

Reductive Self-coupling Reaction of Imines and Aldehydes Induced by Strontium Metal

Norikazu Miyoshi,^{*1} Tadashi Kohno,¹ Makoto Wada,¹ Sei Matsunaga,²
Isao Mizota,² and Makoto Shimizu^{*2}¹Department of Chemistry, Faculty of Integrated Arts and Sciences, The University of Tokushima,
1-1 Minamijosanjima, Tokushima 770-8502²Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu 514-8507

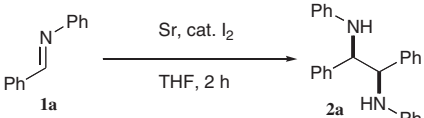
(Received July 30, 2009; CL-090714; E-mail: miyoshi@ias.tokushima-u.ac.jp, mshimizu@chem.mie-u.ac.jp)

Aromatic aldimines reacted with Sr in the presence of a catalytic amount of iodine to give self-coupling products in good yields, whereas aromatic and aliphatic aldehydes underwent a similar reaction effected by the combined use of Sr and Al(OEt)₃.

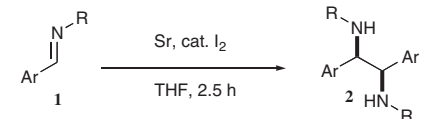
Synthetic reactions using strontium compounds are recently of increasing interest. Although few studies of the preparation and reactivity of organostrontium compounds were found in the literature¹ a decade ago, we have reported the alkylation of aldehydes with alkyl iodides using metallic strontium.² Among other intriguing results, we found that alkylation of imines with alkyl iodides using strontium metal gave the adducts in good yields.³ Compounds incorporating 1,2-diamine, 1,2-hydroxyamine, and 1,2-diol are currently the topics of studies, and their intriguing behaviors offer wide extensions of these particular fields.⁴ Although the reductive coupling of imines or aldehydes seems to be a straightforward way to prepare such compounds, methods under milder conditions for imines⁵ appear to be still needed as compared with their carbonyl counterparts.⁶ Herein we wish to report the reductive self-coupling reaction of imines or aldehydes using metallic strontium as a one-electron transfer agent in the presence of a catalytic amount of iodine and/or aluminum triethoxide.

When *N*-benzylideneaniline (**1a**) was treated with strontium metal, the desired coupling product **2a** was obtained in very low yields, whereas the addition of a catalytic amount of iodine improved the product yield (Table 1). This may be due to the activation effect of the metal surface as well as the ability as a Lewis acid of the resulting strontium iodide. Regarding the solvent, the reaction gave the diamine in good yields in DMF and THF

Table 1. Investigation into the solvents^a

		
Entry	Solvent	Yield/% ^b
1	CH ₂ Cl ₂	No reaction
2	Et ₂ O	No reaction
3	MeCN	No reaction
4	DMF	63
5	THF	88 ^c
6	MeOH	15

^aCarried out according to a typical procedure (Ref. 7).^bIsolated yield. ^cDL:meso = 75:25. The structures were determined by comparison with reported data (Ref. 5b).**Table 2.** Self-coupling reaction of various imines **1**^a

				
Entry	Ar	R	Yield/% ^b	DL:meso ^c
1	Ph	4-MeOC ₆ H ₄	94	63:37 ^d
2	4-MeOC ₆ H ₄	Ph	97	69:31 ^e
3	Ph	4-MeC ₆ H ₄	88	67:33 ^d
4	Ph	4-ClC ₆ H ₄	79	46:54 ^d
5	4-ClC ₆ H ₄	Ph	36	57:43 ^e
6	4-NCC ₆ H ₄	Ph	51	50:50 ^f
7	2-Naphthyl	Ph	95	50:50 ^g
8	1-Naphthyl	Ph	trace	Not determined
9	Ph(C=NPh)Me ^h	Ph	33 ⁱ	14:86 ^d

^aCarried out according to a typical procedure (Ref. 7). ^bIsolated yield. ^cRatio determined by ¹H NMR. ^dFor structure determination, see Ref. 5c. ^eStructure determination (Ref. 5b). ^fStructure determination (Ref. 5d). ^gStructure determination (Ref. 5e). ^hKetimine derived from acetophenone and aniline was used. ⁱ*N*-Phenyl-1-phenylethylamine was also obtained in 16% yield.

(Entries 4 and 5), but a decreased yield was observed in MeOH (Entry 6). The reactions did not take place in CH₂Cl₂, Et₂O, and MeCN (Entries 1–3). Under the optimized conditions a variety of imines were subjected to the imino pinacol coupling, and the results are summarized in Table 2.

Using aldimines prepared from aromatic aldehydes and aromatic amines, the reactions afforded the corresponding self-coupling products in good yields (Entries 1–4 and 7). Aldimines having an electron-withdrawing group on the aromatic ring such as chloro or nitrile slightly decreased the product yields (Entries 5 and 6). However, dimerization of imines having a nitrophenyl group and the *N*-alkyl aldimine prepared from benzaldehyde and benzylamine did not occur. Even in the case of an intramolecular coupling of aldimine such as *N,N'*-dibenzylideneethylene-1,2-diamine, the desired product was not formed. These results indicate that the reaction is effective for aromatic aldimines, and that the electron deficiency of the imines affects the reactivities. 2-Naphthylmethylideneaniline gave the coupling product in 95% yield, while 1-naphthylmethylideneaniline did not (Entries 7 and 8). Using a ketimine from acetophenone and aniline, the coupling product was formed in 33% yield, indicating that the reaction was sensitive to steric congestion (Entry 9).

There are significant differences between imines and carbonyl counterparts in reductive self-coupling reactions.⁶ In fact, pinacol coupling reaction of benzaldehyde did not take place but a simple reduction product, benzyl alcohol, was obtained in 90%

Table 3. Pinacol coupling of aldehydes **3** under various conditions^a

Entry	R	Additive	Temp/°C	Yield/% ^b	Dl:meso ^c
1	Ph	none	rt	0	—
2	Ph	TMSOTf ^d	0 to rt	0	—
3	Ph	TBSOTf ^d	0 to rt	11	91:9
4	Ph	TfOH ^d	0 to rt	0	—
5	Ph	AlEt ₃	0 to rt	37	67:33
6	Ph	Al(OPh) ₃	0 to rt	0	—
7	Ph	Al(O ⁱ Pr) ₃	0 to rt	41	67:33
8	Ph	Al(O ⁱ Pr) ₃ ^d	0 to rt	18	67:33
9	Ph	Al(OEt) ₃	0 to rt	63	75:25
10	Ph	Al(OEt) ₃	−78 to rt	26	67:33
11	4-ClC ₆ H ₄	Al(OEt) ₃	0 to rt	61	60:40
12	4-MeOC ₆ H ₄	Al(OEt) ₃	0 to rt	23	91:9
13	4-MeC ₆ H ₄	Al(OEt) ₃	0 to rt	57	73:27
14	Cy	Al(OEt) ₃	0 to rt	87	62:38
15	PhCH ₂ CH ₂	Al(OEt) ₃	0 to rt	53	76:24

^aCarried out according to a typical procedure (Ref. 7), except for the use of an additive. ^bIsolated yield. ^cRatio determined by ¹H NMR and/or GLC. For structure determination, see Ref. 6b. ^dAdditive (1.0 equiv) was used.

yield under the present conditions (1.3 mmol Sr, cat I₂, THF, rt, 1.5 h). In an effort to find conditions for the pinacol coupling reaction of aldehydes, use of a series of additives was next examined. Table 3 summarizes the results.

As can be seen from Table 3, use of TBSOTf effected the desired coupling (Entry 3), whereas much better results were obtained with aluminum-containing Lewis acids. Among the aluminum compounds, aluminum triethoxide was found to be the most effective to promote the pinacol coupling (Entries 5–10). A branched aliphatic aldehyde serves as a good substrate for the present pinacol coupling (Entry 14).

Useful chemoselectivity was observed. Treatment of a 1:1 mixture of the imine **1b** and the aldehyde **3b** with Sr in the presence of I₂ and Al(OEt)₃ gave selectively the imino pinacol product **2b** in good yield without formation of the pinacol arising from the aldehyde **3b** which was reduced to the alcohol **5** (Scheme 1).

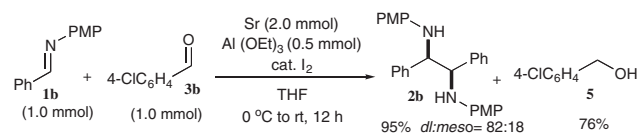
In summary, the reductive self-coupling reaction of aromatic imines with strontium metal gave 1,2-diamines in good yields, while pinacol coupling of aldehydes was successful with the combined use of strontium metal and aluminum triethoxide. Although there is much room for the improvement of diastereoselectivity, this study has opened a possible use of strontium metal as a useful one-electron transfer agent for imine and carbonyl functionalities. Furthermore, the good chemoselectivity ob-

served between imine and carbonyl moieties may make the present procedure a useful addition to the existing methodologies.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas “Advanced Molecular Transformations of Carbon Resources” from MEXT.

References and Notes

- a) N. A. Bell, W. E. Lindsell, in *Comprehensive Organometallic Chemistry*, ed. by G. Wilkinson, F. G. A. Stone, E. W. Abel, Pergamon, Oxford, **1982**, Vol. 1. b) W. E. Lindsell, in *Comprehensive Organometallic Chemistry II*, ed. by E. W. Abel, F. G. A. Stone, G. Wilkinson, Pergamon, Oxford, **1995**, Vol. 1. c) N. Miyoshi, in *Houben-Weyl: Science of Synthesis*, ed. by H. Yamamoto, Thieme, Stuttgart, **2004**, Vol. 7, p. 685, and earlier references therein.
- N. Miyoshi, K. Kamiura, H. Oka, A. Kita, R. Kuwata, D. Ikehara, M. Wada, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 341.
- N. Miyoshi, D. Ikehara, T. Kohno, A. Matsui, M. Wada, *Chem. Lett.* **2005**, *34*, 760.
- a) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. b) For an unprecedented cleavage of 1,2-diamines, see: M. Shimizu, H. Makino, *Tetrahedron Lett.* **2001**, *42*, 8865.
- a) For a recent review on imino pinacol coupling covering literatures from 1960 to 2006, see: V. Faugeron, Y. Genisson, *Curr. Org. Chem.* **2008**, *12*, 751. b) J. G. Smith, I. Ho, *J. Org. Chem.* **1972**, *37*, 653. c) S. Ohtaka, K. Mori, S. Uemura, *Heteroat. Chem.* **2001**, *12*, 309. d) J. G. Smith, I. Ho, *J. Org. Chem.* **1973**, *38*, 2776. e) J. J. Eisch, P. O. Fregene, *Eur. J. Org. Chem.* **2008**, 4482. f) Enantioselective imino pinacol coupling, see: M. Shimizu, T. Iida, T. Fujisawa, *Chem. Lett.* **1995**, 609. g) Crossed imino pinacol coupling of two different imines, see: M. Shimizu, I. Suzuki, H. Makino, *Synlett* **2003**, 1635.
- a) G. M. Robertson, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, Pergamon, Oxford, **1991**, Vol. 3, p. 563, and references therein. b) T. Mukaiyama, N. Yoshimura, K. Igarashi, A. Kagayama, *Tetrahedron* **2001**, *57*, 2499. c) R. Hayakawa, M. Shimizu, *Chem. Lett.* **2000**, 724. d) M. Shimizu, H. Goto, R. Hayakawa, *Org. Lett.* **2002**, *4*, 4097. e) M. Shimizu, H. Okimura, N. Manabe, I. Hachiya, *Chem. Lett.* **2008**, *37*, 28. f) For crossed pinacol coupling between aldehydes and imines, see: M. Shimizu, A. Iwata, H. Makino, *Synlett* **2002**, 1538.
- A typical procedure for the reductive self-coupling of imine is as follows: Under an argon atmosphere, *N*-benzylidene-aniline (182 mg, 1.00 mmol) and I₂ (ca. 10 mg, 0.08 mmol) were added successively to a THF (3 mL) suspension of Sr (116 mg, 1.32 mmol) at rt. After stirring for 2 h, the reaction mixture was quenched with 1 M HCl(aq) (3 mL), and the whole reaction mixture was made basic to litmus with 5% aq Na₂CO₃, filtered through a cake of celite. The organic materials were extracted with Et₂O (30 mL × 3), and the combined organic layers were washed successively with 5% aq NaHSO₃ and brine, and dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was purified by column chromatography on Al₂O₃ (hexane:ethyl acetate = 10:1) to give 1,2-dianilino-1,2-diphenylethane (162 mg, 88% yield, dl:meso = 75:25)^{5b} and *N*-benzylaniline (10 mg, 5% yield).

**Scheme 1.**