Diastereoselective Allylation of Optically Active Imines with Metallic Samarium

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Abstract: Barbier-type allylation of optically active imines such as *N*-benzylidenevalinol methyl ether was performed with metallic samarium, a catalytic amount of iodine, and allyl bromide. This reaction proceeded in a highly diastereoselective manner in THF at room temperature.

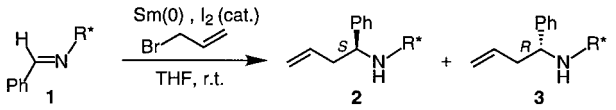
Samarium reagents have quite unique and useful properties such as long ion radius, high coordination number, strong Lewis acidity, and high oxophilicity. So the chemistry of samarium reagents to oxygen functional groups, especially carbonyl groups, has been extensively developed. Recently, several examples where high stereoselectivity was achieved by chelation between the Sm(III) cation and oxygen functional groups were reported.[1] The chemistry of metallic samarium (Sm) is of current interest in organic synthesis. Though samarium iodide (SmI_2) is a good synthetic tool (a mild, neutral and ether-soluble one-electron reductant),[2] its sensitivity to air makes it rather difficult to handle. We have been studying the direct use of Sm to improve on this shortcoming of SmI_2.[3] The mildness and operational simplicity of this new protocol encouraged us to further investigate the scope and utility with a series of representative chiral imines. We report here *the first diastereoselective Barbier-type allylation of optically active imines with Sm and a catalytic amount of iodine*.

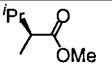
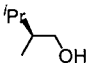
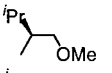
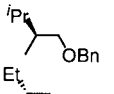
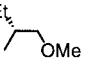
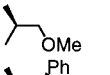
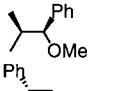
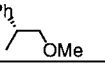
Three types of imines, *N*-benzylideneamino acid alkyl ester (**1a**), *N*-benzylidene amino alcohol (**1b**), and *N*-benzylidene amino alcohol alkyl ethers (**1c-1k**), have been designed for optically active substrates.[4] The former two have been used for Barbier-type allylation of imine to induce chiral amines. No example has been reported on such reaction of *N*-benzylidene aminoalcohol alkyl ether.[5]

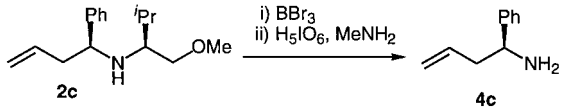
The general allylation procedure is as follows. A mixture of imine (0.30 mmol), Sm (0.63 mmol), iodine (0.03 mmol),[6] and allyl bromide (0.60 mmol) was stirred in THF (2 ml) at room temperature under nitrogen for 30 min. The color changes of the mixture during the reaction served as indicator of the progress of the reaction. After a short induction period, the color of the solution turned to black- purple and then dark blue-green. After the reaction was quenched with 1*N*-hydrochloric acid and the resulting mixture was made basic with 10% NaOH aq., the product was extracted with diethyl ether and was purified by preparative thin-layer chromatography.

Table 1 summarizes the results of the allylation of imines. Among the imines (**1a-1d**), methyl ether type **1c** was the best substrate to give allylation products in good yield (85%) and in high diastereoselectivity (**2c**:**3c**= 96:4) (Entry 3). The absolute configurations of **2c** (*S, S*) and **3c** (*R, S*) were determined by comparison with the authentic samples prepared by *O*-methylation of known products **2b** (*S, S*) and **3b** (*R, S*).[7] Benzyl ether type **1d** gave allylation products in 79% yield and in high diastereoselectivity (**2d**:**3d**= 97:3) (Entry 4). Ester type imine **1a** gave a complex mixture (Entry 1). Alcohol type imine **1b** gave allylation products in 47% yield (**2b**:**3b**= 62:38) (Entry 2). The chiral allylation product was readily converted into optically active homoallic amine (Scheme 1). For example, **2c** was converted into (*S*)-**4c** by demethylation with boron tribromide (BBr_3) followed by oxidative cleavage of the C-N bond (85 % yield).[7b] More bulkiness (phenyl, isopropyl, ethyl, and methyl) at the α position from the amino group in methyl ether type imines increased diastereoselectivity of allylation (Table 1, Entries 8, 3, 5, and 6). Imine **1h** derived from (*R*)-phenylglycinol gave only one diastereomer **3h** in 77% yield and the other diastereomer could not be detected by ^{1}H-NMR (Entry 8). The substituent, such as phenyl, at the β-position of the amino group did not exert any influence upon the diastereoselectivity (Entries 6 and 7).

Table 1. Allylation of imines with Sm(0)-I_2-allyl bromide



Entry	Imine	R*	Product	Yield (%) (2 + 3)	Ratio (2 : 3)
1	**1a**		complex mixture	-	-
2	**1b**		**2b , 3b**	47	62 : 38
3	**1c**		**2c , 3c**	85	96 : 4
4	**1d**		**2d , 3d**	79	97 : 3
5	**1e**		**2e , 3e**	73	7 : 93
6	**1f**		**2f , 3f**	74	90 : 10
7	**1g**		**2g , 3g**	75	91 : 9
8	**1h**		**3h**	77	<1 : >99

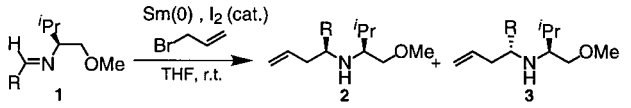


Scheme 1. Preparation of chiral homoallylamine **4c**

Table 2 shows that the substituent in the aldehyde side of imine affects the allylation of (*S*)-valinol methyl ether type imines (**1i-1l**). Imine **1i** which has a 4-cyanophenyl group gave a complex mixture (Entry 1). The reaction of **1j** which has a 4-methoxyphenyl group proceeded smoothly to give allylation products in 93% yield (Entry 2). These results suggest that an electron-donating group helps the reaction. Imine **1k** which has a 2-methoxyphenyl group showed high diastereoselectivity (99:1) (Entry 3). This implies that the 2-methoxy group on phenyl also coordinates to the Sm(III) cation in the intermediate and constructs a stronger stereostructure. Imine **1l** which has a 1-naphthyl group gave the product in 62% yield with some by-products (Entry 4).

Figure 1 shows a plausible reaction mechanism. At the first stage, Sm and allyl bromide would produce an allyl Sm complex in the presence of iodine.[8] The Sm(III) species was probably deposited in the reaction mixture during a short induction period. Because the Sm(III) species is a strong Lewis acid, it would be coordinated by the intramolecular nitrogen and oxygen atoms of the imine in the reactive intermediate complex. In the case of imine **1c** derived from (*S*)-valinol methyl ether,

Table 2. Allylation of imines with Sm(0)-I_2-allyl bromide



Entry	Imine	R	Product	Yield (%) (**2** + **3**)	Ratio (**2** : **3**)
1	**1i**	4-NC-C_6H_4	complex mixture	-	-
2	**1j**	4-MeO-C_6H_4	**2j** , **3j**	93	97 : 3
3	**1k**	2-MeO-C_6H_4	**2k** , **3k**	77	99 : 1
4	**1l**	1-naphthyl	**2l** , **3l**	62	92 : 8

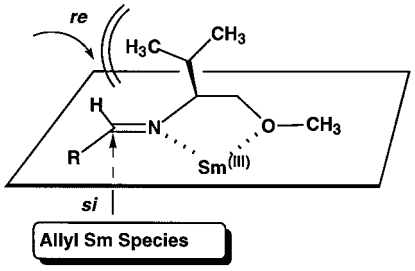


Figure 1. Plausible mechanism of allylation

the bulky isopropyl group is oriented *re* face and obstructs the approach of the allyl samarium species from the *re* face. The allyl samarium species then approaches from the less hindered side *si* face to give the (*S*, *S*) isomer **2c** selectively.

In conclusion, the first diastereoselective Barbier-type allylation of optically active imines was performed with Sm and a catalytic amount of iodine. The induction of other substituents instead of the allyl group is now being investigated.

References and Notes

(1) (a) Molander, G. A.; Kenny, C. *Tetrahedron Lett.*, **1987**, *28*, 4367. (b) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc*., **1989**, *111*, 8236. (c) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.*, **1994**, *59*, 5532. (d) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.*, **1994**, *59*, 6900. (e) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729. (f) Matsuda, F. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 987. (g) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (h) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (i) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, 479.

(2) (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (b) Kagan, H. B. *Nouv. J. Chim.* **1990,** *14*, 453. (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (d) Molander, G. A. *Organic Reactions* **1994**, *46*, 211. (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

(3) (a) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc*., **1992**, *114*, 8729. (b) Ogawa, A.; Nanke, T.; Takami, N.; Sumino, Y.; Ryu, I.; Sonoda, N. *Chem. Lett.*, **1994**, 379. (c) Murakami, M.; Hayashi, M.; Ito, Y. *Synlett*, **1994**, 179.(d) Yanada, R.; Bessho, K.; Yanada, K. *Chem. Lett*. **1994**, 1279. (e) Yanada, R.; Bessho, K.; Yanada, K. *Synlett* **1995**, 443. (f) Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* **1995**, 1261. (g) Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett*. **1996**, *37*, 9313. (h) Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett*. **1997**, *38*, 3271.

(4) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895, and references cited therein.

(5) Examples of Grignard-type allylation to optically active imines (*N*-benzylideneamino alcohol alkyl ether type): (a) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull*. **1983**, *31*, 2895. (b) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T. *Chem. Lett*. **1991**, 1555. (c) Hashimoto, Y.; Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K. *Chem. Lett*. **1995**, 235. (d) Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc., Perkin Trans. 1*. **1998**, 775.

(6) Addition of a catalytic amount of iodine was the best condition for the allylation of **1c**. No reaction occurred without iodine. One mol eq. iodine to **1c** gave **2c** and **3c** (95:5) in 24% yield accompanied with the starting material **1c** (30 %).

(7) (a) Bocoum, A.; Savoia, D.; Umani- Ronchi, A. *J. Chem. Soc., Chem. Commun*. **1993**, 1542. (b) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem*. **1994**, *59*, 7766. (c) Alvaro, G.; Pacioni, P.; Savoia, D. *Chem. Eur. J.* **1997**, *3*, 726.

(8) We can not deny the mechanism in which the imine is reduced at the first stage. But we think the formation of allyl Sm complex is plausible because there is no imine dimer or amine, which is the product from imine radical, under this experimental conditions.