ORGANIC
LETTERS

2011
Vol. 13, No. 15
3968–3971

A Tertiary Amine as A Hydride Donor: Trichlorosilyl Triflate-mediated Conjugate Reduction of Unsaturated Ketones

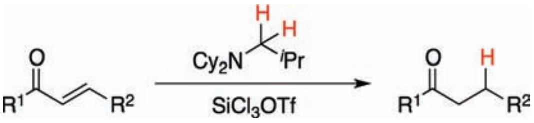
Shunsuke Kotani,*,† Kazuki Osakama,‡ Masaharu Sugiura,‡ and Makoto Nakajima‡

Priority Organization for Innovation and Excellence, Kumamoto University, and
Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi,
Kumamoto, 862-0973, Japan

skotani@gpo.kumamoto-u.ac.jp

Received June 2, 2011

ABSTRACT



Bulky tertiary amines, especially dicyclohexylisobutylamine, smoothly reduced α,β-unsaturated ketones in the presence of trichlorosilyl triflate to give the corresponding saturated ketones in excellent yields. Isotope-labeling studies revealed that an α-hydrogen of the amine was transferred to the enones during reduction.

Amine is one of the most versatile and inexpensive reagents for organic synthesis. Amine is most frequently used as a base, of which the lone pair electrons on the nitrogen atom act as a Brønsted base and accept a proton. Some amines, such as the Hantzsch ester, are hydrogen donors, which can promote reduction of organic compounds.[1] Several other hydrogen transfer reagents containing amino functional groups also have been investigated.[2,3] However, little attention has been paid to tertiary amines as a hydrogen transfer reagent.[4−6]

Recently, we described a trichlorosilyl triflate-mediated enantioselective aldol reaction of cyclohexanone with benzaldehyde using dicyclohexylmethylamine as a Brønsted base and BINAP dioxide (BINAPO) as a Lewis base.[7] While screening the reaction conditions, we were surprised to find that using diisopropylethylamine produced benzyl alcohol as a byproduct (Scheme 1). This finding prompted us to explore the possibility of developing a novel reduction method. Herein, we report that a tertiary amine in the presence of trichlorosilyl triflate mediates the conjugate reduction of α,β-unsaturated ketones and that an α-hydrogen of the amine is transferred into the β-position of the enone.

Initially, reductions of chalcone (**1a**) were conducted under a variety of conditions (Table 1). The conjugate

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[†] Priority Organization for Innovation and Excellence.

[‡] Graduate School of Pharmaceutical Sciences.

(1) For reviews for Hantzsch ester reductions, see: (a) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (b) You, S.-L. *Chem. Asian J.* **2007**, *2*, 820. (c) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407. (d) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084.

(2) For imidazoline or thiazoline-promoted reductions, see: (a) Chikashita, H.; Miyazaki, M.; Itoh, K. *Synthesis* **1984**, 308. (b) Chikashita, H.; Itouh., K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1747. (c) Zhang, Y.; Zhou, G.; Guo, W. *Heterocycles* **2009**, *78*, 1541. (d) Chikashita, H.; Miyazaki, M.; Itoh, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 699. (e) Hasegawa, E.; Hirose, H.; Sasaki, K.; Takizawa, S.; Seida, T.; Chiba, N. *Heterocycles* **2009**, *77*, 1147. (f) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180.

(3) For lithium amide-promoted reductions, see: (a) Woo, E. P.; Mak, K. T. *Tetrahedron Lett.* **1974**, *15*, 4095. (b) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601. (c) Scott, L. T.; Carlin, K. J.; Schultz, T. H. *Tetrahedron Lett.* **1978**, *19*, 4637. (d) Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057. (d) Takeda, K.; Ohishi, Y.; Koizumi, T. *Org. Lett.* **1999**, *1*, 237.

(4) For reductions by amines, see: (a) Nishiguchi, T.; Tachi, K.; Fukuzumi, K. *J. Org. Chem.* **1975**, *40*, 237. (b) Schreiber, S. L. *Tetrahedron Lett.* **1980**, *21*, 1027.

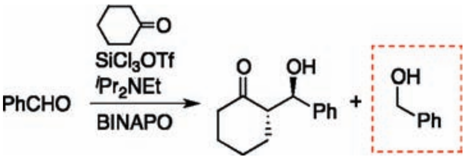
(5) For metal-mediated reductions with tertiary amines, see: (a) Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron Lett.* **2004**, *45*, 1825. (b) Cho, C. S.; Kim, D. T.; Shim, S. C. *Bull. Korean Chem. Soc.* **2009**, *30*, 1931.

(6) For recent papers for intramolecular amine-mediated reductions, see: (a) Mátyus, P.; Éliás, O.; Tapolcsányi, P.; Polomka-Bálint, Á.; Halász-Dajka, B. *Synthesis* **2006**, 2625. (b) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, *38*, 524. (c) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (d) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (e) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (f) Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, *46*, 6593. (g) Haibach, M. C.; Deb, I.; De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100. (h) Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 600.

(7) Kotani, S.; Aoki, S.; Sugiura, M.; Nakajima, M. *Tetrahedron Lett.* **2011**, *52*, 2834.

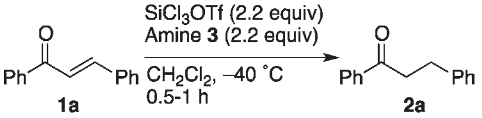
10.1021/ol2014895

Scheme 1. Unexpected Reduction of Benzaldehyde to Benzyl Alcohol



reduction of **1a** was performed using trichlorosilyl triflate[8] (2.0 equiv) and diisopropylethylamine (2.2 equiv) in dichloromethane at −40 °C, yielding not the corresponding alcohol but the 1,4-reduction product **2a** in moderate yield (30%, entry 1). The absence of Lewis base (BINAPO) improved the yield of **2a** (50%, entry 2). Because Lewis bases are essential for conjugate reductions with $HSiCl_3$,[9] the present reaction does not proceed via hypervalent silicon species. A range of solvents was tested, and dichloromethane was found to be optimal for the conjugate reduction of α,β-unsaturated ketones.[10] Next, we screened amines using dichloromethane as the reaction solvent. Reactions with small amines, such as triethylamine (**3b**) or diisopropylmethylamine (**3c**), did not yield any product (entries 3, 4, and 7), whereas sterically hindered amines tended to provide high yields (entries 5, 6, 8, and 9).

Table 1. Optimization of the Reaction Conditions[a]



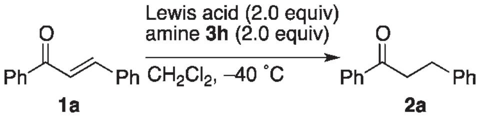
entry	amine, **3**	yield, %[b]
1[c]	^{i}Pr$_2$NEt, **3a**	30
2[d]	^{i}Pr$_2$NEt, **3a**	50
3	Et$_3$N, **3b**	0
4	^{i}Pr$_2$NMe, **3c**	0
5	^{i}Pr$_2$NPr, **3d**	56
6	^{i}Pr$_2$N^{i}Bu, **3e**	92
7	Cy$_2$NMe, **3f**	0
8[d]	Cy$_2$NEt, **3g**	47
9[e]	Cy$_2$N^{i}Bu, **3h**	98

[a] Unless otherwise noted, the reactions were conducted using the ketone **1a** (0.5 mmol), the amine **3** (2.2 equiv), and $SiCl_3OTf$ (2.2 equiv) in CH_2Cl_2 (5 mL) at −40 °C. [b] Isolated yield. [c] With BINAPO (10 mol %). [d] 1,5-Diphenyl-5-oxopentanal (**4a**) was obtained (27% yield in entry 2, 38% yield in entry 8). [e] $SiCl_3OTf$ (2.0 equiv).

Dicyclohexylisobutylamine (**3h**), especially, afforded the corresponding product in 98% yield (entry 9). Small amines might coordinate to trichlorosilyl triflate, thereby suppressing the reaction. On the other hand, the bulkiness of the amines prevented complexation with trichlorosilyl triflate, yielding the corresponding product in excellent yield.

Conjugate reductions using various types of Lewis acids with dicyclohexylisobutylamine (**3h**) were examined (Table 2). Other silyl reagents such as silicon tetrachloride, trimethylsilyl triflate, or boron trifluoride gave no product (entries 2–4). Titanium tetrachloride promoted the reduction,[5a] but the yield was low in comparison with that of trichlorosilyl triflate (entry 5). These observations indicated importance of combining trichlorosilyl triflate with dicyclohexylmethylamine for the reaction the α,β-unsaturated ketone.

Table 2. Reduction of **1a** with Various Lewis Acids[a]



entry	Lewis acid	time, h	yield, %[b]
1	$SiCl_3OTf$	0.5	98
2	$SiCl_4$	2	0
3	TMSOTf	8	0
4	$BF_3 \cdot Et_2O$	4	0
5	$TiCl_4$	0.5	41

[a] All reactions were conducted using the ketone **1a** (0.5 mmol), the amine **3h** (2.0 equiv), and a Lewis acid (2.0 equiv) in CH_2Cl_2 (5 mL) at −40 °C. [b] Isolated yield.

With optimal conditions in hand, the conjugate reductions of various unsaturated ketones were investigated (Table 3). Ketones substituted with aliphatic groups as the R^1 group were cleanly reduced in high yields (entries 2 and 3).[11] Substrates having dibenzylidene moiety gave the partially reduced products in good yields (entries 4 and 5). In the reduction of ketone **1e**, the unreacted olefin moiety partially isomerized (E/Z = 12/1) presumably through addition/elimination of chloride ion to enone. *trans*-1,2-(Dibenzoyl)ethylene (**1f**), with carbonyl groups on the both sides of the olefin was reduced with 4 equiv of trichlorosilyl triflate and the amine **3h** to afford the corresponding adduct **2f** in 96% yield (entry 6). The reductions of enones with fixed *s-trans* geometry proceeded in lower yields (entries 7 and 8). However, it is noteworthy that the $SiCl_3OTf/Cy_2N^{i}Bu$ system reduced the *s-trans* substrates, which were not reduced by $HSiCl_3$ with a Lewis base.[9] These results indicate that the reaction mechanism differs from that of the conjugate reduction with $HSiCl_3$.

We next focused our attention on elucidating the reaction mechanism. A hydrogen transfer reduction assumes to proceed either via ionic species or via radical species.

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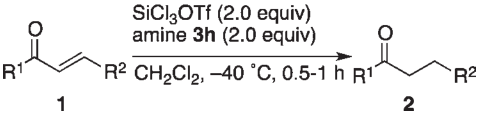
(8) For preparation of trichlorosilyl triflate, see: Bassindale, A. R.; Stout, T. *J. Organomet. Chem.* **1984**, *271*, C1.

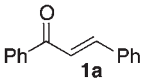
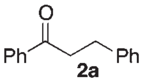
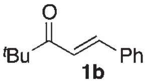
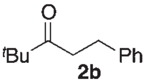
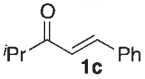
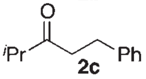
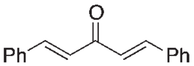
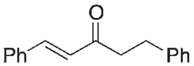
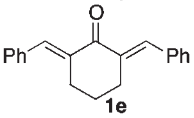
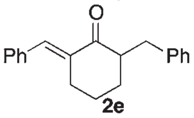
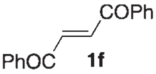
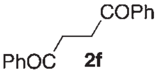
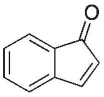
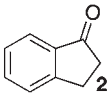
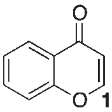
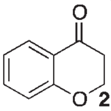
(9) (a) Sugiura, M.; Sato, N.; Kotani, S.; Nakajima, M. *Chem. Commun.* **2008**, 4309. (b) Sugiura, M.; Sato, N.; Sonoda, Y.; Kotani, S.; Nakajima, M. *Chem. Asian J.* **2010**, *5*, 478.

(10) Solvents affected reactivities for the reduction. No products were obtained in tetrahydrofuran (THF) or chloroform. Propionitrile and toluene produced the reduced ketone **2a**, but the yields were low compared to dichloromethane (propionitrile: 21%, toluene: 24%).

(11) Enones bearing aliphatic substituents on R^2 resulted in low yields: 4-methyl-1-phenyl-2-penten-1-one (24%), 4,4-dimethyl-1-phenyl-2-penten-1-one (26%).

Table 3. Conjugate Reduction of Various Enones **1**[a]



entry	substrate, 1	product, 2	yield, %[b]
1	 **1a**	 **2a**	98
2	 **1b**	 **2b**	90
3	 **1c**	 **2c**	88
4	 **1d**	 **2d**	89
5[c,d]	 **1e**	 **2e**	91
6[e]	 **1f**	 **2f**	96
7	 **1g**	 **2g**	28
8[f]	 **1h**	 **2h**	75

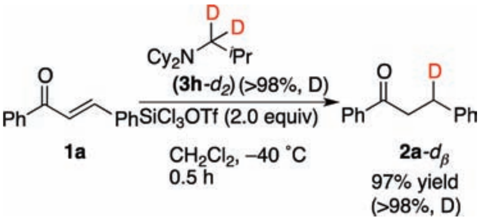
[a] Unless otherwise noted, the reactions were conducted using the ketone **1** (0.5 mmol), the amine **3h** (2.0 equiv), and $SiCl_3OTf$ (2.0 equiv) in CH_2Cl_2 (5 mL) at −40 °C. [b] Isolated yield. [c] At 0 °C . [d] E/Z = 12/1. [e] With $SiCl_3OTf$ and **3h** (4 equiv each). [f] With $SiCl_3OTf$ and **3h** (3 equiv each).

To probe the possibility of a single electron transfer (SET) mechanism, the reduction of benzophenone was examined under optimized conditions, giving only trace amounts (3%) of the alcohol. These results could not completely exclude the SET mechanism; however, it suggested that the reduction most likely proceeded through ionic processes rather than through radical processes.[12]

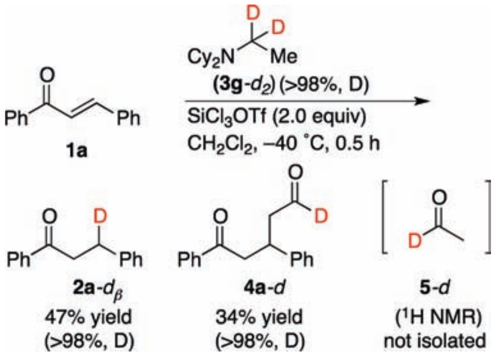
Deuterium-labeling experiments were performed to determine which hydrogen was transferred (Scheme 2). First, the deuterated amine **3h**-d_2 was prepared[13] and applied to the conjugate reduction of ketone **1a**. Because the β-position of the ketone was completely deuterized to give **2a**-$d\alpha$ in 97% yield, an α-hydrogen of amine **3h**-d_2 was transferred to the β-position of the ketone.

We observed a byproduct **4a** in the reaction of **1a** with amine **3a** and **3g** (Table 1, entries 2, and 8). To investigate how **4a** was produced, the deuterized amine **3g**-d_2 was prepared and the reduction of **1a** was performed (Scheme 3). The deuterized **4a**-d was produced in 34% yield, in addition to the reduced product **2a**-$d\beta$. After a hydrogen transfer, an enamine intermediate derived from the amine was generated and reacted with **1a** to produce the **4a**-d, though aldehyde **5** was not detected.[14] Reaction with amine **3h** did not give a Michael adduct, suggesting that the enamine generated from **3h** was unreactive toward the ketone **1a**. On the other hand, 1,4-addition of the reactive enamines to the enone **1a** competed with the reduction and decreased the product yield.

Scheme 2. Deuterium-labeling Experiments Using **3h**-d_2

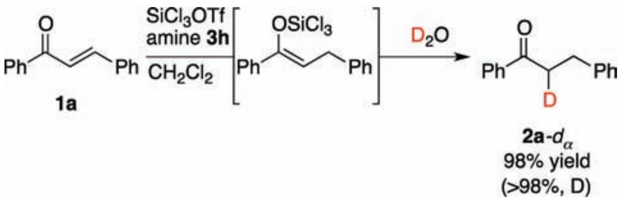


Scheme 3. Deuterium-labeling Experiments Using **3g**-d_2



Next, deuterium oxide was used to quench the reaction of **1a** with $SiCl_3OTf/Cy_2N^iBu$ (Scheme 4). The product **2a** was deuterized only at the α-position. The result suggested that a trichlorosilyl enol ether may be generated in the reaction medium after conjugate reduction and accept a proton in workup to produce **2a**.

Scheme 4. Deuterium-labeling Experiments with D_2O



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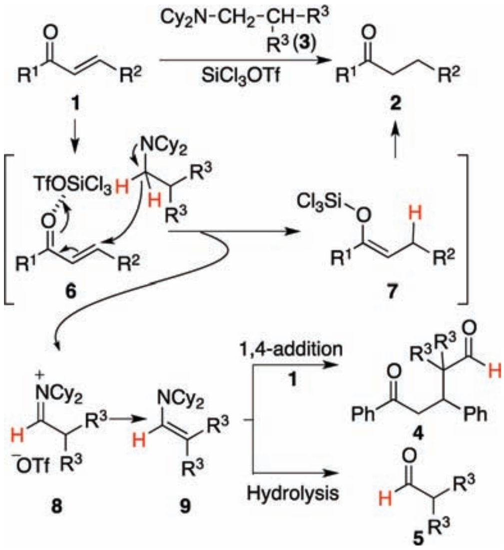
[12] Addition of a radical scavenger did not prevent the reduction, remarkably. 2,6-Di-*tert*-butyl-4-methylphenol (BHT) gave **2a** (95% yield), whereas the yield decreased with galvinoxyl (45%).

[13] The deuterated amines were prepared from *N*,*N*-dicyclohexyl amides and $LiAlD_4$. See Supporting Information.

Scheme 5. Plausible Reaction Mechanism of the Conjugate Reduction



These labeling experiments supported the reaction pathway outlined in Scheme 5 for the reduction. First, $SiCl_3OTf$ coordinates to the oxygen atom of ketone **1** to increase the electrophilicity. This complex **6** accepts a hydrogen from the α-position of amine **3** to afford the trichlorosilyl enol ether **7** and the iminium intermediate **8**.[15] The desired product **2** was obtained by hydrolysis of **7**, whereas the iminium ion **8** was enolized to give the enamine **9**. The 1,4-addition of **9** to ketone **1** afforded a byproduct **4**, whereas hydrolysis of **9** gave the corresponding aldehyde **5**.

In conclusion, we demonstrated that the combination of trichlorosilyl triflate and a tertiary amine reduced α,*β*-unsaturated ketones to afford saturated ketones in good yield. Furthermore, analysis using deuterized amines proved that the α-hydrogen of the amine was transferred to the *β*-position of the ketone. Further investigations to utilize this reduction system in asymmetric reactions are currently in progress.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Note Added after ASAP Publication. Errors were corrected in Tables 1−3 and this paper reposted July 12, 2011.

Supporting Information Available. Experimental details and characterization of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Formation of deuterized hydrocinnamaldehyde was confirmed in the reaction with *N*,*N*-dicyclohexyl-2-phenylethylamine.

[15] For generation of iminium intermediates from tertiary amines, see: (a) Bharathi, P.; Periasamy, M. *Org. Lett.* **1999**, *1*, 857. (b) Kagawa, N.; Sasaki, Y.; Kojima, H.; Toyota, M. *Tetrahedron Lett.* **2010**, *51*, 482.