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Highly Enantioselective Biphasic Iminium-Catalyzed Epoxidation of Alkenes. On the Importance of the Counterion and of N(sp^2)–C(sp^3) Rotamers

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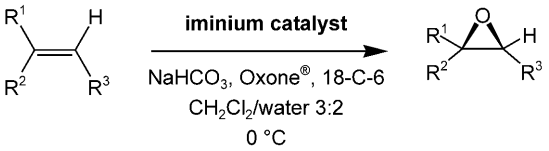
Abstract: Diastereomeric biaryliminium cations made of an (*R*a)-5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyl core and exocyclic appendages derived from (*S*)- or (*R*)-3,3-dimethylbutan-2-amine are effective asymmetric epoxidation catalysts for unfunctionalized alkenes. Herein, we report that the negative counterion of the iminium salts has to be chosen wisely. While the hexafluoroantimonate anion [SbF_6^-] is optimal for reliable results, one has to be careful about other anions and tetraphenylborate [BPh_4^-] in particular. We also detail that the so far unexplained "lack" of stereochemical control from the chiral exocyclic appendage in this type of catalysts is due to the existence of atropisomers around the N(sp^2)–C(sp^3) bond that links the azepinium core to the exocyclic stereocenter. Finally, we develop a general model to predict with certainty the high selectivity in the formation of non-racemic epoxides of defined absolute configuration.

Keywords: counterion; epoxidation; iminium salts; organocatalysis; rotamers

Introduction

Non-racemic epoxides are useful precursors and building blocks in synthetic organic chemistry. Quite a few effective systems have been developed for their preparation,[1] and the catalytic asymmetric epoxidation of olefins has proven to be one of the most powerful approaches. Most of them are based on transition metals such as the Katsuki–Sharpless epoxidation of allylic alcohols with chiral titanium catalysts[2], vanadium-catalyzed epoxidation of allylic[3] and homoallylic[4] alcohols and the Katsuki–Jacobsen protocol for unfunctionalized olefins[5]. During the last decade, much effort has been devoted to the development of organocatalytic systems that afford metal-free procedures, such as asymmetric epoxidation catalyzed by chiral ketones and iminium salts.[6] In this field, three-membered ring heterocycles such as dioxiranes,[7,8] oxaziridines,[9] ammonium and oxaziridinium salts[7] have been shown to be effective oxidation agents.

Oxaziridinium ions are attractive alternatives to the commonly used dioxiranes.[10] These organic salts are effective oxygen transfer reagents towards nucleophilic substrates[11] and electron-rich unfunctionalized olefins in particular. Moreover, the propensity of iminium ions to react with Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) to generate the oxaziridinium species renders the development of catalytic processes possible [Eq. (1)].[12,13]



(1)

In the recent years, quite a few successful enantioselective variants of the reaction have been reported,[14–16] many of them based on configurationally stable biarylazepinium skeletons. Some of these derivatives are doubly bridged biphenyl **1**,[17] binaphthyl **2**[18,19] and 5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyl **3** azepinium cations[20] that are displayed in Figure 1 and Figure 2. Of importance for this study, these catalysts contain an exocyclic chiral appendage R* in addition to the twisted biaryl axis.

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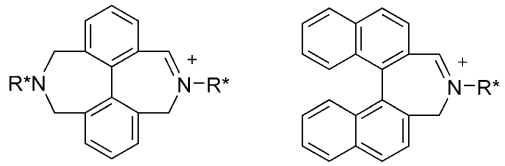
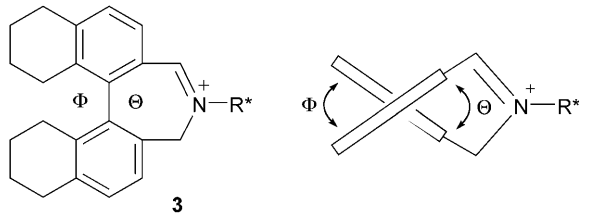


1 **2**

Figure 1. Doubly bridged biphenyl-, **1**, and binaphthyl-, **2**, azepinium cations containing a chiral exocyclic appendage R* (e.g., L-acetonamine or 3,3-dimethylbutan-2-amine).



3

Figure 2. 5,5′,6,6′,7,7′,8,8′-Octahydrobinaphthyliminium **3** catalysts and θ and Φ dihedral angles (measured inside and outside the N-containing seven-membered ring, respectively).

Recently, it was proposed that the larger the dihedral angles θ and Φ around the central bond joining the aromatic rings (Figure 2) are, the stronger is the stereocontrol of the reaction by the biaryl axis over the exocyclic chiral appendage.[20] In fact, salts (*R*a,*S*) and (*R*a,*R*) of catalysts **2** (unlike **1**) provide non-racemic epoxides with the same absolute configuration and with virtually the same enantiomeric purity despite the diastereomeric relationship.[19] Based on this dihedral angle hypothesis, partially hydrogenated azepinium cations of type **3** were prepared and they displayed excellent levels of enantioselectivity for certain olefins such as 1-phenyl-3,4-dihydronaphthalene **5a** (*ee* up to 94%, Oxone/$NaHCO_3$/18-C-6/CH_2Cl_2/H_2O).

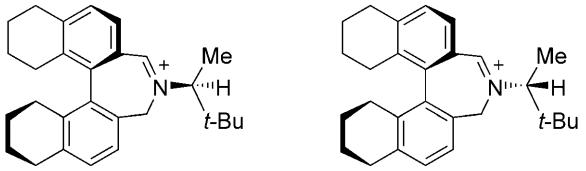
However, for other simple alkenes, such as *trans*-α-methylstilbene, only a moderate level of induction was obtained (*ee* up to 77%). While such a difference in selectivity for these two substrates has been observed in all previously reported examples of epoxidation with chiral iminium catalysts, there has been, to our knowledge, no attempt to account for this difference rationally. No general model has been provided so far to predict with certainty which type of olefins reacts more selectively than others with this class of organocatalysts and which absolute configuration is afforded for the epoxides.

Herein, based on an extensive experimental study, we report a rationalization to foresee with confidence which trisubstituted olefins lead to high levels of enantioselectivity. We also provide details on the solution (and solid-state) behaviour of the iminium biaryl catalysts of type **3** and demonstrate the existence of atropisomers around the N(sp^2)–C(sp^3) bond that links the azepinium core to the chiral appendage. Significantly, these rotameric conformations are the key to an understanding of the lack of the stereochemical influence of the exocyclic stereocenter. Finally, and also importantly, we report on the importance of the counterion associated with the cationic catalytic moieties to afford reliable reactivity in these enantioselective epoxidation reactions.

Results and Discussion

On the Importance of the Counterion

In fact, in our previous study on 5,5′,6,6′,7,7′,8,8′-octahydrobinaphthylazepinium catalysts with appendages derived from (*S*)- and (*R*)-3,3-dimethylbutan-2-amine, catalysts **3a** and **3b** (Figure 3), or from (*S*)- and (*R*)-1-



(*Ra,S*)-**3a** (*Ra,R*)-**3b**

Figure 3. Diastereomeric 5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyliminium catalysts **3a** and **3b** derived from (*S*)- and (*R*)-3,3-dimethylbutan-2-amine, respectively.

phenylpropylamine, a somewhat puzzling observation was made.[20] Rather large differences in enantioselectivity were observed for the reactions performed with the iminium catalysts combined with bromide or with tetraphenylborate counterions respectively. This difference (up to 5% *ee* with **3b** and 14% with the iminiums derived from 1-phenylpropylamine) was dependent upon the nature of the olefin and catalysts at play; the highest *ee* values being observed for the BPh_4 salts.

We thus decided to characterize this effect better and looked more closely at what was happening with the tetraphenylborate salts. First, a study of the enantioselectivity of the epoxidation of 1-phenylcyclohexene as a function of catalyst loading was performed using salt [**3a**][BPh_4]. The results are reported in Table 1. The stereoinduction is greatly affected by the amount of active salt in the medium and, to a bit of our surprise, the larger the amount of catalyst the lower the selectivity.

This unusual observation was difficult to rationalize at first glance. One possible explanation was, at low amount of catalyst, the occurrence of a degradation generating a more selective catalyst *in situ*. Care was then taken to fully characterize the result of these reactions and those performed with the largest amount

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Table 1. Epoxidation of 1-phenylcyclohexene using catalyst [**3a**][BPh_4].[a]

Catalyst [mol%]	*ee*[b] [%]
1.0	90
2.5	90
5	80
10	66

[a] *Conditions:* 1-phenylcyclohexene (0.2 mmol), catalyst (*x* mol%), 2.5 mol% of 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, CH_2Cl_2/H_2O (3:2) , 2 h, 0 °C. Average of at least two runs.

[b] Determined by CSP-GC (Chiraldex Hydrodex β-3P).

of catalysts in particular. Relatively high amounts of biphenyl could be identified in the GC-MS analyses of the reaction mixtures, a compound that was furthermore isolated in pure form from the crudes. Different hypotheses could then account for this observation as biphenyl might (i) be an impurity brought in solution along with the starting alkene, (ii) result from degradation and aromatization under the reaction conditions of *in situ* formed 1-phenylcyclohexene oxide or (iii) be derived from tetraphenylborate anion by an oxidative decomposition pathway.[21]

To distinguish these hypotheses, a few tests were performed. First of all, the purity of 1-phenylcyclohexene (commercial, 98%) was checked by GC-MS and no trace of biphenyl could be found. Then, 1-phenylcyclohexene was submitted to the epoxidation procedure with bromide salts as catalysts (e.g., [**3a**][Br]); no biphenyl was observed rendering unlikely the existence of a pathway from 1-phenylcyclohexene oxide to biphenyl (for details see Supporting Information). Finally, [**3a**][BPh_4] (5 mol%) was treated under the reaction conditions in the absence of alkene and, after two hours of vigorous stirring at 0 °C and filtration of the biphasic mixture, a ^{1}H NMR analysis was performed which revealed a complete disappearance of the tetraphenylborate species and only signals of biphenyl.

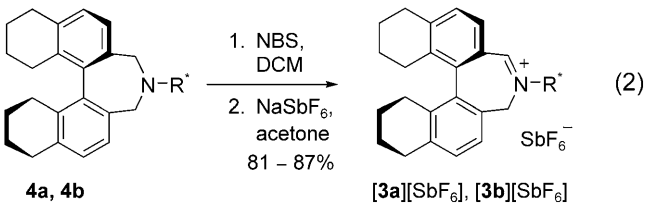
Clearly, under the oxidative reaction conditions,[21] the lipophilic counterion undergoes a decomposition to form biphenyl as by-product. This process is of particular importance as it modifies profoundly the solubility and/or the partition ability of the [iminium/oxaziridinium] species in the two-layer situation of the reaction conditions. The epoxidation, which is most probably occurring in the organic layer exclusively when the lipophilic anion is intact,[15] might now occur at the interface of the heterogeneous solvent mixture or even in the aqueous phase upon degradation.

In view of these results, a search for a stable alternative to BPh_4 was started and that of a "light" counterion rather than a "heavy" TRISPHAT.[22]

Catalyst Preparation

Hexafluorophosphate was first evaluated as an alternative. The PF_6 iminium salts of cations **3a** and **3b** were easily prepared by ion exchange metathesis from the corresponding bromide salts (~70% yield). However, these salts were stable only in the solid state. ^{19}F and ^{31}P NMR spectroscopic analysis of the salts revealed a hydrolysis of the counterion already in CD_2Cl_2 only; the signals of the cations remaining, however, unchanged in the ^{1}H and ^{13}C NMR spectra.

Hexafluoroantimonate, which was studied next, was found to be suitable for the catalysis work (see the next section). The synthesis of catalysts [**3a**][SbF_6] and [**3b**][SbF_6] was performed in two steps following a general and highly-reproducible procedure [Eq. (2) and Experimental Section].



(2)

Tertiary 5,5′,6,6′,7,7′,8,8′-octahydrobinaphthylazepines (*R*a,*S*)-**4a** and (*R*a,*R*)-**4b**, of which a synthesis in 6 steps has been previously reported, were used as starting materials.[20] Their treatment with *N*-bromosuccinimide (NBS) in dichloromethane provided a fast and clean formation of the desired iminium bromide salts in 5 min only. Subsequent anion metathesis in acetone with sodium hexafluoroantimonate (5 min) and trituration in EtOH provided the pure catalysts (*R*a,*S*)-[**3a**][SbF_6] and (*R*a,*R*)-[**3b**][SbF_6] in good yield for two steps (81–87%).

Enantioselective Epoxidation Reactions

Initial Reactivity/Selectivity Screen

The first task at hand was the verification that different loading of salts [**3a**][SbF_6] and [**3b**][SbF_6] would afford non-racemic epoxides with identical levels of enantiomeric excesses. To test this hypothesis, 1-phenylcyclohexene was used as substrate along with the following reaction conditions that are suitable for even very sensitive epoxides (Oxone®/$NaHCO_3$/18-crown-6/CH_2Cl_2/H_2O/0 °C). The results are summarized in Table 2.

The reactions were performed with 2.5, 5.0 and 10 mol% of [**3a**][SbF_6] and [**3b**][SbF_6] to afford (−)-(1*S*,2*S*)-1-phenylcyclohexene oxide with, as desired, invariable 89 and 92% *ee*, respectively. Clearly, cata-

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Table 2. Asymmetric epoxidation of 1-phenylcyclohexene with SbF_6 salts. Catalyst loading influence.[a]

Catalyst [mol%]	[**3a**][SbF_6] *ee*[b] [%]	[**3a**][SbF_6] Conv.[c] [%]	[**3b**][SbF_6] *ee*[b] [%]	[**3b**][SbF_6] Conv.[c] [%]
2.5	89	97	92	60
5.0	89	>99	92	66
10	89	>99	92	68

[a] *Conditions:* 1-phenylcyclohexene (0.2 mmol), catalyst (*x* mol%), 2.5 mol% of 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 2 h, 0 °C. Average of at least two runs.

[b] Determined by CSP-GC (Chiraldex Hydrodex β-3P). In all cases, the absolute configuration of 1-phenylcyclohexene oxide is (−)-(1*S*,2*S*).

[c] Determined by GC analysis of crude reaction mixture using naphthalene as an internal standard.

lyst [**3a**][SbF_6] is more reactive than [**3b**][SbF_6] and it can be used in the epoxidation reaction in amounts as low as 2.5 mol% without significant loss of activity (97% conversion in 2 h). Under the same conditions, only a 60% conversion to the desired epoxide is reached with [**3b**][SbF_6], albeit with a better enantiomeric excess of 92% that remains constant with larger amounts of **3b**. While [**3a**][SbF_6] is the most reactive, [**3b**][SbF_6] is the most selective. It was also noted that the epoxidation reaction was very clean and no traces of ring opening by-products were detected by GC-MS analysis of reaction mixtures. The pure epoxide was obtained by simple filtration through a silica gel plug necessarily buffered though with triethylamine.

In short, both catalysts performed as expected. For further studies, it was decided to use the most selective salt [**3b**][SbF_6] as its reactivity is addressable by increasing either reaction time or catalyst loading.

Initial Substrate Screen

The epoxidation was then performed with a few simple commercially available substrates (Figure 4) looking for leads that would indicate which olefins are best for this asymmetric catalyzed process.

Whereas the epoxidation was highly disappointing with *trans*-stilbene **5b** and α-methylstyrene **5c** (6% and 12% *ee*, respectively), much higher selectivity was obtained with *trans*-β-methylstyrene (**5d**, 64% *ee*) and, as already mentioned, 1-phenylcyclohexene (**5a**, 92% *ee*). In view of these results and considering that one aromatic group is beneficial (as in **5a**), we reasoned that the second aromatic group on **5b** was too large for the chiral pocket of the catalyst and that a methyl or a methylene group at the same *trans*-β-position was, however, favorable; these smaller substituents being actually needed for high selectivity (in comparison with **5c**). Looking at the larger enantiomeric excess of **5a** over **5d**, we reasoned that the presence of a third α-substituent next to the aromatic group was also beneficial. This was tested with *trans*-α-methylstilbene **5e** which afforded its epoxide with a 65% *ee* value, quite a bit better than that of **5b** (6% *ee*); the moderate *ee* value being the result of antagonistic effects of the favorable α-Me and unfavorable β-phenyl substituents.

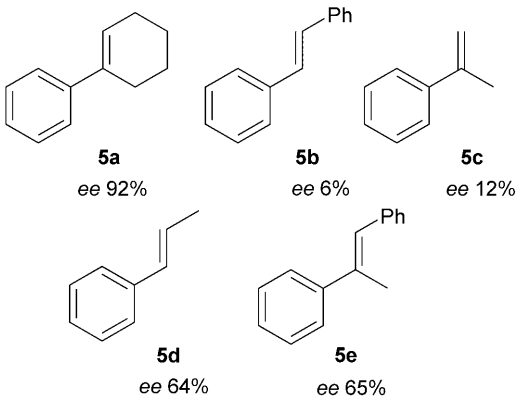

Figure 4. Tested commercial alkenes.

All considered, any alkene of type **6** corresponding to the general formula displayed in Figure 5 should lead to high enantiomeric excesses in the enantioselective epoxidation catalyzed by salt [**3b**][SbF_6]; the size of the α-substituent compatible with the process remaining to be determined in the course of the study.

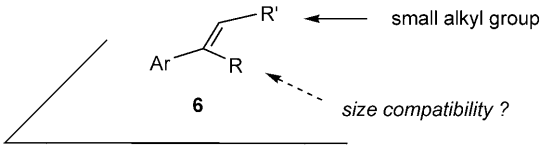

Figure 5. Proposed model type of alkenes giving epoxides with high enantiomeric excesses.

Extended Substrate Screen

To test this hypothesis, a range of substrates was prepared and their asymmetric epoxidation with catalyst [**3b**][SbF_6] performed. All results are presented in Table 3 and Table 4.

It should be mentioned that for all the alkenes, experiments with different catalyst loading (mol%) led, as for 1-phenylcyclohexene, to constant levels of asymmetric induction. For **5a**, full conversion to the desired epoxide was obtained after 24 h at 0 °C. 1-Phenyl-3,4-dihydronaphthalene **5f**, another classical substrate, was very reactive as well. The resulting ep-

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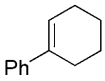
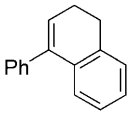
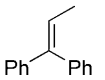
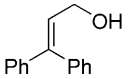
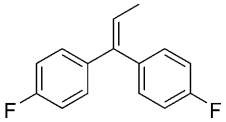
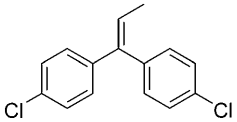
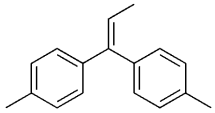
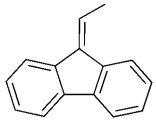
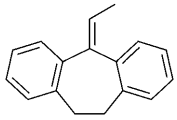
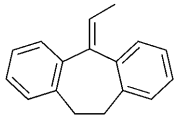
Table 3. Asymmetric epoxidation of various alkenes mediated by catalyst [**3b**][SbF_6].[a]

Substrate		Catalyst, [mol%]	Time [h]	Yield[d] (conversion [%])	*ee* [%]	Configuration[i]
	**5a**	2.5	24	85 (>99[b])	92[e]	(−)-(1*S*,2*S*)
	**5f**	2.5	24	83 (>97[c])	91[f], (98[j])	(+)-(1*R*,2*S*)
	**5g**	5	48	95 (>99[b])	90[g]	(−)-(*S*)
	**5h**	20	48	80 (>97[c])	88[f]	(−)-(*S*)
	**5i**	10	43	87 (>99[b])	91[f]	(−)
	**5j**	10	47	84 (>99[b])	91[f]	(−)
	**5k**	5	24	67 (>99[b])	94[f]	(−)
	**5l**	10	24	94 (>99[b])	90[f]	(−)-(*S*)
	**5m**	20	91	67 (75[b])	98[f]	(+)
	**5m**	10[h]	66[h]	85[h] (>99[h])	93[h]	(+)
	(*E*)-**5n**	2.5	48	91 (>99[b])	90[e]	(−)-(2*S*,3*S*)
	(*Z*)-**5n**[k]	5	48	93[k] (>99[b])	76[e]	–[k]

[a] *Conditions:* substrate (0.2 mmol), catalyst (*x* mol%), 2.5 mol% of 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 0 °C.
[b] Determined by GC-MS (HP-5MS) analysis of the crude reaction mixture.
[c] Determined by ^1H NMR analysis of the crude reaction mixture (400 MHz).
[d] Isolated yields of pure epoxides.
[e] Determined by CSP-GC (Chiraldex Hydrodex β-3P).
[f] Determined by CSP-HPLC (see Supporting Information).
[g] Determined by ^1H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$.
[h] Results obtained with catalyst [**3a**][SbF_6].
[i] The absolute configuration of major enantiomers was determined by comparison of optical rotation with that reported in the literature.
[j] After single recrystallization from *n*-hexane.
[k] A 95:5 mixture of (*Z*)-**5n** and (*E*)-**5n** was used. Due to the stereospecificity of the reaction and the occurrence of a minor diastereomeric epoxide, the optical rotation was not measured.

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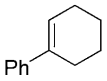
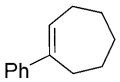
Table 4. Ring size effect on the epoxidation of few cycloalkenes with catalyst [**3b**][SbF_6].[a]

Substrate		Yield[c] (Conversion [%][b])	*ee* [%]	Configuration[f]
	**5a**	85 (>99)	92[d]	(−)-(1*S*,2*S*)
	**5o**	85 (>99)	72[e]	(−)-(1*S*,2*S*)
	**5p**	92 (>99)	83[d]	(−)

[a] *Conditions:* substrate (0.2 mmol), catalyst (2.5 mol%), 2.5 mol% of 18-C-6, 1.1 equiv. Oxone®, 4.0 equiv. $NaHCO_3$, CH_2Cl_2/H_2O (3:2), 24 h, 0 °C.
[b] Determined by GC-MS (HP-5MS) analysis of the crude reaction mixture.
[c] Isolated yields.
[d] Determined by CSP-GC (Chiraldex Hydrodex β-3P).
[e] Determined by CSP-HPLC (OD-H column).
[f] The absolute configuration of major enantiomers was determined by comparison of optical rotation with that reported in the literature.

oxide was isolated in 83% yield and 91% *ee*. Similar results were obtained with 1,1-diphenylprop-1-ene **5g** (90% *ee*); the system being however slightly less reactive. Interestingly, moving from this substrate to the analogous allylic alcohol (**5h**, 88% *ee*), only a very small decrease in enantioselectivity was measured. The reactivity was however much lower as 5 mol% and 20 mol% of catalyst [**3b**][SbF_6] were required to achieve full conversion with **5g** and **5h**, respectively under the same reaction time. This difference in reactivity may be explained by the electron-withdrawing effect of the hydroxy moiety that renders the double bound of allylic alcohol less electrophilic and also possibly by a less favorable partition of the olefin in the biphasic CH_2Cl_2/water layers. Then, a range of substrates structurally analogous to **5g** was prepared bearing either electron-withdrawing (F, Cl: **5i** and **5j**, respectively) or electron-donating (Me: **5k**) groups at the *para*-positions. In the cases of **5i** and **5j**, essentially the same level of asymmetric induction was observed as for **5i** (*ee* 91% *vs.* 90% *ee)*, whereas electronically-rich alkene **5k** led to an increase in the enantiomeric excess value (94% *ee*). If only a moderate impact was seen on the selectivity, it was not the case on the reactivity. While only 5 mol% of catalyst was required to achieve full conversion after 48 h at 0 °C with **5g**, its electron-rich analogue **5k** reacted in half the time for the same catalyst loading. Electron-poor derivatives **5i** and **5j** required however quite a lot more of the catalyst as full conversion was observed only after 2 days with 10 mol% of [**3b**][SbF_6].

We then turned our attention to **5l** and **5m**, cyclic analogues of **5g** derived from 9*H*-fluoren-9-one and dibenzosuberone, respectively. Whereas all carbons are virtually coplanar in **5l**,[23] this is not the case for **5m**. The central cycloheptadiene ring of **5m** adopts a bent conformation intermediate between boat and chair forms and the aromatic groups adjacent to the double bond are twisted by 45 and 65° out of the plane of the alkene.[24] Despite this very large difference, both **5l** and **5m** afforded the corresponding epoxides in high to very high enantiomeric purity (90% and 98% *ee* respectively). The reaction with **5m** was however much slower than others as, with 20 mol% of catalyst and 4 days, the isolated epoxide was obtained in only 67% yield (75% conversion).[25] In view of this result, **5m** was treated with the more active catalyst [**3a**][SbF_6]. As expected, the reaction was faster and only required 10 mol% of iminium salt to yield the epoxide in 85% yield and still a decent 93% *ee* after *ca.* 3 days.

The impact of the olefin geometry was also tested using the *E* and *Z* geometrical isomers of 1-methyl-1-phenylpropene **5n**. If the reaction could be performed with an essentially pure *E* isomer (>99%), that of the *Z* isomer was conducted with a sample only 95% pure in the *cis* form. In the first case, (*E*)-**5n** was epoxidized using just 2.5 mol% of catalyst [**3b**][SbF_6] in 48 h and 90% *ee*, whereas (*Z*)-**5n** afforded its epoxide in only 76% *ee*. Moreover, the *Z* isomer was less reactive; 5 mol% of catalyst being required to achieve full conversion after 48 h.

Finally, after these largely successful examples, two other 1-phenylcycloalkenes, namely the 5- and 7-membered ring **5o** and **5p**, were tested in the epoxidation reaction (Table 4). Only 2.5 mol% of [**3b**][SbF_6] was required to achieve full and clean conversion of olefins to the corresponding epoxides that were isolated in good yields (85–92%), albeit with lower enantiomeric excesses (72 and 83% *ee*, respectively). The results are compared to that of alkene **5a.**

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Validity of the Alkene Model Hypothesis and Absolute Sense of Stereoinduction

Clearly, at this stage, the alkene model type proposed earlier for double bonds that would provide high levels of enantioselectivity in reactions catalyzed by [**3b**][SbF_6] is a working model. From **5f** to (*E*)-**5n**, the lowest *ee* value is 88% – and this corresponds to **5h** that might react differently in the biphasic catalytic system due to the presence of hydroxy group. Having at the *trans*-β-position from the aromatic group a small alkyl moiety R′ of type CH_3, CH_2OH or CH_2 (cyclic) is something favorable. The group at the α-position R can be possibly quite large and even twisted out of the plane of the double bond as in **5m**.

If (*E*)-**5n** also fits the model, it is however not the case for the (*Z*) isomer. For that substrate, the β-methyl group is positioned in a quadrant usually occupied by an H-atom only and this most probably leads to an unsatisfactory interaction with the iminium catalyst and hence the lower enantioselectivity (Figure 6). The exact reasons why 1-phenylcyclopentene **5o** and 1-phenylcycloheptene **5p** lead to lower *ee* values remain undetermined for the moment, the different conformations of the three rings systems possibly play a role.

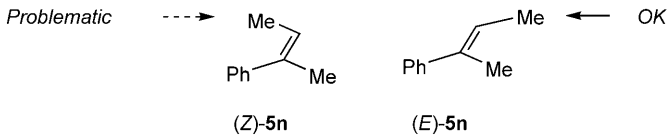

Figure 6. Different recognition of *E* and *Z* isomers.

Finally, the stereochemical outcome was analyzed for the reactions providing epoxides of known absolute configuration and the results are summarized in Figure 7. All the major enantiomers produced come from the addition of the O-atom onto the same prochiral face of the alkene; the top face in the geometrical description provided on Figure 7. For substrates **5a**, **5f**, **5g**, **5l**, (*E*)-**5n** and **5o**, it is the *si* face of the β-carbon of the alkene. For **5h**, due to the presence of the oxygen at the allylic position which changes the priority sequence in the CIP rule, it is the *re* face. It is then highly probable that compounds **5i**, **5j**, **5k**, **5m** and **5p** have reacted in a similar fashion.

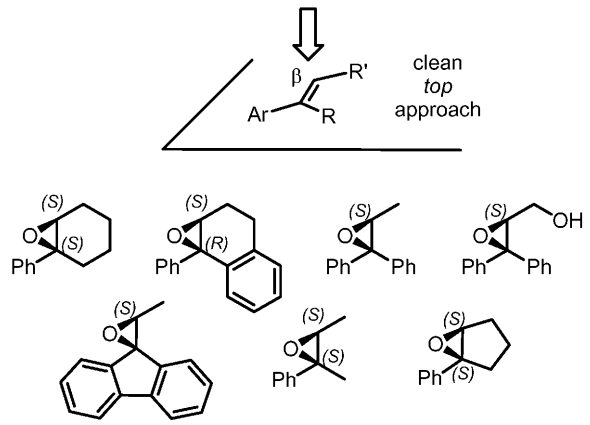

Figure 7. Facial selectivity.

Slow Rotation around the N(sp^2)–C(sp^3) Bond and Importance of the Resulting rotameric Situation

Previously, it has been shown that a slow rotation around N(sp^2)–C(sp^3) bonds can occur when bulky substituents are attached to a stereogenic carbon linked to an sp^2-hybridized nitrogen atom.[26] It results in atropisomeric conformations that can have an impact on the stereochemical outcome of reactions. For some acridinium cations, a rotation barrier of 20.1 kcal·mol^{-1} was recently measured for the 3,3-dimethylbutan-2-amine derivative.[27] In view of this result, it was likely that such a hindered rotation around the N(sp^2)–C(sp^3) bond that links the azepinium core to the chiral appendage would also occur for salts [**3a**][SbF_6] and [**3b**][SbF_6].[16] Care was thus taken to characterize the diarylazepinium cations by variable temperature (VT) NMR in a search for atropisomeric *anti*- and *synperiplanar* conformations.

While the ^{1}H NMR analysis of [**3b**][SbF_6] in CD_2Cl_2 displayed sharp signals at 298 K, a gradual decrease of the temperature led to a broadening of all signals (with a coalescence around 243 K) before they became sharp again at 193 K (Figure 8). Then, two sets of signals appeared indicative of the existence indeed of two atropisomeric conformers and of their slow interconversion on the NMR time scale at 193 K. The signal of the iminium proton at $\delta =$ 8.6 ppm was particularly useful for monitoring. If one considers that the NMR coalescence is reached at 243 K, then an approximate energy barrier in the range of 11–12 kcal·mol^{-1} can be estimated. {The relationship $\Delta G^{\neq} = RT_c[22.96+\ln(T_c/\Delta\nu)]$ was used to determine the activation energy, $\Delta G^{\neq}$, from the coalescence temperature, T_c (243 K), and the frequency separation of the peaks of the iminium protons, $\Delta\nu$ (115.1 Hz at 193 K)}. An atropisomeric enrichment was also observed between the *anti*- and *synperiplanar* conformers and a 85:15 ratio was measured by integration of the respective signals.

In ^{13}C NMR spectroscopy, an analogous behavior was observed although with a broadening of some of the signals appearing already at 298 K; these enlargements disappearing at 193 K along with the splitting of all carbon signals (see Supporting Information).

The determination of the conformations of the major and minor atropisomer in solution was realized

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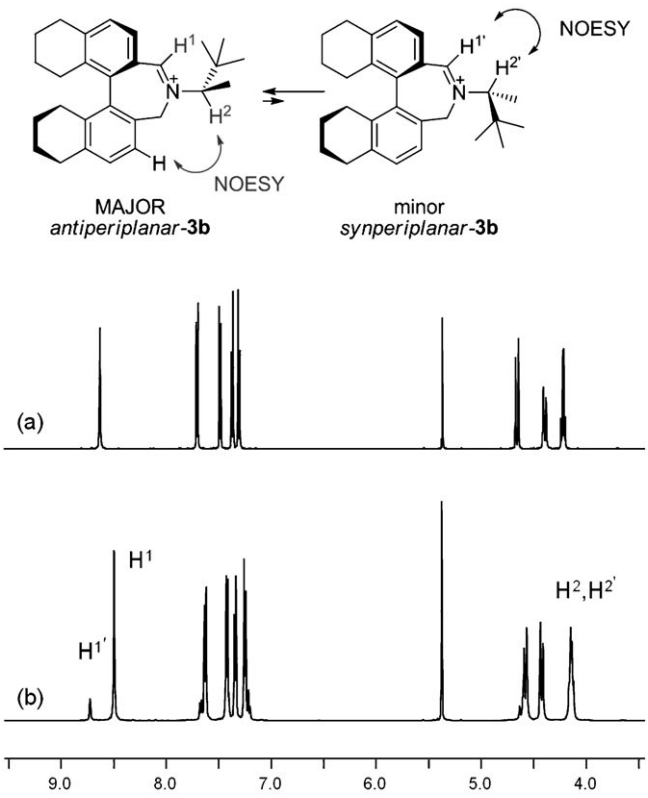

Figure 8. ^{1}H NMR ($\delta = 9.5$–3.5 ppm, CD_2Cl_2, 500 MHz) of [**3b**][SbF_6] at (a) 298 K and (b) 193 K. A color variant of this drawing is included in the Supporting Information.

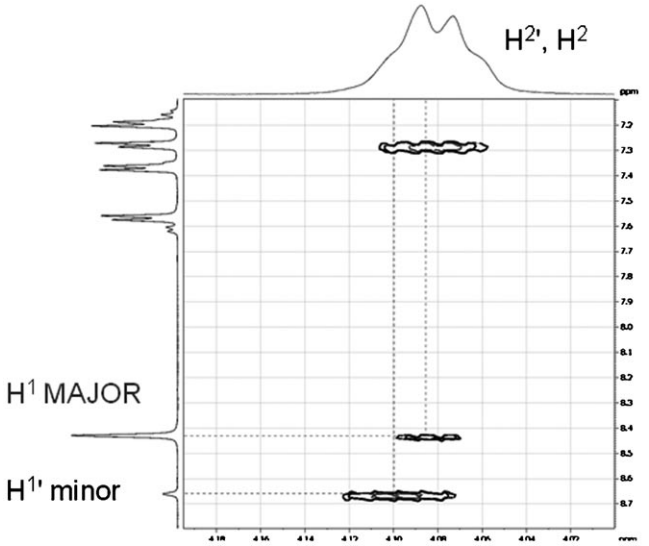

Figure 9. NOESY experiment (CD_2Cl_2, 500 MHz) of [**3b**]-[SbF_6] at 193 K. A color variant of this drawing is included in the Supporting Information.

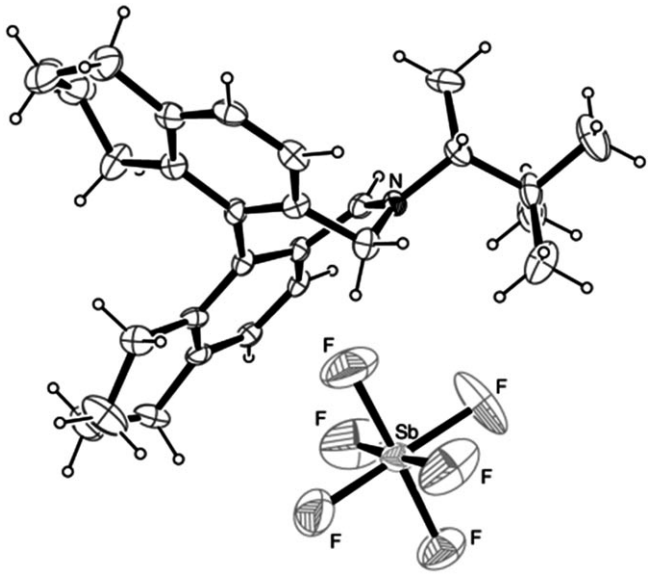

Figure 10. ORTEP view of [**3b**][SbF_6]. Ellipsoids are presented at the 50% probability level.

by a NOESY experiment at 193 K. In the case of the minor conformer, a strong cross-peak was observed between the signal of the iminium proton ($H^{1'}$, $\delta =$ 8.68 ppm) and that of the hydrogen α to *t*-Bu group ($\delta = 4.09$ ppm, Figure 9) whereas, for the major atropisomer, a weak cross-peak was only observed for the analogous signals. For that major isomer, a strong cross-peak was nevertheless seen between the H^2 signal and that of the *ortho*-aromatic proton next to the CH_2N group. It strongly points towards *syn*- and *antiperiplanar* conformations for the minor and major conformers, respectively (Figure 8 and Figure 9).

Monocrystals of compound [**3b**][SbF_6] were obtained and an X-ray structural analysis was performed. The ORTEP view is reported in Figure 10. Clearly, in the solid state, the *antiperiplanar* conformer is the preferred atropisomer as well.[28]

Interestingly, for catalyst [**3a**][SbF_6], a totally different situation was observed (Figure 11).

At 193 K, ^{1}H and ^{13}C NMR analyses revealed a lone set of signals indicating the presence of a single conformer (>98%). A NOESY experiment was performed at low temperature (193 K) and a strong cross-peak was observed between the signal of the iminium proton ($H^{1'}$, $\delta = 8.62$ ppm) and that of the hydrogen α to *t*-Bu group ($\delta = 4.05$ ppm). Then, only a *synperiplanar* geometry can account for the spectrum of the unique atropisomer of **3a**. The reason for this change in the preferred atropisomeric population between **3a** and **3b** is unclear at the moment.

However, this dichotomy in the atropisomeric situation is important as it is a possible reason for (i) the "lack" of observed stereochemical influence from the exocyclic auxiliary and (ii) the higher reactivity of diastereomer **3a** over **3b** during the course of the study.

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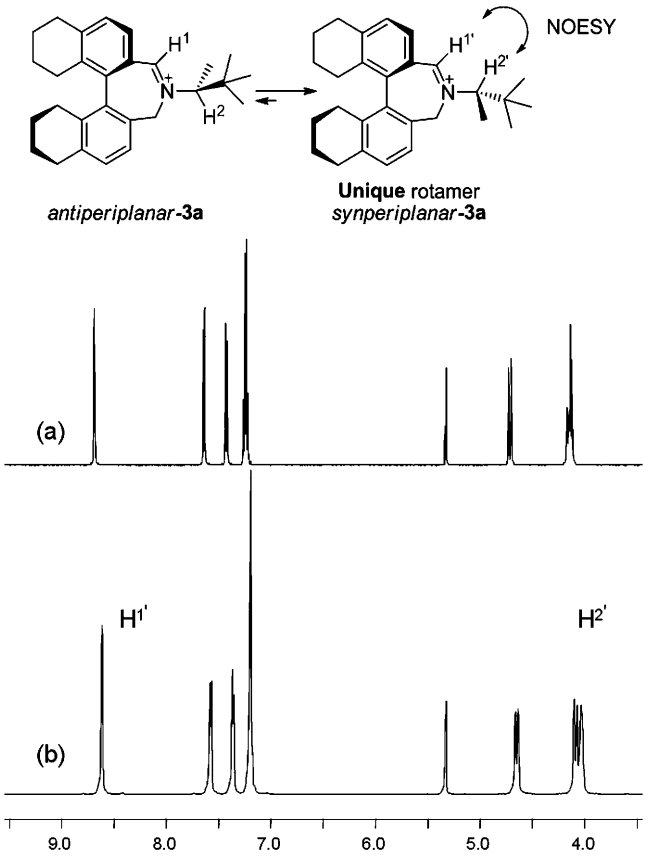

Figure 11. ^{1}H NMR ($\delta = 9.5$–3.5 ppm, CD_2Cl_2, 500 MHz) of [**3a**][SbF_6] at (a) 298 K and (b) 193 K. A color variant of this drawing is included in the Supporting Information.

Indeed, the fact that **3a** and **3b** are exclusively and predominantly *synperiplanar* and *antiperiplanar*, respectively, creates a situation in which the bulky *tert*-butyl side chain of the chiral auxiliary is always positioned on the bottom (*si* face, C1 atom) of the iminium ion irrespective of the diastereomeric situation (Figure 12). As such, iminium ions **3a** and **3b** react with the same sense of stereoinduction and little influence from the chiral auxiliary.

This geometrical arrangement of the side chain furthermore reinforces the natural preference for a top face attack of the peroxymonosulfate anion on the (*R*a)-iminium species to generate oxaziridinium rings of $R_C R_N$ configuration in accordance with the calculations from Washington and Houk[29] and the experimental results from Zavada and collaborators.[30]

Finally, in the case of **3a**, the fact that the atropisomeric situation is shifted towards a single rotamer may also entice a faster reaction of this diastereomer with the peroxymonosulfate anion than with **3b** for which the mixed *antiperiplanar/synperiplanar* population retards possibly the formation of the $R_C R_N$ oxaziridinium species.

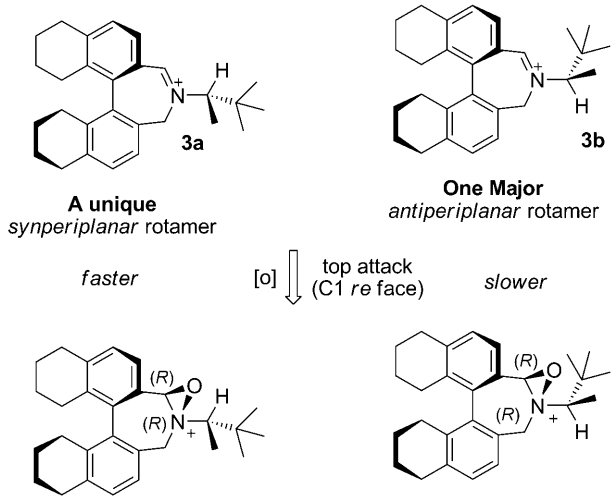

Figure 12. Importance of the rotameric situation for the "lack" of stereochemical influence of the R* appendage. A color variant of this drawing is included in the Supporting Information.

Conclusions

Herein, we have looked for an optimal chiral iminium cation/achiral anion combination and reported on (i) the origin of the lack of stereochemical control from the chiral exocyclic appendage, (ii) the unexpected dangers of using BPh_4 as counterion and (iii) on a general model to predict high selectivity in the formation of non-racemic epoxides of defined absolute configuration.

Experimental Section

For analytical data of all new compounds, HPLC, GC and ^{1}H NMR determination of the enantiomeric purity of the chiral epoxides, see Supporting Information.

General Procedure for the Synthesis of the Iminium SbF_6 Salts

To a solution of substrate (**4a** or **4b**)[20] in CH_2Cl_2 (2 mL for 100 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 hexafluoroantimonate (1.0 equiv. in 1.0 mL of acetone) was added in one portion, and the resulting mixture was stirred for 5 min. The suspension was diluted with CH_2Cl_2 (15 mL), water (15 mL) and the resulting two-phase mixture separated. The aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The crude product was purified by trituration from ethanol. The resulting salts were filtered, washed with a small amount of ethanol, diethyl ether, *n*-pentane and dried under high vacuum at 70 °C for at least one day.

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Typical Biphasic Enantioselective Epoxidation Procedure

All reactions were performed in a standard test-tube equipped with a magnetic stirring bar. $NaHCO_3$ (67.0 mg, 0.80 mmol, 4.0 equiv.) was dissolved in 800 μL of water. Oxone® (132.0 mg, 0.21 mmol, 1.1 equiv.) was then added as a solid in one portion and the solution stirred for few minutes until effervescence subsided. 500 μL of a 0.4 mol/L solution of an alkene (0.20 mmol, 1.0 equiv.) in CH_2Cl_2 were added and the resulting biphasic mixture was cooled to 0 °C with a cryostat bath. A catalyst was added in CH_2Cl_2 (500 μL) in one portion followed by a solution of 18-C-6 (1.0 mg, 5.0 μmol, 2.5 mol%) in CH_2Cl_2 (200 μL) and the resulting mixture was then vigorously stirred (*very important*!) at 0 °C. After the indicated amount of time, the reaction mixture was diluted with dichloromethane (10 mL), water (10 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated under vacuum and purified.

Crystal Structure Determination of [3b][SbF_6]

Cell dimensions and intensities were measured at 150 K on a Stoe IPDS diffractometer with graphite-monochromated Mo*K*α radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (SIR-97),[31] and all other calculations were performed with the XTAL system[32] and ORTEP[33] programs. The Flack parameter (x) was refined to $x = -0.03(3)$ and corresponds to the absolute configurations observed from the syntheses (see Supporting Information for the CD spectra of the measured crystals).

CCDC 713527 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif 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].

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