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Enantioselective Olefin Epoxidation using Axially Chiral Biaryl Azepinium Salts as Catalysts. Rapid *in-situ* Screening and Origin of the Stereocontrol

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Dedicated to Prof. Andreas Pfaltz on the occasion of his 60th anniversary

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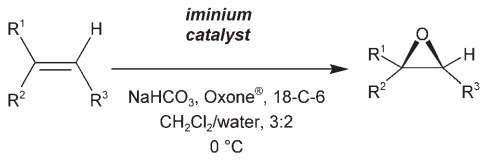
Abstract: To unravel the origin of the stereocontrol in epoxidation reactions of unfunctionalized alkenes by diastereomeric biaryl oxaziridinium salts, two series of novel iminium cations were prepared. These moieties combine (R_a)-dimethylbiphenyl or (R_a)-5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyl cores with chiral exocyclic appendages derived from commercially available (*S*)- or (*R*)-3,3-dimethylbutan-2-amine and (*S*)- or (*R*)-1-phenylpropan-1-amine. Under biphasic enantioselective olefin epoxidation conditions, *in-situ* generated bromide salts of these derivatives have displayed similar or better asymmetric efficiency than the classical binaphthyl derivatives. A structural analysis was performed in search of a correlation between the origin of the stereocontrol/level of enantioselectivity in the products, and dihedral angles around the biaryl twist of the catalysts.

Keywords: atropisomers; catalysis; chiral amines; chirality; epoxidation; *in-situ* formation

Introduction

Chiral non-racemic epoxides are useful precursors in synthetic chemistry, and frequent structures in natural products, often related to their biological activity.[1] Quite a few efficient catalytic methods exist for their preparation from olefins and many of them are based on transition metals such as the Katsuki–Sharpless or Katsuki–Jacobsen protocols.[2,3] In recent years, much effort has been devoted to the development of organocatalyzed epoxidation conditions that afford metal-free procedures; the catalysts being perhydrate, dioxirane, oxaziridine, or oxoammonium moieties as well as ammonium or oxaziridinium salts.[4]

Oxaziridinium ions are attractive alternatives to the commonly used dioxiranes.[5] These organic salts are effective oxygen transfer reagents towards nucleophilic substrates[6] and electron-rich unfunctionalized olefins in particular. Moreover, the propensity of iminium ions to react with Oxone® triple salt to generate the oxaziridinium species renders the development of catalytic processes possible [Eq. (1)].[7] Quite a few successful enantioselective variants of the reaction



(1)

have been reported,[8] many of them using biarylazepinium salts as catalysts. Typical structures are biphenyl **1**,[9] doubly-bridged biphenyl (DBB) **2**,[10] and binaphthyl **3** iminium salts,[9c,e,f,11] which are detailed in Figure 1. Further to the stereogenic biaryl element, most of these chiral salts bear an exocyclic chiral appendage noted R* on the diagram.

Interestingly, in compounds **1** and **2**, the stereocontrol over the reaction is provided by this exocyclic chiral appendage. It is particularly true for the derivatives made from enantiopure L-acetonamine[9a,b] and 3,3-dimethylbutan-2-amine (*S* or *R* enantiomer)[9c] which are the best chiral auxiliaries for this type of catalytic moieties. If this is not surprising for the *tropos* derivatives of type **1**,[12] it is more astonishing for the *atropos* derivatives of type **2** that are configu-

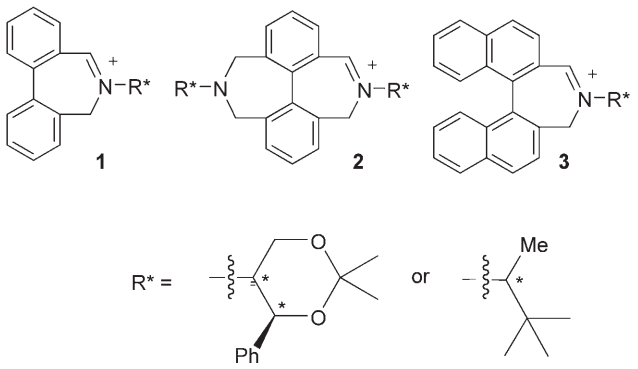


Figure 1. Biphenyl **1**, doubly-bridged biphenyl (DBB) **2**, binaphthyl **3** iminium catalysts and typical chiral exocyclic appendages R* derived from L-acetonamine or 3,3-dimethylbutan-2-amine.

rationally stable at room temperature and under the reaction conditions.[10,13]

For compounds **3**, the origin of the stereocontrol element is exactly the opposite. In this case, the *atropos* binaphthyl core has a overwhelming stereochemical influence. The enantioselectivity of the epoxidation reaction is solely controlled by the configuration of the biaryl moiety and not by the exocyclic appendage.[11b–d] Essentially identical *ee* values are obtained in reactions of prochiral olefins in the presence of diastereomeric iminium salts that differ only by the configuration of the exocyclic appendage, and this in favor of epoxides of identical configurations. In most of these above-mentioned studies with compounds of type **1**, **2** and **3**, the counterion associated with the iminium ions have been either tetraphenylborate or TRISPHAT anions which act *a priori* as liphophilic genenions.[14]

For the stereocontrol of the epoxidation reaction, there was thus a clear dichotomy between the catalytic behavior of biphenyl compounds **1** and **2** on one side and binaphthyl derivatives **3** on the other. To the best of our knowledge, no explanation has been so far given to account for this difference. Minimally, one can consider that the chemical nature of the biaryls at play – biphenyl *vs.* binaphthyl – is the determining factor in the sense of the enantioselective induction. However, a declaration of the presence of two extra aromatic groups is falling short of any rational explanation. For us, it was clear that other parameters could well influence the reaction – and the dihedral angle θ around the central bond joining the aromatic rings in particular (Figure 2). It is indeed known that such a parameter can be crucial on the level of asymmetric induction obtained in enantioselective catalytic reactions.[15] In the present case, we wondered if a low dihedral angle value at the junction of the rings (θ ~ 40–45°) would entice a stronger (dominant) influence of chiral exocyclic appendage R* whereas higher values (θ ~ 53° and higher) would lead to the predominance of the biaryl element for the stereocontrol of the epoxidation reaction; this predominance of the axial over the centered chirality resulting also possibly in higher enantiomeric excesses values for the epoxides.

To test this hypothesis, it was decided to synthesize two configurationally stable biphenyl systems for which the θ dihedral angle would be similar to that of the binaphthyl derivatives. Ideally, the two systems would have (slightly) lower and higher θ values than compounds of type **3**, respectively. In the first instance, a lower level of enantioselectivity ought to be reached with a possible influence of the chiral exocyclic appendage whereas, in the second case, higher levels of stereoinduction should be observed with the biaryl system acting solely for the stereocontrol. Alternatively, this analysis performed with θ values could be performed with the "external" dihedral angle Φ. Herein, in a search for such derivatives, we report the reactivity of 6,6′-dimethylbiphenylazepinium and 5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyl azepinium cations of type **4** and **5** (Figure 3). Structural information on these derivatives is provided by the X-ray analysis of amines or ammonium precursors. Two series of diastereomeric derivatives were prepared from (*S*)- or (*R*)-3,3-dimethylbutan-2-amine and (*S*)- or (*R*)-1-phenylpropan-1-amine, and the results of the epoxidation studies are reported in the following paragraphs. In order to expedite the screening process, a protocol of *in-situ* generation of iminium bromide catalysts was used – some of the results using

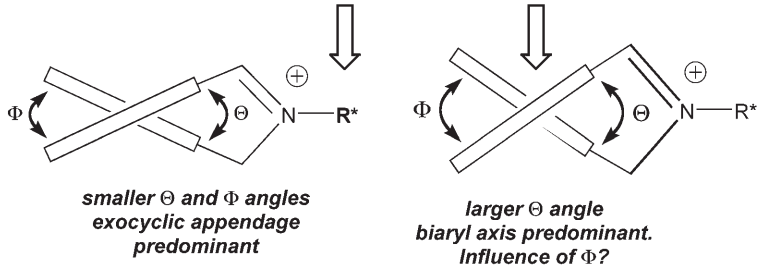


Figure 2. Stereochemical influence as a function of θ and Φ dihedral angles (measured inside and outside the N-containing seven membered-ring respectively).

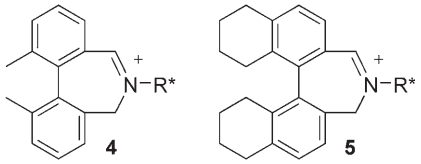


Figure 3.

this protocol being compared with that of fully isolated iminium salts of the tetraphenylborate family.

Results and Discussion

Catalyst Selection and Preparation

As just mentioned, our initial goal was to design, develop and study two novel biphenyl azepinium catalysts for which the θ angle would be similar to that of binaphthyl derivatives with, ideally, (slightly) lower and higher dihedral angle values, respectively. However and unfortunately, at the start of the study, little structural information was found in the literature on biaryl azepines or azepinium salts to help us in the selection of the catalyst skeletons. In fact, an extensive search of the Cambridge Structural Database revealed only 35 structures of seven-membered ring biaryl azepine derivatives with very little structural overlap between the compounds. A precise determination of the nature of the θ angle in this family of compounds was therefore impossible to achieve from literature precedents. Nevertheless, an analysis of the data revealed that some of these compounds could be grouped into sub-families from which some trends could be inferred. These moieties (**6**–**14**) are detailed in Figure 4; the CSD refcodes corresponding to the structures are detailed in the caption text and the dihedral angle(s) θ (and Φ) mentioned on the drawing.

Clearly, two groups could be discerned based on θ values. On the one hand, biphenyl and doubly-bridged biphenyl moieties (**6** to **10**) presented rather low dihedral angle values ($\theta \leq 45.9°$) whereas, on the other hand, quite higher values ($\theta > 52°$) were observed for dimethylbiphenyl and binaphthyl derivatives. Unfortunately, very little difference was noticed between the θ values of latter two classes of compounds (**11** to **14**). This observation was rather disappointing. However, a closer investigation of the second sub-family revealed rather large differences between the θ and Φ dihedral angles measured inside and outside the N-containing seven membered-ring, respectively (see Figure 4). Considering that (i) the Φ (rather than θ) ought to be more sensitive to the nature of the substituents positioned at the 6,6′-position of the biphenyl and (ii) Φ values mentioned on Figure 4 might not be representative of the derivatives under study, we

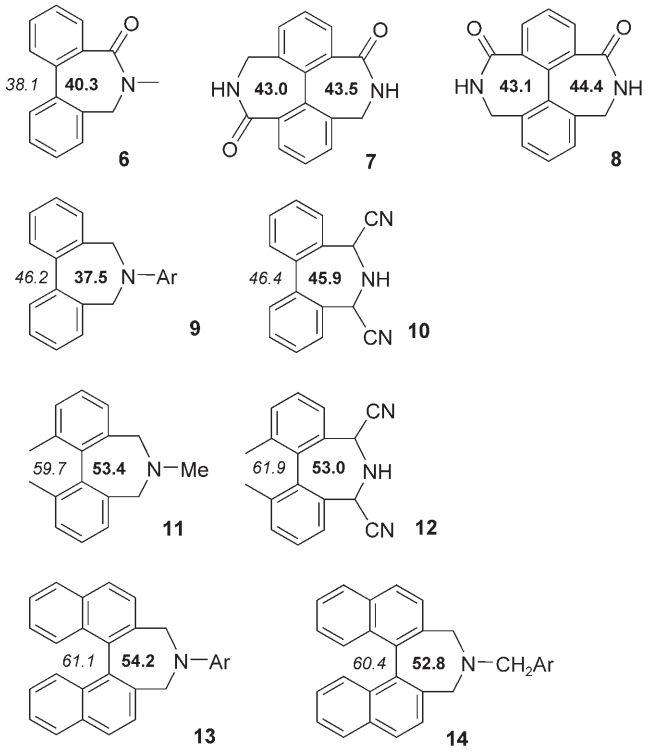
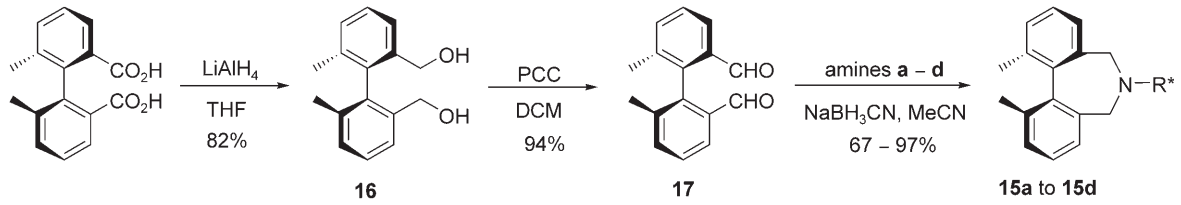


Figure 4. Biaryl azepine derivatives and dihedral angles θ (bold) and Φ (italic): **6** (HMBAZO), **7** (GEMQOE), **8** (GEMQUK), **9** (GAVKET), **10** (WIPJAG), **11** (NUBGOG), **12** (WIPJIO), **13** (XEBNIB), **14** (HOVGII).

decided to investigate dimethylbiphenyl azepinium cations of type **4** as catalysts and verify if a reactivity difference could be found with **3** in the context of the epoxidation chemistry. Furthermore, taking into account the possible importance of Φ, we considered that the second system of study ought to be a 5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyl azepinium cation of type **5** (Figure 3); strong repulsion between the hydrogenated rings leading possibly to higher Φ values than systems **3** and **4** and hence a better selectivity in the epoxidation reactions.

The synthesis of the 6,6′-dimethylbiphenylazepine amines (**15a** to **15d**), precursors to catalysts of type **4**, was realized in three steps starting from highly enantioenriched (−)-(*M*)-6,6′-dimethylbiphenyl-2,2′-dicarboxylic acid (96.7% *ee*, Scheme 1).[16] Reduction with lithium aluminum hydride gave the corresponding diol (**16**, 82%)[17] which was oxidized to the desired dialdehyde (**17**) with excellent yield (94%) following an already reported protocol.[18]

Reductive amination in the presence of enantiopure amines **a** to **d** (Figure 5) using $NaBH_3CN$ in MeCN provided the desired compounds **15a** to **15d** in decent to good yields (67–97%). Diastereomeric **15a/15b** and **15c/15d** were obtained as single enantiomers after purification; no trace of stereomeric entities being evidenced in the ^1H NMR analysis.



Scheme 1. Synthesis of azepines **15a** to **15d**.

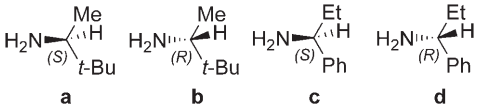
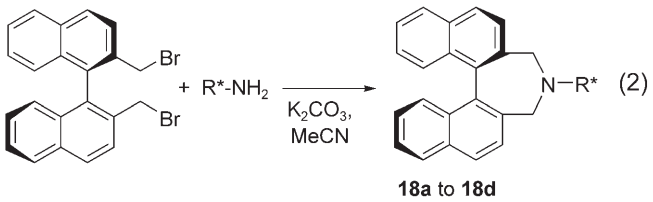


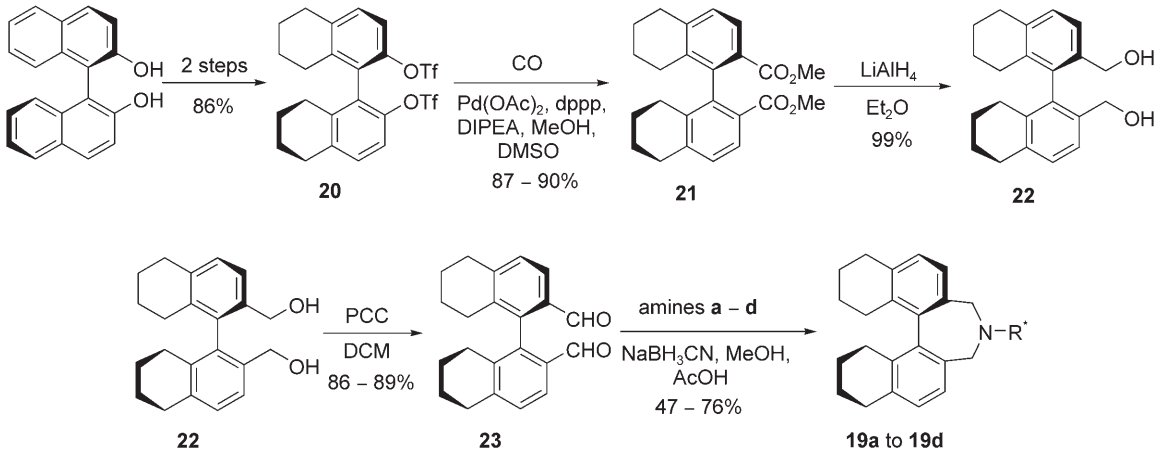
Figure 5. Selected amines for the formation of diastereomeric biphenyl and binaphthyl azepines.

The synthesis of the binaphthyl azepines **18a** and **18b** was previously reported using as starting material (R_a)-2,2′-bis(bromomethyl)-1,1′-binaphthyl.[9e] Two novel binaphthyl azepines **18c** and **18d** were prepared following a procedure similar to the one described above and this in 76% and 72% yield, respectively [Eq. (2)].



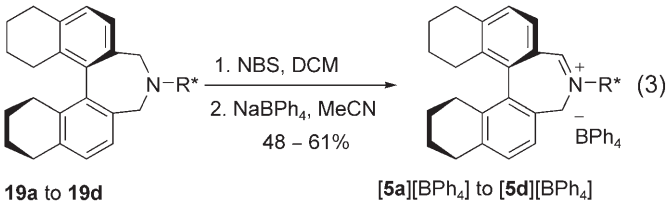
The four novel 5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyl azepines **19a**, **19b**, **19c** and **19d** were prepared in six steps starting from commercially available enantiopure (R_a)-BINOL (Scheme 2).[19]

Catalytic hydrogenation of (R_a)-BINOL (Pd/C, EtOH) and subsequent recrystallization from *n*-heptane provided (R_a)-2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl in more than 99% enantiomeric purity.[20] This compound was then treated with triflic anhydride (CH_2Cl_2, pyridine, 0 °C) to form the (R_a)-2,2′-ditrifluoromethanesulfonyloxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (**20**) in 86% isolated yield. Palladium-mediated carbonylation of the bistriflate [$Pd(OAc)_2$, dppp, $(i\text{-}Pr)_2NEt$, MeOH, DMSO] provided the known 2,2′-bis(carbomethoxy)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (**21**) in good yield (87–90%).[21] The reduction with lithium aluminum hydride in diethyl ether gave the desired bisdiol (**22**) in almost quantitative yield. The subsequent oxidation (PCC, CH_2Cl_2) proceeded smoothly and afforded pure bisaldehyde (**23**) in 86–89% yield which was the starting material for the synthesis of all four octahydrobinaphthyl azepines **19a**, **19b**, **19c** and **19d**. The derivatives were subjected to the reductive amination procedure used for the synthesis of azepines **15a** to **15d** [amines **a** to **d** (2.0 equiv.), **23** (1.0 equiv.), $NaBH_3CN$ (4.0 equiv.), MeCN]. Surprisingly, this protocol was not successful. After 24 h, only a moderate conversion of starting aldehyde was observed. Nevertheless, using a slightly modified protocol [amines **a** to **d** (1.1 equiv.), **23** (1.0 equiv.), $NaBH_3CN$ (2.0 equiv.), MeOH, catalytical amount of glacial AcOH], azepines **19a** to **19d** were provided in



Scheme 2. Synthesis of azepines **19a** to **19d.**

moderate and decent yields (47–76%). With these (R_a)-H_8-binaphthyl azepines in hand, catalysts [**5a**][BPh_4] to [**5d**][BPh_4] were prepared in two steps following the general and reproducible procedure detailed below [Eq. (3)].



(3)

19a to **19d** [**5a**][BPh_4] to [**5d**][BPh_4]

Treatment of tertiary amines **19a** to **19d** with NBS in dichloromethane provided a rapid and clean formation of the desired iminium salts [**5a**][Br] to [**5d**][Br] in 5 min. Subsequent anion exchange metathesis in acetonitrile with sodium tetraphenylborate and trituration/recrystallization in EtOH gave catalysts [**5a**][BPh_4] to [**5d**][BPh_4] in appropriate yields (48–61%) for two steps.

Finally, for four azepine derivatives (or their hydrogen chloride salts), monocrystals were obtained and their structural X-ray analysis was performed.[22] The ORTEP views of **15c**, **18c**·HCl, **19c**·HCl, and **19d** are reported in Figure 6 along with θ and Φ values.

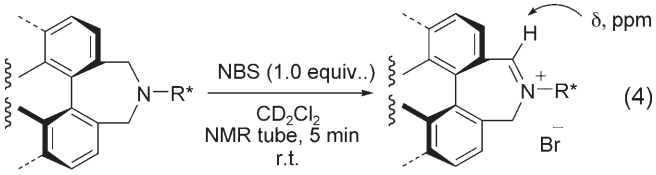
Interestingly, assuming little structural perturbation from the protonation and quite opposite to the Cambridge Structural Database situation, rather strong differences were observed for θ and Φ in the three biaryl series. As it could be expected, the 6,6′-dimethylbiphenyl azepine **15c** presented the lowest dihedral angle values. Comparison with **18c**·HCl to **19c**·HCl indicated that this θ angle changes only moderately, whereas a strong variation of the Φ angle could be noticed with values increasing from 57.5° to 61.0° and 67.0°, respectively. Diastereomeric structures **19c**·HCl and **19d** are also remarkably similar. With that information in hands, the catalysts behavior was studied.

Iminium Salt Formation

As already mentioned, the enantioselective epoxidation of unfunctionalized alkenes is possible using iminium species as organocatalysts – these compounds being usually prepared prior to the epoxidation step and, for instance, by the oxidation of tertiary amine precursors. Oxidation of tertiary amines to iminium salts is indeed feasible and literature precedents have indicated that a mixture of I_2 and KOAc is a useful oxidative combination for that transformation.[9b,23] However, this protocol leads to many by-products and is not appropriate for compounds containing several amine functional groups, and DBB azepines in particular. To overcome this problem, milder reaction conditions were developed [NBS, AIBN (10 mol%), CCl_4, 25 °C].[24] This protocol is indeed more selective than I_2/KOAc. However, the oxidation occurs quite slowly. In our group, it was found that the process can be greatly accelerated (20 min *vs.* hours) by performing the reaction without AIBN and using chloroform or dichloromethane as solvent instead of carbon tetrachloride.[9e,11c] The bromide counterion of the iminium salts was then exchanged to more lipophilic anions of TRISPHAT type in a second series of experiments.

However, recently, we wondered about the necessity of isolating the iminium salts altogether and whether the bromide precursors generated *in-situ* could not be used directly as catalysts. It was thus decided to test this hypothesis with all azepines **15a** to **15d**, **18a** to **18d** and **19a** to **19d** – and then compare the reactivity of one of the systems with that of a classical, isolated, tetraphenylborate salt.

To check the validity of the amine to iminium ion transformation, NMR tube experiments were performed in conditions similar to what would be the reaction conditions [NBS (1.0 equiv.), CD_2Cl_2, see next section]. ^{1}H NMR spectra of the crude reaction mixtures indicated the clean conversion of the azepine moieties to the corresponding iminium bromide salts of the amines [Eq. (4), Table 1]. The formation of the



(4)

unsaturated species [**3a**][Br] to [**3d**][Br], [**4a**][Br] to [**4d**][Br], [**5a**][Br] to [**5d**][Br] was particularly easily to monitor in the 10 to 12 ppm region as singlet signals corresponding to the C*H*=N$^+$ proton appear (e.g., Figure 7). Globally, higher frequencies were observed

Table 1. *In-situ* formation of iminium salts.[a] Chemical shifts of the C*H*=N$^+$ proton (^{1}H NMR).

Iminium salt	δ, ppm	Iminium salt	δ, ppm	Iminium salt	δ, ppm
[**4a**][Br]	10.98	[**3a**][Br]	11.21	[**5a**][Br]	10.79
[**4b**][Br]	10.42	[**3b**][Br]	10.57	[**5b**][Br]	10.25
[**4c**][Br]	10.87	[**3c**][Br]	11.47	[**5c**][Br]	11.00
[**4d**][Br]	11.31	[**3d**][Br]	11.54	[**5d**][Br]	10.99

[a] *Conditions:* 0.2 mmol of azepine, 0.2 mmol of NBS in 0.5 mL of CD_2Cl_2, 5 min, 400 MHz. Chemical shifts are given relative to Me_4Si with the solvent resonance used as the internal standard (CD_2Cl_2 $\delta = 5.32$ ppm).

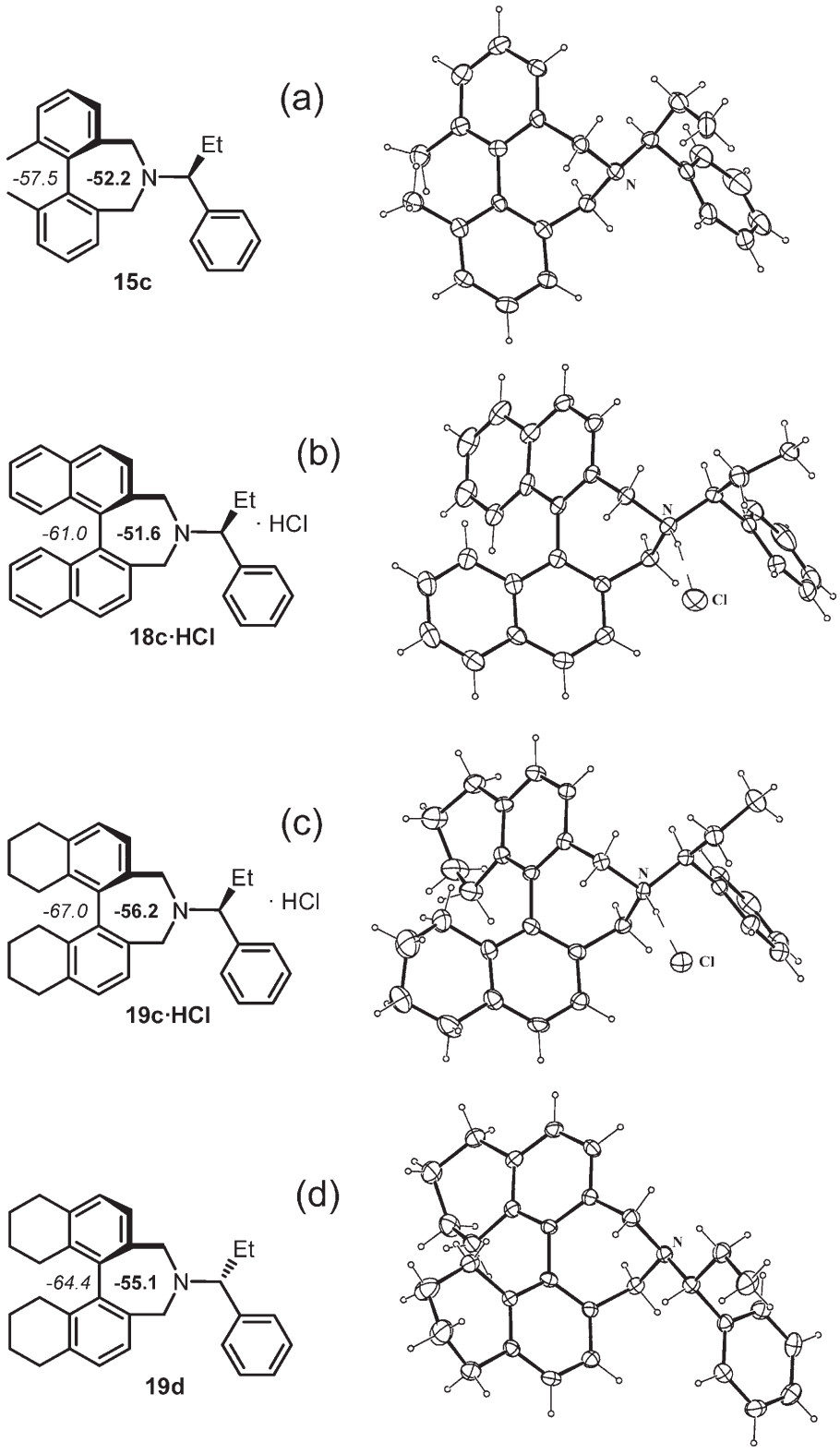


Figure 6. Chemical structures and ORTEP views of (a) **15c**, (b) salt **18c**·HCl, (c) salt **19c**·HCl and (d) **19d**. Ellipsoids are presented at the 50% probability level. Dihedral angles θ (bold) and Φ (italic) are indicated with a mean value of uncertainty of 0.5°.

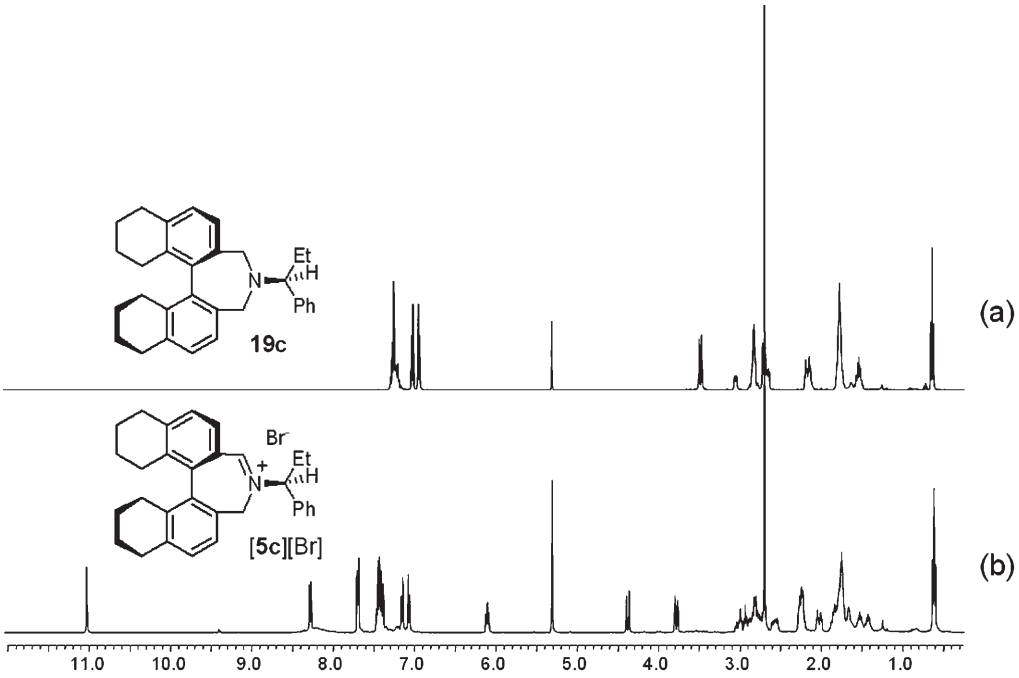


Figure 7. ^{1}H NMR spectra (CD_2Cl_2, 400 MHz) of (a) **19c** and (b) *in-situ* generated [**5c**][Br].

for the chemical shifts of the iminium protons of the derivatives **3** and the lowest values for the derivatives of **5**; derivatives of amines **b** and **d** presenting the lowest and highest frequencies in each series respectively (Table 1).

Enantioselective Epoxidation Reactions

Having established the feasibility of the *in-situ* oxidation of the various biarylazepines to the corresponding iminium salts, we decided to use these species directly for our study on the influence the dihedral angle of the biaryl moieties on the enantioselectivity of the epoxidation reaction.

One set of epoxidation conditions (5 mol% catalyst, Oxone®/CH_2Cl_2/$NaHCO_3$/18-crown-6/H_2O) and three different prochiral trisubstituted unfunctionalized alkenes were selected for the study (Figure 8) – these alkenes being chosen for their proven record of performing well in iminium-catalyzed epoxidation reactions.[7–11] The biphasic CH_2Cl_2/H_2O protocol, which has been detailed previously,[9b,c] is easy to run and usually allows the ready isolation of the epoxides after the oxidation reaction. To perform the reaction with the *in-situ* bromide catalysts derived from **15a** to **15d**, **18a** to **18d** and from **19a** to **19d**, the only modification to the protocol was the separated treatment of the azepines with NBS (CH_2Cl_2, 5 min) and the addition of the resulting solution to a mixture of the other reagents. The results for the various experiments are reported in Table 2, Table 3, Table 4 and Table 5. Only the enantiomeric excesses are reported as the purpose of this study was essentially the evaluation of the sense of induction of the enantioselective transformation and the global asymmetric efficiency of the catalysts. Information about the reactivity will be

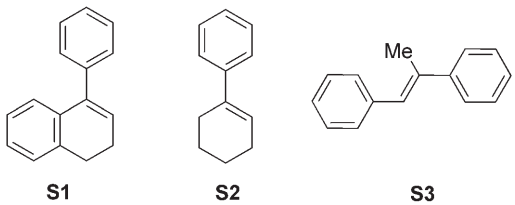


Figure 8. Prochiral trisubstituted alkenes.

Table 2. Epoxidation of olefins **S1**, **S2**, **S3** using catalysts [**4a**][Br], [**3a**][Br], [**5a**][Br]. Enantiomeric excesses (%).[25]

Alkene	[**4a**][Br]	[**3a**][Br]	[**5a**][Br]	Configuration
S1	75	80	87	(+)-(1*R*,2*S*)
S2	78	67	82	(−)-(1*S*,2*S*)
S3	60	46	63	(−)-(1*S*,2*S*)

Table 3. Epoxidation of olefins **S1**, **S2**, **S3** using catalysts [**4b**][Br], [**3b**][Br], [**5b**][Br]. Enantiomeric excesses (%).[25]

Alkene	[**4b**][Br]	[**3b**][Br]	[**5b**][Br]	Configuration
S1	57	85	92	(+)-(1*R*,2*S*)
S2	67	75	83	(−)-(1*S*,2*S*)
S3	44	54	67	(−)-(1*S*,2*S*)

Table 4. Epoxidation of olefins **S1**, **S2**, **S3** using catalysts [**4c**][Br], [**3c**][Br], [**5c**][Br]. Enantiomeric excesses (%).[25]

Alkene	[**4c**][Br]	[**3c**][Br]	[**5c**][Br]	Configuration
S1	68	76	82–88[a]	(+)-(1*R*,2*S*)
S2	63	59	72	(−)-(1*S*,2*S*)
S3	58	42	61	(−)-(1*S*,2*S*)

[a] In the particular case of the epoxidation of 1-phenyl-3,4-dihydronaphthalene with salt [**5c**][Br], and contrary to the other reactions, a large deviation in the enantiomeric excess values was observed while performing multiple runs of the reactions. Rather than indicate an average, we have decided to put the range of the *ee* values observed.

Table 5. Epoxidation of olefins **S1**, **S2**, **S3** using catalysts [**4d**][Br], [**3d**][Br], [**5d**][Br]. Enantiomeric excesses (%).[25]

Alkene	[**4d**][Br]	[**3d**][Br]	[**5d**][Br]	Configuration
S1	85	91	88	(+)-(1*R*,2*S*)
S2	77	69	69	(−)-(1*S*,2*S*)
S3	53	34	57	(−)-(1*S*,2*S*)

given when necessary in the course of the study. Importantly, all iminium salts from [**3a**][Br] to [**3d**][Br], [**4a**][Br] to [**4d**][Br], [**5a**][Br] to [**5d**][Br] behaved as catalysts under this set of conditions. As catalysts of type **4** have in general been less effective than that of type **3** and **5**, data in the tables have indicated with the catalysts positioned in the following order **4**→**3**→**5**, from left to right.

If one compares the selectivity of the diastereomeric catalysts derived from 3,3-dimethylbutan-2-amine together – that is [**4a**][Br] with [**4b**][Br], [**3a**][Br] with [**3b**][Br] and [**5a**][Br] with [**5b**][Br], some definite trends can be observed. First, the levels of stereoinduction in the (R_a,*S*) and (R_a,*R*) series are different. For catalysts [**4a**][Br] and [**4b**][Br] much better *ee* values were observed with (R_a,*S*)-configurated catalyst [**4a**][Br] (Table 2, Table 3). For diastereomeric series [**3a**][Br] and [**3b**][Br], [**5a**][Br] and [**5b**][Br], it is the opposite as better *ee* values were found with (R_a,*R*)-configurated catalysts. This indicates a sensitivity of the reaction to the global stereoisomeric environment of the catalysts. However, importantly, an identical sense of induction was obtained for the epoxides in all experiments. These results indicate that the two new types of biphenyl frameworks are, like in the binaphthyl series, more influential as chiral auxiliaries than the exocyclic appendage derived from 3,3-dimethylbutan-2-amine. In fact, the configuration of the epoxides remains the same while using catalysts with opposite absolute configuration at the chiral exocyclic appendage.

That said, divergences in the outcome can still be found for the diastereomeric catalysts and rather strong differences between the *ee* values of reactions performed with [**4a**][Br] and [**4b**][Br] were observed (e.g., for alkene **S3** the catalyst [**4a**][Br] provided epoxide formation with 60% *ee*, then catalyst [**4b**][Br] with 44% *ee*). This difference is attenuated in the reactions of catalysts [**3a**][Br] and [**3b**][Br] (for substrate **S3** the catalysts [**3a**][Br] and [**3b**][Br] gave epoxide with 46% *ee* and 54% *ee*, respectively) and becomes minimal with [**5a**][Br] and [**5b**][Br] (alkene **S3**, 63% *ee* observed with catalyst [**5a**][Br] and 67% *ee* with catalyst [**5b**][Br]). These results then probably indicate that the H_8-binaphthyl skeleton has a stronger stereochemical influence than the binaphthyl and 6,6′-dimethylbiphenyl structures, respectively.

Now if one compares together the selectivity of the other diastereomeric catalysts derived from 1-phenylpropan-1-amine, that is [**4c**][Br] with [**4d**][Br], [**3c**][Br] with [**3d**][Br] and [**5c**][Br] with [**5d**][Br], the same kind of observations can be made. Again the levels of stereoinduction in the (R_a,*S*) and (R_a,*R*) series can be different, but in this case the (R_a,*R*)-configurated catalysts are most effective in terms of enantioselectivity than the (R_a,*S*)-series. The configuration of the epoxides is again controlled by the axial stereogenic element of the iminium salts and it does not change with an inversion of the configuration of the exocyclic appendage.

From these studies, one can conclude that larger twist angles around the biaryl axes lead indeed to the predominance of the axially chiral stereogenic element over the exocyclic centred one; the chemistry of iminiums **4** and **5** confirming the observations made previously for the binaphthyl series **3**. Furthermore, if one assumes that the crystallographic trends observed for the amine and ammoniums species detailed above, hold for iminium salts as well, then one can draw a correlation between the enantioselectivity of the process and the dihedral angle Φ of the biaryl systems. It can be clearly seen on the results of the epoxidation reactions of [**4b**][Br], [**3b**][Br] and [**5b**][Br]. Moving from the *a priori* smallest dihedral angle to the biggest, from [**4b**][Br] to [**5b**][Br], one can see an increase of the enantioselectivity for all substrates. For the other catalysts, this correlation can also be found for alkene **S1**. For olefins **S2** and **S3**, the situation is different as the two biphenyl series (**4** and **5**) are more selective than the binaphthyl one – the difference between the iminiums **4** and **5** remaining although modest. Globally, the best results in terms of enantioselectivity have been achieved with the catalysts derived from the H_8-binaphthyl skeleton.

However, although interesting, these results were obtained with a "new" untested protocol of epoxidation using *in-situ* generated bromide iminium salts. Care was thus taken to compare this outcome with

Table 6. Epoxidation of olefins **S1**, **S2**, **S3** using catalysts [**5a**][Br], [**5a**][BPh_4], [**5b**][Br], [**5b**][BPh_4]. Enantiomeric excesses (%).[25]

Alkene	[**5a**][Br]	[**5a**][BPh_4]	[**5b**][Br]	[**5b**][BPh_4]	Configuration
S1	87	87	92	91	(+)-(1*R*,2*S*)
S2	82	80	83	81	(−)-(1*S*,2*S*)
S3	63	67	67	72	(−)-(1*S*,2*S*)

Table 7. Enantioselective epoxidation of olefins **S1**, **S2**, **S3** using catalysts [**5c**][Br], [**5c**][BPh_4], [**5d**][Br], [**5d**][BPh_4]. Enantiomeric excesses (%).[25]

Alkene	[**5c**][Br]	[**5c**][BPh_4]	[**5d**][Br]	[**5d**][BPh_4]	Configuration
S1	82–88[a]	88	88	94	(+)-(1*R*,2*S*)
S2	72	67	69	68	(−)-(1*S*,2*S*)
S3	61	77	57	68	(−)-(1*S*,2*S*)

[a] In the particular case of the epoxidation of 1-phenyl-3,4-dihydronaphthalene with salt [**5c**][Br], and contrary to the other reactions, a large deviation in the enantiomeric excess values was observed while performing multiple runs of the reactions. Rather than indicate an average, we have decided to put the range of the *ee* values observed.

that of more classical isolated salts. We selected for the comparison study commercially available tetraphenylborate as lipophilic counterion. The synthesis of the four derived iminium salts, [**5a**][BPh_4] to [**5d**][BPh_4], was detailed earlier. The epoxidation reactions were performed under the same reaction conditions and the novel salts behaved unsurprisingly as catalysts. The results are given in Table 6 and Table 7.

For catalysts [**5a**][Br] and [**5a**][BPh_4], [**5b**][Br] and [**5b**][BPh_4], little difference in the enantioselectivity of the epoxidation reaction is observed (Table 6). For alkenes **S1** and **S2** the *ee* values are either identical or slightly lower, while for substrate **S3** the values are always better by 4–5% with the isolated salt. If one compares [**5a**][BPh_4] with [**5b**][BPh_4], the trends determined for the bromides salts are perfectly applicable.

Surprinsingly, for [**5c**][Br] and [**5c**][BPh_4], [**5d**][Br] and [**5d**][BPh_4], the situation is different (Table 7). Substantial variations in *ee* values can be noticed in all direct comparisons of the bromide and BPh_4 salts. The stronger counterion effect is observed for alkene **S3**. This ionic interplay is something that was not observed previously in our group or others in this field of epoxidation chemistry. At this stage, it is too early to speculate on this counterion effect which is extremely sensitive to the olefin structure at play. Nevertheless, the global trends determined for the bromide salts remained with the tetraphenylborate counterion – just the selectivity can be better with the more lipophilic counterion (with the exception of olefin **S2**).

Conclusions

We have described two new classes of biaryl azepinium salts that behave as effective catalysts for the enantioselective epoxidation of prochiral olefins. We have been able to show that the origin of the predominance of the axially chiral stereogenic element is to be found in the dihedral angle values for the biaryl twist – and the external angle Φ in particular. The larger the angle, the better it is for the asymmetric transfer. We have further used an oxidation protocol that allows a rapid assay for the enantioselective efficiency by *in-situ* oxidation of tertiary amine precursors to bromide iminium salts; the development of this assay revealing a first counterion effect in this iminium-catalyzed epoxidation chemistry.[26]

Experimental Section

For analytical data of compounds **15**, **18**, **19**, **22**, **23** and salts [**5**][BPh_4]. ECD spectra of **15c**, salt **18c**·HCl, salt **19c**·HCl and **19d** and comparison with that of the crystals used in the X-ray structural analyses, see Supporting Information.

General Procedure for the Synthesis of Azepines 15a to 15d

To a solution of (R_a)-6,6′-dimethyl-1,1′-biphenyl-2,2′-dicarboxaldehyde[18] (100 mg, 0.42 mmol, 1.0 equiv.) in MeCN (5 mL) the corresponding enantiopure amine (**a** to **d**, 2.0 equiv.) was added. After 15 min of stirring $NaBH_3CN$ (106 mg, 1.68 mmol, 4.0 equiv.) was added to the reaction mixture and the resulting colorless solution was stirred for 23 h at room temperature. The reaction mixture was quenched by addition of AcOH (0.24 mL, 10.0 equiv.), stirred for 10 min, then diluted with MeOH (1 mL) and DCM (30 mL). The resulting solution was washed with 2 M aqueous solution of NaOH (30 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2× 25 mL). Combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, concentrated under vacuum and purified.

General Procedure for the Synthesis of Azepines 18c and 18d

In a 25-mL round-bottomed flask containing a solution of enantiopure 1-phenylpropylamine (110 mg, 0.818 mmol, 1.2 equiv.) in acetonitrile (10 mL) was added (R_a)-2,2′-bis-(bromomethyl)-1,1′-binaphthyl (300 mg, 0.682 mmol, 1.0 equiv.) and potassium carbonate (376 mg, 2.73 mmol, 4.0 equiv.). The mixture was heated at reflux for *ca.* 5 h

[monitoring by thin layer chromatography (TLC)], allowed to cool down to room temperature and filtered though a Celite plug washed with CH_2Cl_2. Evaporation of the solvent under reduced pressure gave the crude product which was purified by column chromatography.

Synthesis of (R_a)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-binaphthyl-2,2′-dimethanol (22)

To a suspension of $LiAlH_4$ (6.66 mmol, 0.25 g, 2.0 equiv.) in dry diethyl ether (30 mL) (R_a)-2,2′-bis(carbomethyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl[21] was added as a solid in small portions at 0 °C. After the addition, the resulting mixture was stirred at room temperature for 0.5 h, refluxed for 0.5 h and recooled to 0 °C. Water (20 mL) was added carefully *via* an addition funnel and concentrated HCl was added slowly until the mixture became homogeneous. Diethyl ether (20 mL) was added and the resulting two-phase mixture was separated. The aqueous layer was extracted with ether (2×20 mL). The combined organic layers were washed with 10% aqueous solution of $NaHCO_3$ (30 mL), brine (30 mL) and dried under $MgSO_4$. Evaporation of the solvent under reduced pressure provided pure product as a white amorphous solid; yield: 1.06 g (99%).

Synthesis of (R_a)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-binaphthyl-2,2′-dicarboxaldehyde (23)

A round-bottomed flask (100 mL), equipped with a magnetic stirring bar, containing PCC (9.6 mmol, 2.06 g, 3.0 equiv.) was charged with dry CH_2Cl_2 (15 mL). A solution of substrate (3.2 mmol, 1.03 g, 1.0 equiv.) in CH_2Cl_2 (15 mL) was added to the resulting suspension in one portion. The resulting dark mixture was vigorously stirred for 3 h at ambient temperature, then diethyl ether (30 mL) was added. The mixture was stirred for 10 min, filtered through silica gel plug topped with a layer of Celite, which was then washed with ether. The filtrate was concentrated under reduced pressure to provide a green solid. Subsequent purification by column chromatography on silica gel gave pure product as a colorless solid; yield: 86–89%.

General Procedure for the Synthesis of Azepines 19a to 19d

To a suspension of aldehyde **23** (100 mg, 0.314 mmol, 1.0 equiv.) in MeOH (4 mL) the corresponding enantiopure amine (**a** to **d**, 1.1 equiv.) was added. After few minutes of stirring, $NaBH_3CN$ (40 mg, 0.628 mmol, 2.0 equiv.) and glacial acetic acid (2 drops) were added to the reaction mixture and the resulting colorless solution was stirred for 1 day at ambient temperature. The reaction mixture was quenched by addition of an aqueous solution of NaOH (1 M, 25 mL). Diethyl ether (25 mL) was added and the resulting two-phase mixture separated. The aqueous phase was extracted with ether (2×15 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, concentrated under vacuum and purified by preparative TLC on silica gel plates (20×20 cm, 2 mm, EtOAc/hexane, 1:5).

General Procedure for the Synthesis of Iminium Salts [5a][BPh_4] to [5d][BPh_4]

To a solution of substrate in CH_2Cl_2 (5 mL for 200 mg of starting tertiary amine) NBS (1.0 equiv.) was added in small portions (exothermic reaction). The resulting deep yellow solution was stirred for 5 min at ambient temperature. A solution of sodium tetraphenylborate (1.0 equiv. in 2 mL of MeCN) was added in one portion, and the resulting mixture was stirred for 5 min. The suspension was diluted with CH_2Cl_2 (15 mL), washed twice with water (2×15 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by trituration/recrystallization from ethanol. The resulting salts were dried in high vacuum at 80 °C.

Typical Biphasic Enantioselective Epoxidation Procedure with *in-situ* Prepared Catalysts

In a 5-mL flask equipped with a magnetic stirring bar, $NaHCO_3$ (67.0 mg, 0.80 mmol, 4.0 equiv.) was added to 800 μL of water. Oxone® (132.0 mg, 0.21 mmol, 1.0 equiv.) was then added and the solution stirred for 2 min until effervescence subsided. 500 μL of a 0.4 mol/L solution of the alkene (0.20 mmol, 1.0 equiv.) and naphthalene (0.20 mmol, 1.0 equiv., internal reference) in CH_2Cl_2 was added and the resulting biphasic mixture was cooled to 0 °C with an ice-bath. The catalyst was prepared by mixing the azepine precursor and NBS (10.0 μmol each, 5 mol%) in CH_2Cl_2 (500 μL) for five minutes. The resulting solution was added, followed by a solution of 18-crown-6 (1.0 mg, 5.0 μmol, 2.5 mol%) in CH_2Cl_2 (200 μL). After 5 min at 0 °C without any stirring, the reaction mixture was then vigorously stirred at that temperature for 2 h.

Crystal Structures Determination

Cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer with graphite-monochromated Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods (SIR-97),[27] and all other calculations were performed with the XTAL system[28] and ORTEP[29] programs. The Flack parameter (x) was refined for the HCl salt compounds **18c** and **19c** [x = 0.00(8) and −0.01(7), respectively] and was fixed to 0.0 for compound **15c** and **19d** for which the absolute configurations were known from the syntheses (see Supporting Information for the CD spectra of the measured crystals).

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 673551, 673552, 673553, and 673554. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].

Supporting Information

General methods and materials are given in the Supporting Information.

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