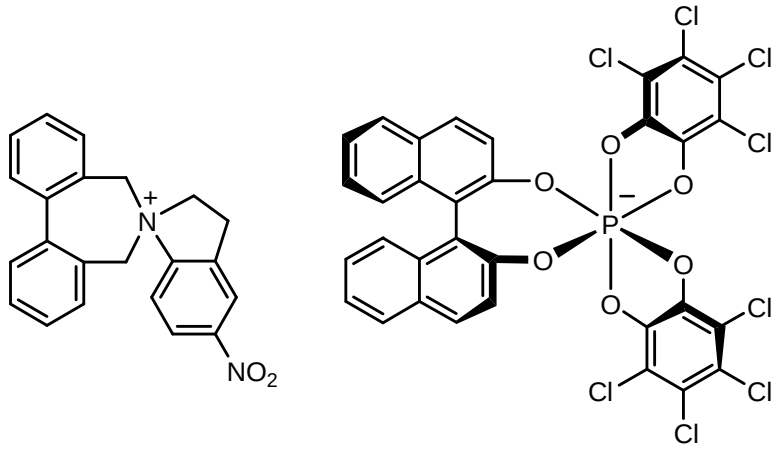
**5'-iodo-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86g][*Δ*-BINPHAT]:**



Starting from 100 mg (0.199 mmol) of [**86g**][Br], salt [**86g**][*Δ*-BINPHAT] was obtained as a white solid after purification by column chromatography (119 mg, 49%).

**M.p.** 227 °C (decomposition); **$[\alpha]_D^{20}$** –100.7 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 2924, 1738, 1592, 1450, 1388, 1229, 992, 952, 818, 781, 751, 724 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 7.86 (d, 2H, BT, *J* = 8.2 Hz), 7.63-7.00 (m, 8H, BT + 8H, *Maj* + 9H, *min*), 6.97 (td, 1H, *Maj*, *J* = 7.2 Hz, *J* = 1.8 Hz,), 6.49 (d, 1H, *Maj*, *J* = 8.5 Hz), 6.39 (d, 1H, *min*, *J* = 8.8 Hz), 6.30 (d, 1H, *min*, *J* = 7.6 Hz), 6.10 (d, 2H, BT, *J* = 8.8 Hz), 5.79 (d, 1H, *Maj*, *J* = 7.2 Hz), 4.45-4.36 (m, 1H, *Maj* + 1H, *min*), 4.13-3.59 (m, 5H, *Maj* + 5H, *min*), 3.31 (d, 1H, *min*, *J* = 12.6 Hz), 3.10-3.05 (m, 1H, *min*), 2.73-2.58 (m, 2H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.6; **MS-ES** (+) *m/z* (rel intensity) 425.4 (36%), 425.4 (100% $[M]^+$), 338.5 (28%), 298.5 (24%), **MS-ES** (-) *m/z* (rel intensity) 807.3 (100% $[M]^-$, BINPHAT).

**5'-nitro-5,7-dihydrospiro[dibenzo[c,e]azepine-6,1'-indolin]-1'-ium][*Δ*-bis(tetrachloro-benzenediolato)mono((*S*)-1,1'-dinaphthyl-2,2'-diolato)phosphate] or [86h][*Δ*-BINPHAT]:**



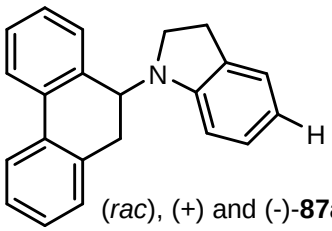
Starting from 85 mg (0.201 mmol) of [**86h**][Br], salt [**86h**][*Δ*-BINPHAT] was obtained as a pale yellow solid after purification by column chromatography (201 mg, 87%).

**M.p.** 219 °C (decomposi- tion); $[\alpha]_D^{20}$ –147.6 (*c* 0.1, $CH_2Cl_2$); **IR** (neat): 3057, 1709, 1591, 1451, 1389, 1228, 992, 953, 818, 781, 753, 726 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 233 K, Major *(Maj)* or minor *(min)* enantiomers of the cation) δ 8.12 (s, 1H, *min*), 8.0 (dd, 1H, *min*, *J* = 8.8 Hz, *J* = 2.5 Hz), 7.86-7.84 (m, 2H, BT + 1H, *Maj*), 7.71-7.20 (m, 8H, BT + 7H, *Maj* + 5H, *min*), 7.04 (t, 1H, *min*, *J* = 8.2 Hz), 6.99-6.92 (m, 2H, *Maj* + 1H, *min*), 6.83 (d, 1H, *min*, *J* = 8.8 Hz), 6.36 (d, 1H, *min*, *J* = 7.0 Hz), 6.05 (d, 2H, BT, *J* = 8.8 Hz), 5.67 (d, 1H, *Maj*, *J* = 7.5 Hz), 4.68-4.64 (m, 1H, *min*), 4.44 (d, 1H, *Maj*, *J* = 14.1 Hz), 4.26-4.05 (m, 4H, *Maj* + 2H, *min*), 3.99-3.83 (m, 1H, *Maj* + 2H, *min*), 3.75 (d, 1H, *min*, *J* = 13.2 Hz), 3.49 (d, 1H, *min*, *J* = 12.9 Hz), 3.26-3.21 (m, 1H, *min*), 2.91-2.85 (m, 1H, *Maj*), 2.65-2.62 (m, 1H, *Maj*); **$^{31}$P-NMR** (202 MHz, $CD_2Cl_2$, 233 K) δ –83.4; **MS-ES** (+) *m/z* (rel intensity) 344.4 (31%), 343.3 (100% $[M]^+$), 338.3 (29%), 122.3 (48%), **MS-ES** (-) *m/z* (rel intensity) 807.3 (100% $[M]^-$, BINPHAT); **HRMS**: Calculated for $C_{22}H_{19}N_2O_2$ 343.1441, found 343.1444 and calculated for $C_{32}H_{12}O_6P^{35}Cl_8$ 802.7885, found 802.7888.

**Typical procedure for the Stevens rearrangement of the dibenzoazepine-indolinium cations:**

To a solution of the required ammonium salt (1.0 equiv.) in dry $CH_2Cl_2$ (0.5 mL per 0.01 mmol of substrate) at –80 °C was added the $P_4$-*t*-Bu base (1 M in Hexane, 1.5 equiv.). After stirring 4 h at –80 °C, under a nitrogen atmosphere, the reaction was quenched by addition of MeOH (0.5 mL per 0.01 mmol of substrate), by cannulation at –80 °C. The mixture was concentrated under reduced pressure. The residue was dissolved in a minimum amount of $CH_2Cl_2$ and the precipitate upon addition of $Et_2O$ filtered. The mother liquors were concentrated in vacuo and the resulting compound was purified by column chromatography or preparative plate chromatography over basic alumina.

**1-(9,10-dihydrophenanthren-10-yl)indoline or 87a:**



(*rac*), (+) and (-)-**87a**

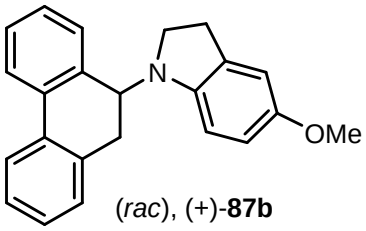
Starting from 15 mg (0.040 mmol) of [**86a**][Br] or 45 mg (0.041 mmol) of [**86a**][*Δ*-BINPHAT] or 45 mg (0.041 mmol) of [**86a**][*Λ*-BINPHAT] ammonium salts, the desired compound **87a** was obtained after purification by column chromatography (basic alumina, $Et_2O$) as a white solid, as (*rac*)-**87a** (92%), (+)-**87a** (90%) and (–)-**87a** (88%) respectively. The enantiomeric excess was measured using a CSP-HPLC (Chiralpak IB; *n*-Hexane/*i*-PrOH/ethanolamine 95:05:0.1%; 0.5 mL.min$^{-1}$, 23 °C).

**M.p.** 131 °C; **IR** (neat): 3067, 2925, 2847, 1606, 1490, 1474, 1450, 1260, 769, 743, 728, 712 cm$^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.85 (dd, 1H, *J* = 7.5 Hz, *J* = 0.8 Hz), 7.80 (d, 1H, *J* = 7.5 Hz), 7.43-7.31 (m, 3H), 7.29-7.23 (m, 3H), 7.06 (m, 1H), 7.01-6.98 (m, 1H), 6.59 (td, 1H, *J* = 7.2 Hz, *J* = 0.9 Hz,), 6.45 (d, 1H, *J* = 7.8 Hz), 4.92 (dd, 1H, *J* = 10.4 Hz, *J* = 5.3 Hz), 3.35-3.22 (m, 3H), 2.99-2.89 (m, 3H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 151.5 ($C^{IV}$), 136.2 ($C^{IV}$), 136.1 ($C^{IV}$), 135.2 ($C^{IV}$), 134.1 ($C^{IV}$), 130.3 ($C^{IV}$), 129.0 (CH), 128.1 (2CH), 128.0 (CH), 127.6 (CH), 127.5 (2CH), 124.9 (CH), 124.3 (CH), 124.0 (CH), 117.3 (CH), 107.3 (CH), 54.0 (CH), 48.5 ($CH_2$), 31.6 ($CH_2$), 28.8 ($CH_2$); **MS-LR** (EI) *m/z* (rel intensity) 297 (27% $[M]^+$), 179 (50% $[MC_{14}H_{11}]$), 119 (100% $[MC_8H_8N+1]$), **MS-ES** (+) *m/z* (rel intensity) 298.5 (27% [M+1]), 179.4 (100% $[MC_{14}H_{11}]$); **HRMS**: Calculated for $C_{22}H_{20}N$ 298.1590, found 298.1590.

(+)-**87a**: **$[\alpha]_D^{20}$** +23.8 (*c* 0.1, $CH_2Cl_2$).

(–)-**87a**: **$[\alpha]_D^{20}$** –23.6 (*c* 0.1, $CH_2Cl_2$).

**1-(9,10-dihydrophenanthren-10-yl)-5-methoxyindoline or 87b:**



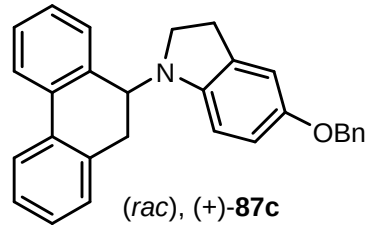

(*rac*), (+)-**87b**

Starting from 30 mg (0.074 mmol) of [**86b**][Br] or 45 mg (0.041 mmol) of [**86b**][*Δ*-BINPHAT] ammonium salts, the desired compound **87b** was obtained after purification by column chromatography (basic alumina, cyclohexane:$Et_2O$ from 90:10 to 80:20) a white solid, as (*rac*)-**87b** (53%) and (+)-**87b** (52%) respectively. The enantiomeric excess was measured using a CSP-HPLC (Chiralpak IB; *n*-Hexane/*i*-PrOH/ethanolamine 99.5:0.5:0.1%; 0.5 mL.min$^{-1}$, 23 °C).

**M.p.** 168 °C; **IR** (neat): 3064, 2925, 2850, 1592, 1490, 1449, 1433, 1249, 1235, 1138, 1034, 806, 749 cm$^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.84 (dd, 1H, *J* = 7.9 Hz, *J* = 0.8 Hz), 7.80 (d, 1H, *J* = 7.9 Hz), 7.46 (m, 1H), 7.39-7.22 (m, 5H), 6.73 (m, 1H), 6.56 (dd, 1H, *J* = 8.3 Hz, *J* = 2.7 Hz), 6.36 (d, 1H, *J* = 8.3 Hz), 4.82 (dd, 1H, *J* = 10.4 Hz, *J* = 5.3 Hz), 3.71 (s, 3H), 3.31-3.19 (m, 3H), 2.96-2.88 (m, 3H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 152.8 ($C^{IV}$), 145.5 ($C^{IV}$), 136.4 ($C^{IV}$), 136.2 ($C^{IV}$), 135.1 ($C^{IV}$), 134.1 ($C^{IV}$), 132.0 ($C^{IV}$), 129.0 (CH), 128.1 (2CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 124.1 (CH), 124.0 (CH), 112.6 (CH), 111.7 (CH), 107.8 (CH), 56.2 ($CH_3$), 54.7 (CH), 49.2 ($CH_2$), 31.0 ($CH_2$), 29.1 ($CH_2$); **MS-LR** (EI) *m/z* (rel intensity) 327 (36% $[M]^+$), 179 (44% $[MC_{14}H_{11}]$), 149 (100% $[MC_9H_{10}NO+1]$), 134 (59%), **MS-ES** (+) *m/z* (rel intensity) 328.4 (36% [M+1]), 179.4 (100% $[MC_{14}H_{11}]$); **HRMS**: Calculated for $C_{23}H_{22}NO$ 328.1695, found 328.1702.

(+)-**87b**: **$[\alpha]_D^{20}$** +17.6 (*c* 0.1, $CH_2Cl_2$).

**5-(benzyloxy)-1-(9,10-dihydrophenanthren-10-yl)indoline or 87c:**



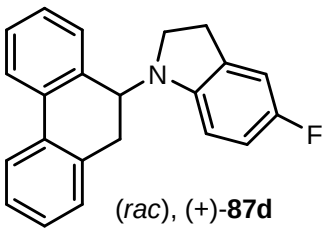
(*rac*), (+)-**87c**

Starting from 25mg (0.052 mmol) of [**86c**][Br] or 45 mg (0.037 mmol) of [**86c**][*Δ*-BINPHAT] ammonium salts, the desired compound **87c** was obtained after purification by column chromatography (basic alumina, cyclohexane:$Et_2O$ from 90:10 to 80:20) a pale yellow solid, as (*rac*)-**87c** (48%) and (+)-**87c** (50%) respectively. The enantiomeric excess was measured using a CSP-HPLC (Chiralpak IB; *n*-Hexane/*i*-PrOH/ethanolamine 98:02:0.1%; 0.5 mL.min$^{-1}$, 23 °C).

**M.p.** 171 °C; **IR** (neat): 3063, 3030, 2924, 2850, 1593, 1488, 1452, 1232, 1139, 1024, 750, 736, 695 cm$^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.83 (dd, 1H, *J* = 7.9 Hz, *J* = 0.9 Hz), 7.80 (d, 1H, *J* = 7.9 Hz), 7.47-7.21 (m, 11H), 6.81 (m, 1H), 6.64 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz), 6.35 (d, 1H, *J* = 8.5 Hz), 4.97 (s, 2H), 4.82 (dd, 1H, *J* = 10.4 Hz, *J* = 5.3 Hz), 3.34-3.19 (m, 3H), 2.96-2.85 (m, 3H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 151.8 ($C^{IV}$), 145.8, ($C^{IV}$), 138.3 ($C^{IV}$), 136.4 ($C^{IV}$), 136.2 ($C^{IV}$), 135.1 ($C^{IV}$), 134.1 ($C^{IV}$), 132.0 ($C^{IV}$), 129.0 (CH), 128.8 (CH), 128.0 (5 CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 124.1 (CH), 124.0 (CH), 113.7 (CH), 113.1 (CH), 107.7 (CH), 54.6 (CH), 71.3 ($CH_2$), 49.1 ($CH_2$), 31.0 ($CH_2$), 29.1 ($CH_2$); **MS-LR** (EI) *m/z* (rel intensity) 403 (15% $[M]^+$), 179 (53% $[MC_{14}H_{11}]$), 134 (100%), **MS-ES** (+) *m/z* (rel intensity) 404.5 (15% [M+1]), 226.5 (52% [$C_{15}H_{14}NO$+2), 179.3 (100% $[MC_{14}H_{11}]$); **HRMS**: Calculated for $C_{29}H_{26}NO$ 404.2008, found 404.2004.

(+)-**87c**: **$[\alpha]_D^{20}$** +18.2 (*c* 0.1, $CH_2Cl_2$).

**5-fluoro-1-(9,10-dihydrophenanthren-10-yl)indoline or 87d:**



(*rac*), (+)-**87d**

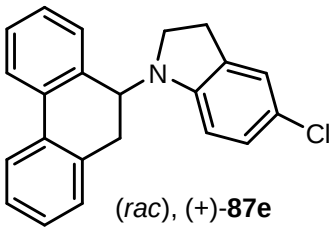
Starting from 35 mg (0.088 mmol) of [**86d**][Br] or 50 mg (0.044 mmol) of [**86d**][*Δ*-BINPHAT] ammonium salts, the desired compound **87d** was obtained after purification by preparative plate chromatography (basic alumina, cyclohexane:$Et_2O$ 99:01) as a pale yellow solid, as (*rac*)-**87d** (48%) and (+)-**87d** (50%) respectively.

The enantiomeric excess was measured using a CSP-HPLC (Chiralpak IB; *n*-Hexane/ *i*-PrOH/ethanolamine 95:05:0.1%; 0.5 mL.min$^{-1}$, 23 °C).

**M.p.** 110 °C; **IR** (neat): 3066, 2923, 2865, 1601, 1494, 1480, 1441, 1247, 1229, 1131, 863, 792, 766, 751, 742, 727 cm$^{-1}$; **H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.84 (dd, 1H, *J* = 7.9 Hz, *J* = 0.9 Hz), 7.80 (d, 1H, *J* = 7.6 Hz), 7.43-7.23 (m, 6H), 6.82 (dt, 1H, $J_{H-H}$ = 2.8 Hz, $J_{H-F}$ = 8.5 Hz), 6.70 (td, 1H, $J_{H-H}$ = 2.8 Hz, $J_{H-F}$ = 8.5 Hz), 6.33 (dd, 1H, $J_{H-F}$ = 4.4 Hz, $J_{H-H}$ = 8.5 Hz), 4.83 (dd, 1H, *J* = 10.4 Hz, *J* = 5.3 Hz), 3.35-3.19 (m, 3H), 2.97-2.89 (m, 3H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 157.2-155.4 (d, $C^{IV}$, $J_{C-F}$ = 233.0 Hz), 147.7 ($C^{IV}$), 136.0 ($2C^{IV}$), 135.1 ($C^{IV}$), 134.0 ($C^{IV}$), 132.1 (d, $C^{IV}$, $J_{C-F}$ = 8.0 Hz), 129.0 (CH), 128.1 (2CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 124.2 (CH), 124.0 (CH), 113.0-112.8 (d, CH, $J_{C-F}$ = 23.0 Hz), 112.6-112.4 (d, CH, $J_{C-F}$ = 23.0 Hz), 107.2-107.1 (d, CH, $J_{C-F}$ = 8.0 Hz), 54.5 (CH), 49.1 ($CH_2$), 31.2 ($CH_2$), 28.8 ($CH_2$); **$^{19}$F-NMR** (212 MHz, $CD_2Cl_2$, 293 K) δ –128.8; **MS-LR** (EI) *m/z* (rel intensity) 315 (20% $[M]^+$), 179 (61% [$MC_{14}H_{11}$]), 137 (100% [$MC_8H_7FN$+1]), **MS-ES** (+) *m/z* (rel intensity) 316.4 (20% [M+1]), 179.1 (100% [$MC_{14}H_{11}$]); **HRMS**: Calculated for $C_{22}H_{19}NF$ 316.1496, found 316.1498.

(+)-**87d**: **$[\alpha]_D^{20}$** +27.9 (*c* 0.1, $CH_2Cl_2$).

**5-chloro-1-(9,10-dihydrophenanthren-10-yl)indoline or 87e:**




(*rac*), (+)-**87e**

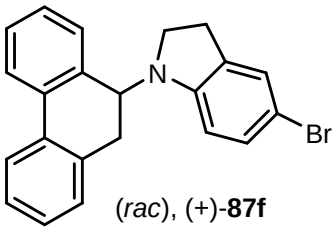
Starting from 35 mg (0.085 mmol) of [**86e**][Br] or 50 mg (0.044 mmol) of [**86e**][*Δ*-BINPHAT] ammonium salts, the desired compound **87e** was obtained after purification by preparative plate chromatography (basic alumina, cyclohexane:$Et_2O$ 99:01) as a pale yellow solid, as (*rac*)-**87e** (46%) and (+)-**87e** (48%) respectively. The enantiomeric excess was measured using a CSP-HPLC (Chiralpak IB; *n*-Hexane/ *i*-PrOH/ethanolamine 95:05:0.1%; 0.5 mL.min$^{-1}$, 23 °C).

**M.p.** 161 °C; **IR** (neat): 3056, 2954, 2918, 2849, 1599, 1494, 1474, 1450, 1436, 1406, 1263, 1161, 806, 769, 753, 728 cm$^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.85 (d, 1H, *J* = 7.9 Hz), 7.80 (d, 1H, *J* = 7.6 Hz), 7.40-7.24 (m, 6H), 7.0 (m, 1H), 6.95 (dd, 1H, *J* = 8.3 Hz, *J* = 2.3 Hz), 6.35 (d, 1H, *J* = 8.3 Hz), 4.86 (dd, 1H, *J* = 10.4 Hz, *J* = 5.3 Hz), 3.37-3.19 (m, 3H), 2.99-2.91 (m, 3H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 150.4 ($C^{IV}$), 135.9 ($C^{IV}$), 135.8 ($C^{IV}$), 135.3 ($C^{IV}$),

134.2 ($C^{IV}$), 132.5 ($C^{IV}$), 129.1 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 125.2 (CH), 124.5 (CH), 124.2 (CH), 107.9 (CH), 54.3 (CH), 48.9 ($CH_2$), 31.8 ($CH_2$), 28.7 ($CH_2$); **MS-LR** (EI) *m/z* (rel intensity) 331 (21% $[M]^+$), 179 (83% $[MC_{14}H_{11}]$), 153 (100% $[MC_8H_7ClN+1]$), **MS-ES** (+) *m/z* (rel intensity) 332.5 (21% [M+1]), 179.4 (100% $[MC_{14}H_{11}]$), 154.3 (46% $[MC_8H_7ClN+1]$); **HRMS**: Calculated for $C_{22}H_{19}N^{35}Cl$ 332.1200, found 332.1216.

(+)-**87e**: **$[\alpha]_D^{20}$** +20.5 (*c* 0.1, $CH_2Cl_2$).

**5-bromo-1-(9,10-dihydrophenanthren-10-yl)indoline or 87f:**



(*rac*), (+)-**87f**

Starting from 35 mg (0.077 mmol) of [**86f**][Br] or 50 mg (0.038 mmol) of [**86f**][*Δ*-BINPHAT] ammonium salts, the desired compound **87f** was obtained after purification by preparative plate chromatography (basic alumina, cyclohexane:$Et_2O$ 99:01) as a yellow oil, as (*rac*)-**87f** (24%) and (+)-**87f** (28%) respectively. The enantiomeric excess was measured using a CSP-HPLC (Chiralpak IB; *n*-Hexane/ *i*-PrOH/ethanolamine 95:05:0.1%; 0.5 mL.min$^{-1}$, 23 °C).

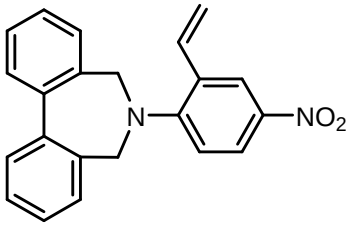
**M.p.** 188 °C; **IR** (neat): 3054, 2922, 2851, 1595, 1493, 1474, 1450, 1436, 1405, 1263, 1161, 804, 769, 753, 729 cm$^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 7.83 (d, 1H, *J* = 7.9 Hz), 7.78 (d, 1H, *J* = 7.6 Hz), 7.38-7.30 (m, 3H), 7.27-7.23 (m, 3H), 7.12 (m, 1H), 7.07 (dd, 1H, *J* = 8.5 Hz, *J* = 2.2 Hz), 6.31 (d, 1H, *J* = 8.5 Hz), 4.84 (dd, 1H, *J* = 10.4 Hz, *J* = 5.3 Hz), 3.35-3.18 (m, 3H), 2.97-2.90 (m, 3H); ; **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 150.7 ($C^{IV}$), 135.8 ($C^{IV}$), 135.6 ($C^{IV}$), 135.2 ($C^{IV}$), 134.0 ($C^{IV}$), 132.8 ($C^{IV}$), 130.0 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 124.3 (CH), 124.0 (CH), 108.4 (CH), 54.1 (CH), 48.6 ($CH_2$), 31.7 ($CH_2$), 28.5 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 378.3 (17%), 376.3 (23% [M+1]), 198.4 (100% $[MC_8H_7BrN+1]$), 179.1 (29% $[MC_{14}H_{11}]$); **HRMS**: Calculated for $C_{22}H_{19}N^{79}Br$ 376.0740, found 376.0740.

(+)-**87f**: **$[\alpha]_D^{20}$** + 16.6 (*c* 0.1, $CH_2Cl_2$).

**Products obtained from the [86h][Br] salt treated under strong basic conditions: the Hofmann elimination product 88h and the product obtained from a benzyne intermediate 89h:**

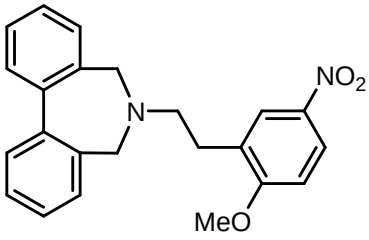
Starting from 30 mg (0.071 mmol) of [**86h**][Br], the compound **88h** and **89h** were obtained as yellow oil after purification by column chromatography over basic alumina using Cyclohexane:$Et_2O$ from 80:20 to 50:50 as eluent, with 25% and 45% respective yields.

**Tertiary amine 88h:**




**IR** (neat): 3069, 3007, 2922, 2853, 1737, 1621, 1595, 1574, 1496, 1482, 1454, 1324, 1307, 1285, 1269, 1214, 1176, 1155, 1080, 977, 932, 899, 817, 752, 740, 716 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 8.37 (d, 1H, *J* = 2.8 Hz), 8.03 (dd, 1H, *J* = 9.0 Hz, *J* = 2.8 Hz), 7.58 (dd, 2H, *J* = 7.8 Hz, *J* = 1.3 Hz), 7.50 (td, 2H, *J* = 7.3 Hz, *J* = 1.3 Hz), 7.37 (td, 2H, *J* = 7.3 Hz, *J* = 1.3 Hz), 7.25 (d, 2H, *J* = 7.0 Hz), 6.98 (d, 1H, *J* = 9.0 Hz), 6.92-6.85 (dd, 1H, *J* = 17.4 Hz, *J* = 10.8 Hz), 5.92-5.87 (dd, 1H, *J* = 17.4 Hz, *J* = 1.0 Hz), 5.42-5.39 (dd, 1H, *J* = 10.8 Hz, *J* = 1.0 Hz), 4.08 (s, 4H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 154.9 ($C^{IV}$), 141.7 ($C^{IV}$), 141.1 ($2C^{IV}$), 134.9 (CH), 134.5 ($2C^{IV}$), 130.4 ($C^{IV}$), 129.9 (2CH), 129.0 (2CH), 128.6 (2CH), 128.0 (2CH), 124.1 (CH), 124.0 (CH), 117.8 (CH), 115.5 ($CH_2$), 55.1 ($2CH_2$); **MS-LR** (EI) *m/z* (rel intensity) 342 (54% $[M]^+$), 181 (100% $[MC_{14}H_{11}+2]$) **MS-ES** (+) *m/z* (rel intensity) 495.4 (38%), 374.3 (35%), 343.3 (100% [M+1]), 179.3 (46%$[MC_{14}H_{11}]$).

**Tertiary amine 89h:**



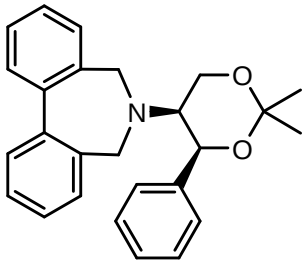

**IR** (neat): 3063, 2927, 2843, 1612, 1590, 1510, 1493, 1451, 1337, 1257, 1090, 1024, 750 $cm^{-1}$; **$^1$H-NMR** (500 MHz, $CD_2Cl_2$, 293 K) δ 8.14-8.09 (m, 2H), 7.52-7.50 (m, 2H), 7.46-7.42 (m, 2H), 7.39-7.34 (m, 4H), 6.97-6.91 (d, 1H, *J* = 10.1 Hz), 3.97 (s, 3H), 3.43 (s, 4H), 3.01-2.96 (m, 2H), 2.81-2.75 (m, 2H); **$^{13}$C-NMR** (126 MHz, $CD_2Cl_2$, 293 K) δ 162.8 ($C^{IV}$), 141.2 ($C^{IV}$), 135.0 ($2C^{IV}$), 130.1 ($2C^{IV}$), 129.7 (2CH), 128.0 (2CH), 127.7 (2CH), 127.6 (2CH), 125.9 ($C^{IV}$), 125.7 (CH), 123.9 (CH), 109.9 (CH), 56.2 ($CH_3$), 55.3 ($2CH_2$), 54.8 ($CH_2$), 28.9 ($CH_2$); **MS-ES** (+) *m/z* (rel intensity) 389.3 (54%), 375.5 (100% [M+1]), 179.3 (56% $[MC_{14}H_{11}]$), 166.3 (30%).

# CHAPTER IV − HOMOLOGOUS AMINE AND IMINIUM CATALYSTS IN ENANTIOSELECTIVE OLEFIN EPOXIDATION

**General procedure for the synthesis of amines 97a, 98a and 99a:**

To a suspension of (+)-L-acetonamine (1.0 equiv) in $CH_3CN$ (4 mL per 50 mg of substrate) was added $K_2CO_3$ (4.5 equiv.) and 2,2'-bis(bromomethyl)-biphenyl / -binaphthyl (1.2 equiv.). The mixture was heated at 80 °C for 3 h. After evaporation of the solvent, the residue was purified by column chromatography over silica gel.

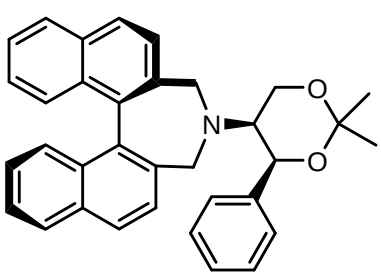
**6-N-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-5H-dibenz[*c*,*e*]azepine or 97a:**




Starting from 99 mg (0.291 mmol) of 2,2'-bis(bromomethyl)biphenyl, compound **97a** was obtained as a white solid (76 mg, 68%) after purification by column chromatography over silica gel using $CH_2Cl_2$:MeOH 99 : 01 as eluent.

**M.p.** 115-120 °C; $\mathbf{[\alpha]_D^{20}}$ +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 ($2C^{IV}$), 136.7 ($2C^{IV}$), 129.4 (2CH), 127.9 (2CH), 127.8 (2CH), 127.4 (4CH), 126.8 (CH), 126.3 (2CH), 99.1 ($C^{IV}$), 74.8 (CH), 62.2 ($CH_2$), 60.9 (CH), 54.0 ($2CH_2$), 30.0 ($CH_3$), 19.0 ($CH_3$); **MS-EI** *m/z* (rel intensity) 386.5 (16 % [M+1]); 179 (100 %)

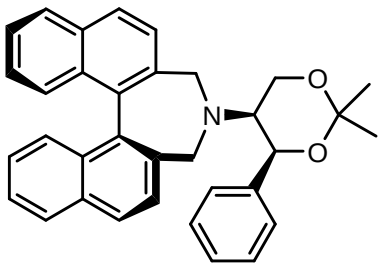
**(*R*)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3H-4-azepine-cyclohepta[2,1-a;3,4-a']dinaphthalene or 98a:**



Starting from 406 mg (0.927 mmol) of (*R*)-2,2'-bis(bromomethyl)-1,1'-binaphthyl, compound **98a** was obtained as a white solid (284 mg, 76%) after purification by column chromatography over silica gel using $CH_2Cl_2$ as eluent.

**M.p.** 102 °C (decomposition); **$[\alpha]^{20}_D$** –130.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat) 3055, 2989, 2859, 1450, 1379, 1197, 1060, 818, 727 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7,91-7.86 (m, 4H), 7.45-7.19 (m, 13H), 5.18 (d, 1H, *J* = 3.3 Hz,), 4.25 (dd, 1H, *J* = 12.5 Hz, *J* = 3.3 Hz), 4.12 (d, 1H, *J* = 12.5 Hz), 3.93 (d, 2H, *J* = 12.1 Hz), 3.36 (d, 2H, *J* = 12.1 Hz), 2.74 (s, 1H), 1.72 (s, 3H), 1.64 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.4 ($C^{IV}$), 135.0 ($2C^{IV}$), 134.8 ($2C^{IV}$), 133.0 ($2C^{IV}$), 131.4 ($2C^{IV}$), 128.5 (2CH), 128.2 (2CH), 128.0 (2CH), 127.8 (2CH), 127.7 (2CH), 126.9 (CH), 126.6 (2CH), 125.6 (2CH), 125.2 (CH), 99.4 ($C^{IV}$), 75.2 (CH), 62.0 ($CH_2$), 60.0 (CH), 53.3 ($2CH_2$), 30.0 ($CH_3$), 19.2 ($CH_3$); **MS-ES** (+) *m/z* (rel intensity) 563.7 (51%), 486.5 (100% [M+1]), 299.5 (28%), 282.3 (77%).

**(*S*)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3*H*-4-azepine-cyclohepta[2,1-a;3,4-a']dinaphthalene or 99a:**



Starting from 459 mg (1.048 mmol) of (*S*)-2,2'-bis(bromomethyl)-1,1'-binaphthyl, compound **99a** was obtained as a white solid (371 mg, 88%) after purification by column chromatography over silica gel using $CH_2Cl_2$ as eluent.

**M.p.** 115 °C (decomposition); **$[\alpha]^{20}_D$** +353.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat) 3053, 2987, 2852, 1449, 1379, 1195, 1061, 817, 751, 697 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7,91-7.86 (m, 4H), 7.51 (m, 2H), 7.43-7.34 (m, 8H), 7.24-7.20 (m, 3H), 5.18 (d, 1H, *J* = 3.8 Hz), 4.19 (dd, 1H, *J* = 12.4 Hz, *J* = 3.8 Hz), 3.96 (dd, 1H, *J* = 12.4, Hz *J* = 2.3 Hz), 3.70 (d, 2H, *J* = 12.6 Hz), 3.50 (d, 2H, *J* = 12.6 Hz), 3.16 (td, 1H, *J* = 3.8 Hz, *J* = 2.3 Hz), 1.50 (s, 3H), 1.1.45 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.2 ($C^{IV}$), 135.2 ($2C^{IV}$), 134.8 ($2C^{IV}$),

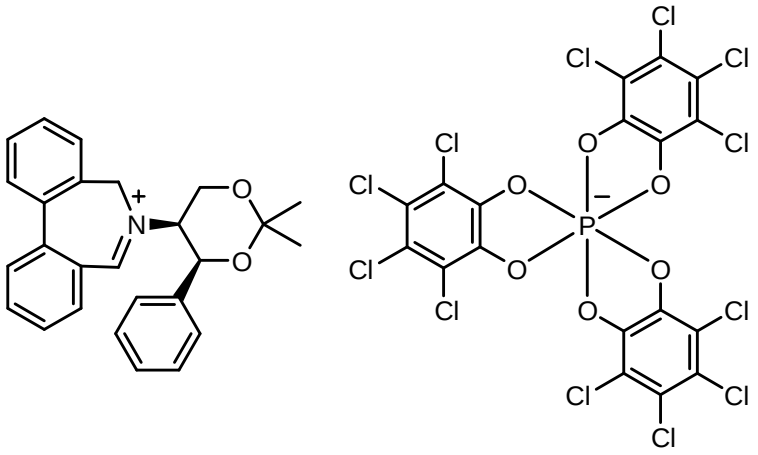
133.0 ($2C^{IV}$), 131.5 ($2C^{IV}$), 128.7 (2CH), 128.3 (2CH), 127.9 (2CH), 127.6 (4CH), 126.9 (CH), 126.3 (2CH), 125.7 (2CH), 125.3 (2CH), 99.1 ($C^{IV}$), 74.6 (CH), 62.7 ($CH_2$), 61.8 (CH), 54.8 ($2CH_2$), 29.2 ($CH_3$), 19.4 ($CH_3$); **MS-ES** (+) *m/z* (rel intensity) 563.7 (39%), 486.5 (100% [M+1]), 299.5 (66%), 282.3 (51%).

**General procedure for the synthesis of the iminium TRISPHAT salts [97i] / [98i] / [99i] [*rac*-TRISPHAT]:**

1)- To a solution of amines **97a, 98a, 99a** (1.0 equiv.) in $CH_2CL_2$ (3 mL per 0.1 mmol of substrate) was added *N*-bromosuccinimide (1.1 equiv.) as solid. The mixture was stirred for 30 min at room temperature. After evaporation of the solvent under reduced pressure, the residue was dissolved in a minimum amount of $CH_2CL_2$ and dropwise addition of $Et_2O$ provided a yellow precipitate, which was collected by filtration over a Buchner funnel, corresponding to iminium bomide salts.

2)- To a solution of this salt in $CH_2Cl_2$ was added a solution of $[Et_2NH_2]$[*rac*-TRISPHAT] (1.2 equiv.) in acetone, and the crude was evaporated under reduced pressure. The desired [iminium][*rac*-TRISPHAT] salts were then isolated by chromatography over silica gel using $CH_2Cl_2$ as eluent.

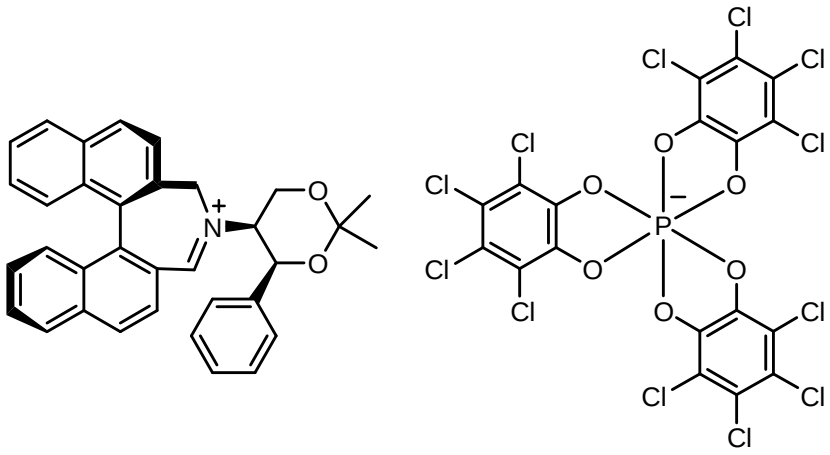
**6-N-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-5H-dibenz[*c*,*e*]azepininium [*rac*-tris-(tetrachlorobenzenediolato)phosphate(V)] or [97i][*rac*-TRISPHAT]:**



Starting from 110 mg (0.285 mmol) of amine **97a**, salt [**97i**][*rac*-TRISPHAT] was obtained as a yellow solid (190 mg, 58%) after purification by column chromatography on basic alumina using $CH_2Cl_2$ as eluent.

**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 (s br, CH=N, 1H), 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, –80.8; **MS-ES** (+) *m/z* (rel intensity) 152.7 (100%), 384.4 (16% $[M]^+$), **MS-ES** (-) *m/z* 769.0 (44% $[M]^-$, TRISPHAT), 113.7 (100%).

**(*R*)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3H-4-azepinium-cyclohepta[2,1-a;3,4-a']dinaphthalene [*rac*-tris(tetrachloro-benzenediolato)phosphate(V)] or [98i][*rac*-TRISPHAT]:**

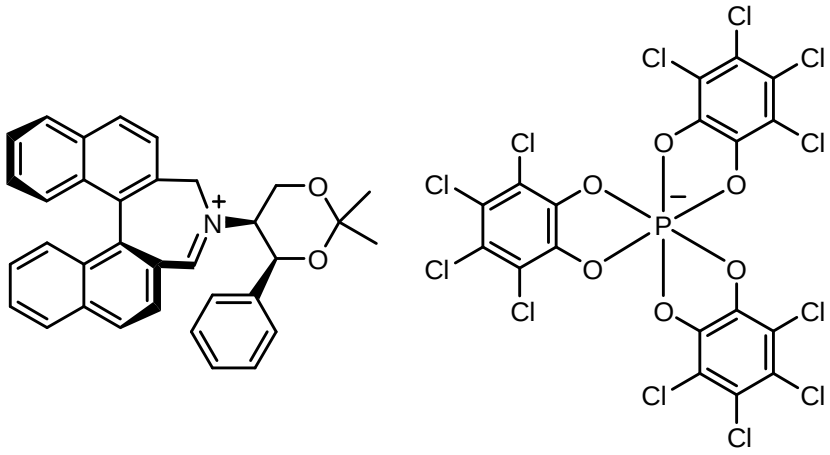


Starting from 47 mg (0.097 mmol) of amine **98a**, salt [**98i**][ *rac*-TRISPHAT] was obtained as a yellow solid (83 mg, 68%) after purification by column chromatography on basic alumina using $CH_2Cl_2$ as eluent.

**M.p** 209 °C (decomposition); **$[\alpha]^{20}_D$** –178.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat) 2923, 2853, 1592, 1446, 1386, 1235, 990, 819 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.05-8.00 (m, 3H), 7.96 (d, 1H, *J* = 8.3 Hz), 7.71 (t, 1H, *J* = 7.8 Hz), 7.63 (d,1H, *J* = 8.3 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 7.49-7.44 (m, 2H), 7.39-7.36 (m, 1H), 7.21 (t, 1H, *J* = 7.8 Hz), 7.03 (m, 2H), 6.89-6.70 (m, 4H), 5.78 (d, 1H, *J* = 13.6 Hz), 5.73 (d, 1H, *J* = 2.0 Hz), 4.61 (d, 1H, *J* = 2.0 Hz), 4.54 (d, 1H, *J* = 13.9 Hz), 4.46 (d, 1H, *J* = 13.9 Hz), 4.35 (d, 1H, *J* = 13.6 Hz,), 1.80 (s, 3H), 1.69 (s, 3H);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ –80.9, –80.8; **MS-ES** (+) *m/z* (rel intensity) 563.7 (54%), 484.3 (100% $[M]^+$), 282.5 (72%), **MS-ES** (-) *m/z* 766.9 (100% $[M]^-$, TRISPHAT).

**(*S*)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3H-4-azepinium-cyclohepta[2,1-a;3,4-a']dinaphthalene [*rac*-tris(tetrachloro-benzenediolato)phosphate(V)] or [99i][*rac*-TRISPHAT]:**



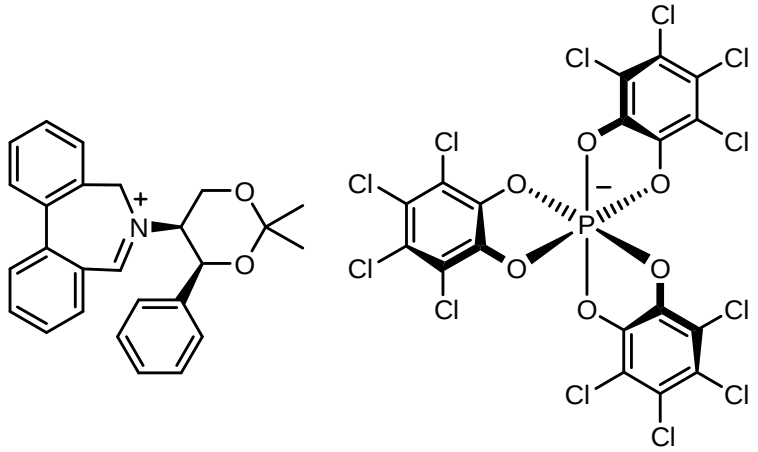
Starting from 90 mg (0.185 mmol) of amine **99a**, salt [**99i**][ *rac*-TRISPHAT] was obtained as a yellow solid (148 mg, 64%) after purification by column chromatography on basic alumina using $CH_2Cl_2$ as eluent

**M.p** 203 °C (decomposition); **$[\alpha]^{20}_D$** +291.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat) 2921, 1590, 1446, 1386, 1235, 1198, 990, 821, 718 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.99-7.89 (m, 3H), 7.76 (d, 2H, *J* = 8.3 Hz), 7.70-7.67 (m, 1H), 7.57-7.53 (m, 1H), 7.36-7.21 (m, 4H), 6.87 (d, 3H, *J* = 8.3 Hz), 6.78-6.74 (m, 1H), 6.64-6.60 (m, 2H), 5,87 (s, 1H), 5.54 (d, 1H, *J* = 12.4 Hz), 5.0 (s, 1H), 4.67 (d, 1H, *J* = 13.6 Hz), 4.52 (d, 1H, *J* = 13.6 Hz), 4.16 (d, 1H, *J* = 12.4 Hz), 1.88 (s, 3H), 1.73 (s, 3H); **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ –80.9, –80.8; **MS-ES** (+) *m/z* (rel intensity) 563.7 (67%), 484.3 (100% $[M]^+$), 282.3 (85%), **MS-ES** (-) *m/z* 766.9 (100% $[M]^-$, TRISPHAT), 339.3 (54%).

**General procedure for the synthesis of the iminium *Δ*-TRISPHAT salts [97i] / [98i] / [99i] [*Δ*-TRISPHAT]:**

To a solution of amines **97a, 98a, 99a** (1.0 equiv.) in $CH_2CL_2$ (3 mL per 0.1 mmol of substrate) was added *N*-bromosuccinimide (1.1 equiv.) as solid. The mixture was stirred at room temperature for 30 min at room temperature, then a solution of [cinchonidinium][*Δ*-TRISPHAT] (1.2 equiv.) 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 [imminium] [*Δ*-TRISPHAT] salt was recovered after column chromatography over basic alumina using $CH_2Cl_2$ as eluent.

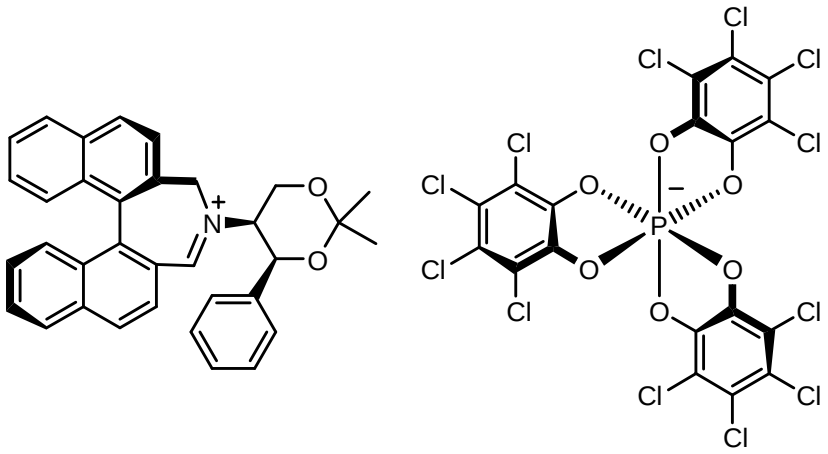
**6-N-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-5H-dibenz[*c*,*e*]azepininium [*Δ*-tris(tetrachlorobenzene-diolato)phosphate(V)] or [97i][*Δ*-TRISPHAT]:**



Starting from 65 mg (0.169 mmol) of amine **97a**, salt [**97i**][*Δ*-TRISPHAT] was obtained as a yellow solid (115 mg, 59%) after purification by column chromatography on basic alumina using $CH_2Cl_2$ as eluent.

**M.p.** 234 °C (decomposition); **$[\alpha]^{20}_D$** –225.3 (*c* 0.1, $CH_2Cl_2$) ; **IR** (neat) 2924, 1632, 1597, 1555, 1446, 1387, 1236, 1201, 990, 819, 718 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.34–8.66 (br, CH=N, 1H), 7.87-6.997 (m, 13H), 5.86 (s, CH-Ar, 1H), 5.00-4.09 (m, $CH_2$-N and CHN and $CH_2$-O, 5H), 1.87 (s, $CH_3$, 3H), 1.78 (s, $CH_3$, 3H); **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ –80.9, –80.8; **MS-ES** (+) *m/z* (rel intensity) 384.1 (100% $[M]^+$), 152.7 (100%), **MS-ES** (-) *m/z* 769.1 (100% $[M]^-$, TRISPHAT).

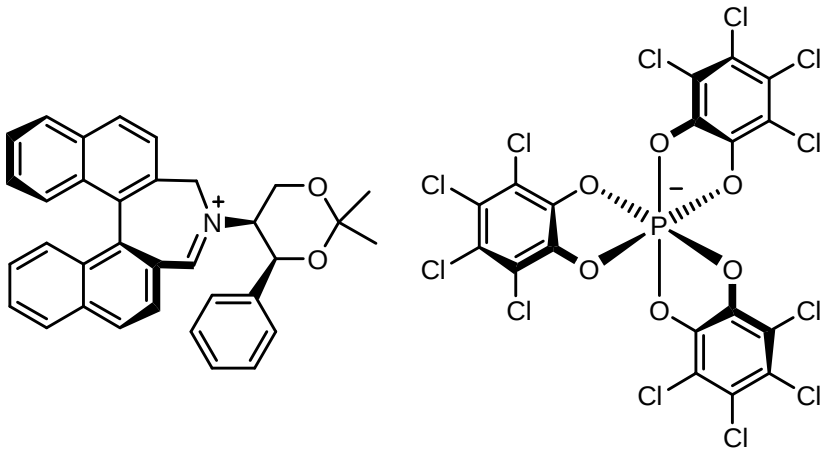
**(*R*)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3*H*-4-azepinium-cyclohepta[2,1-a;3,4-a']dinaphthalene [*Δ*-tris(tetrachlorobenzene-diolato)phosphate(V)] or [98i][*Δ*-TRISPHAT]:**



Starting from 100 mg (0.206 mmol) of amine **98a**, salt [**98i**][*Δ*-TRISPHAT] was obtained as a yellow solid (155 mg, 60%) after purification by column chromatography on basic alumina using $CH_2Cl_2$ as eluent.

**M.p.** 188 °C (decomposition); **$[\alpha]^{20}_D$** –193.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat) 2923, 1593, 1447, 1385, 1236, 990, 819, 719 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.07-8.0 (m, 3H), 7.96 (d, 1H, *J* = 8.3 Hz), 7.71 (t, 1H, *J* = 7.8 Hz), 7.63 (d, 1H, *J* = 8.3 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 7.48-7.46 (m, 1H), 7.40-7.36 (m, 2H), 7.21 (t, 1H, *J* = 7.8 Hz), 7.09 (m, 2H), 6.94-6.79 (m, 4H), 5.78-5.75 (m, 2H), 4.70-4.66 (m, 2H), 4.35-4.29 (m, 2H), 1.81 (s, 3H), 1.71 (s, 3H), **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ –80.9, –80.8; **MS-ES** (+) *m/z* (rel intensity) 563.7 (49%), 484.5 (100% $[M]^+$), 282.3 (74%), **MS-ES** (-) *m/z* 768.9 (100% $[M]^-$, TRISPHAT).

**(*S*)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3H-4-azepinium-cyclohepta[2,1-a;3,4-a']dinaphthalene [*Δ*-tris(tetrachlorobenzene-diolato)phosphate(V)] or [99i][*Δ*-TRISPHAT]:**



Starting from 90 mg (0.185 mmol) of amine **99a**, salt [**99i**][ *Δ*-TRISPHAT] was obtained as a yellow solid (132 mg, 57%) after purification by column chromatography on basic alumina using $CH_2Cl_2$ as eluent.

**M.p.** 184°C (decomposition); **$[\alpha]^{20}_D$** +289.0 (*c* 0.1, $CH_2Cl_2$); **IR** (neat) 2924, 1593, 1447, 1385, 1236, 1197, 990, 821, 719 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.46-9.43 (2s, 1H), 8.11-7.94 (m, 3H), 7.88-7.40 (m, 4H), 7.33-7.13 (m, 6H), 6.99-6.84 (m, 2H), 6.70-6.60 (m, 2H), 5.83 (s, 1H), 5.58 (d, 0.75H, *J* = 12.9 Hz), 4.96-4.92 (m, 1H), 4.81 (d, 0.75H, *J* = 13.9 Hz), 4.39 (d, 0.75H, *J* = 13.9 Hz), 4.18 (d, 0.75H, *J* = 12.9 Hz), 3.84 (d, 0.5H, *J* = 10.6 Hz), 3.48 (d, 0.5H, *J* =10.6 Hz), 1.89 (s, 2H), 1.72 (s, 2H), 1.44 (s, 1H), 1.42 (s, 1H); **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ –80.8, –80.7; **MS-ES** (+) *m/z* (rel intensity) 563.7 (56%), 502.3 (54%), 484.5 (100% $[M]^+$), 282.1(88%), **MS-ES** (-) *m/z* 766.9 (100% $[M]^-$, TRISPHAT), 340.5 (53%).

**Asymmetric epoxidation procedures:**

Condition **A**: A mixture of Oxone (133.2 mg, 0.20 mmol, 2.0 equiv.) and $NaHCO_3$ (42 mg, 0.50 mmol, 5.0 equiv.) was added to a round-bottom flask containing a stirred solution of catalyst (5.0 $\mu$mol, 5.0 mol %), alkene (0.10 mmol, 1.0 equiv.) and naphthalene (0.10 mmol, 1.0 equiv., internal reference) in $CH_3CN$ (250 $\mu$L) and $H_2O$ (25 $\mu$L), at room temperature. The reaction mixture was then stirred at 0 °C for 2 h or 15 min.

Condition **B**: In a 5 mL flask equipped with a magnetic stirring bar, $NaHCO_3$ (33.6 mg, 0.40 mmol, 4.0 equiv.) was added to 400 $\mu$L of water. Oxone (66.6 mg, 0.11 mmol, 1.1 equiv.) was then added, and the solution was stirred for 2 min until effervescence subsided. A 250 $\mu$L portion of a 0.25 mol/L of the alkene (0.10 mmol, 1.0 equiv.) and naphthalene (0.10 mmol, 1.0 equiv., internal reference) in $CH_2Cl_2$ was added. The catalyst (5.0 $\mu$mol, 5.0 mol %), in $CH_2Cl_2$ (300 $\mu$L) was added, followed by a solution of 18-crown-6 (0.5 mg, 2.5 $\mu$mol, 2.5 mol %) in $CH_2Cl_2$ (100 $\mu$L). The reaction mixture was then stirred at 0 °C for 2 h or 15 min.

The enantiomeric excess was determined by Chiral Stationary Phase CSP-GC (Chiral Hydrodex $\beta$-3P; Tinj 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) or CSP-HPLC (Chiralcel OD-H; *n*-Hexane/*i*-PrOH 95:05; 0.5 $mL.min^{-1}$; 23 °C)

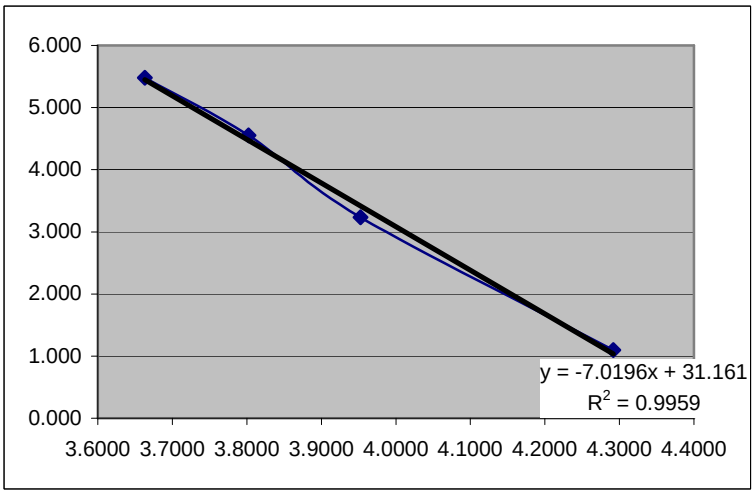
# APPENDIX

## CHAPTER II – TOWARDS AN ENANTIOSELECTIVE [1,2]-STEVENS REARRANGEMENT

Activation parameters of [**61**][I]:

| T [K] | 1000/T |
|---|---|
| 233 | 4.2918 |
| 253 | 3.9526 |
| 263 | 3.8023 |
| 273 | 3.6630 |

| k | ln(k) |
|---|---|
| 3 | 1.099 |
| 25.4 | 3.235 |
| 95 | 4.554 |
| 240 | 5.481 |

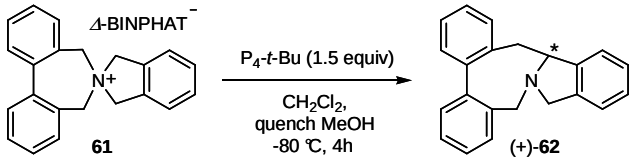


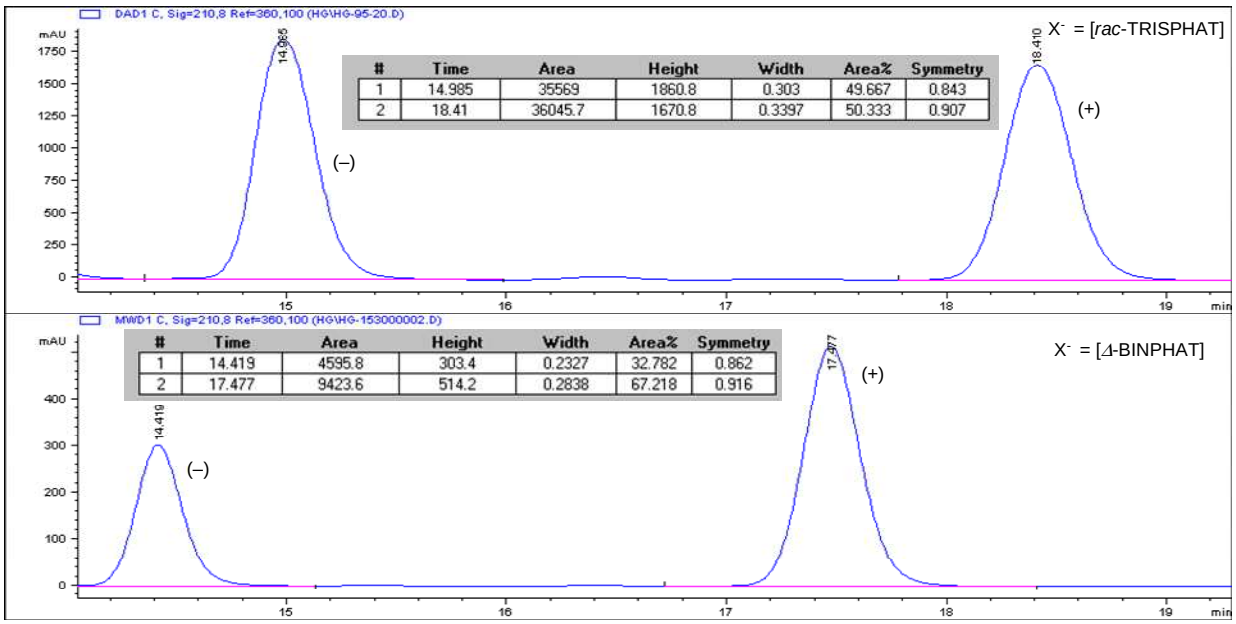

| **ln(k)=f(1000/T)** | | | |
|---|---|---|---|
| slope= | -7.020 | - Ea/R | ±0.32 |
| intercept= | 31.161 | Ln(A) | ±1.26 |
| T | 25 | ℃ | |
| **Ea** | **58.54** | **kJ/mol** | ±2.67 |
| **A** | **3.41E+13** | **s-1** | |

R-square value = **0.996**

| | | | |
|---|---|---|---|
| $\Delta H^{\neq}$ = Ea - RT | 56.057 | kJ/mol | 13.41 kcal/mol |
| $\Delta S^{\neq}$ = R [ln(h*A/k*T)-1] | 5.846 | J/(mol.K) | 1.40 cal/(mol.K) |
| $\Delta G^{\neq}$ | 54.314 | kJ/mol | 12.99 kcal/mol |

Determination of the enantiomeric excess of (+)-**62**:



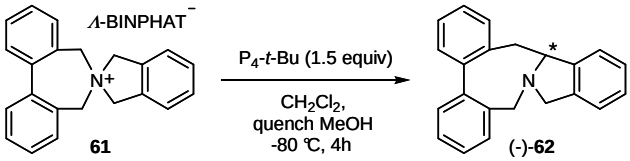



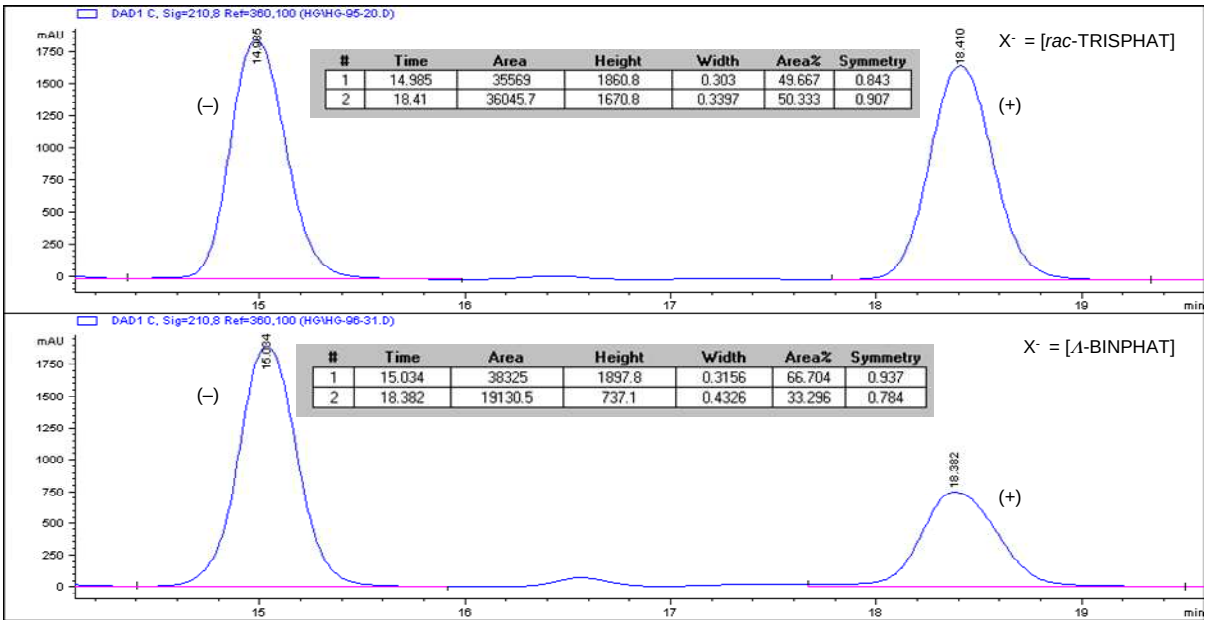

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 14.985 | 35569 | 1860.8 | 0.303 | 49.667 | 0.843 |
| 2 | 18.41 | 36045.7 | 1670.8 | 0.3397 | 50.333 | 0.907 |

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 14.419 | 4595.8 | 303.4 | 0.2327 | 32.782 | 0.862 |
| 2 | 17.477 | 9423.6 | 514.2 | 0.2838 | 67.218 | 0.916 |

**Determined by CSP-HPLC (Chiralpak AD-H); *n*-Hexane / *i*-PrOH 95 : 05; 0.5 mL.min$^{-1}$; 23 °C).**

Determination of the enantiomeric excess of (–)-**62**:

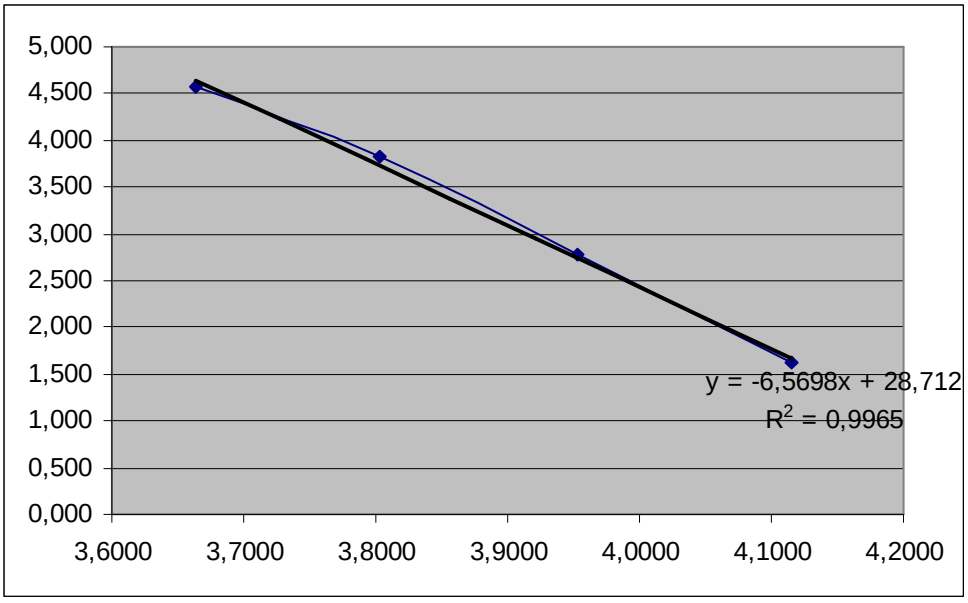



**Determined by CSP-HPLC (Chiralpak AD-H); *n*-Hexane / *i*-PrOH 95 : 05; 0.5 mL.min$^{-1}$; 23 °C).**

Activation parameters of [**73**][Br]:

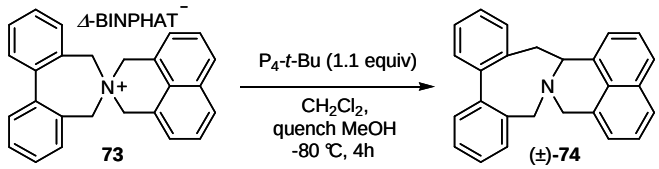
| T [K] | 1000/T | k | ln(k) |
|---|---|---|---|
| 243 | 4.1152 | 5.1 | 1.629 |
| 253 | 3.9526 | 16 | 2.773 |
| 263 | 3.8023 | 45.8 | 3.824 |
| 273 | 3.6630 | 96.8 | 4.573 |

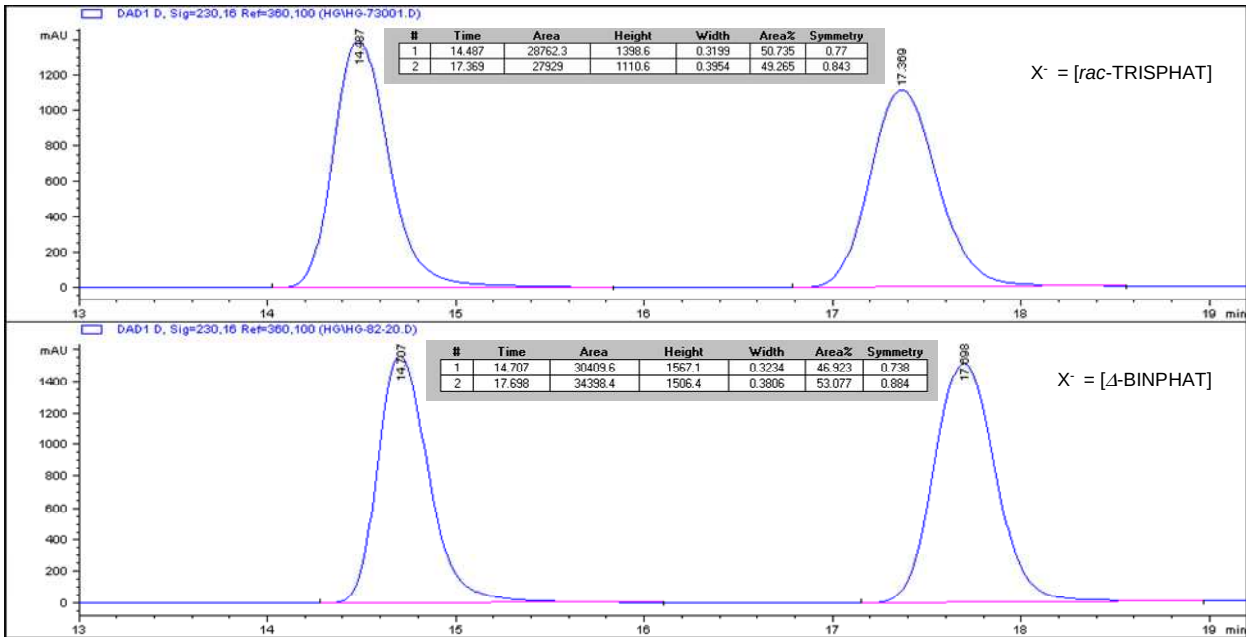



| **ln(k)=f(1000/T)** | | | | |
|---|---|---|---|---|
| slope= | -6.571 | | - Ea/R | ±0.27 |
| intercept= | 28.716 | | Ln(A) | ±1.06 |
| | | | | |
| T | 25 | ℃ | | |
| **Ea** | **54.80** | **kJ/mol** | ±2.28 | |
| **A** | **2.96+12** | **s-1** | | |
| R-square value = | **0.997** | | | |

| | | | | |
|---|---|---|---|---|
| $\Delta H^{\neq}$ = Ea - RT | 52.314 | kJ/mol | 12.51 | kcal/mol |
| $\Delta S^{\neq}$ = R [ln(h*A/k*T)-1] | -14.482 | J/(mol.K) | -3.65 | cal/(mol.K) |
| $\Delta G^{\neq}$ | 56.632 | kJ/mol | 13.54 | kcal/mol |

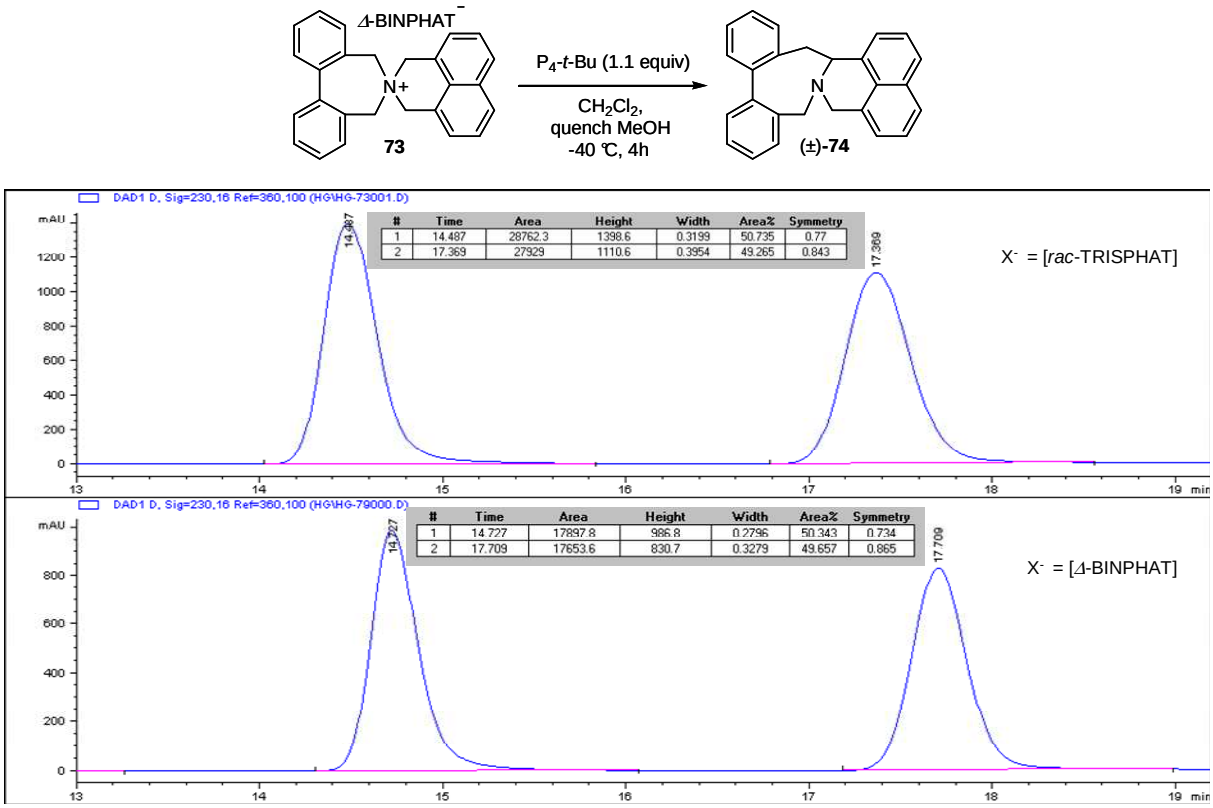
Determination of the lack of enantiomeric excess of (±)-**74**:




**Determined by CSP-HPLC (Chiralpak AD-H); *n*-Hexane / *i*-PrOH 95 : 05; 0.5 mL.min$^{-1}$; 23 °C).**

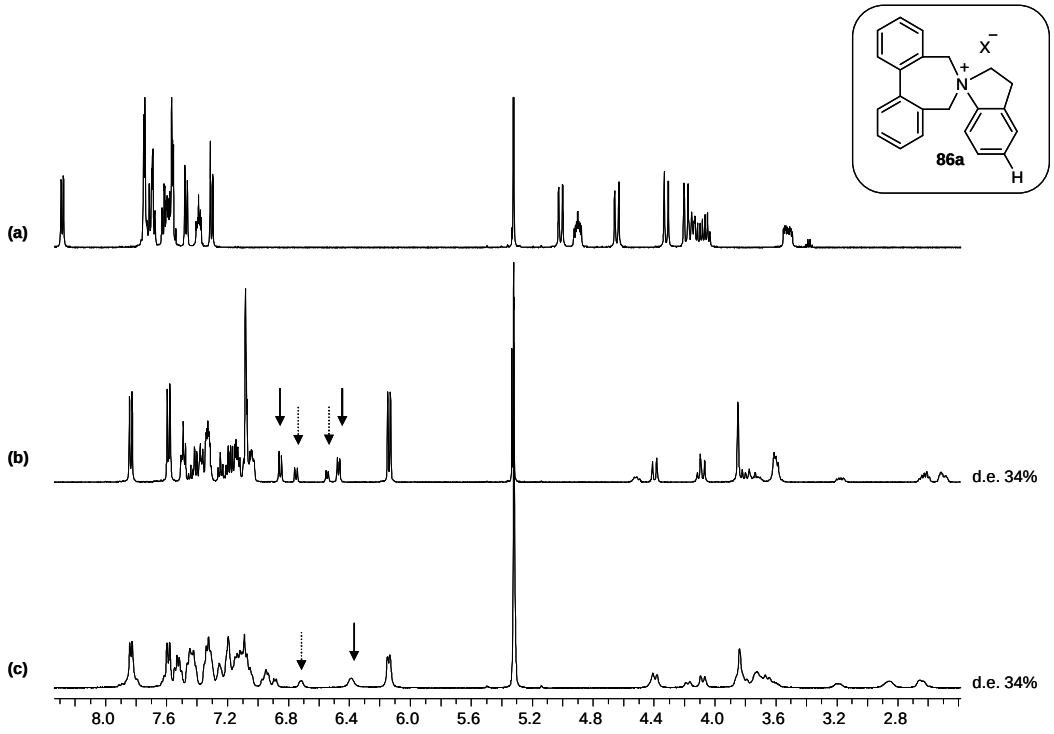
Determination of the lack of enantiomeric excess of (±)-**74**:



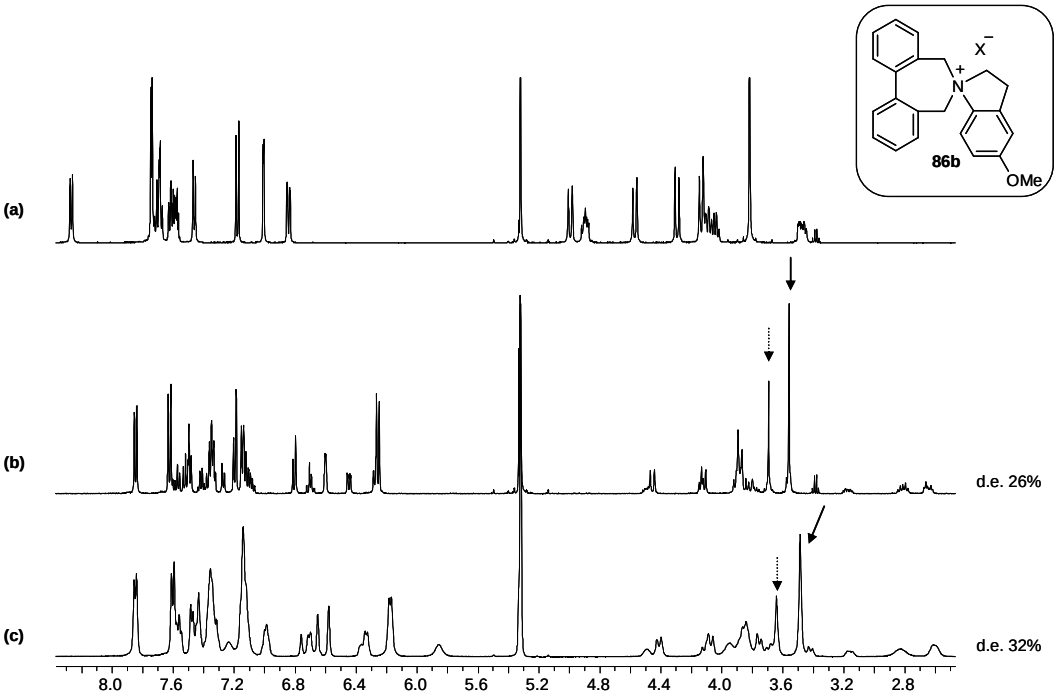

**Determined by CSP-HPLC (Chiralpak AD-H); *n*-Hexane / *i*-PrOH 95 : 05; 0.5 mL.min$^{-1}$; 23 °C).**

## CHAPTER III – ENANTIOSELECTIVE [1,2]-STEVENS REARRANGEMENT AND EXCELLENT TRANFER OF CHIRALITY

Salts of cation **86a** $^{1}$H-NMR (500 MHz, $CD_2Cl_2$):

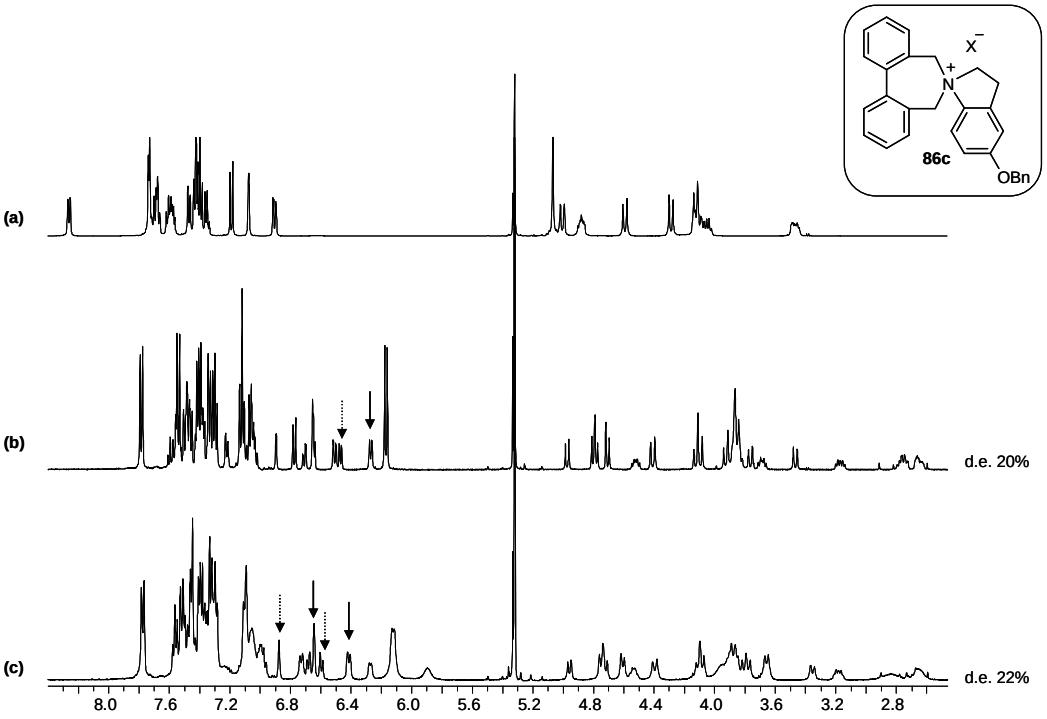



Salts of cation **86b** $^{1}$H-NMR (500 MHz, $CD_2Cl_2$):

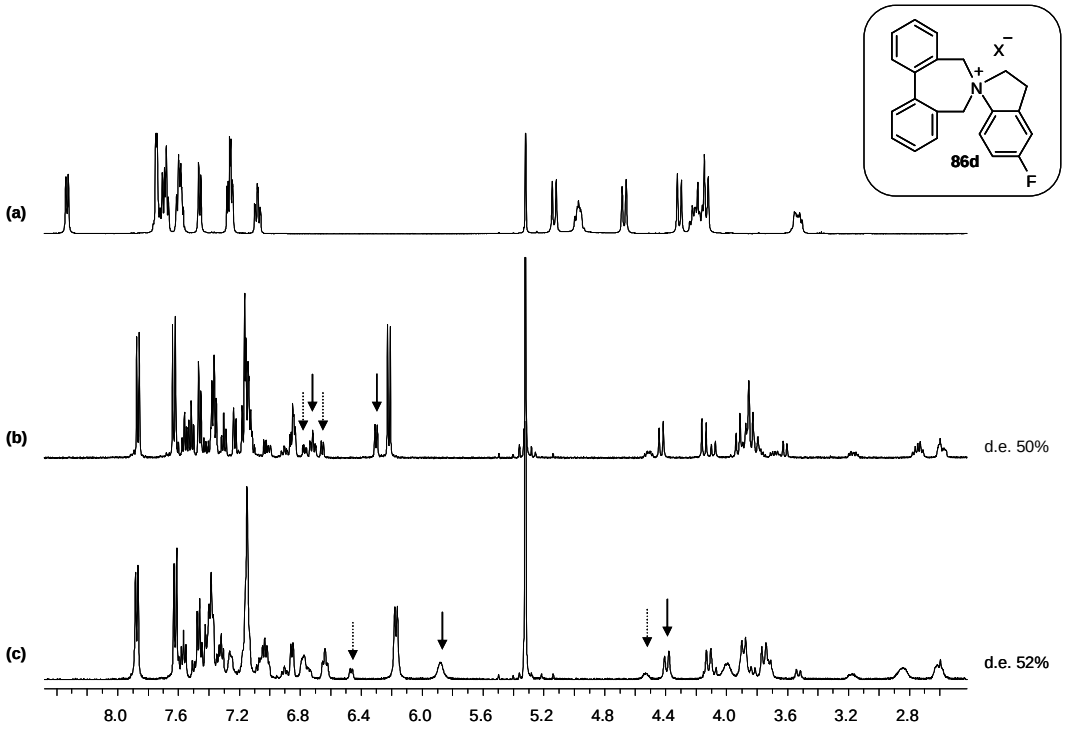



**(a) Bromide salt, 233 K ; (b) BINPHAT salt, 233 K; (c) BINPHAT salt, 193 K.**

Salts of cation **86c** $^{1}$H-NMR (500 MHz, $CD_2Cl_2$):

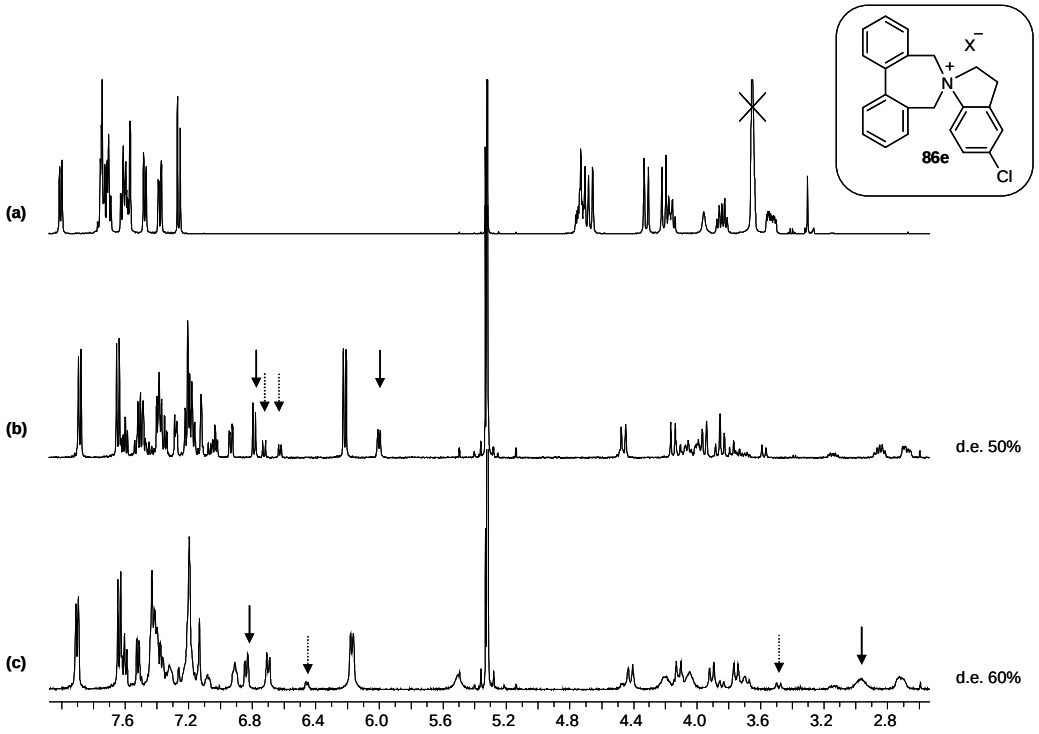



Salts of cation **86d** $^{1}$H-NMR (500 MHz, $CD_2Cl_2$):

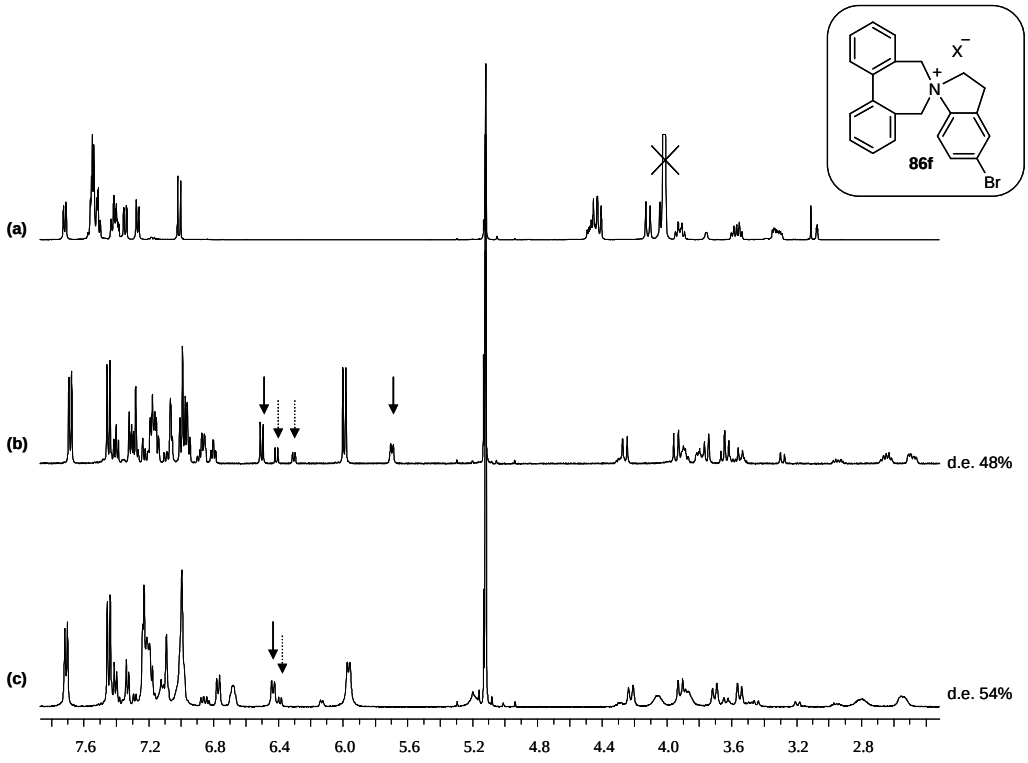



**(a) Bromide salt, 233 K ; (b) BINPHAT salt, 233 K; (c) BINPHAT salt, 193 K.**

Salts of cation **86e** $^1$H-NMR (500 MHz, $CD_2Cl_2$):

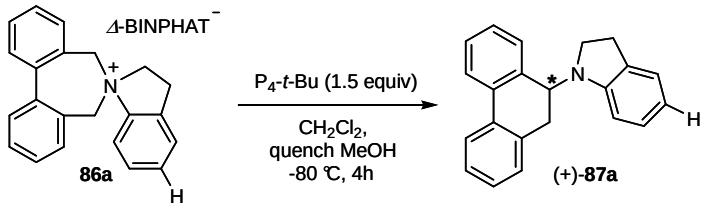


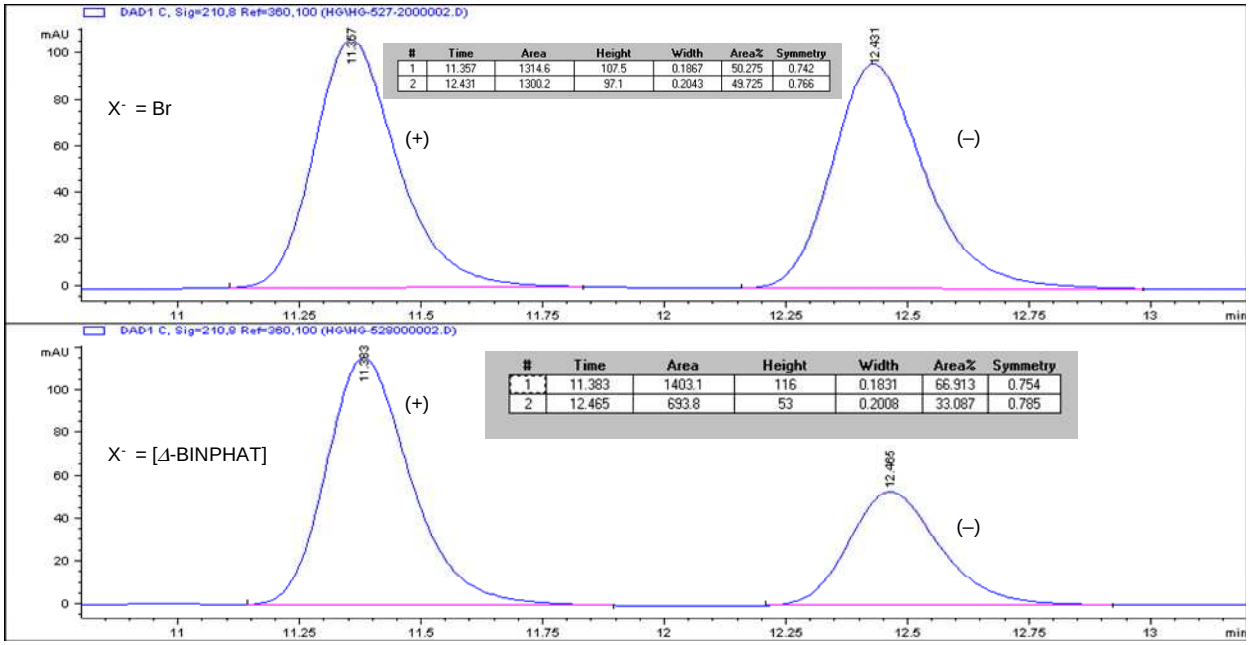

Salts of cation **86f** $^1$H-NMR (500 MHz, $CD_2Cl_2$):




**(a) Bromide salt, 233 K ; (b) BINPHAT salt, 233 K; (c) BINPHAT salt, 193 K.**

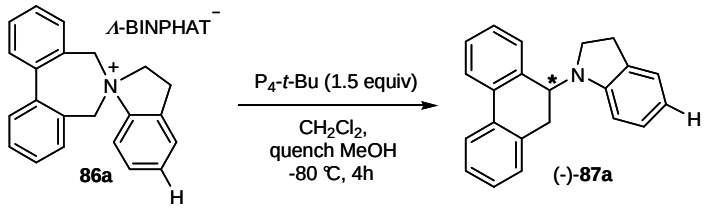
Determination of the enantiomeric excess of (+)-**87a**:

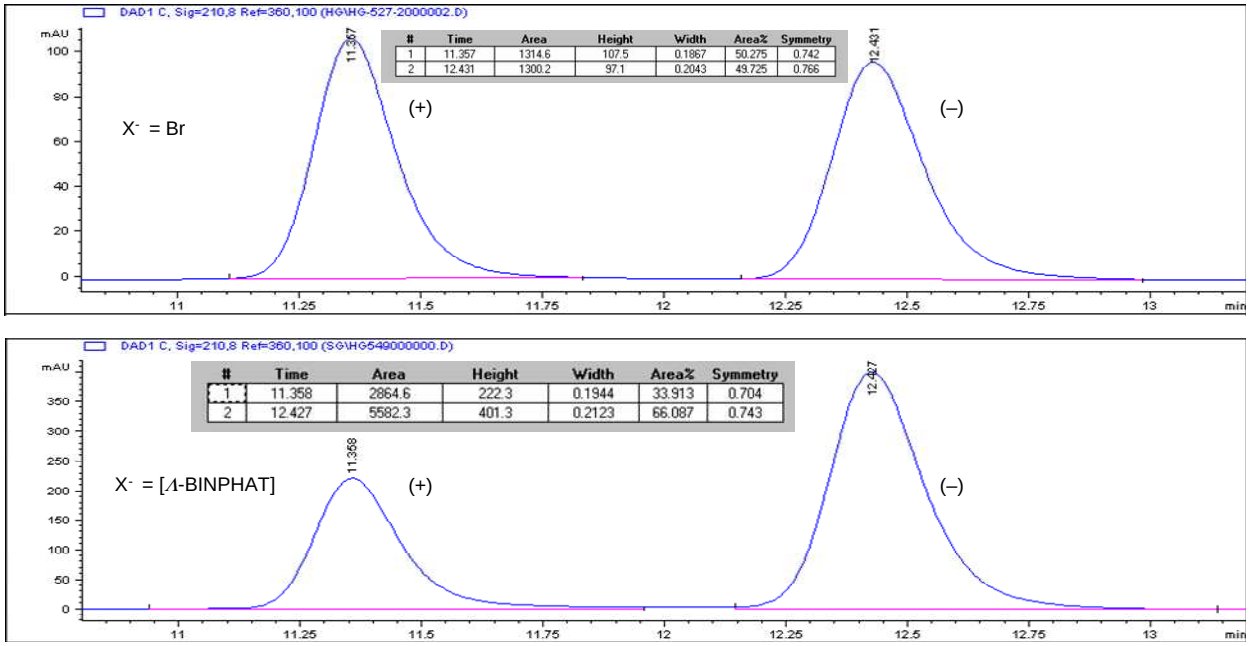



**Determined by CSP-HPLC (Chiralpak IB); *n*-Hexane / *i*-PrOH / ethanolamine 95 : 05 : 0.1%; 0.5 mL.min$^{-1}$; 23 °C).**

Determination of the enantiomeric excess of (–)-**87a**:



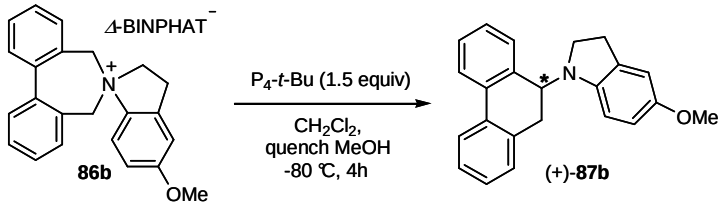



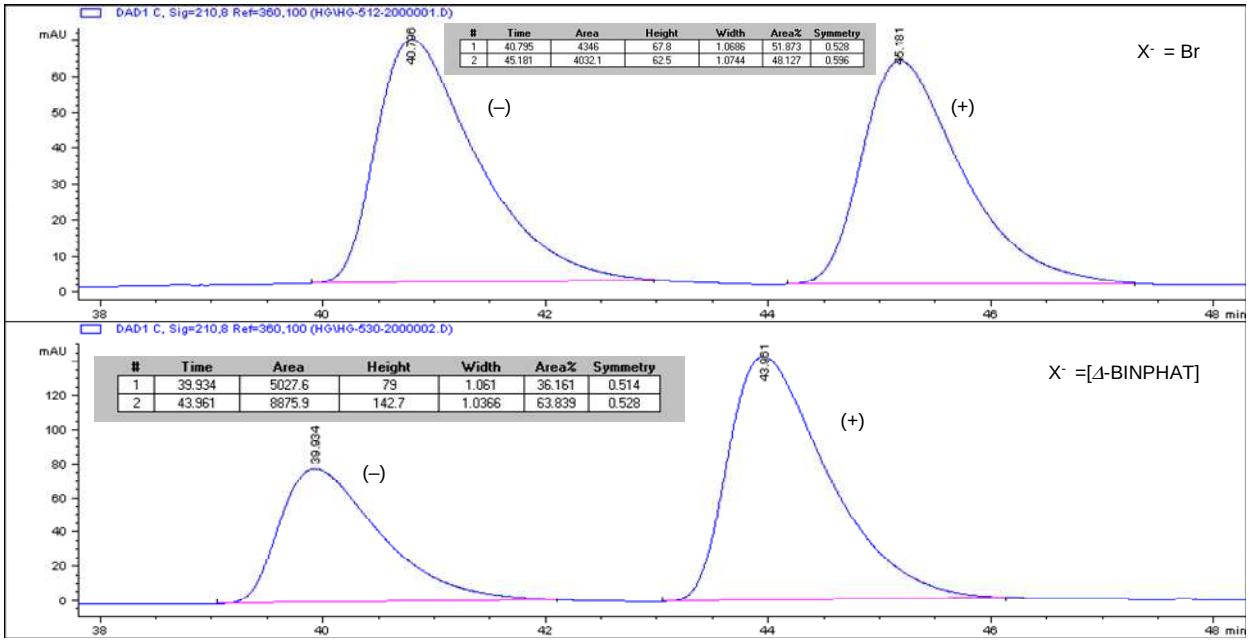

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 11.357 | 1314.6 | 107.5 | 0.1867 | 50.275 | 0.742 |
| 2 | 12.431 | 1300.2 | 97.1 | 0.2043 | 49.725 | 0.766 |

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 11.358 | 2864.6 | 222.3 | 0.1944 | 33.913 | 0.704 |
| 2 | 12.427 | 5582.3 | 401.3 | 0.2123 | 66.087 | 0.743 |

**Determined by CSP-HPLC (Chiralpak IB); *n*-Hexane / *i*-PrOH / ethanolamine 95 : 05 : 0.1%; 0.5 mL.min$^{-1}$; 23 °C).**

Determination of the enantiomeric excess of (+)-**87b**:



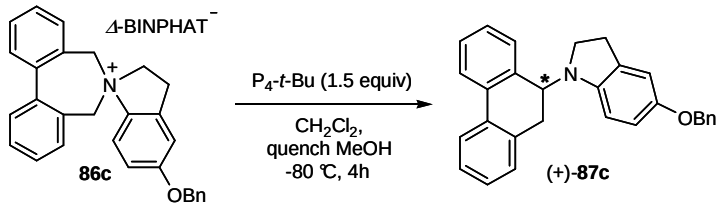



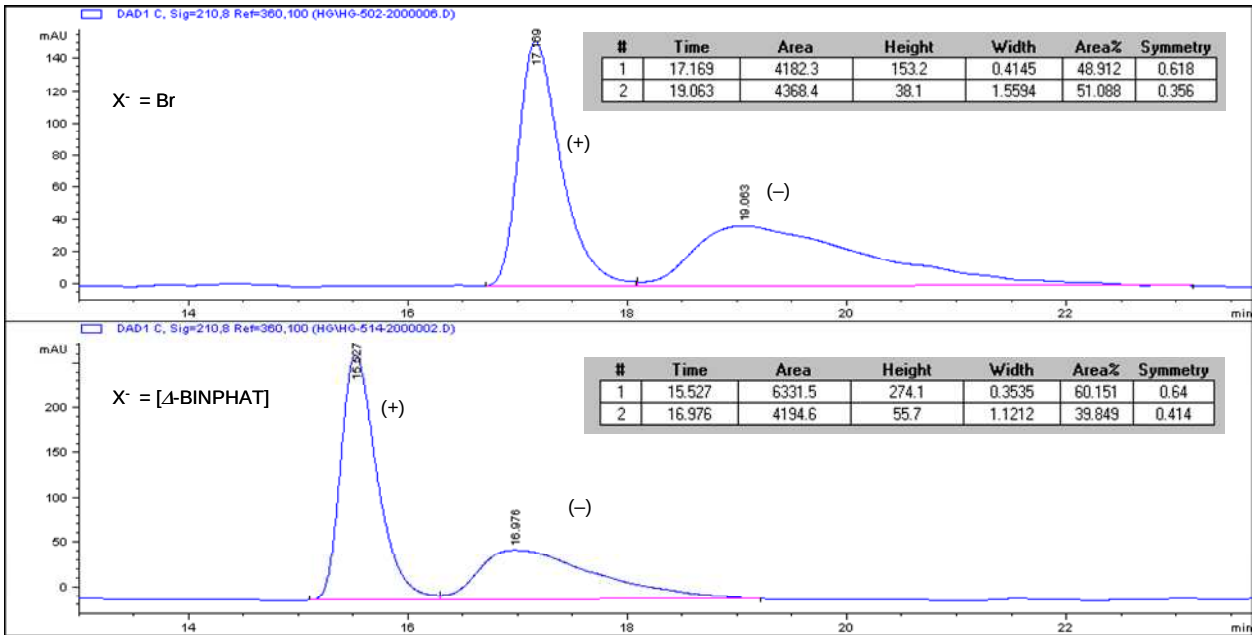

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 40.795 | 4346 | 67.8 | 1.0686 | 51.873 | 0.528 |
| 2 | 45.181 | 4032.1 | 62.5 | 1.0744 | 48.127 | 0.596 |

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 39.934 | 5027.6 | 79 | 1.061 | 36.161 | 0.514 |
| 2 | 43.961 | 8875.9 | 142.7 | 1.0366 | 63.839 | 0.528 |

**Determined by CSP-HPLC (Chiralpak IB); *n*-Hexane / *i*-PrOH / ethanolamine 99.5 : 0.5 : 0.1%; 0.5 mL.min$^{-1}$; 23 °C).**

Determination of the enantiomeric excess of (+)-**87c**



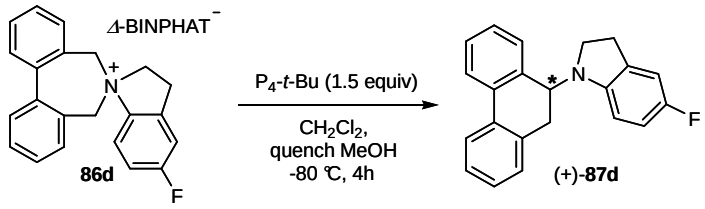



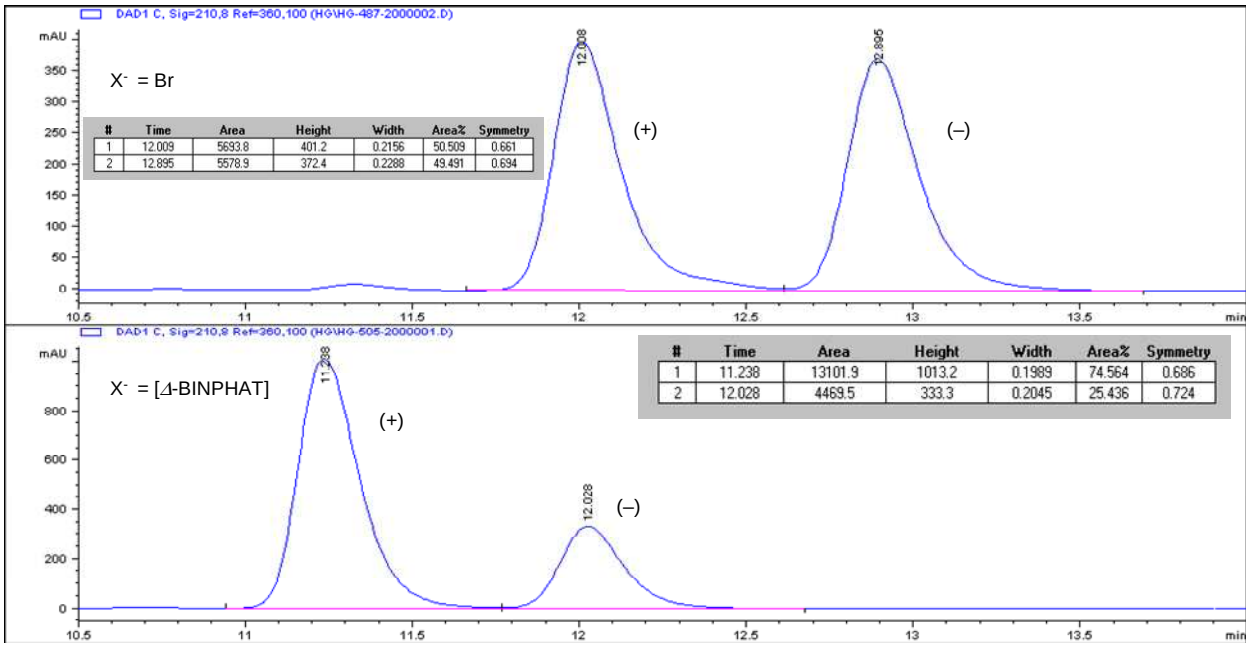

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 17.169 | 4182.3 | 153.2 | 0.4145 | 48.912 | 0.618 |
| 2 | 19.063 | 4368.4 | 38.1 | 1.5594 | 51.088 | 0.356 |

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 15.527 | 6331.5 | 274.1 | 0.3535 | 60.151 | 0.64 |
| 2 | 16.976 | 4194.6 | 55.7 | 1.1212 | 39.849 | 0.414 |

**Determined by CSP-HPLC (Chiralpak IB); *n*-Hexane / *i*-PrOH / ethanolamine 98 : 02 : 0.1%; 1.0 mL.min$^{-1}$; 23 °C).**

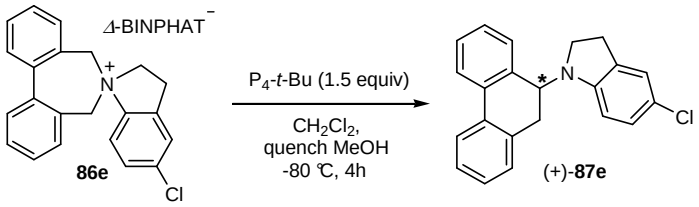
Determination of the enantiomeric excess of (+)-**87d**:

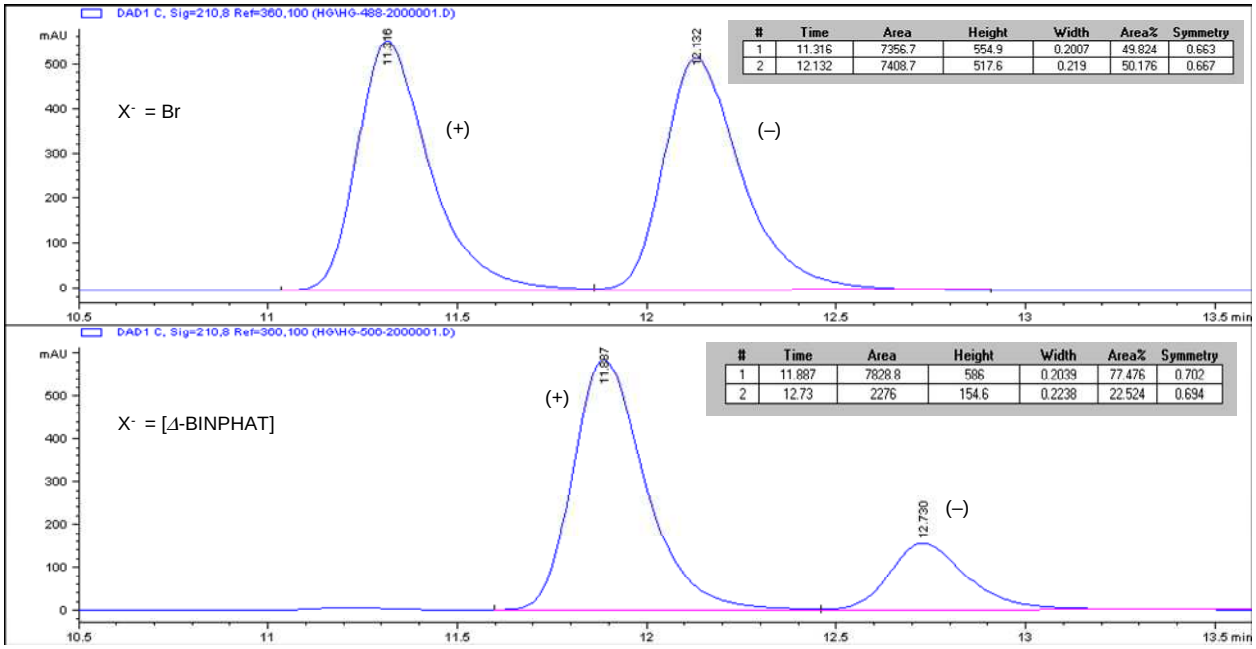



**Determined by CSP-HPLC (Chiralpak IB); *n*-Hexane / *i*-PrOH / ethanolamine 95 : 05 : 0.1%; 0.5 mL.min$^{-1}$; 23 °C).**

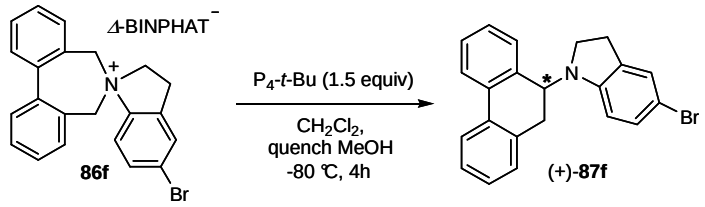
Determination of the enantiomeric excess of (+)-**87e**:

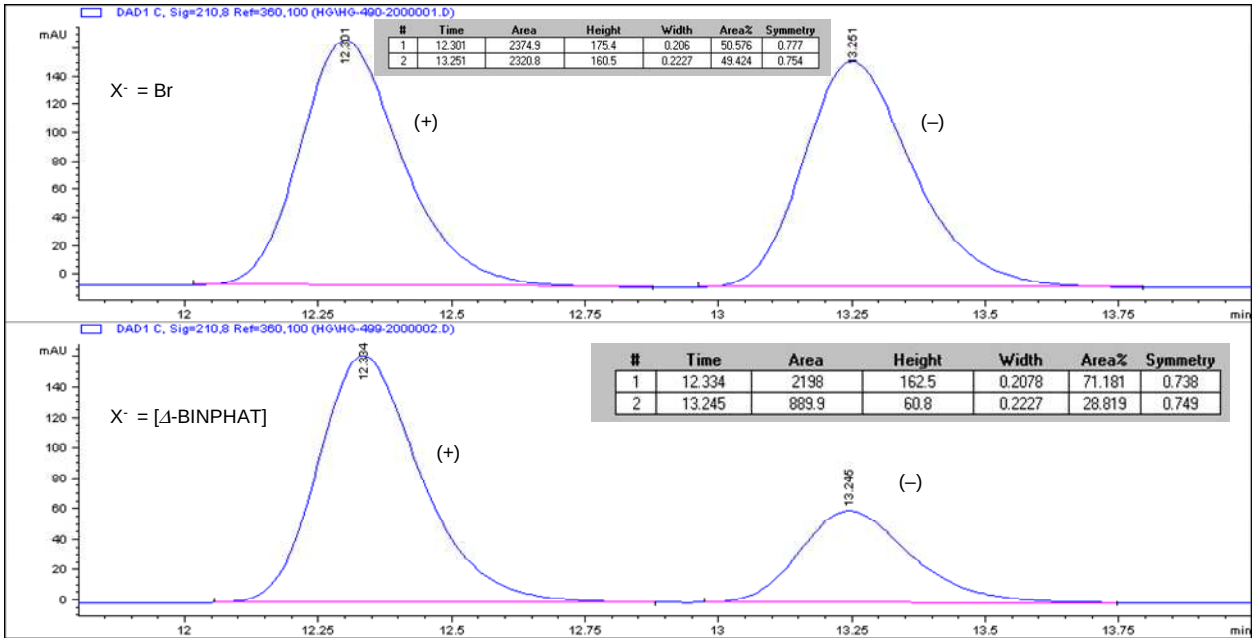



**Determined by CSP-HPLC (Chiralpak IB); *n*-Hexane / *i*-PrOH / ethanolamine 95 : 05 : 0.1%; 0.5 mL.min$^{-1}$; 23 °C).**

Determination of the enantiomeric excess of (+)-**87f**:



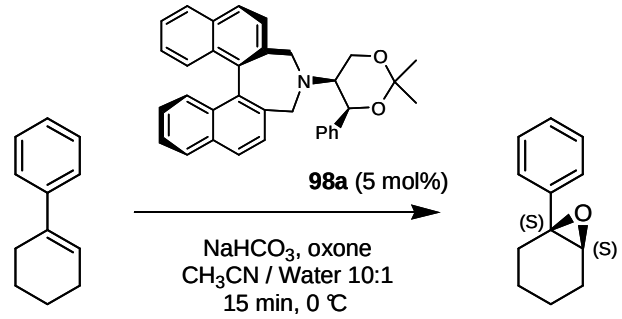

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 12.301 | 2374.9 | 175.4 | 0.206 | 50.576 | 0.777 |
| 2 | 13.251 | 2320.8 | 160.5 | 0.2227 | 49.424 | 0.754 |

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 12.334 | 2198 | 162.5 | 0.2078 | 71.181 | 0.738 |
| 2 | 13.245 | 889.9 | 60.8 | 0.2227 | 28.819 | 0.749 |

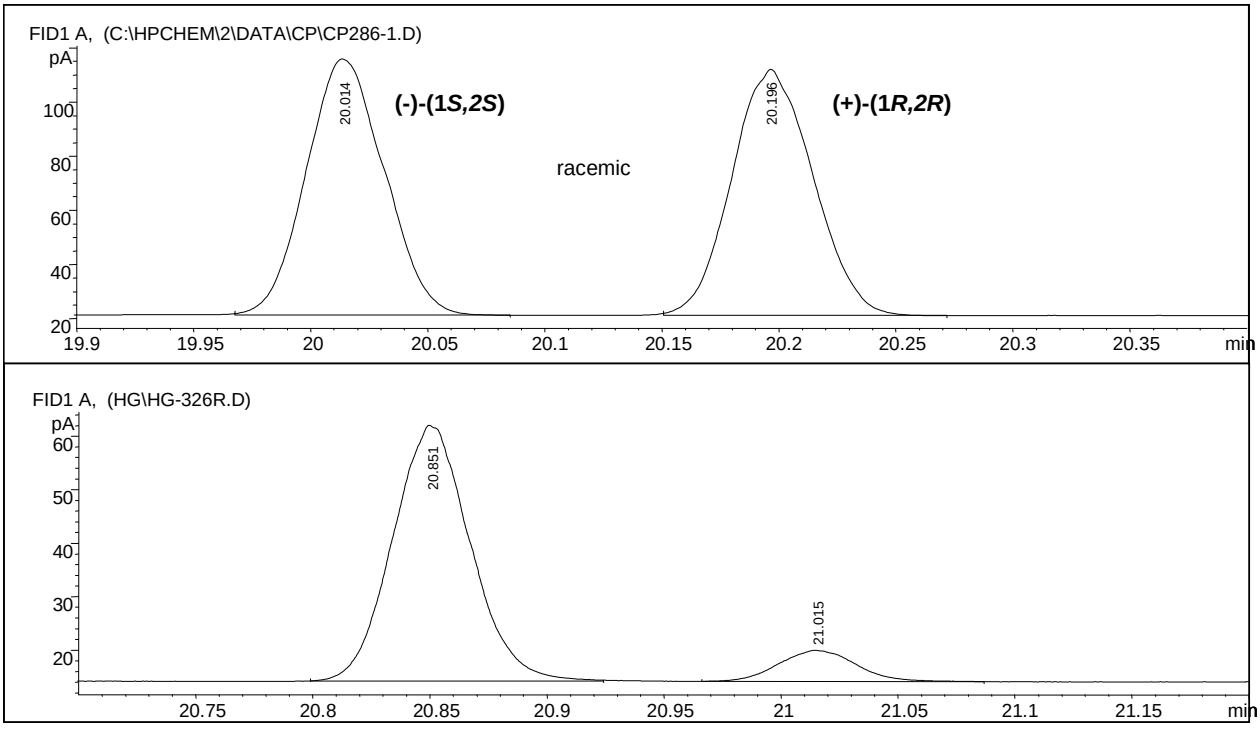
**Determined by CSP-HPLC (Chiralpak IB); *n*-Hexane / *i*-PrOH / ethanolamine 95 : 05 : 0.1%; 0.5 mL.min$^{-1}$; 23 °C).**

# CHAPTER IV − HOMOLOGOUS AMINE AND IMINIUM CATALYSTS IN ENANTIOSELECTIVE OLEFIN EPOXIDATION

Epoxidation of **104** with amine catalyst **98a**:



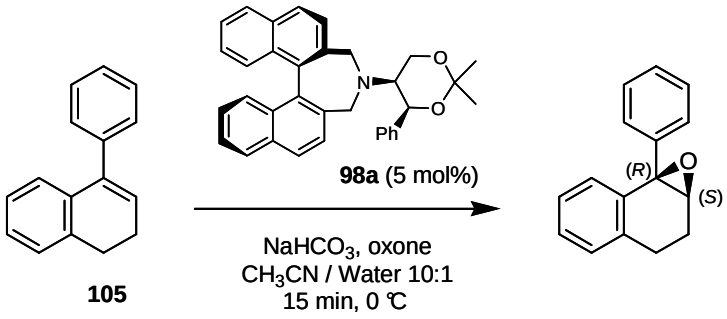

**104**



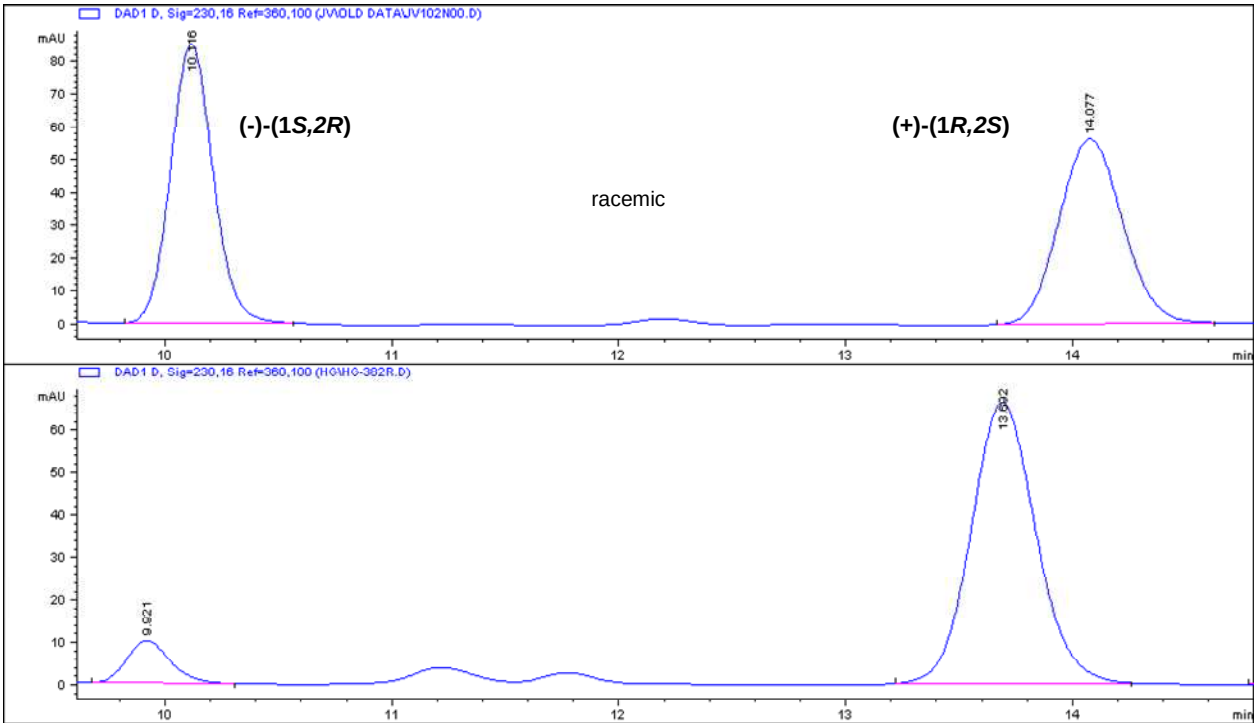

| # | Time | Area | Height | Width | Symmetry |
|---|---|---|---|---|---|
| 1 | 20.851 | 110.4 | 47.9 | 0.0365 | 0.941 |
| 2 | 21.015 | 13.4 | 5.8 | 0.0374 | 0.897 |

**Determined by Chiral Stationary Phase CSP-GC (Chiral Hydrodex *β*-3P; Tinj 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 **105** with amine catalyst **98a**:



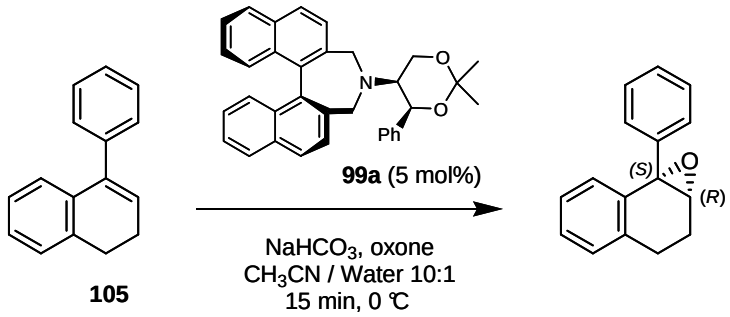

**105**



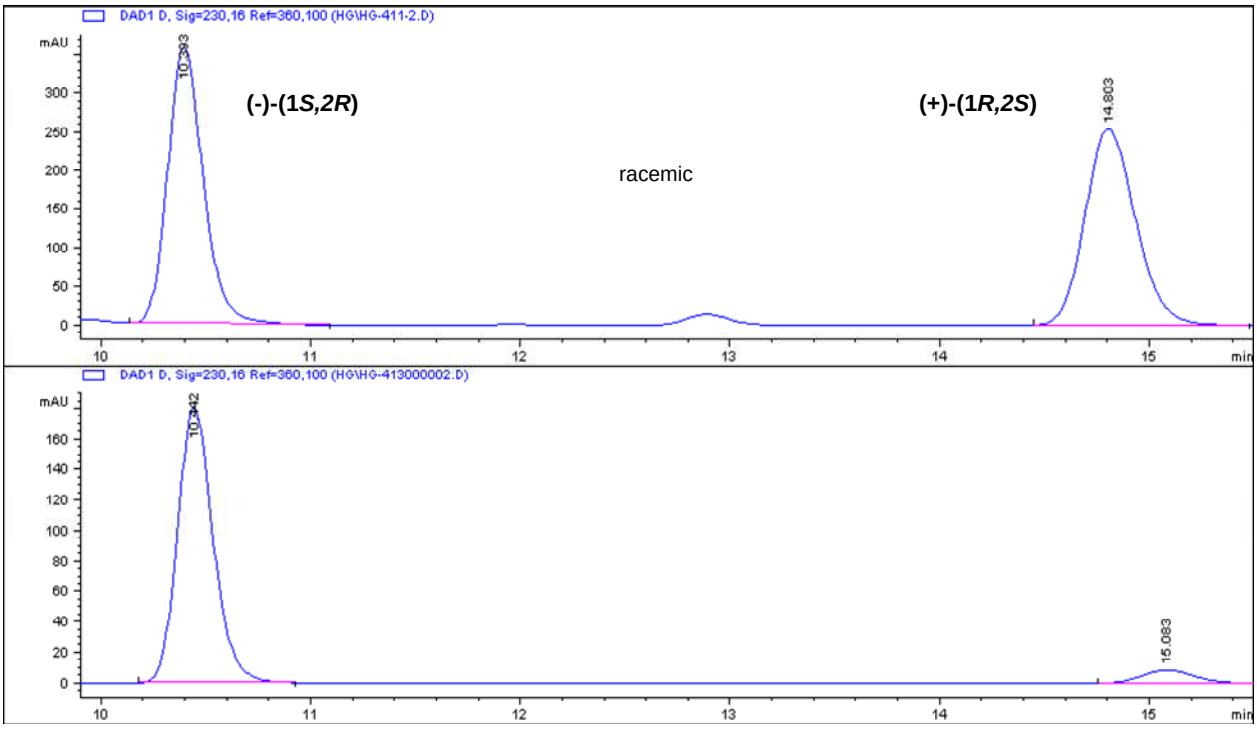

| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 9.921 | 131.6 | 9.9 | 0.2026 | 9.039 | 0.798 |
| 2 | 13.692 | 1323.8 | 66.4 | 0.3087 | 90.961 | 0.902 |

**Determined by CSP-HPLC (Chiralcel OD-H); *n*-Hexane / *i*-PrOH 95 : 05; 0.5 mL.min$^{-1}$; 23 °C.**

Epoxidation of **105** with amine catalyst **99a**:



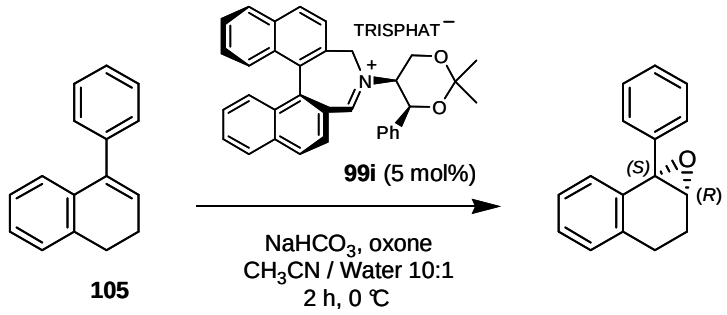

**105**

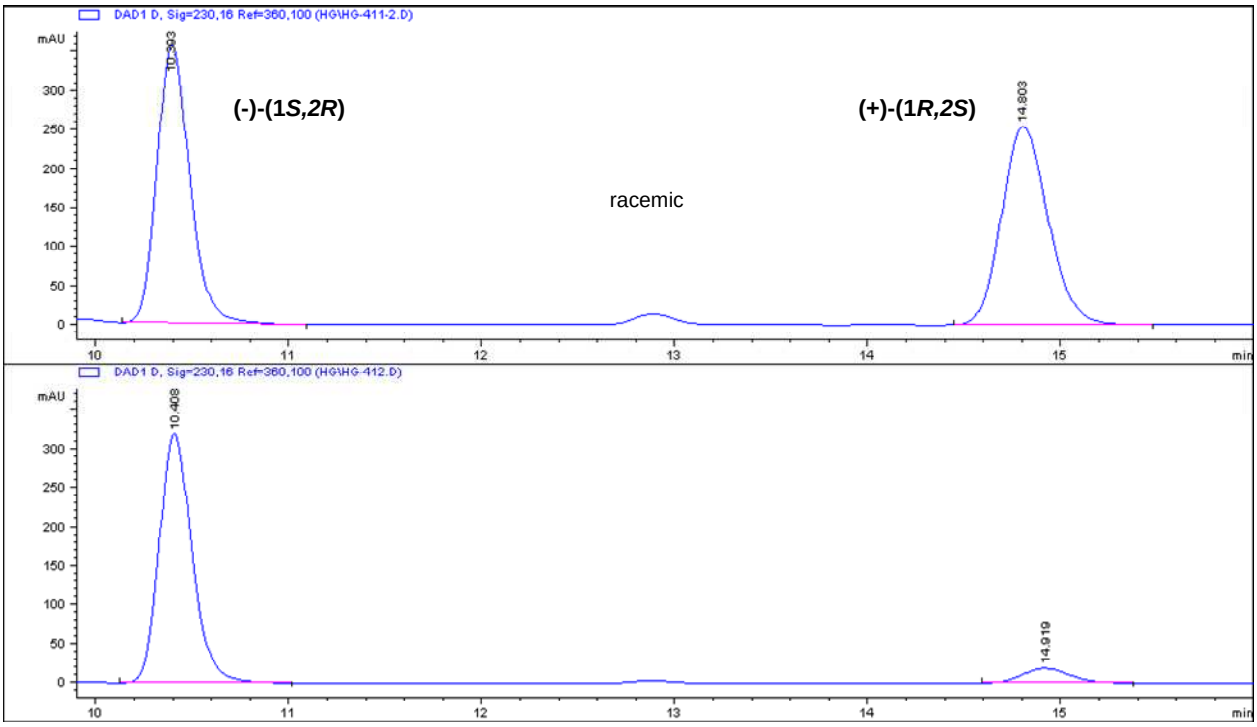



| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 10.442 | 2147.5 | 181.4 | 0.1821 | 93.446 | 0.81 |
| 2 | 15.083 | 150.6 | 8.6 | 0.2734 | 6.554 | 0.872 |

**Determined by CSP-HPLC (Chiralcel OD-H); *n*-Hexane / *i*-PrOH 95 : 05; 0.5 mL.min$^{-1}$; 23 °C.**

Epoxidation of **105** with iminium catalyst **99i**:

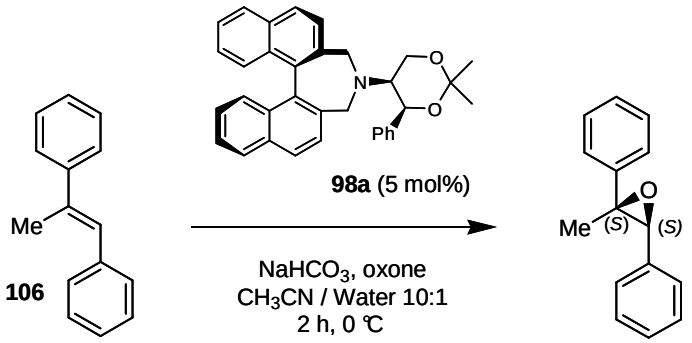


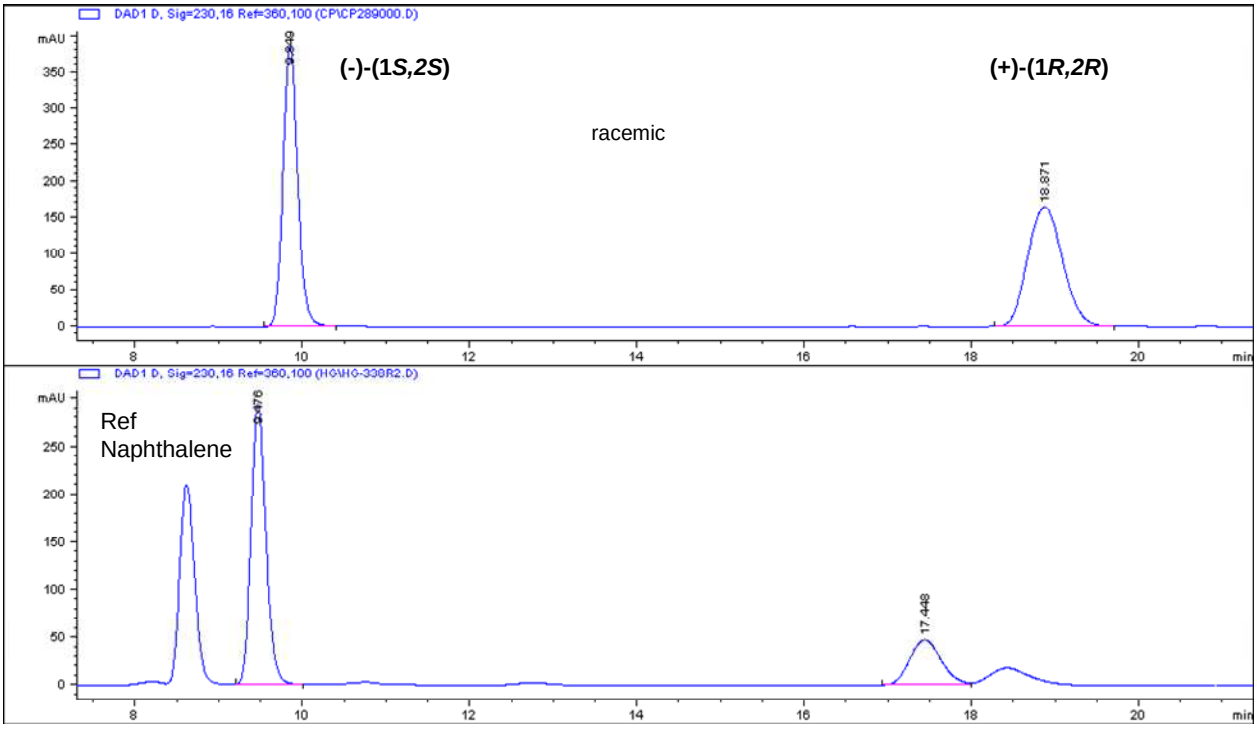




| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 10.408 | 3793.4 | 319.8 | 0.1824 | 91.994 | 0.803 |
| 2 | 14.919 | 330.2 | 19 | 0.2692 | 8.006 | 0.879 |

**Determined by CSP-HPLC (Chiralcel OD-H); *n*-Hexane / *i*-PrOH 95 : 05; 0.5 mL.min$^{-1}$; 23 °C.**

Epoxidation of **106** with amine catalyst **98a**:




| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 9.476 | 3637 | 294.3 | 0.1882 | 74.342 | 0.811 |
| 2 | 17.448 | 1255.2 | 47.4 | 0.415 | 25.658 | 0.858 |

**Determined by CSP-HPLC (Chiralcel OD-H); *n*-Hexane / *i*-PrOH 95:05; 0.5 mL.min$^{-1}$; 23 °C.**