

HETEROCYCLES, Vol. 72, 2007, pp. 127 - 132. © The Japan Institute of Heterocyclic Chemistry
 Received, 21st November, 2006, Accepted, 21st December, 2006, Published online, 22nd December, 2006. COM-06-S(K)23

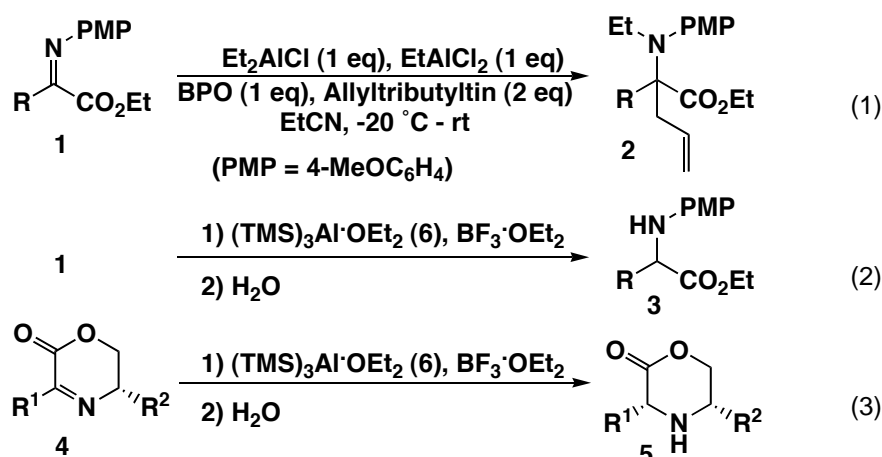
DIASTEREOSELECTIVE REDUCTION OF α -IMINO ESTERS WITH TRIS(TRIMETHYLSILYL)ALUMINUM

Makoto Shimizu,* Yasuki Niwa, Takeshi Nagai, and Iwao Hachiya

Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan. E-mail: mshimizu@chem.mie-u.ac.jp

Abstract – Tris(trimethylsilyl)aluminum was found to be a good chemoselective reducing reagent for α -imino esters to give α -amino esters in good yields. Application to the reduction of 3,5-disubstituted 5,6-dihydro-2*H*-1,4-oxazine-2-ones realized a stereoselective conversion into *cis*-3,5-disubstituted morpholine-2-ones.

For the synthesis of α -amino acids or esters, chemoselective reduction of their α -imino analogues constitutes one of the most straightforward methodologies. When this strategy is applied to chiral cyclic derivatives, an asymmetric version becomes feasible.¹ Although hydrogenation reaction has been usually used for this purpose, development of other stereoselective methods for the transformation of α -imino esters is still a worthwhile goal in terms of substrate flexibility and chemoselectivity.



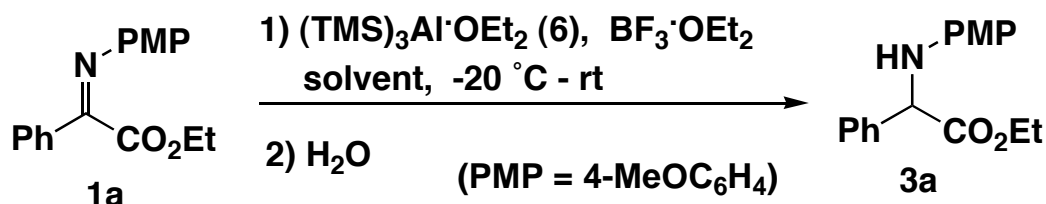
Scheme 1.

 This paper is dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

Nucleophilic addition to the nitrogen atom of simple imines is, in principal, difficult due to the electron negativity of the imino functionality. Only limited examples have been available for the nucleophilic addition to the nitrogen atom of α -imino esters.² We have focused on the reactivity of α -imino esters and have recently disclosed that on treatment of various α -imino esters (**1**) with organoaluminum reagents and allyltributyltin in the presence of benzoyl peroxide (BPO), the tandem reaction proceeds to give the *N*-alkylation-*C*-allylation products (**2**) in good yields (Scheme 1, eq. 1).³ During these studies, tris(trimethylsilyl)aluminum (**6**)⁴ was found to undergo chemoselective addition to α -imino esters (**1**) at the nitrogen atom to give, after hydrolysis, α -amino esters (**3**) in good yields (Scheme 1, eq. 2). This paper describes an intriguing chemoselective reduction of α -imino esters and their cyclic analogues (**4**) with tris(trimethylsilyl)aluminum.

The initial examination was carried out using the reduction of the imine (**1a**) derived from ethyl phenylglyoxylate with tris(trimethylsilyl)aluminum (**6**), and Table 1 summarizes the results.

Table 1. Chemoselective Reduction of **1a** with Tris(trimethylsilyl)aluminum (**6**) under Various Conditions^a



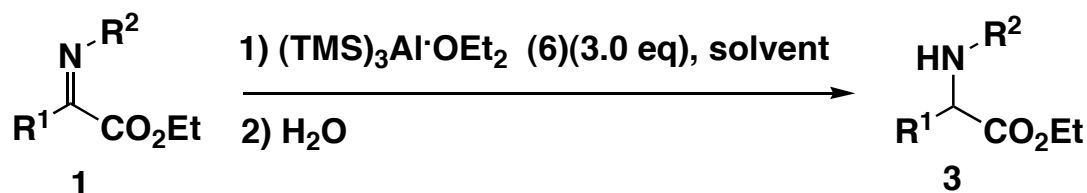
Entry	Solvent	6 /equiv.	BF ₃ ·OEt ₂ /equiv.	Time/h	3a / % ^b
1	CH ₂ Cl ₂	3.0	none	6.0	61
2	EtCN	3.0	none	6.0	70
3	DME	3.0	none	5.5	84
4	Et ₂ O	3.0	none	6.0	81
5	Et ₂ O	2.0	none	6.0	66
6	DME	2.0	1.0	6.0	78
7	DME	1.0	1.0	6.0	84

^aReaction was carried out according to the typical procedure (Ref. 5). ^bIsolated yield.

Among the solvents screened, DME and Et₂O gave the reduction product in good yields, whereas decreased amounts of the desired product were formed in EtCN and dichloromethane (Entries 1 - 4). Regarding the amount of tris(trimethylsilyl)aluminum (**6**), the reaction needed the use of 3.0 equivalents of **6** for completion of the reduction in the absence of BF₃·OEt₂ (Entries 4 and 5). However, the presence of a certain Lewis acid was found to promote the present chemoselective addition reaction of **6** at the imino nitrogen. For example, in the presence of BF₃·OEt₂, the use of an equimolar amount of the reagent

(6) gave a satisfactory result (Entries 6 and 7). Under essentially optimized conditions the reduction of a series of imines derived from various glyoxylates were carried out, and Table 2 summarizes the results.

Table 2. Chemoselective Reduction of Various Imines (**1**) with **6**^a

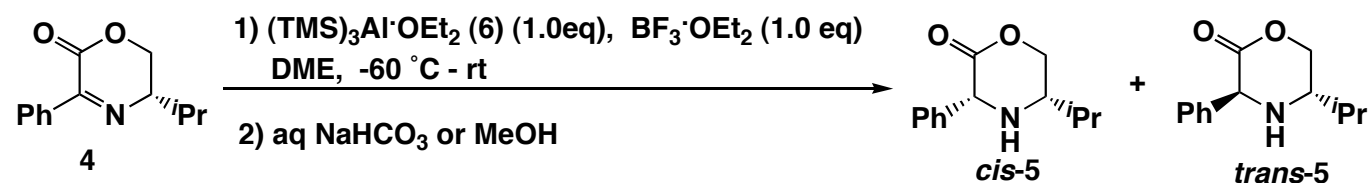


Entry	R ¹	R ²	Solvent	Temp./°C	Time/h	3/% ^b
1	Ph	<i>t</i> -Bu	Et ₂ O	-20 to rt	15.5	46
2	Ph	Ph	Et ₂ O	-20 to rt	7.0	72
3	Ph	4-ClC ₆ H ₄	Et ₂ O	-20 to rt	6.0	68
4	4-MeC ₆ H ₄	4-MeOC ₆ H ₄	DME	-60 to rt	7.5	73
5	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	DME	-60 to rt	10.5	77
6	2-MeOC ₆ H ₄	4-MeOC ₆ H ₄	DME	-60 to rt	7.0	47
7	4-ClC ₆ H ₄	4-MeOC ₆ H ₄	DME	-60 to rt	7.5	81
8	2-Thienyl	4-MeOC ₆ H ₄	DME	-60 to rt	6.0	78
9	Cyclohexyl	4-MeOC ₆ H ₄	DME	-60 to rt	11.5	66

^aReaction was carried out according to the typical procedure (Ref. 5). ^bIsolated yield.

As can be seen from Table 2, regarding the substituents at the nitrogen, a 4-methoxyphenyl group appeared to be the substituent of choice (Entries 1-3 and entry 4 in Table 1). A variety of R¹ groups can be used for this reduction. The phenyl derivatives possessing both electron-donating and –withdrawing groups gave good yields of the reduction products, where the *ortho*-substituent decreased the product yield presumably due to the steric factors (Entries 4-7). Heteroaromatic and alicyclic derivatives also recorded good results (Entries 8-9).

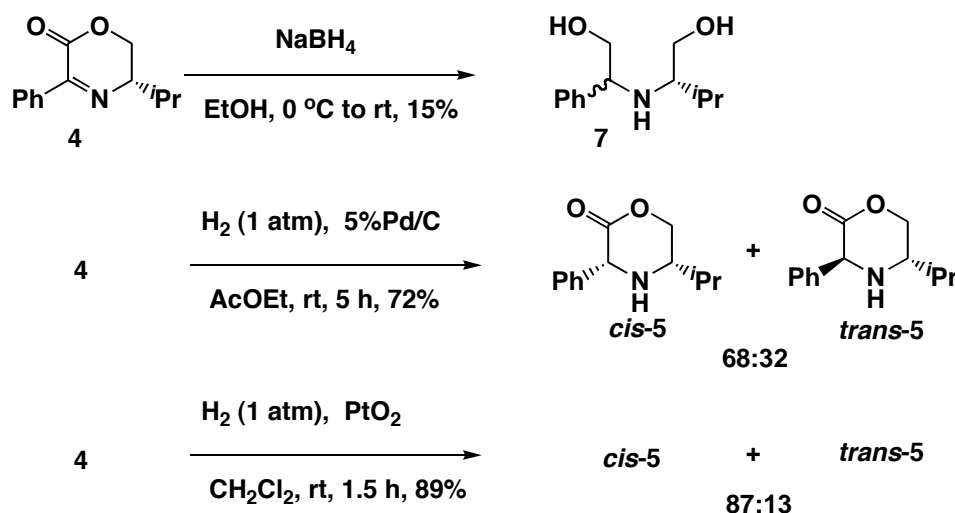
In an effort to apply to the synthesis of chiral materials, cyclic analogues were subjected to the present chemoselective reduction conditions, and Table 3 summarizes the results. In the absence of BF₃·OEt₂ the reduction gave *cis*-**5** as a major product, whereas a slightly better diastereoselectivity was observed in its presence (Entries 1-2). The reduction product (**5**) was sensitive to the basic conditions, and the work-up procedure was found to be crucial for the improvement of the diastereoselectivity. Both quenching the reaction mixture with methanol at low temperature and purification by flash silica gel column chromatography improved the diastereoselectivity (Entries 3-4). Even during the purification by flash silica gel column chromatography, decrease in the diastereoselectivity was observed upon slow elution, and therefore, rapid elution should be taken. Al₂O₃ TLC or column chromatography may also be used for the purification.

Table 3. Stereoselective Reduction of Cyclic Derivative (**4**) with **6**^a

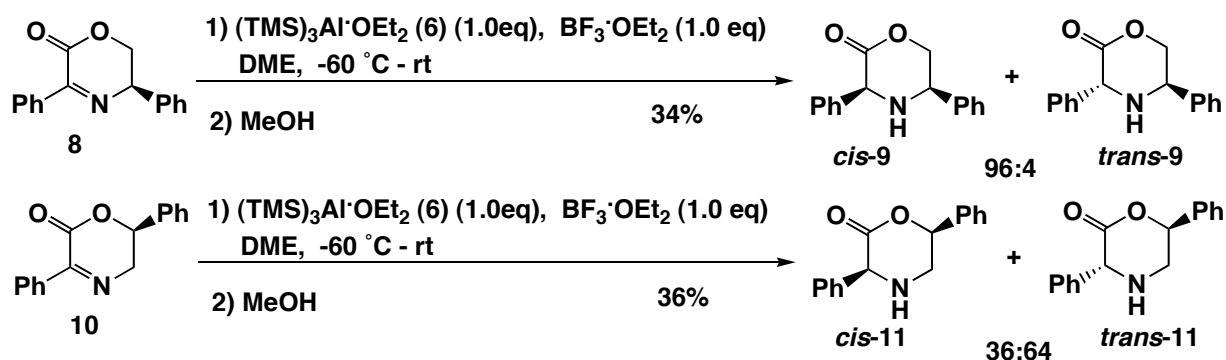
Entry	6 /equiv.	$\text{BF}_3\cdot\text{OEt}_2$ /equiv.	Quench with	5 /% ^b	<i>cis:trans</i> ^c
1	3.0	none	aq. NaHCO_3	51	72:28
2	1.0	1.0	aq. NaHCO_3	47	75:25
3	1.0	1.0	MeOH	50	77:23
4	1.0	1.0	MeOH	54	92:8 ^d

^aReaction was carried out according to the typical procedure (Ref. 5). ^bIsolated yield. ^cDetermined by ^1H NMR and /or HPLC. ^dPurification of the product was conducted using flash SiO_2 column chromatography, and in the other entries using preparative SiO_2 TLC.

By comparison, reduction of **4** with NaBH_4 or Pd-catalyzed hydrogenation was carried out (Scheme 2). As you can see, the use of NaBH_4 gave the ring-opened diol (**7**) in low yield, whereas decreased diastereoselectivities were observed in the hydrogenation reactions using either 5% Pd/C or PtO_2 , indicating that the present tris(trimethylsilyl)aluminum (**6**) mediated reduction appears to be a method of choice in terms of diastereoselectivity.

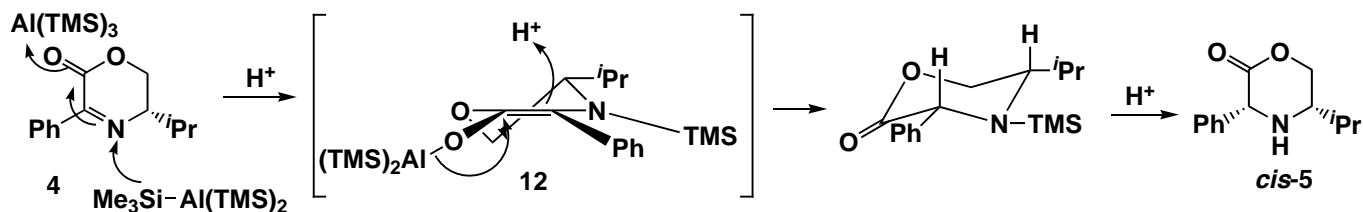
**Scheme 2.**

Reduction of other substrates was also carried out (Scheme 3). Although there is much room for the improvement of the product yields, 3,5-diphenyl derivative (**8**) also recorded good diastereoselectivity, whereas its 3,6-diphenyl isomer (**10**) did not give a satisfactory discrimination. The relatively low yields of the reduction products (**9** and **11**) were mainly due to the undesirable by-products formation arising from the opening of the lactone rings.



Scheme 3.

The following Scheme 4 shows a possible reaction mechanism. First, conjugate addition of tris(trimethylsilyl)aluminum (**6**) to the nitrogen atom of **4** in an “umpolung” manner produces the aluminum enolate (**12**), which in turn is protonated from the stereoelectronically favored axial side followed by desilylation gives *cis*-**5** as a major product.



Scheme 4.

In conclusion, we have found that tris(trimethylsilyl)aluminum (**6**) is a useful reagent for the conjugate addition to α -imino esters in an “umpolung” manner to produce, after hydrolysis, chemoselectively reduced α -amino esters in good yields. Application of this methodology to cyclic counterparts offers a diastereoselective approach to 3,5-disubstituted morpholine-2-ones.

REFERENCES AND NOTES

- (a) G. G. Cox and L. M. Harwood, *Tetrahedron:Asymmetry*, 1994, **5**, 1669. (b) F. Seggat-Dioury, O. Lingibe, B. Graffe, M.-C. Sacquet, and G. Lhommet, *Tetrahedron*, 2000, **56**, 233.
- (a) M. P. Bertrand, L. Feray, R. Nouguier, and P. Perfetti, *Synlett*, 1999, 1148. (b) K. Uneyama, F. Yan, S. Hirama, and T. Katagiri, *Tetrahedron Lett.*, 1996, **37**, 2045. (c) Y. Yamamoto and W. Ito, *Tetrahedron*, 1988, **44**, 5415. (d) M. R. van Vliet, J. T. B. H. Jastrzebski, W. J. Klaver, K. Goubitz, and G. van Koten, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 132. (e) J.-C. Fiaud and H. B. Kagan, *Tetrahedron Lett.*, 1971, **12**, 1019.

3. (a) Y. Niwa and M. Shimizu, *J. Am. Chem. Soc.*, 2003, **125**, 3720. (b) M. Shimizu and Y. Niwa, *Tetrahedron Lett.*, 2001, **42**, 2829. (c) Y. Niwa, K. Takayama, and M. Shimizu, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1819. (d) Y. Niwa, K. Takayama, and M. Shimizu, *Tetrahedron Lett.*, 2001, **42**, 5473. (e) M. Shimizu, H. Itou, and M. Miura, *J. Am. Chem. Soc.*, 2005, **127**, 3296.
4. (a) M. A. Avery, W. K. M. Chong, and C. Jennings-White, *J. Am. Chem. Soc.*, 1992, **114**, 974. (b) M. Nakada, S. Nakamura, S. Kobayashi, and M. Ohno, *Tetrahedron Lett.*, 1991, **32**, 4929. (c) G. Altnau and L. Rösch, *Tetrahedron Lett.*, 1983, **24**, 45. (d) B. M. Trost, J. Yoshida, and M. Lautens, *J. Am. Chem. Soc.*, 1983, **105**, 4494. (e) L. Rösch and G. Altnau, *J. Organomet., Chem.*, 1980, **195**, 47.
5. The following example represents typical experimental procedure: To a solution of (5*S*)-5-isopropyl-3-phenyl-5,6-dihydro-2*H*-1,4-oxazine-2-one (32.6 mg, 0.150 mmol) (**5**) in DME (1.5 mL) was added a solution of BF₃·OEt₂ (21.3 mg, 0.150 mmol) in DME (1.5 ml) at -60 °C under an argon atmosphere. To the resulting solution was added a solution of tris(trimethylsilyl)aluminum (**6**) (0.300 mL, 0.150 mmol, 0.5 M in pentane) at -60 °C. The mixture was allowed to warm to ambient temperature with stirring for 8.0 h. The reaction was cooled to -60 °C and quenched with MeOH (0.122 mL, 3.00 mmol). To the resulting solution was added sat. NaHCO₃ aq, and the whole mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column (*n*-hexane-AcOEt = 4 : 1 as an eluent) gave 5-isopropyl-3-phenylmorpholine-2-one (**5**) (17.8 mg, 54%, a 92:8 mixture of *cis* and *trans* isomers) as a colourless oil; ¹H NMR (500 MHz, CDCl₃) δ: 0.98 (d, *J* = 7.3 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 1.71-1.75 (m, 1H), 1.92 (brs, 1H), 2.83-2.89 (m, 0.08H), 2.99-3.04 (m, 0.92H), 4.23-4.27 (m, 1H), 4.40-4.45 (m, 1H), 4.72(s, 0.92H), 4.86 (s, 0.08H), 7.33-7.50 (m, 5H); ¹³C NMR (126 MHz, CDCl₃) δ : 18.7, 18.9, 30.2, 58.0, 63.6, 72.8, 127.2, 128.3, 128.6, 138.4, 169.2; IR (neat) 3329, 3031, 2963, 1739, 1460, 1369, 1294, 1205, 1092, 1028, 968, 867, 743, 700 cm⁻¹.