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Chiral tertiary amine *N*-oxides in asymmetric epoxidation of α,β-unsaturated ketones

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Abstract

Chiral tertiary amine *N*-oxides have been shown to undergo stereoselective oxygen transfer reaction in the epoxidation of chalcone derivatives with modest to good enantioselectivity.

Chiral amines continue to play a pivotal role in the area of asymmetric reactions as ligands and catalysts.[1] The recent use of chiral secondary amines for the activation of the carbonyl moiety has provided powerful tools for the efficient synthesis of enantiopure molecules in high yield and selectivity.[2] The asymmetric induction using the chiral secondary amines originates from the chiral center embedded in the structure of the amine molecule, such as an α-carbon to the nitrogen. Mechanistically distinct, chiral tertiary amines have been the subject of numerous investigations as nucleophilic catalysts.[3] The asymmetric induction by these catalysts is primarily derived from the nitrogen chiral center and most often a secondary anchoring group is necessary.

Inspired by the reactions of chiral tertiary amines, we have initiated a program to use chiral tertiary amine *N*-oxides as asymmetric oxidants. Although some aromatic *N*-oxides have been used in recent years as chiral ligands for metal-catalyzed reactions,[4] its utility has been mainly limited as an oxidant for low valent transition metals.[5] It had been previously demonstrated that tertiary amine *N*-oxides stereospecifically epoxidize chiral unsaturated bicyclic lactams in high yields at room temperature, although double bonds with two geminal carbonyl groups were necessary for a successful epoxidation.[6] Additionally, the mechanistically similar hydrazinium salt-promoted aziridination of enones has been recently reported.[7] The asymmetric epoxidation of α,β-unsaturated ketones, the net result of asymmetric oxygen transfer, has been the subject of numerous investigation in both transition metal-catalysis[8] and organocatalysis.[9]

Herein, we present the first asymmetric oxidation of chalcone derivatives using chiral tertiary amine *N*-oxides. We hypothesized that the bridgehead position of the tertiary amine *N*-oxide would tolerate common α-hydrogen elimination (Polonovski reaction)[10] and β-hydrogen elimination (Cope reaction),[11] often associated with the decomposition pathways for *N*-oxides. In addition, the bridgehead amine would offer an intrinsic asymmetric environment due to the molecular rigidity created by the bi- or tricyclic ring systems as well as an enhanced nucleophilicity of the amine.[12] To effect oxygen transfer sequence, a conjugate addition of the negatively charged oxygen of *N*-oxide **2** to the β-carbon of electron-deficient olefin **1** was envisioned (Scheme 1). We reasoned that the electron-withdrawing group would stabilize a developing anion in intermediate **3**, initially formed from conjugate addition of *N*-oxides. Subsequent nucleophilic attack of the α-carbon to the oxygen atom in **3** would then furnish an epoxide **5** and a tertiary amine byproduct **4**.

We first examined epoxidation of chalcone with commercially available amine *N*-oxides, trimethylamine

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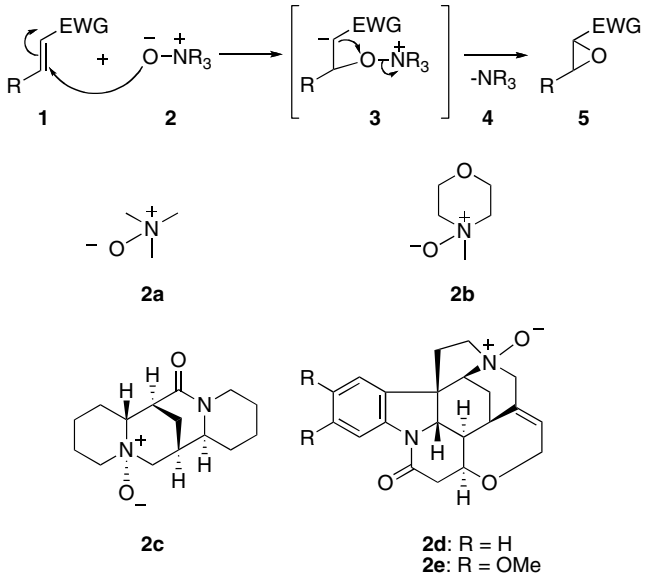
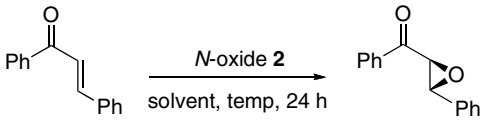


Scheme 1. Oxygen-transfer using tertiary amine *N*-oxide.

N-oxide **2a** (TMANO) and *N*-methylmorpholine *N*-oxide **2b** (NMO) at various temperatures. No reaction had occurred until the reaction temperature reached 100 °C at long reaction times (24 h) in the presence of excess *N*-oxide (2 equiv). Initial product formation, albeit in low yields, encouraged us to test our hypothesis, that bridgehead amine *N*-oxides offer stability to *N*-oxide reagents as well as an asymmetric environment. Known bridgehead amine *N*-oxides, strychinine *N*-oxide **2d** (SNO)[13] and brucine *N*-oxide **2e** (BNO)[14] as well as 17-oxosparteine *N*-oxide **2c**,[15] were then examined. Although *N*-oxide **2c** was completely unreactive upon our reaction conditions, both SNO (**2d**) and BNO (**2e**) improved the yield drastically (Table 1, entries 3–5). Interestingly, BNO (**2e**) was the only *N*-oxide which exerted a modest asymmetric induction (30% ee), although SNO **(2d)** possesses strikingly similar structural features. To find the optimal conditions for the asymmetric induction, a screening was performed with varied temperatures, amount of *N*-oxides, solvents, as well as additives (Table 1, see also Tables 3–7 in Supplementary data).

The screening of varied temperatures showed that the optimal temperature was indeed 100 °C and, rather surprisingly, the asymmetric induction of the product was not influenced by temperature (entries 6–9). Additionally, the amount of *N*-oxide did not affect the asymmetric induction and excess *N*-oxide led to full conversion, although the decomposition of product was accompanied (entries 10 and 11). Among the numerous solvents we screened, dimethoxyethane (DME), propionyl nitrile (*n*-PrCN), and 1,4-dioxane provided somewhat improved asymmetric induction with diminished chemical yields (entries 12–17).[16] The reaction was also found to be dependent on the reaction concentration. Evidently, the asymmetric induction can be improved under high concentrations.

Table 1
Asymmetric epoxidation of chalcone[a]



1a **5a** (α*S*,β*R*)

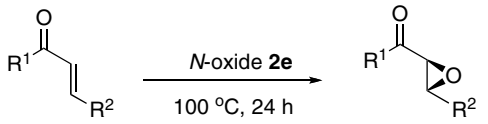
Entry	*N*-Oxide	Solvent	*t* (°C)	Yield[b] (%)	ee[c] (%)
1	**2a**	1,4-Dioxane	100	17	n/a
2	**2b**	1,4-Dioxane	100	10	n/a
3	**2c**	1,4-Dioxane	100	0	n/a
4	**2d**	1,4-Dioxane	100	48	0
5	**2e**	1,4-Dioxane	100	75	30
6	**2e**	1,4-Dioxane	110	60	23
7	**2e**	1,4-Dioxane	90	62	13
8	**2e**	1,4-Dioxane	80	54	17
9	**2e**	1,4-Dioxane	70	19	13
10	**2e**	1,4-Dioxane	100	60[d]	23
11	**2e**	1,4-Dioxane	100	30[e]	33
12	**2e**	DMF[f]	100	26	71
13	**2e**	DMSO[f]	100	17	75
14	**2e**	DME[f]	100	64	47
15	**2e**	*n*-PrCN[f]	100	26	82
16	**2e**	*i*-PrOH[f]	100	5	72
17	**2e**	1,4-Dioxane[g]	100	53	58

[a] Reaction performed with **1** (1 mmol), **2** (2 mmol) in 1,4-dioxane (1.2 mL) at 100 °C for 24 h.
[b] Isolated after flash chromatography.
[c] Determined by chiral HPLC (absolute configuration of **5a** was determined by comparison of the HPLC retention times in Ref. 9a).
[d] Reaction performed with 1 equiv BNO.
[e] Reaction performed with 3 equiv BNO.
[f] Solvent concentrations, see Supplementary data.
[g] Reaction performed in 1,4-dioxane (0.6 mL).

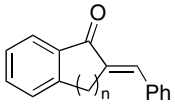
However, the yields are compromised due to the decomposition of the product as well as self-deoxygenation of *N*-oxide **2e**.

After considerable experimentation, three solvents were chosen (DME, *n*-PrCN, 1,4-dioxane), where maximum asymmetric induction was observed. We then turned our attention to expanding the scope of our asymmetric epoxidation. Several chalcone derivatives were reacted in the presence of 2 equiv of BNO at 100 °C for 24 h (Table 2). The results show that several chalcone epoxides could be obtained in moderate enantioselectivity; however, the diverting trends between higher chemical yields and enantioselectivity was the major limiting factor in finding optimal conditions for each substrate. Again the solvents and the reaction concentration largely influenced the outcome of the product (Table 2, entries 1–3, see also Tables 8 and 9 in Supplementary data). Furthermore, the asymmetric epoxidation using chiral tertiary amine *N*-oxides is rather limited to chalcone derivatives, since several α,β-unsaturated carbonyl systems have failed to undergo conjugate addition[17] or the enantioselectivity was largely compromised (entries 10–12). We also screened enolizable ketones, including methyl vinyl ketone and cyclohex-2-enone, without success. We reasoned that the presence of the enolate form of ketones due to high temperature as well as the

Table 2
Asymmetric epoxidation of chalcone derivatives[a]



1a-i **5a-i** ($\alpha S,\beta R$)

Entry	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	Ph	Ph	53[d]	58
2	4-Me–Ph	Ph	33[f]	67
3	4-Cl–Ph	Ph	53[e]	21
4	4-F–Ph	Ph	30[d]	52
5	Ph	4-Me–Ph	42[e]	32
6	Ph	4-Cl–Ph	37[e]	67
7	Ph	4-F–Ph	43[d]	30
8	Ph	4-NO_2–Ph	81[e]	55
9	4-F–Ph	4-F–Ph	32[d]	54
10		**6a** ($n=1$)	14[d]	8
11		**6b** ($n=2$)	56[d]	2
12	**6a-c**	**6c** ($n=3$)	69[f]	16

[a] Reaction performed with **1** (1 mmol), **2** (2 mmol) at 100 °C for 24 h.
[b] Isolated after flash chromatography (not corrected with the recovery of 10–30% of starting materials).
[c] Determined by chiral HPLC (absolute configuration of **5** was determined by comparison of the HPLC retention times with known data).
[d] Reaction performed in 1,4-dioxane (0.6 mL).
[e] Reaction performed in DME (1.2 mL).
[f] Reaction performed in *n*-PrCN (0.6 mL).

presence of chiral tertiary amine could lower the reactivity of carbonyl compounds. However, the reaction also failed when non-enolizable ketones were used, indicating a subtle steric bias upon the interaction between the *N*-oxide and the carbonyl compounds.[18]

In summary, we have demonstrated that the chiral tertiary amine *N*-oxide **2e** can promote the asymmetric epoxidation of chalcone derivatives. Although the detailed structural requirement of the chiral tertiary amine *N*-oxides for asymmetric induction awaits further studies, our results clearly show that the bridgehead amine *N*-oxides are capable of providing a sufficient stability for an asymmetric induction. The present methodology utilizes a chiral reagent **2e** in excess; however, the recovery of brucine from the reaction using 2 equiv of brucine *N*-oxide **2e** can be achieved without loss upon reaction work-up.[19] Furthermore, our oxygen-transfer reaction is extremely simple and convenient and can be performed in a highly concentrated organic medium (1.7 M).[20] We are currently investigating further applications of the chiral tertiary amine *N*-oxides and our results will be reported in due course.

Acknowledgments

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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.2008.01.103.

References and notes

1. Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005.
2. For recent reviews, see: (a) List, B. *Chem. Commun.* **2006**, 819; (b) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79; (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
3. For recent reviews, see: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614; (b) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496; (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; Mcdaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621; (d) France, S.; Guerin, D.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.
4. For recent review, see: Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373.
5. For review on amine *N*-oxides, see: (a) Albini, A. *Synthesis* **1993**, 263; (b) Luh, T.-Y. *Coord. Chem. Rev.* **1984**, *60*, 255.
6. Anres, C. J.; Stetseris, N.; Norton, J. R.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 1613.
7. (a) Armstrong, A.; Baxter, C. A.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Org. Lett.* **2007**, *9*, 351; (b) Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005; (c) Armstrong, A.; Carbery, D.; Lamont, S. G.; Pape, A.; Wincewicz, R. *Synlett* **2006**, 2504; (d) Xu, J.; Jiao, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1491.
8. (a) Wang, X.; Shi, L.; Li, M.; Ding, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6362; (b) Kino, R.; Daikai, K.; Kawanami, T.; Furuno, H.; Inanaga *J. Org. Biomol. Chem.* **2004**, *2*, 1822; (c) Yu, H.-B.; Zheng, X.-F.; Lin, Z.-M.; Hu, Q.-S.; Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 8149 and references cited therein. For a review, see: (d) Porter, M.; Skidmore, J. *Chem. Commun.* **2000**, 1215.
9. For representative α,β-unsaturated ketone examples, see: (a) Li, Y.; Liu, X.; Yang, Y.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 288; (b) Jew, S.-S.; Lee, J.-H.; Jeong, B.-S.; Yoo, M.-S.; Kim, M.-J.; Lee, Y.-J.; Lee, J.; Choi, S.-H.; Lee, K.; Lah, M. S.; Park, H.-G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1383; (c) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579; (d) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. J. *Am. Chem. Soc.* **2004**, *126*, 6844; (e) Lattanzi, A.; Cocilova, M.; Iannece, P.; Scettri, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3751; (f) Aoki, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 187; (g) Adam, W.; Rao, P. B.; Degen, H.-G.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 5654; (h) Arai, S. S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375; (i) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289; (j) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287; (k) Ref. 8b.
10. Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190.
11. Kleinschmidt, R. F.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 1929.
12. (a) Ly, T.; Krout, M.; Pham, D. K.; Tani, K.; Stoltz, B. M.; Julian, R. R. *J. Am. Chem. Soc.* **2007**, *129*, 1864; (b) Kubas, G. J.; Larson, A. C.; Ryan, R. R. *J. Org. Chem.* **1979**, *44*, 3867.
13. (a) Hadden, C. E.; Kaluzny, B. D.; Robins, R. H.; Martin, G. E. *Magn. Reson. Chem.* **1999**, *37*, 325; (b) Edward, J. T.; Whiting, J. *Can. J. Chem.* **1971**, *49*, 3502.
14. (a) Derdau, V.; Laschat, S. *J. Organomet. Chem.* **2002**, *642*, 131; (b) Carpenter, N. E.; Nicholas, K. M. *Polyhedron* **1999**, *18*, 2027; (c) Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Synlett* **1995**, 1085.
15. (a) Derdau, V.; Laschat, S.; Jones, P. G. *Heterocycles* **1998**, *48*, 1445; (b) Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1985**, *63*, 716.

16. To maximize the enantioselectivity of the product, the reaction was stopped upon 50–70% conversion.
17. (*E*)-Cinnamaldehyde, (*E*)-cinnamic acid, (*E*)-ethyl cinnamate, and (*E*)-cinnamamide are all inert to our oxidation conditions.
18. (*E*)-4,4-Dimethyl-1-phenylpent-1-en-3-one and (*E*)-4,4-dimethyl-1-phenylpent-2-en-1-one are inert to our oxidation conditions. For other unsuccessful α,β-unsaturated ketones we screened, see: Supplementary data.
19. After work-up, brucine and BNO are isolated in >95% yield as a 9:1 mixture.
20. For a review on highly concentrated reactions, see: Walsh, P. J.; Li, H.; de Parrodi, C. A. *Chem. Rev.* **2007**, *107*, 2503.