Reductive amination of aldehydes and ketones by a Hantzsch dihydropyridine using scandium triflate as a catalyst

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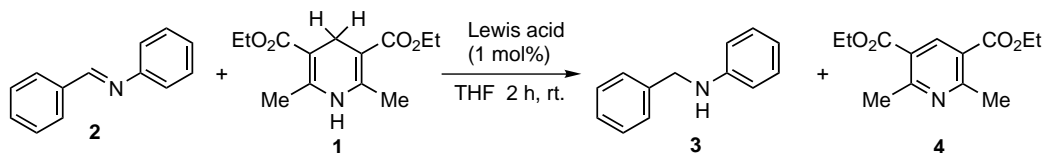
Abstract—Direct reductive amination of aldehydes and ketones was carried out using a Hantzsch dihydropyridine as a reducing agent in the presence of a catalytic amount of a Lewis acid. © 2002 Elsevier Science Ltd. All rights reserved.

Direct reductive amination[1] of aldehydes and ketones is a convenient method for the preparation of secondary and tertiary amines owing to its simple procedure,[2] and recent application of the reaction to combinatorial chemistry is gaining more attention.[3] The overall process involves the formation of an imine or iminium intermediate by condensation of aldehydes or ketones with amines, followed by in situ reduction to an alkylated amine. For the reducing agent, various modified borohydride derivatives have been used which involve NaBH$_3$CN,[4] NaBH(OAc)$_3$,[5] pyridine–BH$_3$,[6] ZnCl$_2$–NaBH$_4$,[7] silica gel–Zn(BH$_4$)$_2$,[8] Ti(OiPr)$_4$–NaBH$_4$,[9] and NiCl$_2$–NaBH$_4$.[10] Many of these reactions, however, require an excess amount of amines to obtain good yields of the products, since carbonyl compounds themselves are also reduced under the conditions. Besides these reagents, alternative metal hydride reagents have recently been developed such as Bu$_3$SnH,[11] Bu$_2$SnClH,[12] Bu$_2$SnIH,[12] Et$_3$SiH–trifluoroacetic acid,[13] Ti(OiPr)$_4$–polymethylhydrosiloxane,[14] and PhSiH$_3$–Bu$_2$SnCl$_2$[15] in order to improve the above drawback. To the best of our knowledge, however, there are no reports using organic compounds as a reductant of imines.

In the course of our study of redox chemistry of heterocycles,[16] we found that a Hantzsch dihydropyridine reduced imines to the corresponding amines in the presence of a catalytic amount of an acid catalyst, and that the reduction was completely selective to imines in the presence of aldehydes or ketones. Thus, direct reductive amination of aldehydes and ketones was performed in the system. Moreover, the reductant was found to be inactive toward aldehydes or ketones *even in the absence of* imines. This paper describes these results.

The Hantzsch dihydropyridine **1** is a classic compound that is readily obtained in multi-gram scale by the reaction of ammonia, formaldehyde, and two equivalents of ethyl acetoacetate.[17] When an imine **2** and Hantzsch dihydropyridine **1** were stirred in a THF solvent, complete recovery of the starting material was observed. In the presence of a catalytic amount of an acid, however, the reaction proceeded smoothly to give the corresponding amine **3** and an aromatized pyridine **4** (Scheme 1 and Table 1).[18]

Quantitative yields were obtained using 1 mol% of Sc(OTf)$_3$ or Sn(OTf)$_2$, and when Yb(OTf)$_3$, Cu(OTf)$_2$

Scheme 1.

Table 1. Reduction of imine **2** with Hantzsch dihydropyridne **1** in the presence of Lewis acid

Entry	1	2	3	4	5	6
Acid	None	Sc(OTf)$_3$	Yb(OTf)$_3$	Sn(OTf)$_2$	Cu(OTf)$_2$	HCl[a]
Yield of **3** (%)	Trace	94	79	99	76	88
Yield of **4** (%)	Trace	96	79	99	78	90

[a] 1N HCl was applied as an aqueous solution.

or HCl was used as an additive, a slight decrease of the yield was observed.

With these data in hand, direct reductive amination was carried out using benzaldehyde (**5**) and acetophenone (**6**) as representative substrates (Scheme 2 and Table 2).

The Lewis acids which gave better results in Table 1 were examined as a candidate for the catalyst. In the case of **5**, the reaction proceeded smoothly with all acids in THF,[19] which is a standard solvent for Sc(OTf)$_3$ reaction.[20] When the reaction of **6** was carried out under the same conditions, however, compound **9** was seldom obtained. Further investigation revealed that product was obtained in a moderate yield using benzene as the solvent in the presence of 5 Å molecular sieves (entry 5).[21] The combination of benzene and molecular sieves was proven to be crucial for the reaction progress, which was shown from the data in entries 4–6.[22] In addition, Sn(OTf)$_2$ and HCl gave poor results

compared with that of Sc(OTf)$_3$. Thus, the reaction conditions were determined as in entry 1 for aldehydes, and in entry 5 for ketones.[23]

The above reaction process was next applied to various aldehydes and ketones, and the results are shown in Scheme 3 and Table 3. The reaction of aldehydes proceeded smoothly in THF or CH$_2$Cl$_2$ without side reactions of other reducible functional groups (entries 2–4). Reductive amination of ketones proceeded slower than that of aldehydes, but in the presence of 5 Å molecular sieves the products were obtained in moderate yields by the use of 10 mol% of the catalyst (entries 6–12).

The difference in the reaction rates between aldehyde and ketone was noteworthy, and it prompted us to study the reaction of an aldehyde in the presence of a ketone, and the result is shown in Scheme 4. In the case of *p*-acetylbenzaldehyde (**12**), the absolute chemoselec-

5 (R=H)
6 (R=Me)

7

1 (1 equiv)
Lewis acid, rt.

8 (R=H)
9 (R=Me)
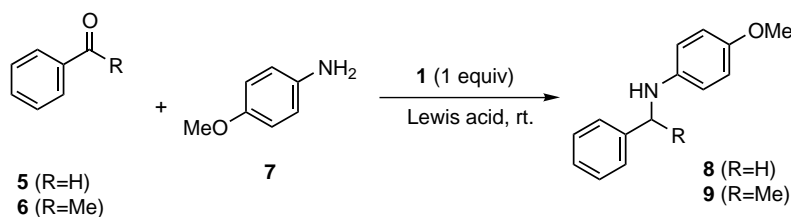
Scheme 2.

Table 2. Reductive amination of benzaldehyde (**5**) and acetophenone (**6**) with *p*-anisidine in the presence of **1** under various conditions[a]

Entry	Substrate	Lewis acid (mol%)	Solvent	Additive	Yield of **8** or **9**
1	**5**	Sc(OTf)$_3$ (2)	THF	–	98
2	**5**	Sn(OTf)$_2$ (2)	THF	–	92
3	**5**	HCl (2)	THF	–	62
4	**6**	Sc(OTf)$_3$ (10)	THF	5 Å MS	14
5	**6**	Sc(OTf)$_3$ (10)	Benzene	5 Å MS	75
6	**6**	Sc(OTf)$_3$ (10)	Benzene	–	4
7	**6**	Sn(OTf)$_2$ (10)	Benzene	5 Å MS	34
8	**6**	HCl (10)[24]	Benzene	5 Å MS	5

[a] Reaction time: 4 h for **5**; 24 h for **6**.

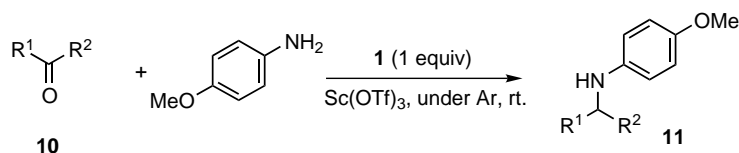
10

1 (1 equiv)
Sc(OTf)$_3$, under Ar, rt.

11

Scheme 3.

Table 3. Direct reductive amination of aldehydes and ketones with **1** in the presence of Sc(OTf)$_3$ as a catalyst

| Entry	R^1	R^2	Sc(OTf)$_3$ (mol%)	Solvent	Additive	Time (h)	Yield of **11** (%)
1	Ph	H	2	THF	–	4	98
2	p-NO$_2$-Ph	H	1	THF	–	34	93
3	p-CN-Ph	H	1	THF	–	22	89
4	(E)-PhCH=CH	H	1	CH$_2$Cl$_2$	–	3	55
5	Cyclohexyl	H	2	CH$_2$Cl$_2$	–	6	98
6	Ph	Me	10	Benzene	5 Å MS	24	75
7	CH$_2$=CHCH$_2$	Me	10	Benzene	5 Å MS	24	67
8	PhCH$_2$CH$_2$	Me	10	Benzene	5 Å MS	24	82
9	Ph	Et	10	Benzene	5 Å MS	72	62
10	2-Naphthyl	Me	10	Benzene	5 Å MS	24	68
11	2-Pyridyl	Me	10	Benzene	5 Å MS	24	82
12	p-NO$_2$-Ph	Me	10	Benzene	5 Å MS	96	69
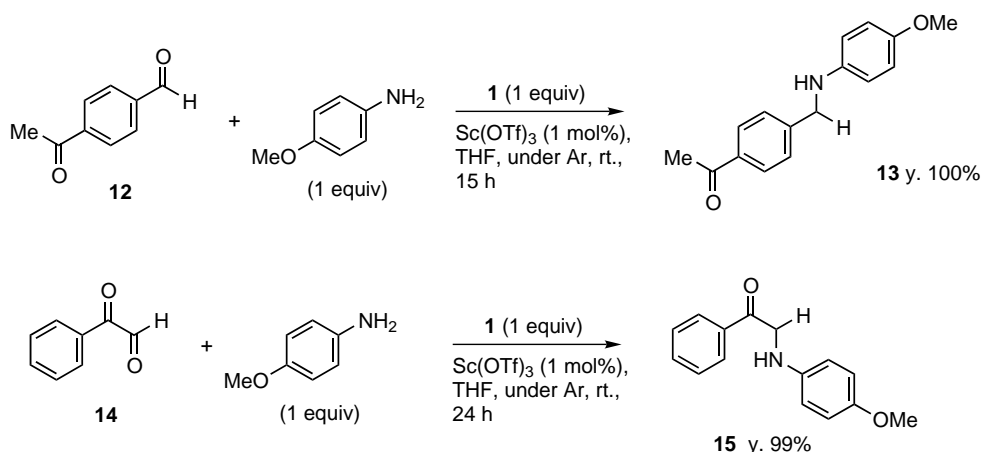
Scheme 4.

tivity toward the aldehyde carbonyl was observed even when equimolar amounts of the substrate, the amine, and the reductant were used. Phenylglyoxal (**14**) also afforded the amino derivative **15** in a good yield of 99%.

In the reaction of imines that use scandium or ytterbium triflate as the catalyst,[25] aldehyde is a potential substrate, and the selection of imine over aldehyde was attributed to the stronger coordination of the former to the Lewis acid than that of the latter.[26]

In the present process, however, the reactions of aldehydes or ketones did not occur even in the absence of imines, as shown in the example (Scheme 5, Eq. (1)). Thus, a selective reductive amination of terephthalaldehyde (**16**) was possible to give a monoamino derivative **17** in a good yield (Scheme 5, Eq. (2)).[27]

Since it has been well established that a p-anisidine moiety is readily removed by an oxidative process,[28] the above method would provide a useful and selective method for the preparation of primary and secondary
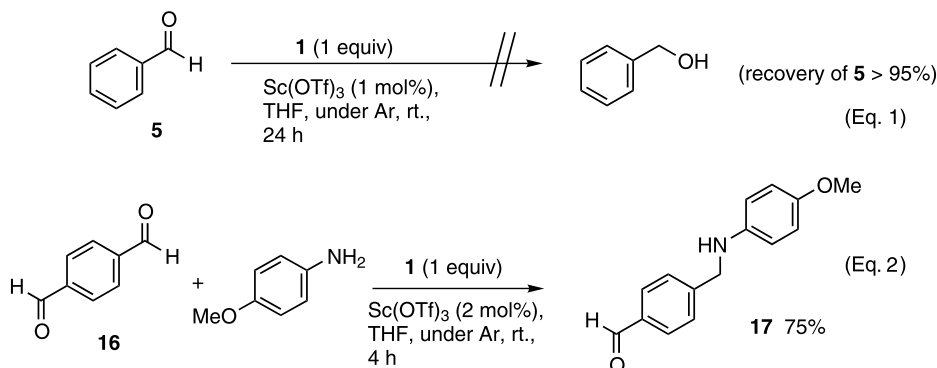
Scheme 5.

amines.[29] A most remarkable point of the reaction is that the reduction is completely selective toward imines. Studies aimed at broadening the scope of the present reaction and understanding its mechanism are now in progress.

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22. Under the same conditions in entry 5 except the solvent, some solvents were investigated, but the yields were found to be low; 14% in THF, 52% in CH_2Cl_2, and 8% in CH_3CN.

23. Typical procedure: In a THF solution (1 ml) of benzaldehyde (0.2 mmol), p-anisidine (0.2 mmol), and **1** (0.2 mmol) under Ar, $Sc(OTf)_3$ (0.004 mmol) were added and the mixture was allowed to react for 4 h at room temperature. Then AcOEt (15 ml) was added and the mixture was washed with 5% Na_2CO_3 (4 ml) and H_2O (4 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a residue, which was chromatographed on silica gel (CH_2Cl_2/AcOEt = 10) to afford the product. The aromatized **4** was readily separated since polarity of **4** was much higher than that of the product. In the case of ketones, a benzene solution (1 ml) of a ketone (0.2 mmol), p-anisidine (0.2 mmol) and 5 Å molecular sieves (400 mg) was treated with **1** (0.2 mmol) and $Sc(OTf)_3$ (0.02 mmol) under Ar for 24 h at room temperature. The work-up procedure was similar to that of aldehydes mentioned above.

24. When trifluoromethanesulfonic acid was used under the same conditions, the yield of **9** was 30%.

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29. A preliminary result showed that oxidation of an amine (obtained from the reaction in Table 3, entry 9) with $(NH_4)_2Ce(NO_3)_6$ in CH_3CN/H_2O afforded the corresponding primary amine in 60% yield.