Lithium Bromide, an Inexpensive and Efficient Catalyst for Opening of Epoxide Rings by Amines at Room Temperature under Solvent-Free Condition

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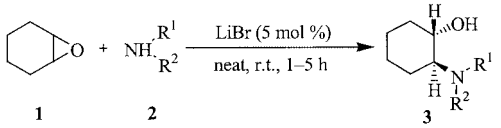
Lithium bromide has been found to be an inexpensive and efficient catalyst for the opening of epoxide rings by amines, and this provides an environmentally friendly method for the synthesis of β-amino alcohols. Aromatic and aliphatic amines react with cycloalkene oxides to exclusively form *trans*-2-(aryl/alkylamino)cycloalkanols in high yields. A 98–100% selectivity in favour of nucleophilic attack at the benzylic carbon atom of styrene oxide is observed with aromatic amines. However, aliphatic amines exhibit a marginal preference for the reaction at the terminal carbon atom of the epoxide ring in styrene oxide. Non-styrenoidal, unsymmetrical alkene oxides undergo selective nucleophilic attack at the sterically less hindered carbon atom by aniline. The chelation effect of the Li^+ ion enables selective opening of the epoxide ring in 3-phenoxypropylene oxide in the presence of styrene oxide.

β-Amino alcohols are versatile synthons for a wide range of biologically active natural and synthetic products,[1] unnatural amino acids[2] and chiral auxiliaries.[3] The classical synthesis of β-amino alcohols by nucleophilic opening of the epoxide ring involves treatment of the epoxides with amines while heating.[4,5] However, the method does not work so well with poor nucleophilic amines and also poses problems when sensitive epoxides are used due to the potential side reactions at high temperatures and the need for excess amine. This led to the necessary use of catalysts to activate the epoxide ring for nucleophilic cleavage. Therefore, continuous efforts have been made to develop various catalysts such as alumina,[6] metal amides and triflamide,[7] alkali metal perchlorates and tetrafluoroborate,[8] metal triflates,[9] metal alkoxides,[10] zirconium sulfophenyl phosphonate,[11] metal halides,[12] silica gel under high pressure,[13] montmorillonite K 10 under microwave irradiation,[14] hexafluoro-2-propanol (HFIP) under reflux,[15] ionic liquids,[16] nBu$_3$P,[17] Yb(OTf)$_3$ in supercritical CO_2 under high pressure at 55 °C,[18] and silica gel.[19] However, some of these methodologies require long reaction times, elevated temperatures, high pressure, air- and moisture-sensitive catalysts, stoichiometric amounts of costly catalysts, special apparatus etc. The rearrangement of the starting epoxide to allylic alcohols[20] and potential hazards in handling pyrophoric/moisture-sensitive reagents in the preparation of the catalyst are also notable disadvantages of some of the reported methodologies Further, in most cases, these methods are applicable to aromatic amines only.[21] Therefore, considering the potential industrial applications of the epoxide ring opening reaction by amines, the development of a cheap and efficient catalyst is in high demand.

We have recently found that the strong oxophilicity of Li^+ activates oxygen-containing electrophiles for nucleophilic attack.[22,23] Herein, we report that lithium bromide efficiently catalyzes the opening of epoxide rings by amines at room temperature under solvent-free conditions to afford a cost-effective and environmentally friendly process for the synthesis of β-amino alcohols.

To find out the best reaction conditions, cyclohexene oxide (**1**) (2.5 mmol) was taken as a symmetrically substituted epoxide and treated with various amines **2** (2.5 mmol) in the presence of LiBr (Scheme 1).



a: $R^1 = H$, $R^2 = C_6H_5$; **b**: $R^1 = H$, $R^2 = 4\text{-MeC}_6H_4$
c: $R^1 = H$, $R^2 = 4\text{-ClC}_6H_4$; **d**: $R^1 = H$, $R^2 = C_6H_5CH_2$
e: $R^1 = R^2 = (CH_2)_4$; **f**: $R^1 = R^2 = (CH_2)_5$

Scheme 1. LiBr-catalyzed epoxide ring opening of **1** with various amines

Use of 5 mol % of LiBr caused the reaction to go to completion at room temperature under neat conditions in 1−5 h (GCMS) (Table 1). No significant amount of the amino alcohol **3a** was formed (GCMS) from **1** and **2a** in the

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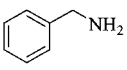
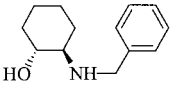
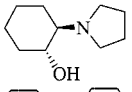
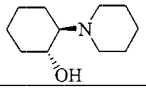
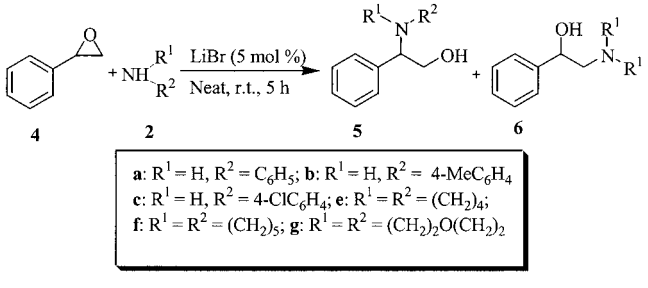
absence of LiBr; the epoxide and the amine remained unchanged. This establishes the need to use LiBr to promote the epoxide opening reaction. Excellent results were obtained with various aromatic amines such as aniline (**2a**), 4-methylaniline (**2b**) and 4-chloroaniline (**2c**): 90, 93, and 88% yields, respectively. The reaction worked well with aliphatic amines such as benzylamine (**2d**), pyrrolidine (**2e**) and piperidine (**2f**) resulting in the formation of the corresponding amino alcohols in 88, 100, and 85% yields, respectively.[21] In each case the resultant 2-(aryl/alkylamino)cyclohexanols were found to be the *trans* diastereoisomer **3** on the basis of NMR spectroscopy.[8,9e,12h]

Table 1. Reactions of **1** with various amines catalyzed by LiBr; cyclohexene oxide (**1**) (2.5 mmol) was treated with the amine (2.5 mmol) in the presence of LiBr (5 mol %) at room temperature under neat conditions

Entry	Amine	Product[a]	Time [h]	Yield [%][b]
1	R = H	R = H	1	90
2	R = 4-Me	R = 4-Me	2	93
3	R = 4-Cl	R = 4-Cl	5	88
4			5	88
5			2	100
6			1.5	85

[a] The ^1H and ^{13}C NMR data confirm the *trans* stereochemistry of the product. [b] Isolated yields of the corresponding amino alcohol.

To evaluate the regioselectivity, styrene oxide (**4**) was chosen as a representative unsymmetrical epoxide and treated with various amines (Scheme 2) under the catalytic influence of LiBr (Table 2).



Scheme 2. Regioselectivity in the LiBr-catalyzed epoxide ring opening of **4** with various amines

The reaction with aromatic amines **2a**−**2c** and aliphatic amines such as pyrrolidine (**2e**), piperidine (**2f**) and morpholine (**2g**) afforded 92−100% yields of the corresponding amino alcohols. The regioisomers obtained from the reaction with **2a** eluted with different retention time, and the regioselectivity was determined by GCMS. In the MS, the regioisomer **5a** exhibits a daughter ion [$M^+ - 31$] due to the loss of CH_2OH, and the diagnostic feature in the mass spectra of **7a** is the ion peak [$M^+ - 106$], which is assigned to the loss of PhCHO. The reactions with **2b** and **2c** afforded a single amino alcohol (GCMS), and the absence of an ion peak [$M^+ - 106$] and the presence of the daughter ion [$M^+ - 31$] as the base peak confirms the formation of the regioisomer **5** on each occasion.

Table 2. Reactions of **4** with various amines catalyzed by LiBr; styrene oxide (**4**) (2.5 mmol) was treated with the amine **2** (2.5 mmol) in the presence of LiBr (5 mol %) at room temperature under neat conditions for 5 h

Entry	Amine	Yield [%][a]	Ratio **5**/**6**[b]
1	R = H	98	92:2
2	R = 4-Me	98	100:0
3	R = 4-Cl	100	100:0
4		92	45:55
5		98	42:58
6		94	48:52

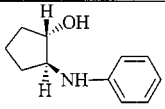
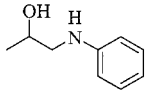
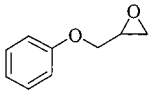
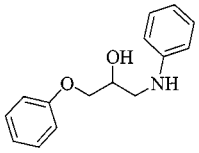
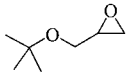
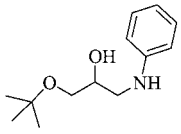
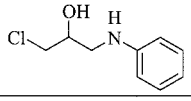
[a] Isolated yields of the corresponding amino alcohols. [b] Determined by GCMS (Entries 1−3) and ^1H NMR spectroscopy (Entries 4−6).

In the case of the aliphatic amines, the regioisomers could not be separated by column chromatography and eluted simultaneously in the GCMS (capillary column). However, the presence of ion peaks [$M^+ - 31$] and [$M^+ - 106$] indicates the formation of **5** and **6**, respectively. The regioselectivity was determined by ^1H NMR spectroscopy on the basis of the integral values of the benzylic methine and methylene proton signals corresponding to **5** and **6**, which appear at $\delta \approx 3.9$ and 4.7 ppm, respectively.[24]

The reaction of **4** with aromatic amines afforded the product obtained from nucleophilic attack at the benzylic carbon atom as the major regioisomer (Table 2, Entries 1−3). Aliphatic amines showed a marginal preference for nucleophilic attack at the terminal carbon atom (Table 2, Entries 4−6). The regioselective formation of **5** in the reaction with aromatic amines may be accounted for by the fact that the phenyl group in **4** induces a carbocationic character at the benzylic carbon atom in the LiBr complex of **4** due to the resonance effect. Thus, aromatic amines react selectively at the benzylic carbon atom of **4** due to their lower nucleophilicity. The relatively better nucleophilicity of aliphatic amines favours an S_N2 process, thus influencing the nucleophilic attack at the terminal carbon atom of **4**. Therefore, the competing electronic effect of the phenyl group in **4** and the increased nucleophilic property of the aliphatic amines, relative to the aromatic amine, result in overall poor regioselectivity.

To evaluate the generality, various epoxides were treated with **2a** in the presence of LiBr (Table 3).

Table 3. Reaction of various epoxides with **2a** catalyzed by LiBr; the epoxide (2.5 mmol) was treated with **2a** (2.5 mmol) in the presence of LiBr (5 mol %) at room temperature under nitrogen in the absence of solvent for 5 h

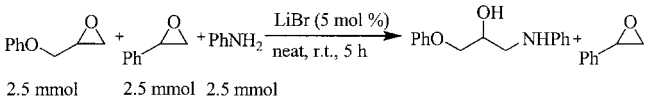
Entry	Amine	Product[a]	Yield [%][b]
1			100
2			100
3			100
4			100
5			100

[a] Determined by GCMS and $^1H/^{13}C$ NMR spectroscopy. [b] Isolated yields of the corresponding amino alcohol.

Quantitative formation of the corresponding amino alcohols demonstrated the efficiency of LiBr. The reaction with cyclopentene oxide resulted in the exclusive formation of the *trans* diastereoisomer (Table 3, Entry 1).[15] In the cases of unsymmetrical epoxides such as methyloxirane, glycidyl phenyl ether and *tert*-butyl glycidyl ether (Table 3, Entries 2−4), complete selectivity for nucleophilic attack at the less hindered carbon atom of the epoxide was observed, which demonstrates the generality of regioselectivity for non-styrenoidal oxides. These observations suggest that the reversal of the regioselectivity (nucleophilic attack at the more hindered benzylic carbon atom) during the reaction of **4** with **2a** and other aromatic amines was controlled by the electronic factor of the phenyl group in **4**.

The reaction of epichlorohydrin (Table 3, Entry 5) exemplified the excellent chemoselectivity that led to quantitative formation of the amino alcohol, corresponding to nucleophilic attack at the terminal carbon atom of the epoxide ring. No product arising from nucleophilic displacement of the chlorine atom could be detected through GCMS analysis of the reaction mixture. The high oxophilicity of Li^+ entails a strong coordination between Li^+ and the alkoxide generated after nucleophilic attack on the LiBr-complexed epoxide, thus prohibiting concommitant elimination of the chloride anion. The quantitative formation of the desired product relative to 81 and 69% yields obtained during the $ZrCl_4$ [12h] and silica-gel[19] catalyzed reactions, respectively, establish that this newly developed catalyst is more effective.

The relative coordinating ability of different epoxides with the Li^+ ion should enable the selective opening of the epoxide ring during intermolecular competition. Thus, a mixture of 3-phenoxypropylene oxide (2.5 mmol) and styrene oxide (2.5 mmol) was treated with aniline (2.5 mmol) in the presence of LiBr (5 mol %) at room temperature for 5 h in the absence of solvent (Scheme 3).



Scheme 3. Selectivity of epoxide ring opening by aniline during intermolecular competition catalyzed by LiBr

The exclusive formation of the amino alcohol from nucleophilic cleavage of the epoxide ring of 3-phenoxypropylene oxide took place, and no significant amount of the amino alcohols resulting from nucleophilic attack by aniline on styrene oxide was detected (GCMS). The selective opening of the epoxide ring in 3-phenoxypropylene oxide may be explained by the chelating ability of the oxygen atoms of the phenoxy group and the epoxide oxygen atom of 3-phenoxypropylene oxide with the Li^+ ion, which leads to a favourable five-membered transition state. The absence of such a chelation effect with styrene oxide results in a less favourable transition state, and selective activation of the epoxide ring in 3-phenoxypropylene oxide takes place.

In conclusion, this study demonstrates that LiBr is a highly efficient catalyst for the opening of epoxides with amines. The mild reaction conditions, applicability with various epoxides and amines (aromatic and aliphatic) and chelation effect leading to selective epoxide activation, offer specific advantages. With increasing environmental concerns,[26] the use of an inexpensive, easy to handle, nontoxic catalyst and solvent-free reaction conditions should fulfil the "triple bottom line"[21] philosophy of green chemistry, and thus the present method is "environmentally friendly" and potentially useful for industrial applications.

Experimental Section

Typical Procedure. 2-(Phenylamino)cyclohexanol: LiBr (10 mg, 5 mol %) was added to a magnetically stirred mixture of **1** (0.25 mL, 2.5 mmol) and **2a** (0.225 mL, 2.5 mmol) at room temperature under nitrogen. After completion of the reaction (1 h, GCMS), the reaction mixture was diluted with water (10 mL) and extracted with Et_2O (2 × 15 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated under vacuum to afford 2-(phenylamino)cyclohexanol (**3a**) (0.428 g, 90%). IR (neat): $\tilde{\nu}$ = 3354, 2931, 2858, 1601, 1500, 1448, 1319, 1067 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03−1.42 (m, 4 H), 1.72−1.78 (m, 2 H), 2.9 (m, D_2O exchangeable, 2 H), 2.10−2.16 (m, 2 H), 3.13 (ddd, *J* = 3.9, 10.0, 10.1 Hz, 1 H), 3.33 (ddd, *J* = 4.2, 10.4, 10.5 Hz, 1 H), 6.7−7.2 (m, 5 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 24.27, 25.02, 31.62, 33.15, 60.17, 74.55, 114.40, 118.38, 129.34, 147.81 ppm. EIMS: *m*/*z* = 191 [M^+]. Identical (^1H and ^{13}C NMR and MS) with an authentic sample.[12h] This general procedure was applied for other

reactions. On each occasion, the product was identified by comparing the spectroscopic data (IR, NMR, MS) with those reported in the literature.

[1] [1a] D. R. Gehlert, D. J. Goldstein, P. A. Hipskind, *Ann. Rep. Med. Chem.* **1999**, 201−210. [1b] E. J. Corey, F. Zhang, *Angew. Chem. Int. Ed.* **1999**, *38*, 1931−1934. [1c] J. De Cree, H. Geukens, J. Leempoels, H. Verhaegen, *Drug Dev. Res.* **1986**, *8*, 109−117. [1d] J. G. Smith, *Synthesis* **1984**, 629−656.

[2] [2a] P. O′Brien, *Angew. Chem. Int. Ed.* **1999**, *38*, 326−329. [2b] G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451−454.

[3] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835−876.

[4] [4a] S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561−2576. [4b] D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, *52*, 14361−14384. [4c] R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437−475. [4d] O. Mitsunobu, in *Comprehensive Organic Synthesis* (Ed.: E. Winterfeldt), Pergamon Press, New York, **1996**, vol. 6, part 1.3.4.1. [4e]A. S. Rao, S. K. Paknikar, J. G. Kirtane, *Tetrahedron* **1983**, *39*, 2323−2367.

[5] [5a] P. A. Crooks, R. Szyudler, *Chem. Ind. (London)* **1973**, 1111−1112. [5b] J. A. Deyrup, C. L. Moyer, *J. Org. Chem.* **1969**, *34*, 175−179. [5c] M. Freifelder, G. R. Stone, *J. Org. Chem.* **1961**, *26*, 1477−1480. [5d] M. Mousseron, J. Jullien, Y. Jolchine, *Bull. Soc. Chim. Fr.* **1952**, 757−766. [5e] R. E. Lutz, J. A. Freek, R. S. Murphy, *J. Am. Chem. Soc.* **1948**, *70*, 2015−2023.

[6] Alumina: G. H. Posner, D. Z. Rogers, *J. Am. Chem. Soc.* **1977**, *99*, 8208−8214.

[7] [7a] Et_2AlNHR: L. E. Overman, L. A. Flippin, *Tetrahedron Lett.* **1981**, *22*, 196−198. [7b] Silicon amides: A. Papini, I. Ricci, M. Taddei, G. Seconi, P. Dembach, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2261−2265. [7c] R_2NMgBr: M. C. Carre, J. P. Houmounou, P. Caubere, *Tetrahedron Lett.* **1985**, *26*, 3107−3110. [7d] R'_3PbNR_2: J.-I. Yamada, M. Yumoto, Y. Yamamoto, *Tetrahedron Lett.* **1989**, *30*, 4255−4258. [7e] Cu amide: Y. Yamamoto, N. Asao, M. Meguro, N. Tsukade, H. Nemoto, N. Adayari, J. G. Wilson, H. Nakamura, *J. Chem. Soc., Chem. Commun.* **1993**, 1201−1203. [7f] $LiNTf_2$: J. Cossy, V. Bellosta, C. Hamoir, J.-R. Desmurs, *Tetrahedron Lett.* **2002**, *43*, 7083−7086.

[8] M. Chini, P. Crotti, F. Macchia, *Tetrahedron Lett.* **1990**, *31*, 4661−4664.

[9] [9a] Ph_4SbOTf: M. Fujiwara, M. Imada, A. Baba, H. Matsuda, *Tetrahedron Lett.* **1989**, *30*, 739−742. [9b] $La(OTf)_3$: M. Chini, P. Crotti, L. Favero, F. Machhia, M. Pineschi, *Tetrahedron Lett.* **1994**, *35*, 433−436. [9c] $Yb(OTf)_3$: M. Meguro, N. Asao, Y. Yamamoto, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597−2601. [9d] LiOTf: J. Auge, F. Leroy, *Tetrahedron Lett.* **1996**, *37*, 7715−7716. [9e] $Cu(OTf)_2$ and $Sn(OTf)_2$: G. Sekar, V. K. Singh, *J. Org. Chem.* **1999**, *64*, 287−289.

[10] [10a] $Ti(OiPr)_4$: S. Sagava, H. Abe, Y. Hase, T. Inaba, *J. Org. Chem.* **1999**, *64*, 4962. [10b] DIPAT (diisopropoxyaluminium trifluoroacetate): S. Rampalli, S. S. Chaudhari, K. G. Akamanchi, *Synthesis* **2000**, 78−80.

[11] M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, *Eur. J. Org. Chem.* **2001**, 4149−4152.

[12] [12a] $CoCl_2$: J. Iqbal, A. Pandey, *Tetrahedron Lett.* **1990**, *31*, 575−576. [12b] $TaCl_5$: S. Chandrasekhar, T. Ramchander, S. J. Prakash, *Synthesis.* **2000**, 1817−1818. [12c] $SmCl_3$: X.-L. Fu, S.-H. Wu, *Synth. Commun.* **1997**, *27*, 1677−1684. [12d] $CeCl_3$: L. R. Reddy, M. A. Reddy, N. Bhanumathi, K. R. Rao, *Synthesis* **2001**, 831−832. [12e] $BiCl_3$: T. Ollevier, G. Lavie-Compin, *Tetrahedron Lett.* **2002**, *43*, 7891−7893. [12f] $ZnCl_2$: L. D. Pachón, P. Gamez, J. J. M. van Bassel, J. Reedijk, *Tetrahedron Lett.* **2003**, *44*, 6025−6027. [12g] VCl_3: G. Sabitha, G. S. K. K. Reddy, K. B. Reddy, J. S. Yadav, *Synthesis* **2003**, 2298−2300. [12h] $ZrCl_4$: A. K. Chakraborti, A. Kondaskar, *Tetrahedron Lett.* **2003**, *44*, 8315−8319.

[13] H. Kotsuki, T. Shimanouchi, M. Teraguchi, M. Kataoka, A. Tatsukawa, H. Nishizawa, *Chem. Lett.* **1994**, 2159−2162.

[14] [14a] R. Gupta, S. Paul, A. K. Gupta, P. L. Kachroo, A. Dandia, *Ind. J. Chem.* **1997**, *36B*, 281−283. [14b] M. M. Mojtahedi, M. R. Saidi, M. Bolourtchian, *J. Chem. Res. (S)* **1999**, 128−129.

[15] U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon, J.-P. Bégué, *J. Org. Chem.* **2000**, *65*, 6749−6751.

[16] J. S. Yadav, B. V. S. Reddy, A. K. Basak, A. V. Narsaiah, *Tetrahedron Lett.* **2003**, *44*, 1047−1050.

[17] R.-H. Fan, X.-L. Hou, *J. Org. Chem.* **2003**, *68*, 726−730.

[18] M. Shi, Y. Chen, *J. Fluorine Chem.* **2003**, *122*, 219−227.

[19] A. K. Chakraborti, S. Rudrawar, A. Kondaskar, *Org. Biomol. Chem.* **2004**, *2*, 1277−1280.

[20] Metal alkylamides induce the rearrangement of epoxides to allylic alcohols. [20a] C. E. Harris, G. B. Fisher, D. Beardsley, L. Lee, C. T. Goralsky, L. W. Nicholson, B. Singaram, *J. Org. Chem.* **1994**, *59*, 7746−7751. [20b] J. Yamada, Y. Yomoto, Y. Yamamoto, *Tetrahedron Lett.* **1989**, *30*, 4255−4258. [20c] J. K. Crandall, M. Apparu, *Org. React.* **1983**, *29*, 345−443. [20d] J. Whitesel, S. W. Felman, *J. Org. Chem.* **1980**, *45*, 755−756. [20e] C. L. Kissel, B. Rickborn, *J. Org. Chem.* **1972**, *37*, 2060−2063.

[21] The reported catalysts such as $CoCl_2$, $Cu(OTf)_2$, HFIP, zirconium sulfophenyl phosphonate, $TaCl_5$, $CeCl_3$/NaI, VCl_3, and $BiCl_3$ are not effective for reactions with aliphatic amines.

[22] A. Basak (née Nandi), M. K. Nayak, A. K. Chakraborti, *Tetrahedron Lett.* **1998**, *39*, 4883−4886.

[23] A. K. Chakraborti, A. Basak (born Nandi), V. Grover, *J. Org. Chem.* **1999**, *64*, 8014−8017.

[24] S. A. Anderson, J. T. Ayers, K. M. Ito, F. DeVries, D. Mendenhall, B. C. Vanderplas, *Tetrahedron: Asymmetry* **1999**, *10*, 2655−2663.

[25] D. E. McClure, B. H. Arison, J. J. Baldwin, *J. Am. Chem. Soc.* **1979**, *101*, 3666−3668.

[26] R. L. Garrett, in *Designing Safer Chemicals* (Eds.: R. L. Garrett, S. C. De Vilto), American Chemical Society Symposium Series 640, Washington DC, **1996**, chapter 1.

[27] J. Elkington, http://www.sustainability.co.uk/sustainability.htm

[28] [28a] A. Solladié-Cavello, M. Bencheqroun, *J. Org. Chem.* **1992**, *57*, 5831−5834. [28b] J. M. Klunder, S. Y. Ko, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 3710−3712.

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