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Lewis Acid-Promoted Diastereoselective Radical Cyclization Using Chiral α,β-Unsaturated Esters

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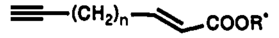
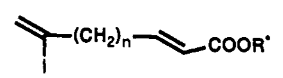
Radical reactions have become important tools for organic synthesis.[2] The generation of new stereo centers using chiral auxiliaries in radical C–C bond formation is of much interest in free radical chemistry,[3] and high α and ρ selectivities[4] have been achieved.[5,6,7b] Although β addition of carbon radicals to the α,β-unsaturated carbonyl system in an inter- or intramolecular manner has been widely employed in organic synthesis, stereocontrol in the radical addition to chiral alkenes with β-attached chiral auxiliaries remains a challenging issue. Recently, Curran introduced a new imide auxiliary which controls the conformation of the O=C—C=C group and the direction of entering radicals, resulting in high β stereoselectivity.[7] However, several steps are required for the preparation of the auxiliary. Therefore, the development of general and convenient strategies to achieve high degrees of β diastereoselectivity is still required.[8] We report here that the intramolecular addition of alkenyl radicals to the β position of 8-phenylmenthyl α,β-unsaturated esters showed good to excellent diastereoselectivity *in the presence of a Lewis acid.*

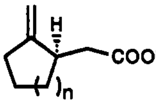
8-Phenylmenthyl alcohol has been widely employed as a chiral auxiliary in diastereoselective reactions.[9–11] In addition to the shielding of the π-face of alkenes, the rotamer distribution with respect to the O=C—C=C bond is important to achieve good diastereoselectivity in radical addition (Figure 1). In contrast to the amide auxiliary the conformation of the ester group exists as an equilibrium mixture of *s-cis* and *s-trans* isomers.[3,12] Radical cyclization of (−)-8-phenylmenthyl (*E*)-2-octen-7-ynoate (**1**)[13] and (−)-8-phenylmenthyl (*E*)-2-nonen-8-ynoate (**2**)[13] under the conditions reported by Oshima and Utimoto (**1** or **2**, 90 mM; *n*-Bu_3SnH, 1.5 equiv; Et_3B, 1.1 equiv; toluene, 0 °C, under Ar)[14] afforded (2-methylenecyclopentyl)acetate **5** and (2-methylenecyclohexyl)acetate **6**, respectively, in good yield. However, only modest diastereoselectivity was observed (Table 1, runs 1 and 5).[15]



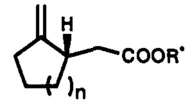
1 : n=3
2 : n=4



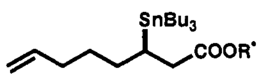
3 : n=3
4 : n=4



(*R*)-5 : n=1
(*R*)-6 : n=2



(*S*)-5 : n=1
(*S*)-6 : n=2



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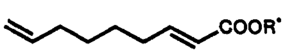

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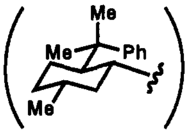
R* = (-)-8-phenylmenthyl



It has been reported that acrylate is fixed in the *s-trans* conformation in the presence of a Lewis acid.[12] Thus, a suitable Lewis acid capable of surviving under the radical conditions[18] would allow reaction to occur predominantly from the *s-trans* conformer. Addition of $BF_3 \cdot OEt_2$ to the reaction under argon clearly accelerated the cyclization of **1** and **2** and increased the proportion of (*R*)-isomer in the product (runs 2 and 3, 6 and 7). Diastereoselectivities of the radical cyclization of **1** and **2** were 76:24 and 86:14, respectively, in the presence of a high

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(1) Hokkaido Institute of Pharmaceutical Sciences.

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(4) For categories of diastereoselective radical reactions, see ref 3.

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(8) (a) Reaction using chiral enamine: Renaud, P.; Schubert, S. *Synlett* **1990**, 624. (b) Radical addition to enolate of chiral amide: Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169. (c) Reaction of dimethylaluminum chloride with chiral α,β-unsaturated *N*-acyloxazolidinones: Rück, K.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 694. Rück, K.; Kunz, H. *Synlett* **1992**, 343. Rück, K.; Kunz, H. *Synthesis* **1993**, 1018.

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(13) The chiral esters **1–4** were prepared by olefination of 8-phenylmenthyl (triphenylphoshoranylidene)acetate and the corresponding aldehydes. Details of the syntheses are described in the supplementary material.

(14) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

(15) Diastereoselectivity was determined by ^{1}H NMR. The configurations of the major diastereoisomers, (*R*)-**5** and (*R*)-**6**, were determined by chemical conversion to known chiral compounds: A diastereo mixture of **5** (*R*:*S* = 1.4:1) was converted to (*S*)-2-undecylcyclopentanone [$[\alpha]_D^{18} = +12.8°$ (*c* 0.99, ether)]. [Enantiomerically pure (*S*)-2-undecylcyclopentanone: $[\alpha]_D = +84.2°$ (*c* 0.83, ether)[16].] A diastereo mixture of **6** (*R*:*S* = 3.3:1) was converted to (*R*)-2-acetonylcyclohexanone [$[\alpha]_D^{20} = +11.4°$ (*c* 4.37, methanol)] [(*R*)-2-Acetonylcyclohexanone of 80% *ee*: $[\alpha]_D = +23.5°$ (*c* 6, methanol).[17]] Details of these transformations are also described in the supplementary material.

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Table 1. Lewis Acid-Promoted Diastereoselective Radical Cyclization

run	substrate[a]	n-Bu_3SnH (equiv)	Lewis acid	[M]	temp (°C)	time (h)	product	yield (%)	ratio[b] (R:S)
1	**1**	1.5	none		0	4.5	**5**	88[c]	58:42
2	**1**	1.5	$BF_3 \cdot OEt_2$	0.72	0	1.5	**5**	90[c]	72:28
3	**1**	4.5	$BF_3 \cdot OEt_2$	2.90	0	2.0	**5**	60[c]	76:24
4	**1**	4.5	$BF_3 \cdot OEt_2$	2.90	0	0.5	**5**	90	76:24
5	**2**	1.5	none		0	7.0	**6**	78[c]	58:42
6	**2**	1.5	$BF_3 \cdot OEt_2$	0.72	0	3.5	**6**	80[c]	81:19
7	**2**	4.5	$BF_3 \cdot OEt_2$	2.90	0	1.5	**6**	39[c,d]	86:14
8	**2**	2.5	$BF_3 \cdot OEt_2$	1.45	0	20 min	**6**	77	84:16
9	**2**	1.5	Me_3Al	0.36	0	1.5	**6**	83	79:21
10	**2**	1.5	Et_3Al	0.45	0	1.5	**6**	76	85:15
11	**2**	1.5	i-Bu_3Al	0.36	0	1.5	**6**	72	87:13
12	**2**	1.5	Me_2AlCl	0.25	0	1.5	**6**	78	79:21
13	**2**	1.5	Et_2AlCl	0.36	0	1.5	**6**	73	83:17
14	**2**	1.5	$EtAlCl_2$	0.18	0	1.5	**6**	53[e]	76:24
15	**1**	1.5	i-Bu_3Al	0.36	0	1.5	**5**	60	81:19
16	**1**	1.5	i-Bu_3Al	0.36	–40	1.5	**5**	50[f]	81:19
17	**3**	1.5	none		–78	1.0	**5**	92	67:33
18	**3**	2.5	$BF_3 \cdot OEt_2$	1.44	–78	0.5	**5**	86	94:6
19	**3**	1.5	i-Bu_3Al	0.36	–78	20 min	**5**	83	90:10
20	**3**	1.5	MAD[g]	0.36	–78	20 min	**5**	79	96:4
21	**4**	1.5	none		0	10 min	**6**	41[h]	57:43
22	**4**	4.5	$BF_3 \cdot OEt_2$	2.90	0	10 min	**6**	82	90:10
23	**4**	1.5	MAD[g]	0.36	–78	0.8	**6**	42[i]	98:2

[a] Concentration of the substrate: 0.09 M. [b] The ratio was determined by ^1H NMR. [c] The reactions were carried out under argon. [d] 53% of **2** was recovered. [e] 16% of **2** was recovered. [f] **7** was obtained in 11% yield. [g] Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide). [h] 41% of **8** was isolated. [i] 42% of **8** was isolated.

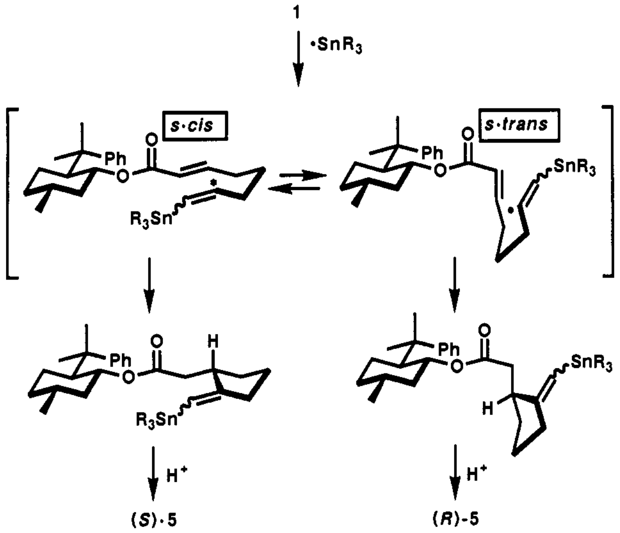

Figure 1. Diastereoselective radical cyclization of **1**.

concentration of $BF_3 \cdot OEt_2$.[19] High concentrations of the Lewis acid appear to be necessary to suppress reaction of the uncomplexed substrate. Although triethylborane can work as a radical initiator under an argon atmosphere, the reaction under dry air proceeded faster with no decrease in the diastereoselectivity (runs 4 and 8). Therefore, the other results presented in Table 1 were obtained under aerobic conditions.[20]

After surveying other Lewis acids,[21] we found that aluminum reagents are effective at lower concentrations of the Lewis acid (runs 9–14). The bulkiness of the alkyl groups on the aluminum reagents affected the diastereoselectivity, and the cyclization of **2** in the presence of $(i\text{-}Bu)_3Al$ afforded the product mixture in 72% yield and in 87:13 selectivity (run 11). The same Lewis acid was also effective in the cyclization of **1** (81:19, run 15). Performing the reaction at a lower temperature (–40 °C) did not improve the selectivity, and the stannylated product **7** was isolated in 11% yield as a single diastereomer (run 16).[22]

To circumvent the difficulties involved in the selective generation of alkenyl radicals from acetylenic substrates at low temperatures, we next examined the radical reaction of vinyl iodides **3** and **4**. The cyclization of **3** proceeded smoothly at -78 °C without Lewis acid, and the selectivity was slightly better (92%, 67:33, run 17) compared to cyclization at 0 °C. Significantly higher selectivity was observed in the presence of the Lewis acids $BF_3 \cdot Et_2O$ (94:6, run 18), $(i\text{-}Bu)_3Al$ (90:10, run 19), and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)[23] (MAD, 96:4, run 20). Although six-membered-ring formation using **4** without Lewis acid was inefficient (41%, 57:43, run 21),[24] cyclization in the presence of $BF_3 \cdot Et_2O$ proceeded efficiently and with high diastereoselectivity (82%, 90:10) even at 0 °C (run 22). The highest diastereoselectivity was recorded at -78 °C in the presence of MAD (98:2, run 23), although a considerable amount of the side product **8** was obtained.

In conclusion, we have reported here an efficient and convenient diastereoselective radical cyclization which shows a high degree of β selectivity. The presence of a suitable Lewis acid is essential to achieve a high level of selectivity.

Supplementary Material Available: Syntheses of **1–4**, representative experiments (runs 4, 8, 20, and 23 in Table 1), and chemical conversions of **5** and **6** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(19) Even under conditions using a high concentration of $BF_3 \cdot OEt_2$, the reaction appeared to proceed *via* a radical mechanism. Without n-Bu_3SnH or Et_3B, no reaction was observed.

(20) Representative procedure (run 4 in Table 1): To a solution of **1** (70.5 mg, 0.20 mmol) in toluene (2 mL) was added $BF_3 \cdot OEt_2$ (807 μL, 6.4 mmol), Et_3B (1.0 M n-hexane solution, 0.21 mL, 0.21 mmol), and n-Bu_3SnH (242 μL, 0.9 mmol) in sequence at 0 °C under dry air. The mixture was stirred for 0.5 h and was quenched by addition of a solution of sodium bicarbonate. The usual workup, followed by silica gel column chromatography, afforded a diastereo mixture of **5** (64 mg, 90%, R:S = 76:24). Destannylation occurred from the initial cyclized products under these conditions.

(21) Other Lewis acids were investigated. No effect on the reaction was observed in the presence of $Zn(OTf)_2$, $Sn(OTf)_2$, and $MgBr_2$ because of their insolubility in the reaction media; TMSOTf and $TiCl_4$ inhibited the reaction by consuming the tin reagent and triethylborane.

(22) The stereochemistry of **7** was tentatively assigned as shown on the basis of the transition-state model.

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(24) Product **8** was isolated in 41% yield which would be formed *via* hydrostannation of the triple bond followed by destannylation.