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Fluorinated Chiral Secondary Amines as Catalysts for Epoxidation of Olefins with Oxone

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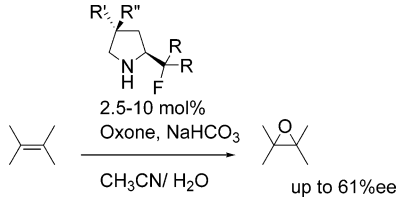
Received September 14, 2004



We have synthesized a series of chiral cyclic secondary amines having different substitution patterns and have screened them as catalysts for the asymmetric epoxidation of olefins using Oxone. The highest enantiomeric excess (61%) occurred for the epoxidation of 1-phenylcyclohexene catalyzed by a secondary amine bearing a fluorine atom at the β-position relative to the amino center. Our experimental results provide further support to the notion that the amine plays a dual role—as a phase transfer catalyst and an Oxone activator—in these epoxidation reactions. The slightly acidic reaction conditions we employed in this work obviate the need to preform ammonium salts, which are the actual catalysts that mediate the epoxidations.

Introduction

The development of efficient methods for asymmetric epoxidation of alkenes has attracted considerable attention[1,2] because chiral epoxides are versatile building blocks in organic synthesis.[3] In addition, many biologically active compounds and natural products contain epoxide functionalities.[4] Over the years, our research group has devoted considerable effort toward the development of methods for the stereoselective epoxidation of alkenes.[2a,5,6]

Recently, we developed an asymmetric epoxidation protocol that uses chiral iminium salts generated in situ from amines and aldehydes under slightly acidic conditions.[6] Interestingly, we found that some cyclic secondary amines could promote epoxidation of alkenes when using Oxone as the oxidant. During our ongoing studies on these iminium salt-catalyzed epoxidations, Aggarwal and co-workers reported that amines and amine·HCl salts could catalyze alkene epoxidation.[7a,b] More recently,

(1) For reviews on asymmetric epoxidation of allylic alcohols, see: (a) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, pp 621−648. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; New York, 1993; pp 103−158.

(2) For recent reviews on asymmetric epoxidation, see: (a) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497−505. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488−496. (c) Adam, W.; Saha-Moeller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499−3548. (d) Frohn, M.; Shi, Y. *Synthesis* **2000**, *14*, 1979−2000. (e) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, pp 649−678. (f) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847−859. (g) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; New York, 1993; pp 159−202.

(3) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67−80.

(4) For examples of the total syntheses of natural products containing epoxides, see: (a) José, M. C.; María, T. M.; Shazia, A. *Chem. Rev.* **2004**, *104*, 2857−2900. (b) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095−5106. (c) Yang, D.; Ye, X. Y.; Xu, M. *J. Org. Chem.* **2000**, *65*, 2208−2217. (d) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543−2552. (e) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1946**, *11*, 3526−3527. (f) Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Finlay, M. R. V.; Boddy, C. N. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 81−84. (g) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268−272.

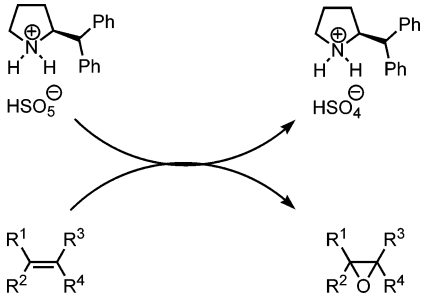
(5) For asymmetric epoxidations with chiral dioxiranes, see: (a) Yang, D.; Jiao, G. S.; Yip, Y. C.; Lai, T. H.; Wong, M. K. *J. Org. Chem.* **2001**, *66*, 4619−4624. (b) Yang, D.; Yip, Y. C.; Chen, J.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 7659−7660. (c) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943−5952. (d) Yang, D.; Wang, X. C.; Wong, M. K.; Yip, Y. C.; Tang, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 11311−11312. (e) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491−492.

(6) For asymmetric epoxidations with iminium salts generated in situ from amines and aldehydes, see: Wong, M. K.; Ho, L. M.; Zheng, Y. S.; Ho, C. Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587−2590.

(7) For amine-catalyzed epoxidations, see: (a) Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317−8318. (b) Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A *J. Am. Chem. Soc.* **2002**, *124*, 11223. (c) Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596−7601.

10.1021/jo048378t CCC: $30.25
Published on Web 01/08/2005

SCHEME 1. Epoxidation Mechanism Proposed Recently by Aggarwal et al.



Aggarwal et al. proposed a new mechanism for the epoxidation in which the amine·HCl salts most likely function as phase transfer catalysts and Oxone activators (Scheme 1).[7c,8]

In this paper, we report our results obtained from a systematic investigation of the amine-catalyzed epoxidation. In particular, we have discovered that substituents on the cyclic skeleton of the secondary amine exert significant effects on the catalytic efficiency and enantioselectivity of the epoxidation.

Results and Discussion

Preliminary Screening of Amine Catalysts for Epoxidation of Alkenes. During our studies on the asymmetric alkene epoxidation catalyzed by chiral iminium salts generated in situ from amines and aldehydes, we found that amines themselves could promote epoxidation under slightly acidic reaction conditions.[6] To investigate the substituent effect that the amines have on the epoxidation, we screened a variety of amines using our previously reported epoxidation conditions (Table 1). We conducted the epoxidation reactions by adding a mixture of Oxone (0.4 mmol) and $NaHCO_3$ (1 mmol) to a solution of amine (0.1 mmol) and *trans*-stilbene (0.1 mmol) in CH_3CN (2.0 mL) and H_2O (0.2 mL) at room temperature.

We found that cyclic secondary amines are better catalysts than are acyclic primary and secondary amines in terms of their activity in catalyzing the epoxidation of *trans*-stilbene (cf. entries 1 and 2 with entries 3, 4, and 8). It is noteworthy that the use of amine **4**, which possesses an oxygen atom β to the amino group, resulted in a faster reaction than did amine **3** (cf. entries 3 and 4). Other secondary amines, such as **5** and **6**, that bear β-hydroxyl groups also displayed high conversions (up to 89%) and yields (92−96%) for *trans*-stilbene epoxidation within 3 h (cf. entries 5 and 6 with entry 2).[9] It is worth highlighting that these simple, cheap, and commercially available achiral amines (amines **5** and **6**) are effective epoxidation catalysts. Amine **6** can be applied to the complete epoxidation of *trans*-stilbene, *trans*-methylstilbene, and β-methylstyrene in 90% isolated yield after 5 h. In contrast, we found that primary amino alcohol **7** was ineffective: it resulted in <1% alkene conversion (entry 7). These preliminary screening results indicate that incorporating the structural features of a cyclic skeleton and a β-hydroxyl substitutent into secondary amines can improve their catalytic efficiency in the epoxidation of olefins.

Next we examined a series of 2-substituted pyrrolidines (**8b**−**h**) for their catalytic activities. Amines **8b**−**d** that bear either a β-hydroxyl or OMe group gave better conversions and yields than did pyrrolidine itself (cf. entries 9−11 with entry 8). Notably, amine **8c**, which bears a bulky CPh_2OH substituent, gave moderate conversion, yield, and enantioselectivity (78% yield based on 59% conversion, 33% ee; entry 10).[7c,10] In addition, while amine **8e** bearing a β-amino group also gave high alkene conversion (90%; entry 12), we found that L-proline **8f** and its carboxylic acid derivatives **8g**,**h** were not effective in promoting epoxidation (conversion <22%; entries 13−15).

Furthermore, we discovered that substituents on the 4-position of the pyrrolidine ring exhibited a remarkable effect on the substrate conversion:[11] Whereas amine **9a**, which bears an acetoxy group at the 4-position, gave <5% conversion (entry 16), amines **9b** and **9c**, which feature hydroxyl and OMOM groups, respectively, at the 4-position resulted in up to 96% conversion of the alkene (entries 17 and 18). These results suggest that the incorporation of a suitable heteroatom β to the pyrrolidine amino group can be beneficial to the catalytic efficiency.

Design of Amines That Provide High Catalytic Efficiency and Better Chiral Induction in Epoxidation. As described in the previous section, amine **8c** bearing a bulky CPh_2OH group at the 2-position of the pyrrolidine ring gave good reactivity, but moderate enantioselectivity. We decided to improve the reactivity and the enantioselectivity by systematically modifying the structure of **8c**. Accordingly, we synthesized amines **10**, **12a**−**g**, and **13a**−**c**, which have various heteroatom substituents positioned β to the amino group, and performed epoxidation reactions of 1-phenylcyclohexene catalyzed by 5 mol % of those amines in the presence of lower amounts of Oxone (2 equiv) and $NaHCO_3$ (5 equiv);[11] Table 2 summarizes our results. Under these reaction conditions, 1-phenylcyclohexene epoxide was the major product, along with 1-phenylcyclohexene-1,2-*cis*-diol.[12] We found that amine **10** and Aggarwal's amine **11a**, which bear OMe and H groups, respectively, at their benzylic positions, gave higher conversions and yields (100% conversion, 73−87% yield; entries 2−3) than did **8c**, which bears an OH group (58% conversion, 41% yield; entry 1).[7c,10] More importantly, **12a**, which bears a fluorine atom located β to the amino center, provided the highest catalytic efficiency and enantioselectivity (100% conversion, 87% yield, 50% ee; entry 4).[13−15] Further increases in enantioselectivity (up to 56% ee) were

(8) Armstrong, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1460−1462.

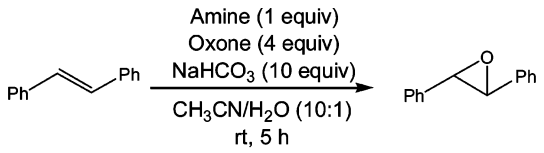
(9) The reasons why β-hydroxylamines efficiently promote epoxidation of olefins are under investigation.

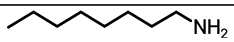
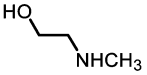
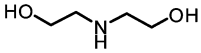
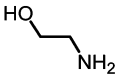
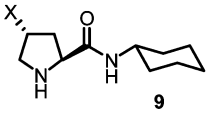
(10) In the amine-catalyzed epoxidation of *trans*-stilbene with amine **8c**, the amine subsequently decomposed to give benzophenone and nitrone. (a) Su, Z.; Mariano, P. K.; Falvey, D. E.; Yoon, U. C.; Oh, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 10676−10686. (b) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170−6172.

(11) The procedures for the preparation of amines **9a**−**c**, **10**, **12b**−**g**, **13a**−**c**, and **14** are provided in the Supporting Information.

(12) We found that under our slightly acidic reaction system, *cis*-1,2-diol is the major hydrolysis product of 1-phenylcyclohexene oxide. This finding is in agreement with literature reports that the *cis*-1,2-diol is more stable than the *trans*-1,2-diol. (a) Berti, G.; Bottari, F.; Macchia, B.; Macchia, F. *J. Org. Chem.* **1952**, *17*, 6227−6234. (b) Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kantam, M. L. *Tetrahedron* **1965**, *12*, 3277−3283.

TABLE 1. Amine-Catalyzed Epoxidation of *trans*-Stilbene[a]



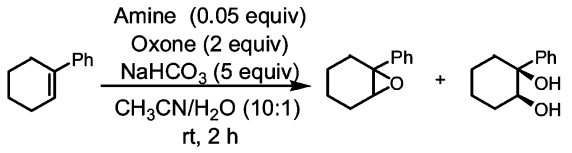
entry	amine			conversion (%)[b]	yield (%)[c]	ee (%)[d]
1		**1**		6	n.d.	–
2		**2**		< 5	n.d.	–
3		**3**		34	n.d.	–
4[e]		**4**		56	98	–
5[e]		**5**		74	92	–
6[e]		**6**		89	96	–
7[e]		**7**		<1	n.d.	–
8	 **8**	**8a**	X = H	19	50	–
9[e,f]		**8b**	X = CH_2OH	84	99	1
10[e]		**8c**	X = CPh_2OH	59	78	33
11[e]		**8d**	X = CH_2OMe	26	65	10
12[e]		**8e**	X = $CH_2N(CH_2)_4$	90	67	5
13		**8f**	X = COOH	<5	n.d.	n.d
14		**8g**	X = $CONH_2$	12	17	8
15		**8h**	X = COOMe	22	68	4
16[g]	 **9**	**9a**	X = OAc	<5	100	20
17[g]		**9b**	X = OH	96	92	7
18[g]		**9c**	X = OMOM	86	86	13

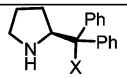
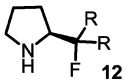
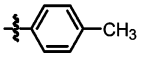
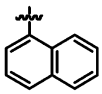
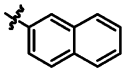
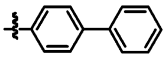
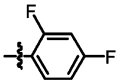
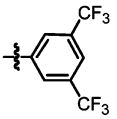
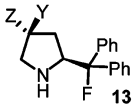
[a] Unless otherwise indicated, all epoxidation reactions were performed at room temperature over 5 h with 0.1 mmol of *trans*-stilbene, 0.1 mmol of amine, 0.4 mmol of Oxone, and 1 mmol of $NaHCO_3$ in 2 mL of CH_3CN and 0.2 mL of H_2O. [b] Conversion calculated from the recovery of *trans*-stilbene after flash column chromatography. [c] Yield based on conversion after flash column chromatography. [d] Determined by chiral HPLC analysis (Daicel OD column); the major enantiomer of the epoxide has the (*S*,*S*) configuration. [e] 3 h. [f] Using D-prolinol, the configuration of the major enantiomer of the epoxide was (*R*,*R*). [g] 40 min.

achieved when the epoxidation reactions were conducted at 0 or −20 °C (entries 5 and 6). Although the reaction proceeded more slowly at −20 °C, no diol side product was formed. These results reflect the importance of incorporating an electronegative atom (fluorine) at the β-position relative to the amino group.

Aggarwal et al. reported that increasing the steric bulk of the aryl group of the amine catalyst (from phenyl to α-naphthyl) led to an increase in the enantioselectivity of 1-phenylcyclohexene epoxidation (from 46% to 59%; Scheme 2).[7c] We also attempted to improve the enantioselectivity of the epoxide formation by modifying the aryl

TABLE 2. Amine-Catalyzed Epoxidation of 1-Phenylcyclohexene[a]



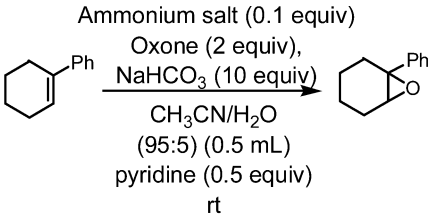
entry	amine			conversion (%)[b]	yield (%)[b]	ee (%)[c]	diol (%)[b]
1		**8c**	X = OH	58	41	43	5
2		**10**	X = OMe	100	83	43	12
3		**11a**	X = H	100	73	31	17
4		**12a**	X = F	100	87	50	12
5[d,e]		**12a**		100	74	56	12
6[d,f]		**12a**		61	96	54	0
7		**12b**	R = 	100	76	52	13
8[d,f]		**12b**		69	92	61	0
9		**12c**	R = 	96	79	45	14
10		**12d**	R = 	94	82	45	9
11		**12e**	R = 	100	66	46	20
12		**12f**	R = 	43	86	33	13
13		**12g**	R = 	31	68	0	14
14		**13a**	Z = OH Y = H	52	65	23	19
15		**13b**	Z = OMe Y = H	52	79	37	7
16		**13c**	Z = F Y = F	16	41	5	0

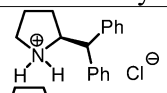
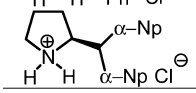
[a] Unless otherwise indicated, all of the epoxidation reactions were performed at room temperature for 2 h with 0.4 mmol of 1-phenylcyclohexene, 5 mol % of amine catalyst, 0.8 mmol of Oxone, and 2 mmol of $NaHCO_3$ in 1 mL of CH_3CN and 0.1 mL of H_2O. [b] Based on conversion and determined by integration of ^1H NMR spectra relative to an internal standard (nitrobenzene). [c] Enantioselectivities determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ (Aldrich no. 16,474-7) as a chiral shift reagent; the configuration of the major enantiomer of the epoxide was (*S*,*S*). [d] 4 h. [e] Reaction performed at 0 °C. [f] Reaction performed at −20 °C.

group of the amine catalysts (Table 2; entries 7−13). In contrast to Aggarwal's findings,[7c] we found that introducing sterically more demanding groups to our amines did not provide any significant improvement in the enantioselectivity of epoxidation. We obtained similar ee values for the epoxidation catalyzed by **12b**−**e** at room temperature (45−52% ee; entries 4, 7, and 9−11). At −20 °C, we achieved the highest enantioselectivity (61% ee) with complete suppression of diol formation when the epoxidation was catalyzed by amine **12b**.

Interestingly, we found that the electronic properties of the aryl ring of the amine have a significant influence on alkene conversion and enantioselectivity (entries 12 and 13).[16,17] The introduction of electron-withdrawing substituents (F and CF_3 groups) on the aryl ring led to decreases in the values of conversion, yield, and ee. As

SCHEME 2. Effect That the Steric Demand of the Amine Catalyst Has on the Enantioselectivity of 1-Phenylcyclohexene Epoxidation Reported by Aggarwal et al.[7c]



amine catalyst	reaction time	yield (%)	ee (%)
	20 min	93	46
	60 min	89	59

indicated in Table 2, amine **12g**, which bears two CF_3 groups on the aryl rings, gave racemic epoxide in 31% conversion (entry 13). Because the corresponding ammonium salts are the actual catalysts for the epoxidation reactions,[7c] the presence of electron-withdrawing substituents on the aryl ring may disfavor protonation of the amine by means of inductive or electrostatic effects that, consequently, decrease the catalyst's concentration, which results in lower values of conversion and ee.[16,17] Another explanation is that the extra F substituents on the aryl ring may increase the hydrophobicity of the amine catalysts, which makes the amine less effective as a phase transfer catalyst.[18]

On the basis of our observation that amines possessing hydroxyl or OMOM groups at the 4-position (**9b** or **9c**) exhibited good reactivity in promoting epoxidation (Table 1, entries 17 and 18), we screened amines **13a**−**c**, which have hydroxyl, methoxy, and difluoro substituents at the 4-position of **12a**, for their catalytic activities (Table 2; entries 14−16).[11,16,17] We found that these functionalities (OH, OMe, and F) at the 4-position of the pyrrolidine ring resulted in low catalytic efficiencies (16−52% alkene conversion, 5−37% ee; entries 14−16), especially for **13c**, which bears two fluorine atoms. These results are similar to the trend we observed for amines **12a**, **12f**, and **12g**.

Asymmetric Epoxidation of Various Alkenes Catalyzed by Amine 12a. We selected amine **12a** as the catalyst for the epoxidation of alkenes having different substitution patterns; Table 3 summarizes the results. We found that the epoxidation proceeded smoothly in the presence of 5−10 mol % of **12a** for most of the substrates (entries 1−6), except for *cis*-stilbene and *trans*-4-octene (entries 7 and 8).[19] We obtained higher enantioselectivities for the epoxidation of 1-phenylcyclohexene (entry 1) than for any of the other substrates (entries 2−5). It is interesting to note that our fluorinated amine gave significantly higher ee values for the epoxidation of aryl olefins than for aliphatic olefins (entries 1 and 2). In the epoxidation of 1-phenylcyclohexene, 2.5 mol % of catalyst **12a** could be employed to give 73% conversion within a reaction time of 3 h, with the ee value of the product epoxide remaining essentially the same (50%). In contrast to Aggarwal's case, the epoxidation of *trans*-stilbene can be achieved by using 10 mol % of amine **12a** without the need to preform the ammonium·HSO_5 complex and use excess amounts of the catalyst (entry 3).[7c] For epoxidation of *trans*-methylstilbene and β-methylstyrene (entries 4 and 5), we required the addition of 10 mol % of amine to effect epoxidation. In the epoxidation of α-methylstyrene, complete conversion was obtained within 3 h. However, the corresponding epoxide was not stable in the reaction system and readily hydrolyzed to the corresponding diol (entry 6).

Mechanistic Studies. We conducted a series of experiments to gain insight into the identity of the active oxidizing species that are responsible for the epoxidation reactions. Our experimental results support Aggarwal's proposal: the secondary amines act as phase transfer catalysts and Oxone activators.[7c]

Aggarwal et al. reported that the oxidation products of amines, such as nitrones, hydroxylamines, and *N*-hydroxylactams, were not the active oxidizing species responsible for epoxidation.[7c] In our current study, we also found that the oxidation products of **12a**[20] were inactive toward epoxidation: no substrate conversion was observed when **12a** was left to stir under the reaction conditions for 1 h prior to the addition of 1-phenylcyclohexene.

In Figure 1 we plot the conversion of 1-phenylcyclohexene against the reaction time when 5 mol % of **12a**

(13) Fluorinated amine **12a** was first prepared and studied as a potential auxiliary for asymmetric alkylation reactions and as a chiral shift agent for the analysis by ^{1}H NMR spectroscopy of the enantiomeric purities of chiral carboxylic acids and alcohols. See: (a) O'Hagan, D.; Royer, F.; Tavasli, M. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2033−2036. (b) Bailey, D. J.; O'Hagan, D.; Tavasli, M. *Tetrahedron*: *Asymmetry* **1997**, *8*, 149−153.

(14) For examples of the use of fluorinated compounds as enzyme substrate mimics, see: (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley & Sons: New York, 1991. (b) Seebach, D. *Angew Chem.*, *Int. Ed. Engl.* **1990**, *29*, 1320−1367. (c) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381−436. (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197. (e) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441−451.

(15) For the X-ray crystallographic structure of amine **12a**·HCl salts, see: Batsanov, A. S.; Howard, J. A. K. *Acta Crystallogr.*, *Sect. C* **2000**, *C56 10*, e467−e468.

(16) For recent examples of electronic effects of catalysts affecting enantioselectivity, see: (a) Cavallo, L.; Jacobsen, H. *J. Org. Chem.* **2003**, *68*, 6202−6207. (b) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Gueler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948−954. (c) Yang, D.; Yip, Y. C.; Chen, J.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 7659−7660. (d) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325−6326. (e) Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem.*, *Int. Ed. Engl.* **1995**, *34*, 931−933. (f) Park, S. B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron*: *Asymmetry* **1995**, *10*, 2487−2494. (g) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939−1942. (h) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *5*, 669−672. (i) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703−6704.

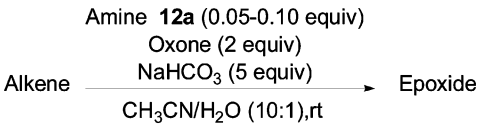
(17) For examples of electronic field effects and inductive effects affecting chemical reactivity, see: (a) Yang, D.; Yip, Y. C.; Jiao, G. S.; Wong, M. K. *J. Org. Chem.* **1998**, *63*, 8952−8956. (b) Bowden, K.; Grubbs, E. J. *Chem. Soc. Rev.* **1996**, 171−177. (c) Stock, L. M. *J. Chem. Educ.* **1972**, *49*, 400−404.

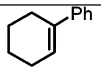
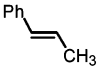
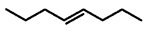
(18) For the use of fluorine atoms to improve the hydrophobicity of a catalyst, see: Wu, J. J.; Fu, L.; Chuang, K. T. *Appl. Catal.* **1991**, *72*, 71−80.

(19) For the determination of the ee values of *trans*-stilbene oxide and *trans*-β-methylstyrene oxide, see: (a) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328−2329. For *trans*-α-methylstilbene oxide, see: (b) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378−4380.

(20) A nitrone was detected by ESI-MS analysis to be the major oxidation product of amine **12a**. For catalytic oxidation of secondary amines to nitrones, see: (a) Murahashi, S. I. *Angew. Chem.*, *Int. Ed. Engl.* **1995**, *34*, 2443−2465. (b) Murahashi, S. I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736−1744.

TABLE 3. Synergistic Effect Observed in the Heterogeneous Epoxidation System[a]



entry	alkene	time (h)	conversion (%)[b]	yield (%)[b]	ee (%)[c]	epoxide configuration	diol (%)[b]
1		2 h	100	87	50	(*S*,*S*)	12
2		2 h	80	80	8	n.d.	–
3[d]		4 h	100	80	28	(*S*,*S*)	–
4[d]		2 h	100	88	33	(*S*,*S*)	–
5[d]		3 h	100	86	15	(*S*,*S*)	–
6[d]		3 h	100	–	–	–	94
7		2 h	20	97	–	–	–
8		2 h	15	25	n.d.	n.d.	–

[a] Unless otherwise indicated, all of the epoxidation reactions were performed at room temperature with 0.4 mmol of alkene, 5 mol % of amine, 0.8 mmol of Oxone, and 2 mmol of $NaHCO_3$ in 1 mL of CH_3CN and 0.1 mL of H_2O. [b] Based on conversion and determined by integration of ^1H NMR spectra relative to an internal standard (nitrobenzene). [c] Enantioselectivities determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ (Aldrich no. 16,474-7) as a chiral shift reagent. [d] 10 mol % of amine was used.

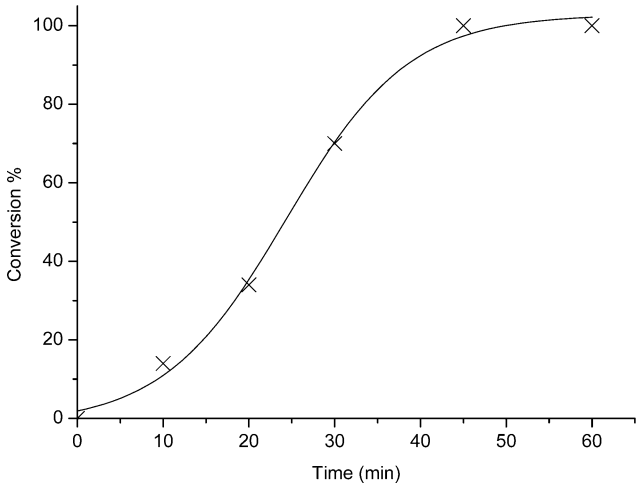


FIGURE 1. A plot of conversion percent versus time for the epoxidation of 1-phenylcyclohexene catalyzed by amine **12a**. Reaction conditions: 0.4 mmol of 1-phenylcyclohexene, 5 mol % of catalyst, 0.8 mmol of Oxone, and 2 mmol of $NaHCO_3$ in 1 mL of CH_3CN and 0.1 mL of H_2O at room temperature. The conversions were determined by integration of ^1H NMR spectra relative to an internal standard (nitrobenzene).

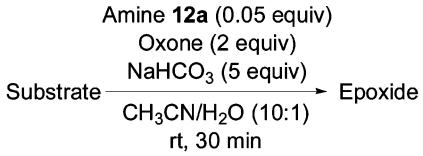
was used as the catalyst for epoxidation. The sigmoidal curve we obtained reveals that an initial induction period was required for the epoxidation. In addition, the value of ee of the chiral epoxide remained essentially unchanged (ca. 50% ee) during the course of the reaction, which indicates that there was a consistent chiral intermediate responsible for the asymmetric epoxidation. It is likely that **12a** was converted into its corresponding ammonium salt under the slightly acidic conditions at the beginning of the reaction (0−10 min). After the complete protonation of **12a**, the epoxidation rate reached a maximum value (10−40 min) and then leveled off after 40 min.

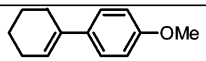
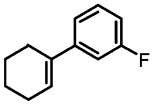
Electrophilic Nature of the Active Oxidizing Species. To probe the electronic nature of the active oxidizing species in our reaction system, we conducted epoxidation reactions of several 1-arylcyclohexenes that bear substituents on the phenyl ring that have different electronic properties (*p*-OMe, H, and *m*-F) using 5 mol % of **12a** as the catalyst;[21,22] Table 4 summarizes the results. We note that, within a 30-min reaction time,

(21) For substrate syntheses, see: (a) Collins, D. J.; Molinski, T. F.; Sjoevall, J. *Aust. J. Chem.* **1983**, *36*, 361−370. (b) Shabarov, Y.; Blagodatskikh, S. A.; Levina, M. I. *Zh. Org. Khim.* **1975**, *11*, 1223−1225.

(22) For recent examples of substrate electronic effects affecting enantioselectivity, see: (a) Wang, M.-X.; Lin, S.-J.; Liu, C.-S.; Zheng, Q.-Y.; Li, J.-S. *J. Org. Chem.* **2003**, *68*, 4570−4573. (b) Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Bhadbhade, M. M.; Suresh, E. *J. Mol. Catal. A*: *Chem.* **1999**, *1−2*, 185−194. (c) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002−8003. (d) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153−9156.

TABLE 4. Catalytic Epoxidation of Alkenes with Amine 12a[a]



entry	substrate	conversion (%)[b]	yield (%)[b]	ee (%)[c]
1		60	80[d]	n.d.[e]
2		53	70	48
3		21	95	48

[a] Unless otherwise indicated, all the epoxidation reactions were performed at room temperature for 30 min with 0.4 mmol of substrate, 5 mol % of amine catalyst, 0.8 mmol of Oxone, and 2 mmol of $NaHCO_3$ in 1 mL of CH_3CN and 0.1 mL of H_2O. [b] Based on conversion and determined by integrating ^1H NMR spectra relative to an internal standard (nitrobenzene). [c] Enantioselectivities were determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ (Aldrich no. 16,474-7) as a chiral shift reagent; the configuration of the major enantiomer of the epoxide was (*S*,*S*). [d] Yield of the corresponding diol: the epoxide was not stable in the reaction system and was readily hydrolyzed. [e] The value of ee of the diol was not determined.

higher conversion occurred for the electron-rich *p*-OMe-substituted substrate (60% conversion; entry 1) than for the electron-deficient *m*-F-substituted one (21% alkene conversion; entry 3). The lower reaction rate for the less-electron-rich alkene indicates that the active oxidizing species has an electrophilic nature. This trend is in agreement with the phase transfer catalyst mechanism proposed by Aggarwal in which the electrophilic ammonium ion·HSO_5 complex is the active oxidizing species.[7c]

Epoxidation with Free Amines and Amine·HCl Salts. Aggarwal and co-workers reported that preforming the amine·HCl salts provides more reproducible results and higher enantioselectivities relative to the use of free amines to catalyze the epoxidation of olefins.[7c] This finding led us to perform experiments side-by-side to compare the reactivities of free amines **12a**, **12b**, and **14** with those of the corresponding amine·HCl salts toward epoxidation (Table 5).

Under our reaction system, we did not observe any significant improvement in conversion, yield, or enantioselectivity when using the HCl salts of our fluorinated amines **12a** and **12b** (entries 1−4); only the preformed HCl salt of the nonfluorinated amine **14** displayed an enhanced enantioselectivity (cf. entries 5 and 6).

We speculate that the discrepancy between our results and those reported by Aggarwal may arise from differences in the reaction systems and the amines used (Scheme 3).

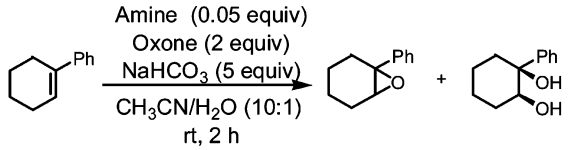
Relative to Aggarwal's amine-catalyzed epoxidation system,[7c] our system uses lower amounts of $NaHCO_3$ and no pyridine is added; thus, we provide a more acidic reaction medium to facilitate the protonation of amines. Under our slightly acidic reaction conditions,[6] the free amines are readily converted in situ to the corresponding ammonium salts necessary for epoxidation. The induction period of the first 10 min of the sigmoidal curve indicated in Figure 1 might be the time required for the amine protonation. It is worth noting that using free amines as catalysts under our epoxidation conditions provided reproducible results. In addition, the presence of electronegative fluorine atoms may stabilize the positively charged ammonium salts through favorable charge-dipole interactions or mild hydrogen bond formation with an ammonium proton (Figure 2).[23] We believe that the presence of the fluorine atom on the amines and the slightly acidic reaction medium we employed are the reasons why we had no difficulty in reproducing the epoxidation results when using free amines. At this stage, however, it is still difficult to draw a clear conclusion of the transition state geometry to explain the configuration of the epoxides.

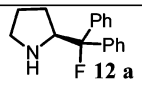
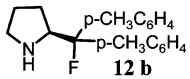
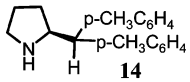
Amines as Both Phase Transfer Catalysts and Oxone Activators Demonstrated in a Heterogeneous Epoxidation System. We employed amine **12a** also for the epoxidation of 1-phenylcyclohexene in a heterogeneous solvent system (1 mL of CH_2Cl_2 and 0.5 mL of H_2O); Table 6 summarizes the results. The alkene conversion was only 22% (entry 1) when the amine catalyst **12a** was used alone. It is known that 18-crown-6 is a good phase transfer catalyst and can increase the solubility of Oxone in the organic solvents, which favors epoxidation.[24] In the absence of our amine catalyst to provide Oxone activation, however, the use of 18-crown-6 alone resulted in only a 7% conversion of the alkene (entry 2). Notably, the conversion increased significantly to 53% when amine **12a** and 18-crown-6 were both added as cocatalysts (entry 3). These results reveal that, although Oxone transfer to the organic layer has an important effect on the rate of this catalysis, the efficient

(23) For studies on fluorine atoms as hydrogen bond acceptors using the Cambridge Structural Database System, see: (a) Howard, J. A. K.; Hoy V. J.; O'Hagan, D.; Smith G. T. *Tetrahedron* **1996**, *38*, 12613−12622. (b) Shimoni, L.; Glusker, J. P. *Struct. Chem.* **1994**, *5*, 383−397. (c) Murray-Rust, P.; Stalling, W. C.; Monti, C. T.; Preston, R. K.; Glusker, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 3206−3214.

(24) For a heterogeneous solvent system that uses 18-crown-6 and Oxone to perform epoxidation, see: Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8257−8260.

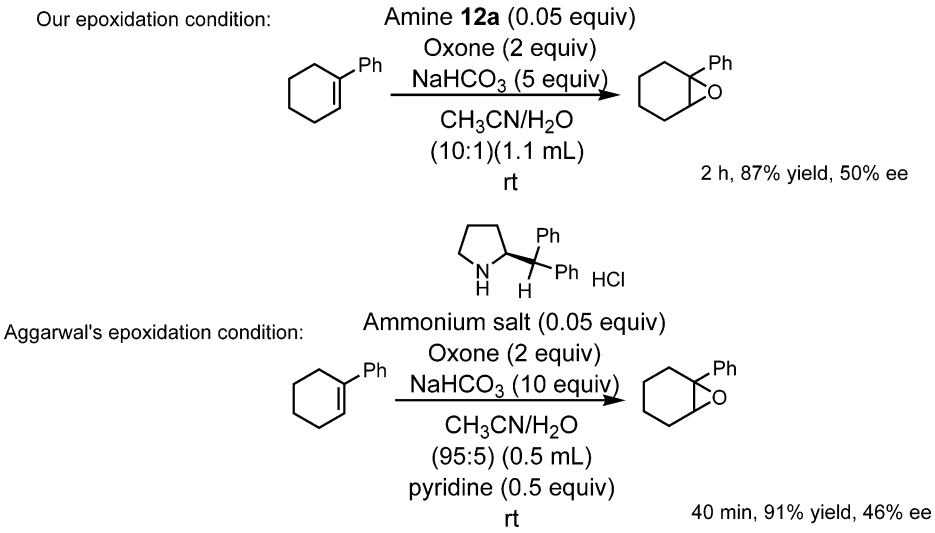
TABLE 5. Effects That the Electronic Properties of the Substrates Have on the Rates of Epoxidation[a]



entry	amine	conversion (%)[b]	yield (%)[b]	ee (%)[c]	diol (%)[b]
1	 **12 a**	100	87	50	12
2	**12a**·HCl salt[d]	89	81	45	10
3	 **12 b**	100	76	52	13
4	**12b**·HCl salt[d]	100	85	53	14
5	 **14**	91	72	26	16
6	**14**·HCl salt[d]	61	92	42	8

[a] Unless otherwise indicated, all of the epoxidation reactions were performed at room temperature for 2 h with 0.4 mmol of 1-phenylcyclohexene, 5 mol % of amine catalyst, 0.8 mmol of Oxone, and 2 mmol of $NaHCO_3$ in 1 mL of CH_3CN and 0.1 mL of H_2O. [b] Based on conversion and determined by integrating ^1H NMR spectra relative to an internal standard (nitrobenzene). [c] Enantioselectivities were determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ (Aldrich no. 16,474-7) as a chiral shift reagent; the configuration of the major enantiomer of the epoxide was (*S,S*). [d] The HCl salt of the amine was prepared by adding an excess amount of 3 M HCl in Et_2O to the corresponding amine in CH_2Cl_2 solution at 0 °C and then concentrating the solution.

SCHEME 3. The Differences between Aggarwal's and Our Epoxidation Conditions



activation of Oxone provided by amine **12a** is equally important to alkene conversion. Once a sufficient amount of Oxone is transferred to the organic layer by 18-crown-6, our amine catalyst **12a** can activate Oxone toward alkene epoxidation.

Conclusion

In summary, we have developed an efficient protocol for the asymmetric epoxidation of olefins catalyzed by chiral fluorinated secondary amines. Through a systematic investigation of the effects that the substituents of the amines have on epoxidation, we discovered that cyclic secondary amines are efficient catalysts and that an electronegative fluorine atom located at the β-position relative to the amino group is beneficial and can further improve the catalytic efficiency. Under our slightly acidic reaction conditions, the fluorinated amine can be protonated in situ, which obviates the need to preform the ammonium salts that are necessary for epoxidation. The role proposed for the amines by Aggarwal and coworkers—that they act as phase transfer catalysts and Oxone activators—is supported by our experimental results. The insights obtained from this study should

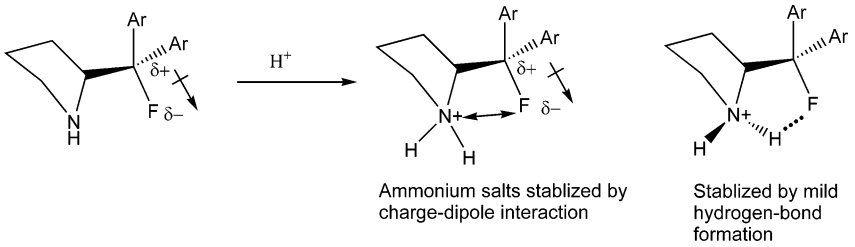
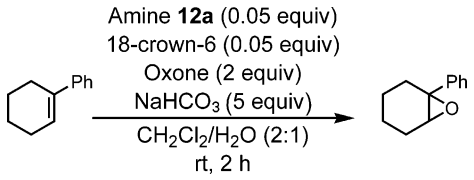


FIGURE 2. Stabilization of the ammonium salts by the fluorine substituent.

TABLE 6. Parallel Tests of the Effects of Using Free Amines and Their Corresponding HCl Salts to Promote Epoxidation[a]



entry	amine loading (mol %)	18-crown-6 loading (mol %)	conversion (%)[b]	yield (%)[b]	ee (%)[c]
1	5		22	56	11
2		5	7	97	n.d.
3	5	5	53	75	39

[a] Unless otherwise indicated, all of the epoxidation reactions were performed at room temperature with 0.4 mmol of 1-phenylcyclohexene, the indicated mol % of catalyst, 0.8 mmol of Oxone, and 2 mmol of $NaHCO_3$ in 1 mL of CH_2Cl_2 and 0.5 mL of H_2O. [b] Based on conversion and determined by integrating ^1H NMR spectra relative to an internal standard (nitrobenzene). [c] Enantioselectivities were determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ (Aldrich no. 16,474-7) as a chiral shift reagent; the configuration of the major enantiomer of the epoxide was (*S*,*S*).

further stimulate the development of new generations of organocatalysts for asymmetric reactions.

Experimental Section

General Procedure for the Amine-Catalyzed Epoxidation of *trans*-Stilbene (Table 1, entry 8). A mixture of Oxone (0.4 mmol) and $NaHCO_3$ (1 mmol) was added to a round-bottom flask containing a solution of pyrrolidine (0.1 mmol) and *trans*-stilbene (0.1 mmol) in CH_3CN (2.0 mL) and H_2O (0.2 mL) at room temperature. After being stirred for 5 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ solution (3 × 20 mL). The organic layer was 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 (1.7 mg, 50% yield based on 19% conversion) as a white solid.

General Procedure for the Amine-Catalyzed Epoxidation of 1-Phenylcyclohexene (Table 2, entry 1). A mixture of Oxone (0.8 mmol) and $NaHCO_3$ (2 mmol) was added to a round-bottom flask containing a stirred solution of amine **12a** (5 mol %) and 1-phenylcyclohexene (0.4 mmol) in CH_3CN (1 mL) and H_2O (0.1 mL) at room temperature. After being stirred for 2 h, the mixture was filtered through $NaHSO_3$ and $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to ^1H NMR spectroscopic analysis to determine the percentage conversion and the yield of epoxide and diol by using nitrobenzene as an internal standard. The enantiomeric excess of the epoxide was determined by ^1H NMR spectroscopy by using $Eu(hfc)_3$ (Aldrich no. 16,474-7) as a chiral shift reagent.

General Procedure for the Amine-Catalyzed Epoxidation of Other Substrates (Table 3). The experimental procedure is the same as reported for the amine-catalyzed epoxidation of 1-phenylcyclohexene, with the exception that the amine catalyst loading was increased.

Procedure for the Amine-Catalyzed Epoxidation of 1-Phenylcyclohexene in the Presence of 18-Crown-6. A mixture of Oxone (0.8 mmol) and $NaHCO_3$ (2 mmol) was added to a round-bottom flask containing amine **12a** (5 mol %), cocatalyst 18-crown-6 (5 mol %), and 1-phenylcyclohexene (0.4 mmol) in CH_2Cl_2 (1 mL) and H_2O (0.5 mL) at room temperature. After being stirred for 2 h, the reaction mixture was filtered through $NaHSO_3$ and $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to ^1H NMR spectroscopic analysis to determine the percentage conversion and the yield of epoxide and diol by using nitrobenzene as an internal standard. The enantiomeric excess of the epoxide was determined by ^1H NMR spectroscopy by using $Eu(hfc)_3$ (Aldrich no. 16,474-7) as a chiral shift reagent.

Acknowledgment. This work was supported by the University of Hong Kong, the Hong Kong Research Grants Council, and the HKU Generic Drug Research Program. We thank Dr. M. S. M. Yuen for preliminary screening of the amines.

Supporting Information Available: Experimental details for the preparation of amine catalysts and spectral characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048378T