Reiko Yanada,^{*a} Nobuyuki Negoro,^a Masanori Okaniwa,^a Yoshihisa Miwa,^a Tooru Taga,^a Kazuo Yanada,^b Tetsuro Fujita^b

^aGraduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan Fax +81 (75) 7612698

^bFaculty of Pharmaceutical Sciences, Setsunan University, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan *Received 23 February 1999*

Abstract: The intermolecular pinacol-like coupling of optically active imines was performed stereoselectively with metallic samarium and a catalytic amount of iodine to give chiral C_2 -2,2'ethylenediimino-diethanol derivatives.

Key words: samarium, imines, reductive coupling, diastereoselective, C_2 -2,2'-ethylenediiminodiethanol derivatives

The reductive coupling of optically active imines is a useful method for the synthesis of chiral C_2 -1,2-ethylenediamine derivatives, which are important as chiral catalysts in stereoselective reactions¹ and medicinal chemistry.² Their preparation generally includes optical resolution.³ Metal-promoting coupling of imines has been examined but stereoselectivity and chemical yield have not been sufficiently improved.⁴ Only one example of high diastereoselectivity was achieved with very bulky and activated special imines, tricarbonyl(benzaldimine)chromium complex.⁵

Samarium reagents have quite unique and useful properties such as long ion radius, high coordination number, strong Lewis acidity, and high oxophilicity. Recently, some examples have shown high stereoselectivity in free radical reactions by chelation between the Sm(III) cation and oxygen functional groups.⁶ Previously, we reported diastereoselective Barbier-type allylation of optically ac-





Table 1. Reductive Coupling of Imines with Sm and I_2

	R	, P'			r	R R'			_	D.
+ م	I ∕=n	OR" -	m, l ₂ (cat	:.) (۳ ۲		ץ" ריי	+		ΎΓ
Ar	6a -	6g	r. t., 2 ħ	4	* ^1		[™] 8a - 8g 9a - 9g 10a - 10g		ArCH ₂ NH 11a -	0R* 11g
Run	Imine 6	Ar	R	R'	R"	8(%)	Dimer 9 (%)	10 (%)	8 · 9 ±10	$\frac{\text{Amine}}{11(\%)}$
1	a	Ph	ⁱ Pr	Н	Me	78 (<i>R</i> , <i>R</i>)	2 (<i>R</i> , <i>S</i>)	-	98:2	10
2	b	Ph	Et ₹	н	Me	60 (<i>S</i> , <i>S</i>)	10 (<i>R</i> , <i>S</i>)	5 (<i>R</i> , <i>R</i>)	80 : 20	11
3	c	Ph	Ph ₹	н	Me	80 (<i>S</i> , <i>S</i>)	-	-	>99 : <1	2
4	d	Ph	Me I	Ph	Me	75 (R, R)	4 (<i>R</i> , <i>S</i>)	-	95 : 5	5
5	e	Ph	ⁱ Pr	H	Bn	65 (R, R)	1 (<i>R</i> , <i>S</i>)	1 (<i>S</i> , <i>S</i>)	97 : 3	16
6	f	MeO-	– ⁱ Pr	Н	Me	79 (<i>R</i> , <i>R</i>)	trace	-	>99 : <1	trace
7	g		ⁱ Pr V	Н	Me	70 (<i>R</i> , <i>R</i>)	-	-	>99 : <1	1
8	h	Br	ⁱ Pr V	Н	Me	47 (<i>R</i> , <i>R</i>)	-	-	>99 : <1	-

tive imines with metallic samarium(Sm) and a catalytic amount of iodine.⁷ The reaction suggests that both nitrogen and oxygen atoms of imine may coordinate to Sm(III) in an intermediate of the reaction. We observed also that reductive coupling products of imines were sometimes produced as by-products.

The mildness and operational simplicity of our new protocol with Sm encouraged us to further investigate the scope and utility with a series of representative chiral imines. Here we would like to report that *intermolecular pinacollike coupling of optically active imines was achieved diastereoselectively with samarium and a catalytic amount of iodine to afford chiral* C_2 -2,2'-*ethylenediiminodiethanol derivatives.*

The coupling reaction⁸ was affected by the structure of substrate imines (Figure 1). Both *N*-benzylideneaniline(1) and N-benzylidenebenzylamine(2) gave the coupling products in good yield (95%) but in low diastereoselectivity (*dl:meso* = 1.4:1). (*R*)-*N*-Benzylidene- α -methylbenzy $lamine(3)^9$ was reacted in 95% and gave better diastereoselectivity (dl:meso = 5.7:1) than 1 and 2. These results imply that the diastereoselectivity of the reaction might be affected by the bulkiness at the α -position of the nitrogen atom. Among three imines derived from L-valine derivatives, N-benzylidene-L-valinol(4), methyl N-benzylidene-L-valinate(5), and N-benzylidene-O-methyl-Lvalinol(6a), ether-type 6a was the best substrate for this coupling reaction. Alcohol type 4 was reduced only at the C = N double bond to give *N*-benzylvalinol(7) quantitatively. Ester-type 5 was inert under these reaction conditions and the starting material was recovered (90%).

Various ether-type imines(6) gave the coupling products (major 8 and minor 9 and/or 10) with accompanying amines(11) (Table 1).^{9,10} The diastereoselectivity (8:(9+10)) was from predominantly to 80:20. The ratio of 8 increased when the bulkiness of α substituent R become more (Ph > *i*-Pr > Et) (Runs 3, 1, and 2). The bulkiness of β -substituent R' also affected the diastereoselectivity. The selectivity of 8d (R = Me, R' = Ph) was higher than that of 8b (R = Et, R' = H) (Runs 4 and 2).

Unexpectedly, unusual C_2 -dimer 12 was produced in 8% yield during the coupling reaction of imine 6g as a byproduct. Its structure was confirmed by the coupling reaction of imine 6h. The compound 12 was produced in 31% yield with accompanying C_2 -dimer 8h (Run 8). The reason has not been clarified why the *o*-methoxy group on the phenyl ring was removed and why the CC bond formation occurred. To our knowledge, such a bond-formation has no precedent in samarium chemistry.

The absolute configuration of **8** at the newly produced benzylic center was R, R (S, S), if imine **6** had S (R) absolute configuration at the α -position of nitrogen. For example, (S)-**6a** gave (R, R)-**8a** at two benzylic centers. Its absolute structure was confirmed by the synthesis of **8a** via another route (eq. 1). The known C_2 -ester(**13**) was prepared from (S)-**5** by Shono's method.^{4c} The compound **13** was reduced with LiAlH₄ and then methylated to give **8a**. The X-ray crystallography of **8d** further confirmed our experimental rule (Fig. 2).¹¹ It shows that **8d** has (RSRRSR) absolute configuration. These results are useful to visualize the reaction mechanism.



Proposed Mechanism of the Stereoselective Intermolecular Reductive Imine Coupling

Scheme 1



Crystal structure of (R,S,R,R,S,R) - 8d

Figure 2

The high stereoselectivity in the coupling of **6** is explained by the high coordination number and Lewis acidity of samarium(III) reagents and the steric interaction of R and R' groups.¹² Scheme 1 illustrates the proposed mechanism for the coupling reaction. Imine **6a** is reduced with Sm and a catalytic amount of iodine. The nitrogen and oxygen atom of the produced imine radical coordinate to the generated Sm(III) species.¹³ Among three plausible radical intermediates(**8a', 9a', 10a'**), the steric interaction seems minimum in **8a'** to give the main product (*R*, *R*)-**8a** (78% yield).

In conclusion, we have achieved excellent to complete diastereoselective intermolecular coupling reactions of optically active imines with Sm and a catalytic amount of iodine to give C_{2} .2,2'-ethylenediiminodiethanol derivatives. Optically active aminoalcohols have extensively been used as catalysts in alkylation of aldehyde with alkyllithium¹⁴ or dialkylzinc,¹⁵ reduction of ketones with borane or borates,¹⁶ and dihydroxylation of a double bond with osmium tetroxide.¹⁷ We are trying now to use our C_{2} -chiral compounds for these reactions as asymmetric ligands.

References and Notes

- (1) (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581-1590.
 (b) Tomioka, K. *Synthesis* **1990**, 541-549. (c) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69.
 (d) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (e) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161-3195.
- (2) (a) von Angerer, E.; Egginger, G.; Kranzfelder, G.; Bernhauer, H.; Schönenberger, H. J. Med. Chem. 1982, 25, 832-837. (b) Pasini, A.; Zunino, F. Angew. Chem. Int. Ed. Engl. 1987, 26, 615-624. (c) Reedijk, J. J. Chem. Soc., Chem. Commun. 1996, 801-806.

- (3) (a) Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa, M. Bull. Chem. Soc. Jpn. 1986, 59, 931-932. (b) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. J. Am. Chem. Soc. 1989, 111, 5493-5495.
- (4) For recent reports: (a) Takaki, K.; Tsubaki, Y.; Tanaka, S.; Beppu, F.; Fujiwara, Y. *Chem. Lett.* **1990**, 203-204. (b) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141-1142. (c) Shono, T.; Kise, N.; Oike, H.; Yoshimoto, M.; Okazaki, E. *Tetrahedron Lett.* **1992**, *33*, 5559-5562. (d) Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609-610. (e) Dutta, M. P.; Baruah, B.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Synlett* **1998**, 857-858. (f) Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873-874. (g) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1998**, *39*, 3333-3336.
- (5) Taniguchi, N.; Uemura, M. Synlett 1997, 51-53.
- (6) (a) Molander, G. A.; Kenny, C. Tetrahedron Lett. 1987, 28, 4367-4370. (b) Molander, G. A.; Kenny, C. J. Am. Chem. Soc. 1989, 111, 8236-8246. (c) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. J. Org. Chem. 1994, 59, 5532-5534. (d) Kawatsura, M.; Matsuda, F.; Shirahama, H. J. Org. Chem. 1994, 59, 6900-6901. (e) Matsuda, F. J. Synth. Org. Chem., Jpn. 1995, 53, 987-998. (f) Molander, G. A.; Harris, C. R. Chem. Rev. 1996, 96, 307-338. (g) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. Synlett 1996, 373-376. (h) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. Synlett 1996, 1057-1060. (i) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. Synlett 1997, 479-480. (j) Renaud, P.; Gerster, M. Angew. Chem. Int. Ed. Engl. 1998, 37, 2562-2579.
- (7) Negoro, N.; Yanada, R.; Okaniwa, M.; Yanada, K.; Fujita, T. Synlett **1998**, 835-836.
- (8) The general procedure is as follows. A mixture of imine (10 mmol), Sm (10 mmol), and iodine (1 mmol) in THF (8 ml) was stirred at room temperature under argon for 2 h. The volume of THF was very important. The minimum volume of THF gave the maximum yield of the dimer 8 and minimum yield of by-product amine 7. Other solvents examined did not give the C₂-coupling products. The use of SmI₂ gave mainly amine 7 because of the low concentration of SmI₂ (0.1 M).
- (9) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895-1946 and references cited therein.

- (10) When allyl bromide is present in the reaction system,⁷ the reductive addition of allyl bromide to the imines proceeds preferentially.
- (11) Crystallographic data for **8d**: $C_{34}H_{40}N_2O_2$, M = 508.7, orthorhombic, space group $P_{2_12_12_1}$, Colorless prism, a = 12.150(4) Å, b = 20.370(9) Å, c = 6.158(2) Å, V = 1524.1Å³, Z = 4, and Dc = 1.1083 gcm⁻³. The reflection data of 1320 reflections with $0<\theta<60^\circ$ were collected on a Rigaku AFC-5 diffractometer using monochromated Cu*Ka* radiation and ω - 2θ scan technique ($0\le h\le 13$, $0\le k\le 22$, $0\le l\le 6$). The structure was solved by the direct method and refined by the fullmatrix least-squares method. The final *R* value was 0.047 for 1260 observed reflections (wR = 0.052, $w = 1/[\sigma^2(F)+0.023F^2]$).
- (12) Shono et al. reported as follows in Ref. (4c). 1) The intermolecular coupling of chiral imine (5) did not give satisfactory stereoselectivity by reduction with zinc and methanesulfonic acid. 2) The intramolecular coupling of diimines, in which two molecules of 5 were linked by a carbon chain, gave good stereoselectivity. 3) The stereoselectivity was explained by steric interaction of isopropyl groups in the diprotonated intermediate. Shono's method is the most practical synthesis of chiral 1,2-diarylethylenediamines.
- (13) A clear yellow-green supernatant was observed during the mild exothermic reaction. After the imine was consumed, it turned to purple and the excess of Sm(0) remained at the bottom. It is generally known that Sm(II) solution is purpleblue and Sm(III) solution is yellowish. The change of the color

implies that the generated Sm(II) in the reaction mixture reacts immediately with imine to generate the Sm(III) species during the reaction and that Sm(II) remained after the imine was consumed.

- (14) Mukaiyama, T.; Suzuki, K. Chem. Lett. 1980, 255-256.
- (15) (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. J. Am. Chem. Soc. **1986**, 108, 6071-6072. (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. J. Am. Chem. Soc. **1987**, 109, 7111-7115. (c) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. J. Chem. Soc., Chem Commun. **1987**, 1690-1691. (d) Bolm, C.; Zehnder, M.; Bur, D. Angew. Chem. Int. Ed. Engl. **1990**, 29, 205-207. (e) Kunieda, T.; Ishizuka, T. J. Synth. Org. Chem., Jpn. **1997**, 55, 1018-1028.
- (16) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. J. Am. Chem. Soc. 1987, 109, 5551-5553. (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. J. Org. Chem. 1988, 53, 2861-2863.
- (17) (a) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131-134. (b) Tomioka, K.; Shinmi, Y.; Shiina, K.; Nakajima, M.; Koga, K. *Chem. Pharm. Bull.* **1990**, *38*, 2133-2135. (c) Ogino, Y.; Chen, H.; Kwong, H. -L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965-3968.

Article Identifier:

1437-2096,E;1999,0,05,0537,0540,ftx,en;Y04399ST.pdf