Construction of Chiral Quaternary Carbon Centers by Catalytic Enantioselective Radical-Mediated Allylation of α-Iodolactones Using Allyltributyltin in the Presence of a Chiral Lewis Acid

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Asymmetric induction in radical-mediated reactions is currently the focus of attention in synthetic organic chemistry. Extensive search for asymmetric radical reactions has been reported, and diastereoselective radical reactions using substrates bearing chiral auxiliaries have proven to be reliable methods for the synthesis of optically active compounds.[1] Recently, several enantioselective radical reactions using organotin reagents have appeared.[2] When chiral Lewis acids are employed, enantioselective radical reactions are reported to give optically active products.[2a−h] Another approach using chiral tin hydrides is also known.[2i,j] However, there are no examples of enantioselective radical reactions for the construction of chiral quaternary carbon centers, although the chiral creation of these carbon centers has received great attention in asymmetric synthesis.[3] In our continuing study of asymmetric induction in radical reactions,[2a] we planned to examine the utility of *tert*-alkyl radicals in the formation of chiral quaternary carbon centers, because the characteristics of the radicals were expected to readily lead to the connection of hindered carbons.[4] Here, we describe the first example of the formation of chiral quaternary carbon centers by both stoichiometric and catalytic enantioselective radical reactions using an organotin reagent: an efficient enantioselective radical-mediated allylation of α-alkyl-α-iodolactones is realized by use of a chiral Lewis acid, which is generated from a chiral ligand **3** and Me₃Al in the presence of Et₂O.

The examples achieving a high degree of asymmetric induction in enantioselective radical reactions utilize oxazolidinones as bidentate substrates to Lewis acids.[2c,e,f,h] We chose α-methyl-α-iodolactone **1** as a model substrate to examine the possibility of radical-mediated asymmetric induction using a monodentate substrate. Among several Lewis acids [MgI₂, MgBr₂, Zn(OTf)₂, Et₂AlCl, Me₃Al] examined, an aluminum

Scheme 1. Enantioselective Radical-Mediated Allylations of **1** and **4a−c**
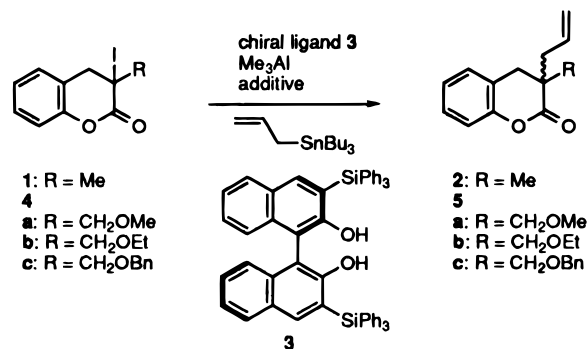
reagent seemed to be a suitable Lewis acid, because the allylation of **1** was most activated with Me₃Al to give the desired product cleanly after 1 h at −78 °C in toluene.[5] This allylation did not proceed without triethylborane as the initiator, and galvinoxyl inhibited the reaction. These findings support that the allylation proceeds through a radical mechanism. Therefore, we focused on the chiral Lewis acid prepared from an aluminum reagent in our radical-mediated asymmetric allylations. At first, reaction of **1** with 1 equiv (each) of allyltributyltin and triethylborane using a stoichiometric amount of the chiral Lewis acid generated from **3**[6] and Me₃Al was explored (Scheme 1). However, the reaction in toluene at −78 °C was very sluggish and took a long time (24 h) to reach completion, and the enantiomeric excess (ee) of allylated product **2** was only 27% (entry 1 in Table 1).[7,8] Subsequently, the effect of an additive on this asymmetric reaction was examined. Surprisingly, the degree of asymmetric induction was improved dramatically to 81% ee by use of the chiral Lewis acid generated from Me₃Al and **3** in the presence of 1 equiv of Et₂O (entry 2).[9]

Next, the reactions of α-(alkoxymethyl)-α-iododihydrocoumarins **4a−c**, the ether moieties of which may interfere with the role of Et₂O in asymmetric induction, were examined (Scheme 1).[10] In all cases, the best results were obtained by use of the chiral Lewis acid containing Et₂O, and the effect of Et₂O was remarkable (entries 3−11).[11] The degree and sense of asymmetric induction were essentially independent of the

(1) For reviews of asymmetric radical reactions see: (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296−304. (b) Smadja, W. *Synlett* **1994**, 1−26. (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995.

(2) (a) Murakata, M.; Tsutsui, H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481−482. (b) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576−3577. (c) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029−11030. (d) Nishida, M.; Hayashi, H.; Nishida, A.; Kawahara, N. *Chem. Commun.* **1996**, 579−580. (e) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200−9201. (f) Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067−2070. (g) Fhal, A.-R.; Renaud, P. *Tetrahedron Lett.* **1997**, *38*, 2661−2664. (h) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800−3801. (i) Nanni, D.; Curran, D. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2417−2422. (j) Blumenstein, M.; Schwarzkopf, K.; Metzger, J. O. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 235−236 and references cited therein.

(3) Extensive search for the chiral creation of quaternary carbon centers has been reported, and several methodological developments have been attained to create these carbon centers enantioselectively. For reviews on the creation of quaternary carbon centers, see: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066 and references cited therein.

(4) (a) Menapace, L. W.; Kuivila, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 3047−3051. (b) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734−745. (c) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H.; Fukuzumi, S. *J. Am. Chem. Soc.* **1991**, *113*, 4028−4030.

(5) The reaction using Et₂AlCl gave the desired allylated product along with unidentified products.

(6) The chiral ligand **3** was prepared using literature procedures, see: Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975−2976.

(7) The ee of allylated product **2** was determined by a chiral HPLC analysis of the reduced product, 3-methyl-3-propyldihydrocoumarin, which was obtained by hydrogenation of **2** [H₂, Pd/C, 1 atm, 97%]. The ees of allylated products **5a−c** were determined directly by HPLC using a chiral column. See the Supporting Information for details.

(8) The absolute configuration of **2** was determined to be *R* by the CD spectrum of 2-methyl-2-propyl-4-methoxyindanone, which was synthesized from **2**. For circular dichroism spectra of indanones having a quaternary carbon center at the 2-position, see: Kuroyanagi, M.; Fukuoka, M.; Yoshihira, K.; Natori, S. *Chem. Pharm. Bull.* **1979**, *27*, 731−741 and references cited therein. The absolute configuration of **5a** was determined by chemical correlation with methyl 2-methyl-2-[(2-methoxyphenyl)methyl]-pentanoate obtained from (*R*)-**2**. The absolute configurations of **5b** and **5c** were determined by chemical correlation with 3-(hydroxymethyl)-3-propyldihydrocoumarin obtained from (*R*)-**5a**. See the Supporting Information for details.

(9) The chiral Lewis acid was prepared from Me₃Al and **3** in the presence of Et₂O at room temperature, and then **1** was added at −78 °C.

(10) It is reported that ether moieties in β-alkoxy-α-halo esters coordinate to Lewis acids, see: Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528−12535.

(11) As for the amounts of Et₂O, 1 equiv of Et₂O for the chiral Lewis acid was found to be the most effective. The ee of the product decreased with excess Et₂O (2−5 equiv of Et₂O, 74−48% ee). Addition of *i*-Pr₂O or THF exhibited a slightly weak effect to increase the ee values (entries 5 and 6), compared with Et₂O. A nitrogen donor as an additive was not effective (entry 7).

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Table 1. Enantioselective Radical-Mediated Allylations of **1** and **4a−c**[a]

entry	substrate	chiral Lewis acid (equiv)	additive	yield (%)[b]	ee (%)[c]	config[d]
1	**1**	1.0	none	72	27	*R*
2	**1**	1.0	Et$_2$O	84	81	*R*
3	**4a**	1.0	none	75	10	*S*
4	**4a**	1.0	Et$_2$O	85	82	*R*
5	**4a**	1.0	*i*-Pr$_2$O	83	43	*R*
6	**4a**	1.0	THF	71	33	*R*
7	**4a**	1.0	*N*-methyl-pyrrolidine	59	3	*R*
8	**4b**	1.0	none	77	6	*S*
9	**4b**	1.0	Et$_2$O	85	85	*R*
10	**4c**	1.0	none	72	3	*S*
11	**4c**	1.0	Et$_2$O	76	91	*R*
12	**1**	0.5	Et$_2$O	82	81	*R*
13	**1**	0.2	Et$_2$O	81	80	*R*
14	**1**	0.1	Et$_2$O	83	72	*R*
15	**4a**	0.5	Et$_2$O	81	81	*R*
16	**4a**	0.2	Et$_2$O	78	80	*R*
17	**4a**	0.1	Et$_2$O	76	74	*R*
18	**4b**	0.2	Et$_2$O	79	83	*R*
19	**4b**	0.1	Et$_2$O	74	70	*R*
20	**4c**	0.2	Et$_2$O	73	82	*R*
21	**4c**	0.1	Et$_2$O	78	71	*R*

[a] For experimental procedures, see the Supporting Information. [b] Isolated yield. [c] See ref 7. [d] See ref 8.

substrates used (**1** and **4a−c**) in the presence of Et$_2$O, indicating that compounds **4a−c** act as monodentate substrates to the Lewis acid.

These results mentioned above (asymmetric allylations of **1** and **4a−c**) demonstrate that the chiral Lewis acid complex generated from **3** and Me$_3$Al in the presence of Et$_2$O is responsible for these highly enantioselective radical-mediated reactions. Usually, organoaluminum complexes exist as four-coordinate complexes.[12] However, when the Et$_2$O molecule is coordinated to the chiral aluminum complex, the aluminum would have a satisfactory coordination sphere (tetravalency) so that α-iodolactone could not coordinate to the chiral aluminum complex. Thus, a five-coordinate aluminum complex derived from the chiral ligand **3** with Et$_2$O may play a key role in these asymmetric allylations.[13]

In the course of developing this system, we turned naturally our attention to a catalytic reaction.[14] The rates of achiral allylations of **1** and **4a−c** in the absence of Lewis acid in toluene at −78 °C are very slow, while a stoichiometric amount of chiral Lewis acid containing Et$_2$O accelerates asymmetric allylations (less than 4 h). These findings on the difference in the reactivity between achiral and chiral conditions open a route to the formation of the chiral quaternary carbon centers by catalytic radical-mediated reactions. Asymmetric allylations with a

catalytic amount of chiral Lewis acid containing Et$_2$O took place effectively to give desired allylated products.

The allylation of **1** in the presence of 0.5 equiv of the chiral Lewis acid proceeded smoothly to give **2** in 81% ee with 82% yield (entry 12). Similarly, the reaction of **4a** gave **5a** in 81% ee with 81% yield (entry 15). It is noteworthy that the ee values were essentially equal to those attained with a stoichiometric amount. Thus, it was found that the chiral Lewis acid−product complex could dissociate to continue the catalytic cycle. Even when 0.2 equiv of the chiral Lewis acid was used, allylated products **2** and **5a−c** were obtained in more than 80% ee in these catalytic systems (entries 13, 16, 18, and 20). Further lowering of the catalyst (0.1 equiv) slightly decreased the degrees of asymmetric induction; however, moderate to good ees of **2** and **5a−c** (74−70% ees) were obtained (entries 14, 17, 19, and 21). To the best of our knowledge, these results are the first catalytic radical reactions using a chiral aluminum reagent and monodentate substrates to the Lewis acid.

In conclusion, we have found the first asymmetric construction of the chiral quaternary carbon center in novel stoichiometric and catalytic enantioselective radical reactions, which were mediated by a chiral Lewis acid containing Et$_2$O. Furthermore, an efficient carbon−carbon bond formation was found to occur enantioselectively with lactones as monodentate substrates to a Lewis acid. Although clarification of the role of Et$_2$O in this reaction and improvement of the selectivity remain, the results mentioned here should be useful for the preparation of optically active lactones having chiral quaternary carbon centers and the development of a new way to enantioselective radical reactions. Further studies are in progress.

(12) Kagan. H. B. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 8, pp 463−498.

(13) (a) Assuming that the Et$_2$O and the substrate carbonyl are axial in this trigonal bipyramidal complex, the ether oxygen in the substrate is not bound to the metal and has no effect on the ee and sense of asymmetric induction (a referee's comment). We acknowledge the referee for this valuable suggestion.
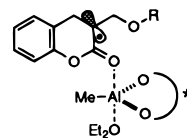
(b) For aluminum complexes: Robinson, G. H. *Coordination Chemistry of Aluminum*; VCH: New York, 1993. (c) An asymmetric Diels−Alder reaction by use of a five-coordinate aluminum complex has been reported, see: Rebiere, F; Riant, O; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 199−214 and references cited therein.

(14) As for catalytic asymmetric radical-mediated reactions, to date only a few examples have been reported, see: refs 2e, f, and h.