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Enantioselective radical-mediated allylation of α-iododihydrocoumarins using Lewis acids generated from chiral sulfonamides

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Abstract

Enantioseletive radical-mediated allylation using chiral Lewis acids generated from sulfonamides is described. Asymmetric allylation took place in 54% enantiomeric excess to form a chiral quaternary carbon center with *R* configuration. The present reaction proceeded equally well with a substoichiometric amount of a chiral Lewis acid as with a stoichiometric amount.

1. Introduction

Enantioselective radical reactions by use of chiral Lewis acids and organo–tin reagents are the current focus in asymmetric synthesis.[1] Methods employing chiral diamines,[1a] binaphthol and its derivatives,[1b,d,g,k] bisoxazolines[1c,e,f,h–j] and diols[1g] as chiral ligands have been developed to create asymmetric carbon centers enantioselectively. However, very little has been described regarding the asymmetric construction of quaternary carbons in enantioselective radical-mediated reactions,[1k] although methodological developments of the synthesis of optically active compounds having these carbon centers have received wide attention.[2] We have already reported an efficient enantioselective radical-mediated reaction catalyzed by a chiral Lewis acid generated from $(Ph_3Si)_2$BINOL containing Et_2O to form stereogenic quaternary carbon centers.[1k] Recently, one example of an enantioselective radical reaction using a sulfonamide as a chiral ligand to form a stereogenic tertiary carbon center in 20% ee has been reported by Renaud et al.[1g] Independently, we have examined a Lewis acid generated from a chiral sulfonamide in our continuing studies on radical-mediated asymmetric induction of α-alkyl-α-iododihydrocoumarins **1**.[1a,k] We describe herein our preliminary results on the asymmetric creation of

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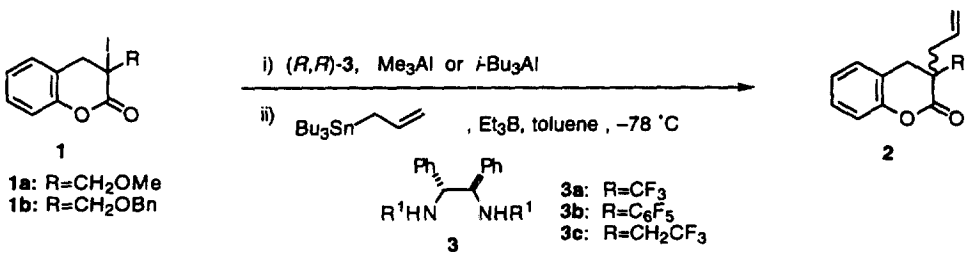
stereogenic quaternary carbon centers by enantioselective radical-mediated allylation of **1** using Lewis acids generated from chiral sulfonamides.

2. Results and discussion

2.1. Enantioselective radical-mediated allylation of α-alkyl-α-iododihydrocoumarins 1 using trifluoromethanesulfonamides 3

The reaction of α-iodo-α-methoxymethyldihydrocoumarin **1a** with allyltributyltin in the presence of Me_3Al and triethylborane as a radical initiator without a chiral sulfonamide at −78°C for 1 h proceeded to afford an allylated product **2a** in 63% isolated yield. Similarly, the reaction of α-benzyloxymethyl-α-iododihydrocoumarin **1b** gave **2b** in 65% yield. Next, the radical-mediated allylation by employing trifluoromethanesulfonamide **3a**[3] was explored (Scheme 1). The asymmetric reactions of **1** in the presence of chiral Lewis acids generated from **3a** afforded allylated products with unsatisfactory enantiomeric excess (ee), and took 1 h at least to reach completion. The results are listed in Table 1. Employment of the chiral Lewis acid prepared from Et_2AlCl gave allylated products in low ees along with some by-products (entries 1 and 3). The reaction of **1b** with the chiral Lewis acid generated from Me_3Al was found to give a higher ee than that of **1a** (entry 2 versus 4).



Scheme 1.

We have also examined the asymmetric induction in the allylation of **1b** using a more bulky chiral ligand **3b**[4] (containing a pentafluorophenyl moiety). However, ees of allylated products in the reactions of **1b** with the chiral Lewis acid prepared by 1 equiv. each of **3b** and Me_3Al (for **1b**) at 80°C were not reproducible.[†] These results seemed to be due to solubility (a heterogeneous solution) of the chiral Lewis acid used. Therefore, several attempts were made to prepare a homogeneous solution of chiral Lewis acid in toluene. Employment of excess toluene did not lead to a homogeneous solution. The desired solution was obtained when preparation of a chiral Lewis acid was carried out under reflux conditions; however, the product **2b** was obtained in low ee (9%). Fortunately, we found that treatment of **3b** with 1.5–2 equiv. of Me_3Al (for **3b**) at 80°C gave homogeneous solutions of chiral Lewis acids, and the degree of asymmetric induction was improved (entries 6 and 7). The allylation of **1b** using the chiral Lewis acid generated from 1.5 equiv. of Me_3Al (for **3b**) in toluene at −78°C gave the desired product in 54% ee (entry 6). When 2 equiv. of Me_3Al (for **3b**) was used, **2b** was obtained in 51% ee (entry 7). Use of Et_2AlCl as an aluminum reagent did not give a satisfactory result as well as in the case of using **3a** (entry 8). The reaction with the chiral Lewis acid generated from *i*-Bu_3Al gave a slightly lower ee (entry 9). Furthermore, a catalytic cycle of the chiral Lewis acid was found to be possible. Asymmetric allylation proceeded essentially equally well with 0.5 equiv. of **3b** for the substrate as with a stoichiometric amount

[†] The chiral sulfonamides **3a–c** were recoverable in high yields and were reusable.

Table 1
Enantioselective radical-mediated allylation of **1** using a chiral Lewis acid generated from **3**[a]

entry	substrate	**3** (eq for **1**)	Lewis acid (eq for **3**)	c.y. (%)	ee (%)	confign
1	**1a**	**3a** (1)	Et_2AlCl (1)	29	5	*R*
2	**1a**	**3a** (1)	Me_3Al (1)	50	5	*R*
3	**1b**	**3a** (1)	Et_2AlCl (1)	19	0	–
4	**1b**	**3a** (1)	Me_3Al (1)	75	25	*R*
5	**1b**	**3a** (1)	*i*-Bu_3Al (1)	62	16	*R*
6	**1b**	**3b** (1)	Me_3Al (1.5)	73	54	*R*
7	**1b**	**3b** (1)	Me_3Al (2)	76	51	*R*
8	**1b**	**3b** (1)	Et_2AlCl (1.5)	76	3	*R*
9[b]	**1b**	**3b** (1)	*i*-Bu_3Al (2)	75	43	*R*
10	**1b**	**3c** (1)	Me_3Al (1)	76	13	*S*
11	**1b**	**3c** (1)	*i*-Bu_3Al (1)	68	42	*S*
12	**1b**	**3b** (0.5)	Me_3Al (2)	72	54	*R*
13[c]	**1b**	**3b** (0.5)	*i*-Bu_3Al (2)	72	37	*R*
14	**1b**	**3b** (0.5)	Me_3Al (3)	75	10	*R*

[a] The chiral Lewis acid was generated from **3** and Lewis acid for 2 h at 80 °C in toluene (3 ml), unless otherwise noted. For details, see experimental section. [b] The treatment of **3b** with aluminum reagents gave a suspension, and the reaction was performed under this state. [c] The chiral Lewis acid was generated in toluene (4 ml).

(entries 6 and 7 versus 12 and 13). When 3 equiv. of Me_3Al for **3b** was used, however, the poor ee (10%) was observed in the reaction with 0.5 equiv. of **3b** for **1b** (entry 14).[‡]

On the other hand, the treatment of **3c** (containing a trifluoroethyl moiety) with 1 equiv. of Me_3Al or *i*-Bu_3Al (for **3c**) at 80°C gave homogeneous chiral Lewis acids. Surprisingly, the sense of asymmetric induction changed to afford allylated product **2b** having *S* configuration. Both with Me_3Al and *i*-Bu_3Al, *S* configuration was formed predominantly (entries 10 and 11).

Although the mechanism of the chiral induction in the reaction of **1** with **3a–c** is not interpreted at this time, the nature of the sulfonyl group in the chiral Lewis acid is found to be responsible for the sense of enantioselection (entries 1–9 versus 10 and 11).

In conclusion, we found that enantioselective radical-mediated reactions catalyzed by Lewis acid generated from chiral sulfonamides took place to form dihydrocoumarins having a stereogenic quaternary

[‡] Since the structures and aggregations of chiral Lewis acids prepared from **3** and excess Lewis acids in solutions have not been determined, clarification of the role of excess Lewis acid used remains.

carbon center. Further investigation toward development of more effective chiral Lewis acids and the clarification of the origin of enantioselection are under way.

3. Experimental

3.1. General

All melting points were measured on a Yanagimoto (hot plate) melting point apparatus and are uncorrected. IR spectra were performed with a Hitachi 260-10 or a Horiba FT-210 spectrophotometer. ^{1}H NMR (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were recorded with a JEOL EX-270 spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard, unless otherwise noted. Mass spectra were measured on a JEOL JMS-SX102A spectrometer. Specific rotation was measured on a JASCO DIP-360 digital polarimeter. Column chromatography was performed on silica gel.

3.2. Preparation of (1R,2R)-N,N′-bis(pentafluorobenzenesulfonyl)-1,2-diphenylethylenediamine 3b[4]

To a solution of commercially available (*R*)-1,2-diphenylethylenediamine (425 mg, 2.0 mmol) in CH_2Cl_2 (4 ml) containing Et_3N (0.6 ml, 4.4 mmol) was added a solution of pentafluorobenzenesulfonyl chloride (1.17 g, 4.4 mmol) in CH_2Cl_2 (6 ml) at −40°C. The mixture was warmed to room temperature, and then stirred for 7 h. The reaction was quenched with water at 0°C. The mixture was extracted with CH_2Cl_2 (20 ml×2). The extracts were washed successively with 0.5 N HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **3b** (1.32 g, 98%) as colorless crystals: mp 273–275°C, colorless needles ($CHCl_3$); $[\alpha]^{27}_D$ +71.0 (*c* 1.01, acetone); ^{1}H NMR (acetone-d_6) δ 4.96–4.98 (2H, m), 7.00–7.09 (6H, m), 7.18–7.21 (4H, m), 8.51 (2H, br); IR (KBr) 3257, 1649, 1431, 1370, 1298, 1270, 1173, 1101 cm^{-1}; MS (FAB$^+$) *m/z* 673 (M^++H); HRMS (FAB$^+$) calcd for $C_{26}H_{15}F_{10}N_2O_4S_2$ 673.0313 (M^++H), found 673.0313.

3.3. Preparation of (1R,2R)-N,N′-bis(2,2,2,-trifluoroethanesulfonyl)-1,2-diphenylethylenediamine 3c

To a solution of commercially available (*R*)-1,2-diphenylethylenediamine (425 mg, 2.0 mmol) in CH_2Cl_2 (4 ml) containing Et_3N (0.6 ml, 4.4 mmol) was added a solution of 2,2,2,-trifluoroethanesulfonyl chloride (803.2 mg, 4.4 mmol) in CH_2Cl_2 (6 ml) at −40°C. The mixture was warmed to room temperature, and then stirred for 7 h. The reaction was quenched with water at 0°C. The mixture was extracted with CH_2Cl_2 (20 ml×2). The extracts were washed successively with 0.5 N HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **3c** (802.0 mg, 80%) as colorless crystals: mp 188–190°C, colorless needles ($CHCl_3$–petroleum ether); $[\alpha]^{26}_D$ +12.9 (*c*, 1.05, $CHCl_3$); ^{1}H NMR δ 3.21–3.44 (4H, m), 4.83–4.85 (2H, m), 6.61 (2H, br), 7.22–7.27 (10H, m); ^{13}C NMR δ 55.4, 62.8, 119.2, 127.6, 128.8, 129.0, 136.2; IR (KBr) 3280, 1618, 1457, 1346, 1321, 1270, 1253, 1167, 1137 cm^{-1}; MS (Fab+) *m/z* 527 (M^++H+Na); HRMS (FAB+) calcd for $C_{18}H_{19}F_6N_2O_4NaS_2$ 527.0508 (M^++H+Na), found 527.0513 (M^++H+Na).

3.4. Preparation of chiral Lewis acids

The chiral Lewis acids (entries 1–5, 10 and 11 in Table 1) were generated from **3a** or **3c** (0.2 mmol) when reacted with 1 equiv. of Lewis acid [Me_3Al, Et_2AlCl or i-Bu_3Al (1 N hexane solution)] for 2 h at 80°C in toluene (3 ml): a homogeneous solution.

The chiral Lewis acids (entries 6–9 in Table 1) were generated from **3b** (0.2 mmol) when reacted with the quantities of Lewis acid shown in Table 1 [Me_3Al, Et_2AlCl or i-Bu_3Al (1 N hexane solution)] for 2 h at 80°C in toluene (3 ml): entries 6–8, homogeneous solutions; entry 9, heterogeneous solutions.

The chiral Lewis acid (entry 12 in Table 1) was generated from **3b** (0.1 mmol) when reacted with Me_3Al (0.2 mmol, 1 N hexane solution) for 2 h at 80°C in toluene (3 ml): a homogeneous solution.

The chiral Lewis acid (entry 13 in Table 1) was generated from **3b** (0.1 mmol) when reacted with i-Bu_3Al (0.2 mmol, 1 N hexane solution)] for 2 h at 80°C in toluene (4 ml): a homogeneous solution.

The chiral Lewis acid (entry 14 in Table 1) was generated from **3b** (0.1 mmol) when reacted with Me_3Al (0.3 mmol, 1 N hexane solution) for 2 h at 80°C in toluene (3 ml): a homogeneous solution.

3.5. The radical-mediated enantioselective allylation: general procedure

A solution or suspension of the chiral Lewis acid prepared as described above was cooled to −78°C, and then stirred for 30 min. A solution of α-alkoxymethyl-α-iododihydrocoumarin **1a** or **1b** (0.2 mmol) in toluene (2 ml) was added, and the mixture was stirred for 1 h at −78°C. Allyltributyltin (0.2 mmol) and Et_3B (0.2 mmol, 1 N hexane solution) were added successively, and the resulting mixture was stirred at −78°C. After the time at which point tlc analysis indicated complete disappearance of iodolactone **1** (1–5 h), saturated NH_4Cl was added. The mixture was extracted with benzene (20 ml×2). The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. Concentration followed by purification through silica gel column chromatography (benzene) gave (*R*)-**2a** or (*R*)-**2b** as an oil: (*R*)-**2a**: colorless oil; bp 150–160°C/1.5 mmHg (bulb-to-bulb distillation); $[\alpha]^{25}_D$ +0.4 (*c* 1.02, acetone) for 5% ee; ^1H NMR, IR, mass spectra were identical to those reported in the literature.[1k] (*R*)-**2b**: colorless oil; bp 215–220°C/1.5 mmHg (bulb-to-bulb distillation); $[\alpha]^{27}_D$ −4.2 (*c* 1.05, acetone) for 54% ee; ^1H NMR, IR, mass spectra were identical to those reported in the literature.[1k] The ees were determined by HPLC analysis using chiral columns [**2a**: chiralcel OD; hexane:*i*-PrOH=50:1, 0.5 ml/min; R*t*: 16.5 min (major enantiomer), 18.5 min (minor enantiomer), **2b**: chiralcel OJ; hexane:*i*-PrOH=9:1, 1.0 ml/min; R*t*: 16.8 min (minor enantiomer), 21.5 min (major enantiomer)]. The absolute configurations were determined by comparison with the R*t* of the major enantiomer in HPLC and/or specific rotation reported by us previously.[1k]

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