Radical Cyclization

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Enantioselective PhSe-Group-Transfer Tandem Radical Cyclization Reactions Catalyzed by a Chiral Lewis Acid**

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Tandem radical cyclization, which is a powerful method for the synthesis of polycyclic compounds, is used widely in the syntheses of natural products.[1] Only a few asymmetric tandem radical cyclization reactions are known,[2,3a] however, and no enantioselective group-transfer radical reactions have been reported.[4] Herein we report a catalytic enantioselective group-transfer radical cyclization reaction and its applications in tandem reactions.

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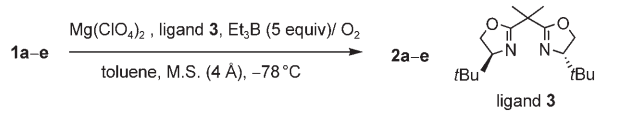
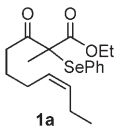
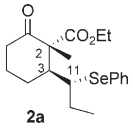
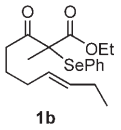
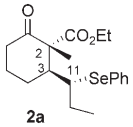
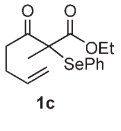
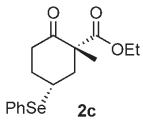
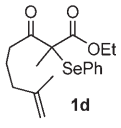
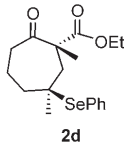
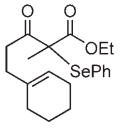
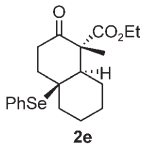
To investigate the enantioselective PhSe-group-transfer radical cyclization reactions of unsaturated α-phenylseleno-β-ketoesters, we prepared compounds **1a–e** and subjected them to cyclization conditions, with Et_3B/O_2 as the radical initiator (Table 1). In the absence of a Lewis acid, no cyclization reaction occurred, and only reductive dephenylselenate products were obtained (data not shown). Clearly Lewis acids promoted this phenylseleno-transfer radical cyclization reaction. We found that the complex formed between $Mg(ClO_4)_2$ and the bisoxazoline ligand[5] **3** was the most suitable catalyst for the cyclization reaction.[6]

Table 1: Chiral Lewis acid catalyzed group-transfer radical monocyclization reactions.[a]



Entry	Substrate	LA[b] [equiv]	*t* [h]	Product	Yield [%][c]	*ee* [%][d]
1	 **1a**	1.0	6	 **2a**	82	89
2[e]		1.0	8		80	89
3		0.3	10		81	84
4[e]		0.3	12		< 5	
5	 **1b**	1.0	7	 **2a**	71	81
6		0.3	10		66	87
7	 **1c**	1.0	8	 **2c**	63	69
8	 **1d**	1.0	9	 **2d**	65	66
9	 **1e**	1.0	8	 **2e**	75	87
10		0.3	9		62	58

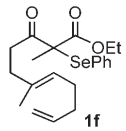
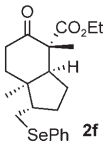
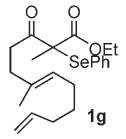
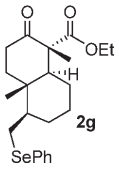
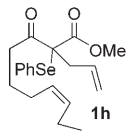
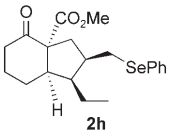
[a] Unless otherwise indicated, all reactions were performed with 0.2 mmol of the substrate at a concentration of 0.025 M in toluene in the presence of activated 4-Å molecular sieves (powder, 500 mg mmol^{-1} substrate) and the indicated amount of $Mg(ClO_4)_2$ and (*S*,*S*)-**3** (ligand/Lewis acid = 1.1:1). [b] LA = Lewis acid. [c] Yield of isolated product. [d] The enantiomeric excess was determined through HPLC analysis by using a Chiralcel AD column. [e] In the absence of the 4-Å molecular sieves (M.S.).

As Table 1 indicates, cyclization of **1a,** after purification by column chromatography, gave the 6-*exo* product **2a** as a single diastereoisomer in 82% yield with 89% *ee* (Table 1, entry 1). Although the addition of activated 4-Å molecular sieves did not improve the *ee* value, it accelerated the reaction dramatically and made it possible to use a catalytic amount of the chiral catalyst (Table 1, entries 2–4).[7] Substrate **1b**, the *trans* olefin analogue of **1a**, gave the same product (+)-**2a** in comparable yield and enantioselectivity (Table 1, entries 5 and 6). When we used a catalytic amount (0.3 equiv) of the chiral Lewis acid, the yield decreased slightly but the enantioselectivity increased to 87% *ee* (Table 1, entry 6). The absolute configuration of (+)-**2a** was determined to be (2*R*,3*S*,11*R*).[8] The excellent control of the configuration at the contiguous stereogenic centers is in contrast to the results obtained from the corresponding bromine-atom-transfer radical cyclization reactions, in which two diastereomeric products were obtained in a poor ratio.[3b] Substrate **1c** gave exclusively the 6-*endo* product **2c** in 63% yield with 69% *ee* (Table 1, entry 7). For the cyclization of **1d**, the α-radical center attacked the less-substituted side of the alkene to form the seven-membered ring product **2d** exclusively in moderate yield and enantioselectivity (Table 1, entry 8). The cyclization of substrate **1e** proceeded smoothly to produce the bicyclic product **2e** with 87% *ee*. A lower catalyst loading (0.3 equiv) led to a large decrease in the *ee* value (Table 1, entries 9 and 10). These results represent the first known enantioselective group-transfer radical cyclization reactions catalyzed by chiral Lewis acids.

Because PhSe-transfer radical cyclization reactions have been demonstrated previously to have great potential for use in tandem cyclization reactions,[9] we expected to obtain bicyclic PhSe-transfer products when applying our new method to a series of diene substrates (Table 2). In contrast to the low yields and enantioselectivities (< 33%) in the corresponding Br-transfer radical cyclization,[3a] substrate **1f** gave the *cis*-6,5-fused ring product **2f** in 70% yield with 73% *ee* (Table 2, entry 1). The use of 0.3 equivalents of chiral Lewis acid did not decrease the yield or the *ee* value significantly (Table 2, entry 2). Substrate **1g** underwent 6-*endo*/6-*exo* cyclization (Table 2, entry 3) to give the 6,6-*trans*-fused ring product **2g** with excellent enantioselectivity (97% *ee*) albeit in low yield (31%); high selectivity (87% *ee*) was attained even when using 0.3 equivalents of the chiral Lewis acid catalyst (Table 2, entry 4). In this case we also isolated approximately of the monocyclization product because the 1,3-diaxial interactions of two methyl groups rendered the second cyclization unfavorable. Substrate **1h**, which has an allyl substituent in the α-position, underwent sequential 6-*exo* and 5-*exo* cyclizations in the presence of a stoichiometric amount of the chiral Lewis acid to give the bicyclic product **2h** in 44% yield with 91% *ee* (Table 2, entry 5). Each of these tandem cyclization reactions successfully creates four stereogenic centers in a single step with moderate to high enantioselectivity, which further demonstrates the power of this chiral Lewis acid promoted PhSe-group-transfer radical cyclization.

The model proposed to account for the high stereoselectivity is similar to that for the corresponding Br-transfer

Table 2: Chiral Lewis acid catalyzed group-transfer radical tandem cyclization reactions.[a]

Entry	Substrate	LA[b] [equiv]	*t* [h]	Product	Yield [%][c]	*ee* [%][d]
1	 **1f**	1.0	9	 **2f**	70	73
2		0.3	10		70	67
3	 **1g**	1.0	12	 **2g**	31	97
4		0.3	12		33	87
5	 **1h**	1.0	12	 **2h**	44	91

[a] Unless otherwise indicated, all reactions were performed with 0.2 mmol of the substrate at a concentration of 0.025 M in toluene in the presence of activated 4-Å molecular sieves (powder, 500 mg mmol^{-1} substrate) and the indicated amounts of $Mg(ClO_4)_2$ and (*S*,*S*)-**3** (ligand/Lewis acid = 1.1:1). [b] LA = Lewis acid. [c] Yield of isolated product. [d] The enantiomeric excess was determined through HPLC analysis by using a Chiralcel OD or AD column.

radical cyclizations we reported earlier (Figure 1). We assume that the dicarbonyl moiety of substrate **1a** chelates to the magnesium center, which adopts an octahedral geometry in which ClO_4^- ions occupy the two axial positions.[10] To avoid steric interactions with the α-*tert*-butyl group, the olefin moiety prefers to approach from the *Re* face of the α-radical center (transition states **A** and **B**). In TS **B**, steric interactions are found between the olefin group and the β-*tert*-butyl group. Thus TS **A** would be favored over TS **B**, affording the cyclic radical intermediate **C**. For the most stable conformer of radical intermediate **C**, SePh abstraction takes place preferentially from the less-hindered *Re* face to yield product **2a** as a single diastereoisomer. Thus, the lower transfer rate of the SePh group to the alkyl radical—relative to that of Br-atom transfer—and its bulk cause the SePh abstraction to be more stereoselective.[11]

In conclusion, we have developed Lewis acid catalyzed, highly enantioselective PhSe-group-transfer radical cyclization reactions for the construction of a variety of monocyclic and bicyclic compounds that include the core structures of many biologically interesting natural products.

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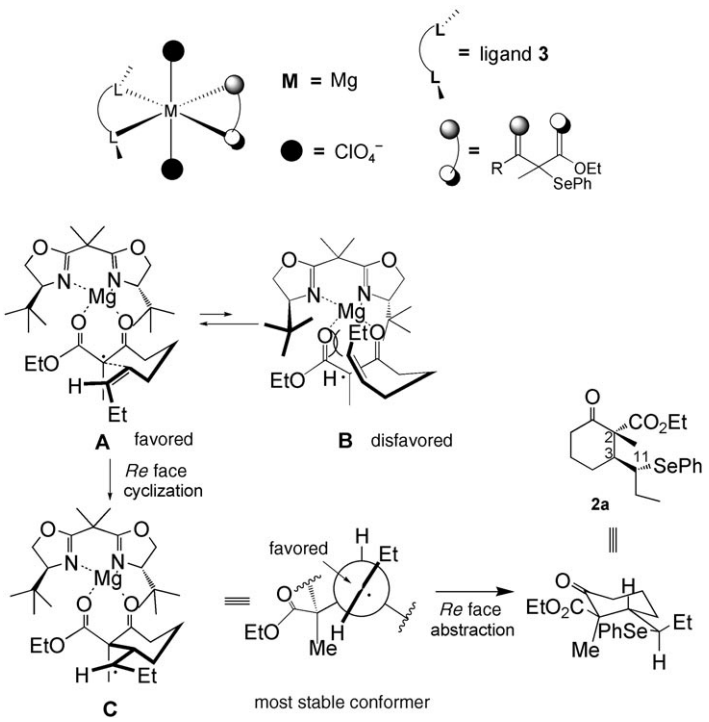

Figure 1. Transition-state model proposed for the enantioselective group-transfer radical cyclization.

[1] For recent reviews on tandem radical cyclization reactions, see: a) M. Malacria, *Chem. Rev.* **1996**, *96*, 289–306; b) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339–363; c) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195–206; d) A. J. McCarroll, J. C. Walton, *Angew. Chem.* **2001**, *113*, 2282–2307; *Angew. Chem. Int. Ed.* **2001**, *40*, 2224–2248; for recent reviews on free radical reactions used in the synthesis of natural products, see: e) C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.* **1991**, *91*, 1237–1286; f) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195–206.

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[3] a) D. Yang, S. Gu, Y.-L. Yan, H.-W. Zhao, N.-Y. Zhu, *Angew. Chem.* **2002**, *114*, 3140–3143; *Angew. Chem. Int. Ed.* **2002**, *41*, 3014–3017; b) D. Yang, S. Gu, Y.-L. Yan, N.-Y. Zhu, K.-K. Cheung, *J. Am. Chem. Soc.* **2001**, *123*, 8612–8613.

[4] For references on atom- and group-transfer radical reactions, see: a) D. P. Curran, M.-H. Chen, D. Kim, *J. Am. Chem. Soc.* **1986**, *108*, 2489–2490; b) D. P. Curran, C.-T. Chang, *J. Org. Chem.* **1989**, *54*, 3140–3157; c) D. P. Curran, M.-H. Chen, D. Kim, *J. Am. Chem. Soc.* **1989**, *111*, 6265–6276; d) D. P. Curran, M.-H. Chen, E. Spletzer, C. M. Seong, C.-T. Chang, *J. Am. Chem. Soc.* **1989**, *111*, 8872–8878; e) D. P. Curran, J. Tamine, *J. Org. Chem.* **1991**, *56*, 2746–2750; f) for a recent review, see: J. Byers in *Radicals in Organic Synthesis, Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, chap. 1.5.

[5] For reviews on the use of C_2-symmetric chiral bisoxazoline ligands in asymmetric catalysis, see: a) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; b) A. K. Ghosh, P.

Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1 – 45.

[6] We found that the use of other Lewis acids, including $Yb(OTf)_3$, $Cu(OTf)_2$, and $Sc(OTf)_3$, was ineffective.

[7] The role of activated molecular sieves in the cyclization reactions is not yet fully understood. One possibility is that molecular sieves absorb water, as $Mg(ClO_4)_2$ is moisture sensitive. A similar effect was found in our Br-atom-transfer radical cyclization reactions.[3b]

[8] The relative configuration of **2a** was determined by X-ray crystallographic analysis of a 2,4-DNP (DNP = dinitrophenylhydrazine derivative of (±)-**2a**; the absolute configurations of the stereogenic centers C2 and C3 were determined by comparison of optical rotation data of the reductive dephenylseleno product of (+)-**2a** with those of the reductive debromo product of a known compound (see Supporting Information for details).

[9] a) D. Yang, Q. Gao, O.-Y. Lee, *Org. Lett.* **2002**, *4*, 1239 – 1241; b) D. Yang, Q. Gao, B.-F. Zheng, N.-Y. Zhu, *J. Org. Chem.* **2004**, *69*, 8821 – 8828.

[10] For a Mg^{II}–bisoxazoline complex with octahedral geometry, see: a) G. Desimoni, G. Faita, P. P. Righetti, *Tetrahedron Lett.* **1996**, *37*, 3027 – 3030; b) G. Desimoni, G. Faita, A. G. Invernizzi, P. P. Righetti, *Tetrahedron* **1997**, *53*, 7671 – 7688; c) J. M. Takacs, E. C. Lawson, M. J. Reno, M. A. Youngman, D. A. Quincy, *Tetrahedron: Asymmetry* **1997**, *8*, 3073 – 3078; d) S. Yao, M. Johannsen, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **1998**, *63*, 118 – 121.

[11] D. P. Curran, A. A. Martin-Esker, S.-B. Ko, M. Newcomb, *J. Org. Chem.* **1993**, *58*, 4691 – 4695.

