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Enantioselective olefin epoxidation using homologous amine and iminium catalysts—a direct comparison

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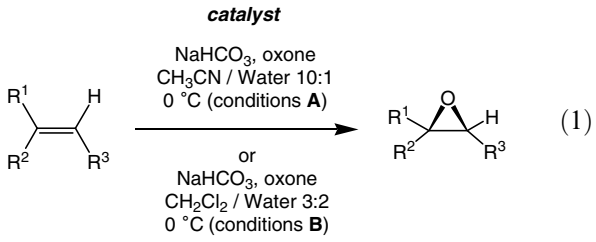
Abstract—Homologous biphenyl and (diastereomeric) binaphthyl tertiary azepines and quaternary iminium salts were prepared from (+)-(*S*,*S*)-L-acetonamine. Both the amines and iminium ions behave as effective catalysts for the enantioselective epoxidation of unfunctionalized olefins (ee up to 83%).

Chiral non-racemic epoxides are not only useful precursors for organic chemists, but also frequently met structures in natural products, often related to their biological activities (Eq. 1).[1] A number of efficient methods exist for their preparation from olefins and many of them use transition metal catalysts such as the Katsuki–Sharpless or Katsuki–Jacobsen protocols.[2] In the 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.[3]



(1)

Oxaziridinium ions are interesting alternatives to the commonly used dioxiranes.[4] Such organic salts are effective oxygen transfer reagents towards nucleophilic substrates 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.[5] The first example of an enantioselective iminium catalyzed reaction was reported in 1993.[6] Since this pioneering work, several successful enantioselective variants of the reaction have been reported,[7–9] among which are studies using biphenyl **1i**[10] and binaphthyl **2i** and **3i** iminium salts;[11] these compounds were derived from (+)-L-acetonamine used as an exocyclic chiral auxiliary (Fig. 1).[12]

In the case of **1i**, the twisted [7]-membered ring is conformationally labile and single enantiomers are readily prepared (vide infra). Two different types of salts, namely compounds [**1i**][BPh_4] and [**1i**][TRISPHAT],

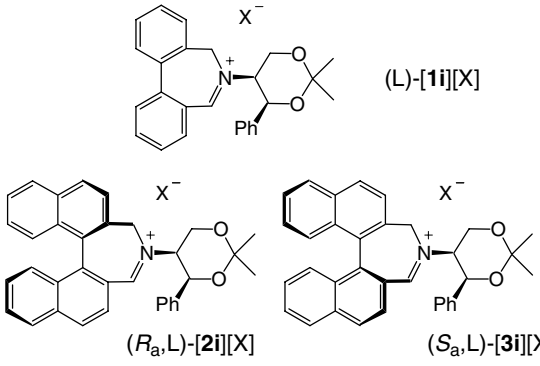


Figure 1. Selected non-racemic iminium salts and their absolute configuration, X^- being a lipophilic non-coordinating anion (BPh_4 or TRISPHAT).

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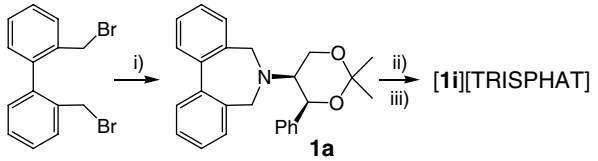
have been utilized previously in epoxidation reactions—no major differences being observed between the two ion pairing systems.[10,13] In the case of **2i** and **3i**, the presence of the stereogenic configurationally rigid binaphthyl core creates a diastereomeric relationship. Both salts (−)-[**2i**][BPh_4] and (+)-[**3i**][BPh_4] of (R_a,L) and (S_a,L) configuration, respectively, were prepared. An interesting matched/mismatched behaviour was characterized; salt [**2i**][BPh_4] leading to quite higher conversions than its diastereomer. On the whole, compound (−)-[**2i**][BPh_4] is one of the most effective iminium salt catalysts to date (ee up to 95%).[11]

Whereas the epoxidation of olefins catalyzed by iminium salts has been known for quite some time, the mediation of the reaction by amines and/or ammonium salts is still a new topic.[14] It was only in 2000 that the catalyzed enantioselective epoxidation of olefins by secondary amines was reported (ee up to 66%), the involvement of ammonium species in the key oxidation transfer step only being described in 2003.[15,16] Recently, various secondary amines were studied in this context and a beneficial influence of electron-withdrawing atoms (such as fluorine) at the β-position relative to the amino group was demonstrated. In that report, the influence of the reaction medium was also examined and different outputs resulted from the reactions that were performed in slightly acidic conditions: type **A**: $CH_3CN/NaHCO_3/H_2O$ and type **B**: $CH_2Cl_2/NaHCO_3$/18-crown-6/H_2O.[17]

So far, the most selective amine/ammonium catalysts have been α-substituted pyrrolidine moieties for which no stable iminium analogues can be found.[18] As such, it has been difficult to compare the catalytic activity and selectivity of ammonium moieties with that of related iminium species. It was therefore debatable as to which of these two classes of related catalysts is the most effective—if either. Herein, we report a study in which tertiary amines **1a**, **2a** and **3a** (Scheme 1 and Fig. 2), directly related to iminium cations **1i**, **2i** and **3i**, have been synthesized, and all these derivatives were tested as catalysts for the enantioselective epoxidation of olefins.

As indicated above, iminium salt [**1i**][TRISPHAT] is an effective catalyst for the asymmetric epoxidation of prochiral alkenes. This compound can be prepared in three steps from 2,2′-bis(bromomethyl)biphenyl using standard reactions (Scheme 1): (i) an alkylation with (+)-L-acetonamine to afford amine **1a** (88%); (ii) a subsequent elimination with *N*-bromosuccinimide to form



Scheme 1. Reagents and conditions: (i) (+)-L-acetonamine (1.0 equiv), CH_3CN, reflux, 88%; (ii) NBS (1.1 equiv), CH_2Cl_2, 20 °C; (iii) [R_3NH]-[TRISPHAT] (1.2 equiv), chromatography (basic Al_2O_3, CH_2Cl_2), 60% (two steps).

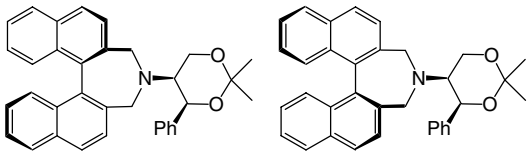
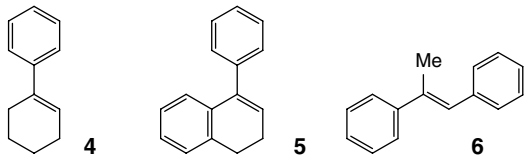


Figure 2. Tertiary amines **2a** and **3a** directly related to iminium cations **2i** and **3i**.

the iminium salt; and (iii) an ion pair metathesis with an ammonium TRISPHAT salt to afford the final product (60%, two steps).[19] With both compounds **1a** and [**1i**][TRISPHAT] available, there was thus a unique opportunity to perform an amine/ammonium versus iminium comparison—tertiary amines of type **1a** being undocumented prior to this study as catalysts in (enantioselective) olefin epoxidation reactions.



Two different sets of epoxidation conditions (**A** and **B**, vide supra) and three different prochiral trisubstituted unfunctionalized alkenes (**4**–**6**) were selected for the study. The results are reported in Table 1. Significantly, both reagents **1a** and [**1i**][TRISPHAT] behaved as effective catalysts under the two sets of experimental conditions.[20] Non-racemic epoxides of analogous absolute configurations were isolated from the reactions with **1a** and [**1i**][TRISPHAT]. Whereas amine **1a** performed better in terms of conversions and enantiomeric excesses in CH_3CN/H_2O (conditions **A**), iminium salt [**1i**][TRISPHAT] gave better (overall) results in biphasic CH_2Cl_2/H_2O medium (conditions **B**). Enantiomeric excesses up to 51% and 68% (alkene **5**) were obtained with **1a** and [**1i**][TRISPHAT], respectively, the 51% value being in fair comparison with that previously obtained with secondary amine/ammonium salts.[15,17]

To extend the scope of the study, and potentially increase the selectivity of the amine/ammonium catalyzed reactions, compounds **2a** and **3a** were prepared following the protocol detailed above (Scheme 1) with (*R*)- and (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl as substrates, respectively, these compounds being further derived into the diastereomeric iminium salts [**2i**][TRISPHAT] and [**3i**][TRISPHAT].

Olefins **4**–**6** were then treated under conditions **A** and **B** with substoichiometric amounts (5 mol %) of **2a**, **3a**, [**2i**][TRISPHAT] and [**3i**][TRISPHAT]. The results are reported in Tables 2 and 3; all four derivatives behave as catalysts. Careful analysis of the data reveals a number of subtleties, but some general trends can be found.

As far as solvent effects are concerned, CH_3CN/H_2O conditions (**A**) were better overall than biphasic

Table 1. Enantioselective epoxidation of olefins **4**–**6** using **1a** and [**1i**][TRISPHAT] as catalysts

Alkene[c]	Amine **1a**						Iminium [**1i**][TRISPHAT]					
	Conditions **A**[a]			Conditions **B**[b]			Conditions **A**[a]			Conditions **B**[b]		
	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.
4	90[e,f]	53	(−)-(*S*,*S*)	78[d]	26	(−)-(*S*,*S*)	75[e,f]	54	(−)-(*S*,*S*)	81[d]	54	(−)-(*S*,*S*)
5	50[e,f]	51	(+)-(1*R*,2*S*)	66[d]	23	(+)-(1*R*,2*S*)	36[e,f]	57	(+)-(1*R*,2*S*)	85[d]	68	(+)-(1*R*,2*S*)
6	97[d]	36	(−)-(*S*,*S*)	73[d]	21	(−)-(*S*,*S*)	95[d]	33	(−)-(*S*,*S*)	88[d]	36	(−)-(*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 (**4**, Chiraldex Hydrodex β-3P) or CSP-HPLC (**5** and **6**, Chiralcel OD-H); the conversions using an internal standard (naphthalene).
[d] 2 h reaction time.
[e] 15 min reaction time.
[f] Complete conversion was observed in 2 h along with some product decomposition. Care was thus taken to select a shorter reaction time.

Table 2. Enantioselective epoxidation of olefins **4**–**6** using **2a** and [**2i**][TRISPHAT] as catalysts

Alkene[c]	Amine **2a**						Iminium [**2i**][TRISPHAT]					
	Conditions **A**[a]			Conditions **B**[b]			Conditions **A**[a]			Conditions **B**[b]		
	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.
4	100[e,f]	78	(−)-(*S*,*S*)	90[d]	65	(−)-(*S*,*S*)	64[e,f]	79	(−)-(*S*,*S*)	99[d]	77	(−)-(*S*,*S*)
5	99[e,f]	80	(+)-(1*R*,2*S*)	87[d]	45	(+)-(1*R*,2*S*)	34[e,f]	71	(+)-(1*R*,2*S*)	90[d]	78	(+)-(1*R*,2*S*)
6	94[d]	48	(−)-(*S*,*S*)	58[d]	48	(−)-(*S*,*S*)	88[d]	47	(−)-(*S*,*S*)	80[d]	46	(−)-(*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 eq 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 (**4**, Chiraldex Hydrodex β-3P) or CSP-HPLC (**5** and **6**, Chiralcel OD-H); the conversions using an internal standard (naphthalene).
[d] 2 h reaction time.
[e] 15 min reaction time.
[f] Complete conversion was observed in 2 h along with some product decomposition. Care was thus taken to select a shorter reaction time.

Table 3. Enantioselective epoxidation of olefins **4**–**6** using **3a** and [**3i**][TRISPHAT] as catalysts

Alkene[c]	Amine **3a**						Iminium [**3i**][TRISPHAT]					
	Conditions **A**[a]			Conditions **B**[b]			Conditions **A**[a]			Conditions **B**[b]		
	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.	Conv. (%)	ee (%)	Conf.
4	99	76	(+)-(*R*,*R*)	70	77	(+)-(*R*,*R*)	98	81	(+)-(*R*,*R*)	54	78	(+)-(*R*,*R*)
5	97	78	(−)-(1*S*,2*R*)	<5	57	(−)-(1*S*,2*R*)	99	83	(−)-(1*S*,2*R*)	33	69	(−)-(1*S*,2*R*)
6	97	52	(+)-(*R*,*R*)	23	53	(+)-(*R*,*R*)	85	52	(+)-(*R*,*R*)	15	54	(+)-(*R*,*R*)

[a] Conditions **A**: 5 mol % of catalyst, 2.0 equiv Oxone®, 5.0 equiv $NaHCO_3$, CH_3CN/H_2O (10:1), 0 °C, 2 h. 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, 2 h. Average of at least two runs.
[c] The enantiomeric excesses were determined by CSP-GC (**4**, Chiraldex Hydrodex β-3P) or CSP-HPLC (**5** and **6**, Chiralcel OD-H); the conversions using an internal standard (naphthalene).

CH_2Cl_2/H_2O (**B**), better conversions occurred in the more polar conditions. In several instances, the reactions were complete in 15 min using conditions **A**, whereas a time of 2 h was necessary with the halogenated solvent mixture. This is true for all catalysts and compound **2a** in particular (e.g., olefin **4**, **A**: 15 min, 100% versus **B**: 2 h, 90%). This trend also holds true for the enantiomeric excesses, which were higher in the more polar conditions (olefin **5**, catalyst **2a**, **A**: ee 80% versus **B**: ee 45%).[21]

If one now compares the selectivity of the diastereomeric catalysts together—that is **2a** with **3a**, and **2i** with **3i**—one generally observes analogous levels of stereoinduction in the (R_a,L) and (S_a,L) series, the only major difference being reversal of the sense of induction for the non-racemic epoxides. It 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 **2i** performed better than **3i**—as previously reported.[11] Amine **2a** also catalyzed

the reaction better than **3a**, in biphasic CH_2Cl_2/water conditions in particular (e.g., olefin **5**, conditions **B**, **2a**: 87% versus **3a**: <5%).

If one now compares the selectivity of the homologous amine and iminium salts—that is **2a** with **2i**, and **3a** with **3i**—one notices that the amines and iminium salts (i) induce the same sense of stereoselective induction into the non-racemic epoxides, and (ii) lead to comparable levels of enantiomeric excesses (with the 'exception' of olefin **5**).[22] A subtle solvent effect is observed for compounds **2a** and **2i**, the amine performing slightly better in conditions **A** and the iminium in CH_2Cl_2/water (conditions **B**). For derivatives **3a** and **3i**, the iminium cation leads to slightly better results in both solvent conditions.

To conclude, amines **1a**–**3a** perform essentially as well as their iminium salts **1i**–**3i** as catalysts for the enantioselective epoxidation of some prochiral olefins—in particular in the acetonitrile/water conditions. As making the amines requires less synthetic steps than the preparation of the iminium salts, it is therefore advantageous to use these 'simpler' reagents for synthetic applications.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.132.

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18. Appropriate pyrrolidine and carbonyl moieties can react together to generate iminium species. Unfortunately, most of these species, in particular the most hindered ones, are prone to solvolysis in the reaction conditions: see Ref. 8.
19. TRISPHAT is chiral. However, it was shown (see Ref. 10b) that its configuration plays no role in the enantioselective epoxidation reaction. For ease of synthesis and better chemical yields in ion pair exchange metathesis, enantiopure [cinchonidinium][Δ-TRISPHAT] was used as a source of hexacoordinated phosphate anion.
20. In view of the previous results by the group of Yang (Ref. 17), one can reason that the presence of two electron-withdrawing oxygen atoms at β-position relative to the amino group in L-acetonamine activates the catalytic activity of the amine/ammonium salt.
21. 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, see Refs. 15 and 17.
22. It is remarkable that the amines and iminium salts leads to such similar enantiomeric excess values. Although it is

reasonable to consider a single mechanistic pathway for the two processes, we have no evidence for it. Under conditions **A** or **B**, no products of oxidation of amines **1a**–**3a** could be characterized or, for that matter, could iminium cations **1i**–**3i** be recovered at the end of the reactions.