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Asymmetric Epoxidation of Olefins Catalyzed by Chiral Iminium Salts Generated in Situ from Amines and Aldehydes

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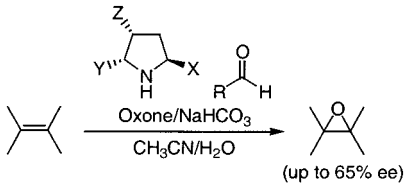
ABSTRACT



A new approach for catalytic asymmetric epoxidation of olefins was developed that utilized chiral iminium salts, generated in situ from chiral amines and aldehydes, as catalysts. Epoxidation reactions can be conducted with 20 mol % of amines and aldehydes. The enantioselectivity of epoxides can be up to 65%. This modular approach obviates the difficulties inherent in the preparation and isolation of unstable exocyclic iminium salts.

Chiral epoxides are important and versatile building blocks in organic synthesis, and development of efficient catalysts for asymmetric epoxidation of olefins has received considerable attention.[1] Oxaziridinium salts, either used in isolated form or generated in situ from iminium salts and Oxone, are powerful electrophilic oxidants for olefin epoxidation.[2] Chiral iminium salts[3−7] have been employed as catalysts for asymmetric epoxidation of olefins with Oxone as the primary oxidant (Figure 1). Generally, the chemical yields were good

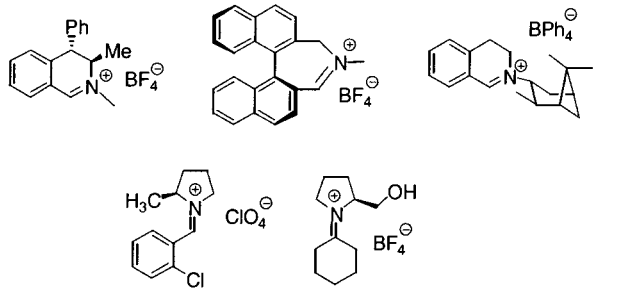


Figure 1.

but the enantioselectivities were only moderate. This could be due to the poor chiral recognition by the flat aryl ring attached to the central carbon of the iminium salts. However, aryl-substituted iminium salts are more stable and more easily

(1) For reviews on asymmetric epoxidation of allylic alcohols, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1. (b) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 621. For a recent review on asymmetric epoxidation of unfunctionalized olefins, see: (c) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 649.

(2) (a) Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727. (b) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 3941.

(3) (a) Bohe, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271. (b) Bohe, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141.

(4) Aggarwal, V. K.; Wang, M. F. *J. Chem. Soc., Chem. Commun.* **1996**, 191.

(5) (a) Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774. (b) Page, P. C. B.; Rassias, G. A.; Barros, D, Bethell, D.; Schilling, M. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, *19*, 3325.

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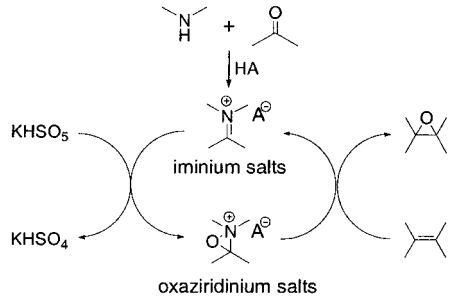
isolated than the alkyl-substituted ones. The intrinsic requirement for an aryl ring severely limits the design and use of chiral iminium salts as catalysts in epoxidation. Alternatively, iminium salts can be generated in situ from the corresponding amines and aldehydes under the conditions for oxidation. In this way, a variety of iminium salts can be generated for screening without prior preparation and purification. Here, we report a new approach for olefin epoxidation promoted by in situ generated iminium salts and its applications in catalytic asymmetric epoxidation.

It is known that iminium salts can be generated from the condensation of a ketone or an aldehyde with a secondary amine. This reaction is catalyzed by acids, which facilitate the aminol dehydration step. On the basis of this mechanism, we can in principle generate a significant amount of iminium salts in situ from amines and aldehydes under slightly acidic conditions (Scheme 1). Then oxaziridinium salts can be

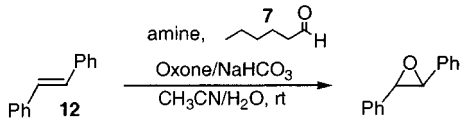
Scheme 1

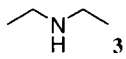
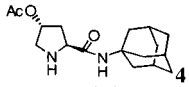
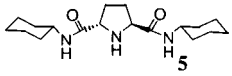


formed by treatment with Oxone and used in olefin epoxidation. After oxygen transfer to olefins, the resulting iminium salts react with an additional 1 equiv of Oxone to generate oxaziridinium salts and complete the catalytic cycle.

With this idea in mind, epoxidation of olefins was conducted by mixing amines and aldehydes in CH_3CN and H_2O followed by the addition of Oxone and $NaHCO_3$. The ratio of Oxone to $NaHCO_3$ was fixed to 1:2.5 in order to provide slightly acidic reaction conditions. As illustrated in Table 1, epoxidation of *trans*-stilbene (**12**) in the presence of a 1:1 ratio of pyrrolidine (**1**) and hexanal (**7**) provided *trans*-stilbene epoxide in 84% yield (based on 77% conversion) in 5 h (entry 1).[8] While no epoxide was obtained in the absence of amine, it is interesting to note that without

Table 1. Asymmetric Epoxidation of *trans*-Stilbene[a]



entry	amine	time	conversion (%)[b]	yield (%)[c]	ee (%)[d]	conversion (%)[b,e]
1	 1	5 h	77	84	--	19
2	 2	5 h	32	99	--	34
3	 3	5 h	33	48	--	<5
4	 4	25 min	95	99	30	<5
5[f]	 5	3 h	63	92	40	<5

[a] Unless otherwise indicated, all epoxidation reactions were carried out at room temperature with 0.1 mmol of *trans*-stilbene, 0.1 mmol of amine, 0.1 mmol of hexanal, 0.4 mmol of Oxone, and 1.0 mmol of $NaHCO_3$ in 2.0 mL of CH_3CN and 0.2 mL of H_2O. [b] Conversion calculated from the recovery of *trans*-stilbene by flash column chromatography. [c] Yield based on conversion after flash column chromatography. [d] Determined by chiral HPLC (OD column); the configuration of the major enantiomer of the epoxide was found to be (*S*,*S*). [e] Reaction performed in the absence of hexanal. [f] Using 0.05 mmol of *trans*-stilbene, 0.05 mmol of amine, 0.05 mmol of hexanal, 0.2 mmol of Oxone, and 0.5 mmol of $NaHCO_3$ in 1.0 mL of CH_3CN and 0.1 mL of H_2O.

the addition of hexanal, the combination of pyrrolidine (**1**) (or piperidine (**2**)) with Oxone effected epoxidation of *trans*-stilbene (**12**) (entries 1 and 2).[9] Epoxidation reactions using six-membered ring piperidine (**2**) and acyclic amine **3** were slower than that with five-membered ring pyrrolidine (**1**) (entries 1 vs 2 and 3). Incorporation of substituents at the 2-

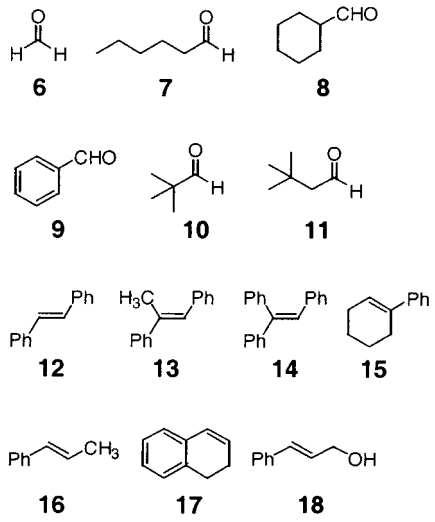


Figure 2.

(6) (a) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K. *Synlett* **1997**, 1075. (b) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341.

(7) Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, *12*, 1810.

(8) **General Procedure for Epoxidation Reactions (Table 1, entry 4).** To a solution of amine **4** (0.1 mmol), hexanal (0.1 mmol), and *trans*-stilbene (0.1 mmol) in CH_3CN (2.0 mL) and H_2O (0.2 mL) at room temperature was added a mixture of Oxone (0.4 mmol) and $NaHCO_3$ (1.0 mmol). After stirring for 25 min, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to provide *trans*-stilbene epoxide (18.4 mg, 99% yield based on 95% conversion) as a white solid. The enantioselectivity of the epoxide was determined to be 30% by chiral HPLC (Chiralcel OD column).

and 4-positions of pyrrolidine significantly influenced the reaction rates. As illustrated in entry 4, epoxidation with amine **4** bearing an acetoxy group at the 4-position and an amide group at the 2-position proceeded faster than that with pyrrolidine (**1**) (entries 1 vs 4) and afforded *trans*-stilbene epoxide with 30% ee in 25 min. When the epoxidation was performed in the presence of C_2 symmetric amine **5** and hexanal (**7**), *trans*-stilbene epoxide was obtained with 40% ee in 3 h (entry 5). Interestingly, unlike amines **1** and **2**, epoxidation reactions with amines **3**−**5** only gave a small amount of *trans*-stilbene epoxide in the absence of hexanal (**7**) (entries 1 and 2 vs 3−5).

With amines **4** and **5** in hand, we investigated the effect of aldehydes in epoxidation (Figure 2), and the results are illustrated in Table 2. It was noticed that the reaction rates

Table 2. Asymmetric Epoxidation of *trans*-Stilbene **12**[a]

entry	amine	aldehyde	time	conversion[b] (%)	yield[c] (%)	ee[d] (%)
1	**4**	**6**	25 min	100	100	16
2	**4**	**7**	25 min	95	99	30
3	**4**	**8**	25 min	<2		
4	**4**	**9**	25 min	0		
5	**4**	**10**	25 min	0		
6	**4**	**11**	2 h	96	100	50
7[e]	**5**	**6**	3 h	79	91	16
8[e]	**5**	**7**	3 h	63	92	40
9[e]	**5**	**11**	3 h	66	97	54
10[e,f]	**5**	**11**	3 h	80	93	65

[a] Unless otherwise indicated, all epoxidation reactions were carried out at room temperature with 0.1 mmol of *trans*-stilbene, 0.1 mmol of amine, 0.1 mmol of aldehyde, 0.4 mmol of Oxone, and 1.0 mmol of $NaHCO_3$ in 2.0 mL of CH_3CN and 0.2 mL of H_2O. [b] Conversion was calculated from the recovery of *trans*-stilbene by flash column chromatography. [c] Yield based on conversion after flash column chromatography. [d] Determined by chiral HPLC (OD column); the configuration of the major enantiomer of the epoxide was found to be (*S*,*S*). [e] Using 0.05 mmol of *trans*-stilbene, 0.05 mmol of amine, 0.05 mmol of aldehyde, 0.2 mmol of Oxone, and 0.5 mmol of $NaHCO_3$ in 1.0 mL of CH_3CN and 0.1 mL of H_2O. [f] At 0 °C.

decreased as the steric bulkiness of aldehydes at the α-position increased (entries 1−5). Epoxidation reactions with sterically less hindered formaldehyde (**6**) and hexanal (**7**) gave almost complete conversion in 25 min, whereas reactions with more bulky cyclohexanecarboxaldehyde (**8**), benzaldehyde (**9**), and trimethylacetaldehyde (**10**) gave less than 2% conversion in the same reaction time (entries 1 and 2 vs 3−5). This may be due to the steric effect, which disfavors the formation of iminium salts. More interestingly, the structure of aldehydes plays an important role on enantioselectivity. In the epoxidation reactions with amine **4**, the enantioselectivities increased from 16% to 30% when formaldehyde (**6**) was replaced by hexanal (**7**) (entries 1 vs 2). When a *β*-branching aldehyde **11** was employed, a further increase in ee was observed (50%; entry 6). The same trend was observed in the epoxidation reactions when C_2 symmetric amine **5** was used (entries 7−9). When the reaction temperature was lowered to 0 °C, the ee value increased from 54% to 65% (entries 9 vs 10).

As iminium salts are known to be highly reactive catalysts, we anticipated that less than stoichiometric amounts of amines and aldehydes could be used for epoxidation. Indeed, we were pleased to find that epoxidation could proceed smoothly with 20−50 mol % of amine **4** and aldehyde **11**, and the results are summarized in Table 3.[10] It was noted

Table 3. Catalytic Asymmetric Epoxidation of Olefins Using Amine **4** and Aldehyde **11**[a]

entry	olefin	cat. loading (mol %)	time (h)	conversion[b] (%)	yield[c] (%)	ee[d] (%)	epoxide config[e]
1	**12**	50	5	81	86	46	(*S*,*S*)
2	**13**	50	0.5	100	100	51	(*S*,*S*)
3[f]	**13**	20	1.5	96	95	51	(*S*,*S*)
4[g]	**13**	50	1.3	100	99	59	(*S*,*S*)
5	**14**	50	2	98	91	54	(*S*)
6[f]	**14**	20	2.5	81	93	52	(*S*)
7	**15**	50	1.5	85	94	46[h]	(*S*,*S*)
8	**16**	50	8	97	73	25[h]	(*S*)
9	**17**	50	8	81	51	26	n.d.
10	**18**	50	8	94	75	17	(*S*,*S*)

[a] Unless otherwise indicated, all epoxidation reactions were carried out at room temperature with 0.1 mmol of olefins, 0.05 mmol of amine, 0.05 mmol of aldehyde, 0.4 mmol of Oxone, and 1.0 mmol of $NaHCO_3$ in 1.0 mL of CH_3CN and 0.1 mL of H_2O. [b] Conversion was calculated from the recovery of olefins by flash column chromatography. [c] Yield based on conversion after flash column chromatography. [d] Determined by chiral HPLC (OD column). [e] The configuration of the major enantiomer of the epoxides was determined by correlation to the known chiral epoxides. [f] Using 0.02 mmol of amine and 0.02 mmol of aldehyde. [g] At 0 °C. [h] Determined by ^1H NMR using chiral shift reagent $Eu(hfc)_3$ (Aldrich no. 16,474-7).

that amine **4** and aldehyde **11** gave higher catalytic efficiency and enantioselectivities for epoxidation of *trans*-stilbene (**12**) (entry 1) and trisubstituted olefins **13**−**15** (entries 2−7) than *trans*-*β*-methyl styrene (**16**) (entry 8), *cis*-olefin **17** (entry 9), and allylic alcohol **18** (entry 10). For trisubstituted olefins **13** and **14**, only 20 mol % of amine and aldehyde were required to effect epoxidation without compromise on reactivity and enantioselectivity (entries 2 vs 3; entries 5 vs 6). For *trans*-*β*-methyl stilbene (**13**), a further increase in enantioselectivity from 51% to 59% was observed when the reaction was conducted at 0 °C. Epoxidation of 1-phenylcyclohexene (**15**) proceeded smoothly to afford the chiral epoxide with 46% ee. However, for less reactive olefins **16**−**18**, longer reaction time was required, and the enantioselectivities of epoxides were low.

(9) While our work was ongoing, Aggarwal and co-workers reported that amines could be used as catalysts for epoxidation with Oxone as the primary oxidant, and the reaction conditions were quite similar to ours; see: Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317.

(10) Control experiments were performed in the absence of aldehyde for epoxidation reactions in Table 3, and it was found that less than 5% conversion of olefins were observed for olefins **12**−**15** within the indicated reaction time. However, for olefins **16**−**18**, up to 48% conversion of styrene **16** and 25% conversion of olefins **17** and **18** were observed in 8 h. The origin of these amine promoted epoxidation reactions is under investigation.

To provide mechanistic insights on the epoxidation reactions, a series of epoxidation reactions of *trans*-stilbene (**12**) were performed with different ratios of amine **4** to hexanal (**7**) at room temperature, and the reaction time was fixed to 25 min. The % conversion of *trans*-stilbene (**12**) was plotted against the mole fraction of amine **4**, and a bell-shape curve (Job plot) was obtained (Figure 3).[11] The maximum substrate

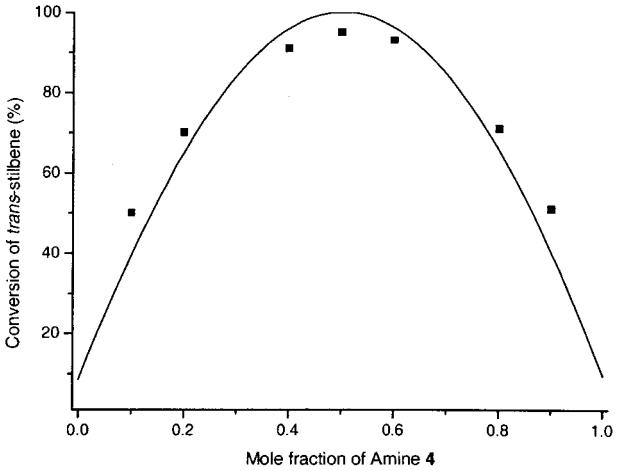


Figure 3. Job plot of mole fraction of amine **4** against the percentage conversion of *trans*-stilbene (**12**).

conversion was observed when the mole fraction of amine **4** was 0.5, suggesting that the reactive intermediate in the epoxidation reactions probably came from a 1:1 adduct of amine and aldehyde. The enantioselectivity of the epoxides were found to be essentially the same (~30% ee) regardless of the ratio of the amine to aldehyde, indicating that the same chiral intermediate was generated for epoxidation. These experimental evidences suggested that chiral iminium salts were most likely the catalysts responsible for epoxidation.

In summary, we have developed an efficient protocol for asymmetric epoxidation of olefins catalyzed by iminium salts generated in situ from chiral amines and aldehydes. This method allows fine-tuning of the steric and electronic properties of iminium salts by simple combination of various amines and aldehydes. Future work will be directed at understanding the mechanism of chiral induction as well as developing better iminium salt catalysts in terms of catalytic efficiency and enantioselectivity.[12]

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Supporting Information Available: Experimental procedures for the preparation of amines **4** and **5**; ee determination of chiral epoxides by HPLC and NMR; ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Job, D. *Ann. Chim. (Paris)* **1928**, *9*, 113.

(12) In principle, upon treatment with Oxone the iminium salt generated from C_2 symmetric amine **5** and an aliphatic aldehyde may provide two diastereomeric oxaziridinium salts (with opposite configurations of the oxaziridinium ring), which may afford epoxides of different configurations and enantioselectivities. Without knowledge on the reactivities and relative ratio of the two diastereomeric oxaziridinium salts, it is difficult to draw a clear conclusion for the transition state geometry and the origin of asymmetric induction. For recent theoretical calculations favoring a spiro transition state for epoxidation by oxaziridinium salts, see: Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 2948.