Enantioselective Radical-mediated Reduction of α-Iodolactone using Tributyltin Hydride in the Presence of a Chiral Amine and a Lewis Acid

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Enantioselective radical-mediated reduction of α-methoxymethyl-α-iododihydrocoumarin **1** using tributyltin hydride is realized in up to 62% enantiomeric excess (e.e.) (88% chemical yield) by combination of chiral diamine **2** and magnesium iodide.

Asymmetric induction in radical-mediated reactions is a current focus in synthetic organic chemistry.[1] Radical reactions of the substrates bearing chiral auxiliaries have proceeded diastereoselectively to give optically active compounds.[2] Furthermore, chirality transfer using stereogenic centres adjacent to the radical centre has also been observed.[2] More recently, some Lewis acids have been proved to influence diastereoselective radical reactions.[3–5] Although diastereoselective radical reactions as mentioned above have been reported, there is no method for enantioselective radical reactions using organotin reagents in the presence of a Lewis acid. We describe here the first example of an efficient enantioselective radical-mediated reduction of α-methoxymethyl-α-iodolactone that can be realized by treatment with tributyltin hydride (Bu_3SnH) coupled with a chiral amine and magnesium iodide (MgI_2) as Lewis acid.

The symmetrical π-system of achiral enol radical[6] complexed by a Lewis acid and a chiral ligand was expected to exist in a chiral environment, which could influence the direction and rate of the reaction with hydrogen radical as depicted in Fig. 1. To realize this expection, we chose α-methoxymethyl-α-iodolactone **1**† as a model substrate in the present study.‡

At first, chiral imines or amines as chiral ligands to coordinate with MgI_2 (Lewis acid)§ were explored. Among them, C_2-symmetric diamine **2**¶ was found to be a suitable chiral ligand for enantioselective radical-mediated reduction. Next, the effect of the solvent was determined (CH_2Cl_2, Et_2O, toluene), with CH_2Cl_2 giving the best result. The reaction of α-methoxymethyl-α-iododihydrocoumarin **1** with Bu_3SnH in the presence of chiral diamine (*S*)-**2** and MgI_2·Et_2O in CH_2Cl_2 at −78 °C proceeded smoothly to afford optically active α-methoxymethyldihydrocoumarin **3** in 62% e.e. (88% chemical yield) (Scheme 1).‖ The results are listed in Table 1.**

The degree and sense of asymmetric induction were essentially independent of the conversion of each reaction (runs 3, 4 and 5 in Table 1) even when the amounts (1.0, 0.9 and 0.5 equiv.) of Bu_3SnH were changed.

Interestingly, the degree of asymmetric induction was shown to be sensitive to the concentration of the substrate. The reaction under high dilution conditions gave low enantioselectivity (run 1 in Table 1), which could be due to the presence of the substrate uncomplexed with chiral ligand and MgI_2. The reaction with a bulky organotin reagent such as triphenyltin hydride resulted in poor enantioselectivity, whereas the use of tris(trimethylsilyl)-silane did not give the desired product (runs 7 and 8 in Table 1).

It is noteworthy that the radical-mediated asymmetric reduction using Bu_3SnH took place effectively even in the enantioselective reaction.

A typical experimental procedure (run 2 in Table 1) is as follows. To a solution of MgI_2 (0.2 mmol) in diethyl ether (0.13 mol dm^{-3} solution) was added a CH_2Cl_2 (2 ml) solution of the chiral diamine [(*S*)-**2**] (0.2 mmol). The mixture was stirred for 5 min at room temp. The resulting clear solution was cooled to −78 °C. A solution of α-iodolactone **1** (0.2 mmol) in CH_2Cl_2 (2 ml) was added, and stirring was continued for 10 min. Bu_3SnH (0.2 mmol) was added at −78 °C to the solution obtained above, and the whole was stirred for 40 min at the same temperature. After addition of aq. ammonium chloride, the product was isolated by usual work-up and purification [column chromatography (silica gel, benzene : diethyl ether = 100 : 1) followed by bulb-to-bulb distillation (120 °C at 2 mmHg)] to give optically active α-methoxymethyldihydrocoumarin **3** {$[\alpha]_D^{25}$ −12

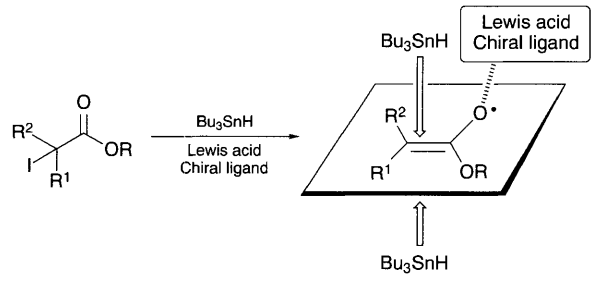
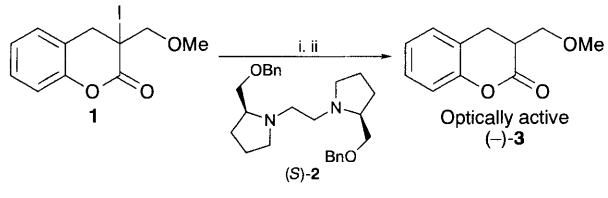


Fig. 1



Scheme 1 *Reagents*: i, (*S*)-**2**, MgI_2; ii, Bu_3SnH or Ph_3SnH

Table 1 Enantioselective radical-mediated reduction of α-iodolactone **1**[a]

Run	Concentration of the substrate/ mmol dm^{-3}	Reagent (equiv.)	Yield (%)[b]	E.e. (%)[c]
1	21	Bu_3SnH (1.0)	81	18
2	36	Bu_3SnH (1.0)	88	62
3	67	Bu_3SnH (1.0)	83	52
4	36	Bu_3SnH (0.9)	84	62
5	36	Bu_3SnH (0.5)	39	57
6	36	Bu_3SnH (1.0)	50	43[d]
7	36	Ph_3SnH (1.0)	74	39
8	36	$(Me_3Si)_3SiH$ (1.0)	[e]	—

[a] For general procedure, see text. Reaction was carried out in the presence of chiral diamine **2** (1 equiv.) and MgI_2·OEt_2 (1 equiv.) in CH_2Cl_2 at −78 °C, unless otherwise noted. Reaction time was 40 min in runs 2–4 and 6, 1 h in runs 1, 5 and 8, and 12 h in run 7. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column (Daicel chiralcel OB) [hexane–propan-2-ol = 50 : 1, flow rate 0.5 ml min^{-1}; t_R (min) 34 (minor enantiomer) and 37 (major enantiomer)]. [d] Reaction was carried out at −50 °C. [e] No reaction.

(*c* 1.01, benzene)} in 62% e.e. (88% chemical yield). The e.e. was determined by HPLC analysis using Daicel chiralcel OB.

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Footnotes

† Compound **1** was prepared from commercially available dihydrocoumarin [lithium hexamethyldisilazide, THF, −78 °C, 45 min, then $MeOCH_2Cl$ (5 equiv.), −45 °C, 16 h, oil 120 °C/2 mmHg, 58%; LDA, THF, −78 °C, 30 min, then I_2, −78 °C, 15 min, mp 97–98 °C, 51%].

‡ It is known that Lewis acids are effective additives in the diastereoselective radical-mediated reactions of α-alkoxymethyl-α-haloesters using tributyltin hydride or allyltributyltin.[4] There is a report[4a] that MgI_2 is an effective Lewis acid in the diastereoselective radical-mediated reduction of α-alkoxymethyl-α-iodoesters without initiator. Other Lewis acids for radical initiators, see ref. 5.

§ The reaction with $Mg(ClO_4)_2$, $TiCl_4$, ZnI_2, $AlCl_3$ and $Eu(tfc)_3$ did not give satisfactory results.

¶ Optically pure (*S*)-**2** {bp >250 °C/1 mmHg (bulb-to-bulb distillation), $[\alpha]_D^{27}$ −88.8 (*c* 1.03, $CHCl_3$)} was prepared from (*S*)-proline by the conventional method.

‖ All new compounds described in the text provided satisfactory analytical and/or spectroscopic data.

** The absolute configuration was not determined.

References

1 *Cf.* B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 969.

2 Reviews: N. A. Porter, B. Giese and D. P. Curran, *Acc. Chem. Res.*, 1991, **24**, 296; W. Smadja, *Synlett*, 1994, 1 and references cited therein.

3 P. Renaud and M. Ribezzo, *J. Am. Chem. Soc.*, 1991, **113**, 7803; T. Toru, Y. Watanabe, M. Tsusaka and Y. Ueno, *J. Am. Chem. Soc.*, 1993, **115**, 10464; K. Rück and H. Kunz, *Synthesis*, 1993, 1018; M. Nishida, E. Ueyama, H. Hayashi, Y. Ohtake, Y. Yamaura, E. Yanaginuma, O. Yonemitsu, A. Nishida and N. Kawahara, *J. Am. Chem. Soc.*, 1994, **116**, 6455; D. P. Curran and L. H. Kuo, *J. Org. Chem.*, 1994, **59**, 3259; P. Renaud, N. Moufid, L. H. Kuo and D. P. Curran, *J. Org. Chem.*, 1994, **59**, 3547.

4 (*a*) Y. Guindon, J.-F. Lavallée, M. Llinas-Brunet, G. Horner and J. Rancourt, *J. Am. Chem. Soc.*, 1991, **113**, 9701; (*b*) H. Nagano and Y. Kuno, *J. Chem. Soc., Chem. Commun.*, 1994, 987.

5 Y. Yamamoto, S. Onuki, M. Yumoto and N. Asao, *J. Am. Chem. Soc.*, 1994, **116**, 421 and references cited therein.

6 W. Strub, E. Roduner and H. Fischer, *J. Phys. Chem.*, 1987, **91**, 4379; D. J. Hart and R. Krishnamurthy, *J. Org. Chem.*, 1992, **57**, 4457; D. P. Curran and P. S. Ramamoorthy, *Tetrahedron*, 1993, **49**, 4841.