Highly Enantioselective Atom-Transfer Radical Cyclization Reactions Catalyzed by Chiral Lewis Acids

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Free radical reactions are powerful and versatile tools for the formation of carbon−carbon bonds.[1] In recent years, significant progress has been made in enantioselective conjugate radical addition reactions[2] catalyzed by chiral Lewis acids.[3] However, no success was reported for the enantioselective atom-transfer radical reactions.[4] Here we report highly enantioselective atom-transfer radical cyclization reactions catalyzed by chiral Lewis acids.

A typical atom-transfer radical cyclization reaction involves the transfer of a halogen atom from one carbon center to another with concomitant ring formation (Scheme 1).[5,6] The advantage of this reaction over other radical reactions is that the halogen atom is retained in the product, which allows for further functionalization. A recent study by Porter and co-workers showed that Lewis acids could catalyze intermolecular atom-transfer radical addition reactions.[4a] We have been focused on atom-transfer radical cyclization reactions, as they hold promise for highly selective formation of multiple chiral centers.

A series of unsaturated β-keto esters **1a**−**d** were used to probe the conditions for atom-transfer cyclization reactions with Et_3B/O_2 as the radical initiator (Table 1).[7] Without the addition of any Lewis acid, no cyclization reaction occurred, and only reductive debromination products were obtained (data not shown). In the presence of 0.3−0.5 equiv of $Yb(OTf)_3$, intramolecular atom-transfer radical cyclization reactions of **1a**−**d** took place efficiently in Et_2O, providing compounds **2a**−**d** as the major products in high yields (entries 1, 4, 7, and 10).[8] For substrate **1a**, the catalyst loading could even be reduced to 5 mol % without significant decrease in yield (entry 2). In the cyclization of substrate **1b** or **1c** of *trans*- or *cis*-olefinic double bonds, respectively, only two isomers **2b/c** differing in the stereochemistry of the exocyclic chiral center were isolated (entries 4−9). After reductive debromination of **2b/c** with tin hydride, a single product **3** was isolated in 92% yield (eq 1). When the atom-transfer radical cyclization reactions were carried out in CH_2Cl_2 or toluene, $Mg(ClO_4)_2$ turned out to be the best Lewis acid (entries 3, 5, 6, 8, 9, and 11). Thus the reaction systems of $Yb(OTf)_3/Et_2O$, $Mg(ClO_4)_2$/toluene, and $Mg(ClO_4)_2/CH_2Cl_2$ were found to be suitable for almost all the substrates.

Scheme 1

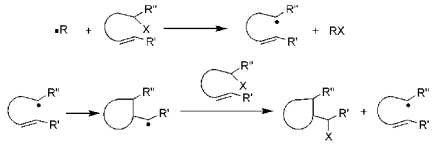
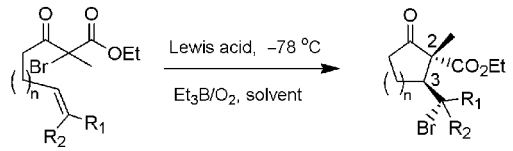


Table 1. Lewis Acid-Catalyzed Atom-Transfer Radical Cyclization Reactions[a]

entry	substr	Lewis acid (equiv)	solvent	time[b] (h)	yield[c] (%)
1	**1a**	$Yb(OTf)_3$ (0.5)	Et_2O	9.5	70
2	**1a**	$Yb(OTf)_3$ (0.05)	Et_2O	9.5	60
3	**1a**	$Mg(ClO_4)_2$ (0.4)	toluene	6.5	62
4	**1b**	$Yb(OTf)_3$ (0.3)	Et_2O	5	78 (2.4/1)[d]
5	**1b**	$Mg(ClO_4)_2$ (0.3)	CH_2Cl_2	4.5	75 (1.3/1)[d]
6	**1b**	$Mg(ClO_4)_2$ (0.3)	toluene	4.5	84 (1/1.9)[d]
7	**1c**	$Yb(OTf)_3$ (0.3)	Et_2O	5	74 (2.5/1)[d]
8	**1c**	$Mg(ClO_4)_2$ (0.3)	CH_2Cl_2	4.5	78 (1/1.1)[d]
9[e]	**1c**	$Mg(ClO_4)_2$ (0.3)	toluene	4.5	81 (1/2.2)[d]
10	**1d**	$Yb(OTf)_3$ (0.5)	Et_2O	10	71
11	**1d**	$Mg(ClO_4)_2$ (0.3)	toluene	9	55

[a] Unless otherwise indicated, all reactions were carried out at −78 °C with 0.2−0.3 mmol of substrate, the indicated amount of Lewis acid, 10 mL of solvent, 2 equiv of Et_3B/O_2 for substrates **1a** and **1d**, or 5 equiv of Et_3B/O_2 for substrates **1b** and **1c**. [b] Time for complete reaction. [c] Isolated yield. [d] Ratio of **2b** and **2c**. [e] 1 mmol of substrate.



1a n = 1, R_1 = R_2 = Me
1b n = 2, R_1 = Et, R_2 = H
1c n = 2, R_1 = H, R_2 = Et
1d n = 2, R_1 = R_2 = Me

2a n = 1, R_1 = R_2 = Me
2b n = 2, R_1 = Et, R_2 = H
2c n = 2, R_1 = H, R_2 = Et
2d n = 2, R_1 = R_2 = Me

Note that those Lewis acid-catalyzed atom-transfer radical cyclization reactions exhibited excellent stereocontrol: only products **2a**−**d** with the 2-ester group trans to the 3-alkyl group were obtained. In contrast, atom transfer radical cyclization of **1b/c** using the $(Me_3Sn)_2/h\nu$ conditions reported by Curran et al. gave mainly the cis products.[9] This indicates that Lewis acids cannot only promote the atom-transfer radical cyclization but also dramatically affect the stereochemical outcome of those reactions.

(1) (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I.; Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.2. (b) Curran, D. P. *Synthesis* **1988**, 417−439. (c) Curran, D. P. *Synthesis* **1988**, 489−513. (d) Giese, B. *Radicals in Organic Synthesis. Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1986.

(2) (a) For an excellent review on enantioselective radical reactions, see: Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171. (b) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200−9201. (c) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800−3801. (d) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955−5958. (e) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501−4504. (f) Nishida, M.; Hayashi, H.; Nishida, A.; Kawahara, N. *Chem. Commun.* **1996**, 579−580.

(3) For an excellent review on the use of Lewis acids in free radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562−2579.

(4) (a) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155−5160. For examples of enantioselective allyl transfer radical reactions, see: (b) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713−11714. (c) Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067−2070. (d) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702−6703. (e) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029−11030. (f) Nagano, H.; Kuno, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 987−988.

(5) (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157. (b) Curran, D. P.; Chen, M.-S.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265−6276. (c) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872−8878. (d) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746−2750. (e) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041−11047.

(6) For recent examples of copper-catalyzed atom-transfer radical cyclization reactions, see: (a) Clark, A. J.; Campo, F. D.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastecoueres, D.; Thomas, G. H.; Verlhac, J.-B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671−680. (b) Clark, A. J.; Filik, R. P.; Haddleton, D. M.; Radigue, A.; Sanders, C. J.; Thomas, G. H.; Smith, M. E. *J. Org. Chem.* **1999**, *64*, 8954−8957.

(7) No reaction took place in the absence of Et_3B/O_2.

(8) Other solvents such as toluene, CF_3CH_2OH, and CH_2Cl_2 gave much lower yields. With Et_2O as the solvent, other Lewis acids such as $Sc(OTf)_3$ and $Zn(OTf)_2$ were found to be less efficient than $Yb(OTf)_3$.

(9) Curran, D. P.; Morgan, T. M.; Schwartz. C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607−6617.

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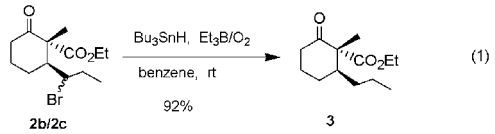


We then investigated the chiral Lewis acid-catalyzed atom-transfer cyclization reactions. In the presence of chiral ligands such as bisoxazoline **4**,[10] the reactions catalyzed by $Yb(OTf)_3$ in Et_2O were found to be very slow and only racemic cyclization products were obtained. But the $Mg(ClO_4)_2/CH_2Cl_2$ and $Mg(ClO_4)_2$/toluene systems were found to be effective, especially with chiral ligand **4**. As shown in Table 2, the reactions carried out in toluene generally gave better ee values than those reactions in CH_2Cl_2 (entries 1 vs 2; 8 vs 9; 11 vs 12). Most notably, the addition of activated 4 Å molecular sieves not only led to a dramatic increase in yield and ee, but also made it possible for the use of catalytic amounts of the chiral catalyst (entries 4, 5, 9, 10, 13, 14, and 17).[11] The loading of Lewis acid can be reduced to as low as 30% in many cases without significant compromise in yield and ee. Up to 95% ee was obtained for the cyclization of **1a**−**d**.[12] These are the first enantioselective radical cyclization reactions catalyzed by chiral Lewis acids.[13] Here activated molecular sieves most likely act as a drying agent, supported by the fact that the addition of 1 equiv of water resulted in a decrease in the rate and ee for the radical cyclization of **1a** (entries 2 vs 6).

To account for the high stereoselectivity, the following model is proposed (Figure 1). The *β*-keto ester group of substrates **1a**−**d** is assumed to chelate to the chiral Mg/**4** complex in a planar geometry. Considering the steric interactions between the substrates and the *tert*-butyl groups of the chiral ligand (*S*,*S*)-**4**, the radical cyclization from the *re*-face (transition states **A** and **B**) should be more favorable than that from the *si*-face (not shown). In addition, due to the lack of steric interactions between substituents on the olefinic C═C bond and the *β*-dicarbonyl group, transition state **B** would be favored over **A**, resulting in the cyclization product **2** of (2*R*,3*S*) configuration and a trans relationship between the 2-ester group and the 3-alkyl group.

In summary, we have developed a Lewis acid-catalyzed, highly enantioselective atom-transfer radical cyclization method for the formation of cyclic 2,3-disubstituted ketones. Applications of this method in enantioselective total synthesis of natural products will be reported in due course.

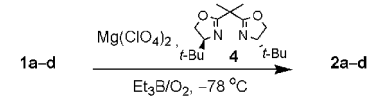
(10) For reviews on the use of C_2-symmetric chiral bisoxazoline ligands in asymmetric catalysis, see: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, 33, 325−335. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(11) For examples on the use of MS 4A in catalytic asymmetric reactions, see: (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922−1925. (b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimoto, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949−3954. (d) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329. (e) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783−4784.

(12) While the absolute configurations of the radical cyclization products **2a** and **2b/c** were determined by X-ray analysis, the stereochemical assignments of **2d** were made by correlation of CD spectra of the debromination products of **2b** and **2d**. See Supporting Information for details.

(13) For a related Lewis acid-catalyzed enantioselective iodocarbocyclization reaction via an ionic pathway, see: Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191−1199.

Table 2. Asymmetric Atom-Transfer Radical Cyclization Reactions[a]



entry	substr	catalyst (equiv)	solvent	time[b] (h)	yield[c] (%)	ee[d,e] (%)
1	**1a**	1.1	CH_2Cl_2	7.5	68	71
2	**1a**	1.1	toluene	5	67	94
3	**1a**	0.6	toluene	7	63	85
4[f]	**1a**	0.5	toluene	7	65	93
5[f,g]	**1a**	0.3	toluene	7	68	92
6[h]	**1a**	1.1	toluene	9	53	21
7	**1b**	1.0	toluene	9.5	57 (1/1.2)[i]	68/78[j]
8	**1b**	1.0	CH_2Cl_2	7	62 (1.3/1)[i]	44/54[j]
9[f]	**1b**	1.0	toluene	6.5	68 (1/1.3)[i]	83/91[j]
10[f]	**1b**	0.3	toluene	12	58 (1/1)[i]	74/87[j]
11	**1c**	1.0	CH_2Cl_2	4	60 (1/1.1)[i]	50/72[j]
12	**1c**	1.0	toluene	6.5	62 (1/1.3)[i]	52/78[j]
13[f]	**1c**	1.0	toluene	4	82 (1/1.4)[i]	70/92[j]
14[f,g]	**1c**	0.3	toluene	9.5	81 (1/1.4)[i]	74/95[j]
15	**1d**	1.1	toluene	7.5	62	93
16	**1d**	0.6	toluene	10	22	82
17[f]	**1d**	0.5	toluene	7.5	53	94

[a] Unless otherwise indicated, all reactions were carried out at −78 °C with 0.2 mmol of substrate, the indicated amount of $Mg(ClO_4)_2$, (*S*,*S*)-**4** (1.1-fold relative to $Mg(ClO_4)_2$), 10 mL of solvent, 3 equiv of Et_3B/O_2 for substrates **1a** and **1d**, or 5 equiv of Et_3B/O_2 for substrates **1b** and **1c**. [b] Time for complete reaction. [c] Isolated yield. [d] The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD or AD column. [e] The absolute configuration of the product was determined to be (2*R*,3*S*). [f] Activated 4 Å molecular sieves (powder, 500 mg/mmol substrate) was added to the reaction mixture. [g] 1 mmol of substrate. [h] 1.0 equiv of water was added to the reaction mixture. [i] Ratio of **2b** and **2c**. [j] The ee values for **2b** and **2c**, respectively.

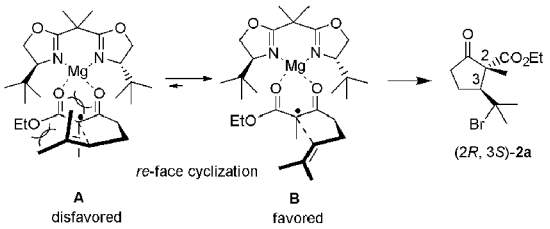


Figure 1.

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Supporting Information Available: Experimental details; determination of the absolute configurations of products **2a**−**d**; HPLC analysis of enantiomeric excesses of products **2a**−**d**; X-ray structural analysis of products **2a**, **2c**, and the 2,4-DNP derivative of **2b** containing tables of atomic coordinates, thermal parameters, bond lengths, and angles (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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