Thiourea-Catalyzed Transfer Hydrogenation of Aldimines

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Abstract: The present letter reports on the thiourea-catalyzed transfer hydrogenation of imines through hydrogen-bonding activation with Hantzsch 1,4-dihydropyridine as the hydrogen source. A variety of aromatic as well as aliphatic aldimines can be reduced to give the respective amines under acid- and metal-free reaction conditions.

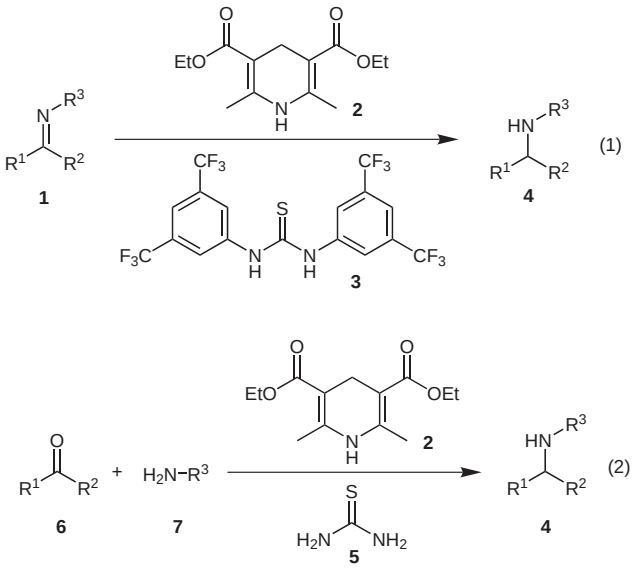
Key words: Hantzsch dihydropyridine, hydrogen bonds, organocatalysis, thiourea, transfer hydrogenation

The organocatalytic hydrogenation of imines and the reductive amination of carbonyl compounds represent a contemporary challenge.[1] There are many metal-based approaches to this transformation, and molecular hydrogen as the reductant activated by chiral metal complexes is a powerful method for the preparation of amines,[2] even on industrial scale.[3] Transfer hydrogenations using isopropyl alcohol or formic acid as sources of hydrogen also are effective.[4] However, expensive and toxic metal ions were used in most of these transformations, so that the organocatalytic hydrogenation of imines and reductive aminations were eagerly anticipated. These include hydrosilylations catalyzed by chiral Lewis bases[5] and hydrogen-transfer reactions catalyzed by chiral phosphoric acid derivatives in combination with the NADH analogous Hantzsch ester.[6]

In the course of our studies on noncovalent organocatalysis mediated through hydrogen bonding, we have demonstrated that thiourea derivatives catalyze Diels–Alder-reactions,[7] acetalizations,[8] epoxide openings[9] as well as several other reactions.[10] We envisioned that activation of imines **1** by hydrogen bonding with electron-poor biaryl thiourea **3** would promote hydrogen transfer from the Hantzsch ester **2** to generate amine **4** (Scheme 1, eq. 1).

Recent work by Menche et al. on the reductive amination of ketones[11] and aldehydes[12] with thiourea (**5**) itself (Scheme 1, eq. 2) encouraged us to utilize **3**, which has proven to be generally a more effective catalyst. First, we attempted to reproduce the findings by the Menche group and compared the catalytic activity of **3** and **5** (Table 1).

Much to our surprise, the reductive amination of acetophenone (**6a**) was ineffective (entries 6–8). When the reaction was carried out using *unactivated* 5 Å MS as dehydrating agent (entry 9), the conversion at 50 °C was



Scheme 1 Thiourea-catalyzed transfer hydrogenation

smooth (89%) even *without* a thiourea catalyst added. This is in stark contrast to the previous report by Menche et al. who reported a maximum yield of 5%;[11] the reasons for using unactivated MS is not clear to us but complies with the data given in the original publications.[11,12]

Conversely, activated MS gives the product in less than 5% yield in the presence of 10 mol% of **5**, while Menche et al. report 88% yield when using unactivated 5 Å MS. As a consequence, we conclude that commercially available 5 Å MS contains some water or other relatively volatile components that could catalyze the reaction as well.

Our attempts at reproducing the published protocol[12] for the reductive amination of aldehydes were equally puzzling at first (entries 1–5). We found that benzaldehyde (**6b**) could be condensed and reduced to the corresponding amine **4b** *without* catalyst with 78% yield in 24 hours! Naturally, we assumed that the auto-oxidation of **6b** had produced sufficient quantities of benzoic acid that could catalyze the reaction as well. Hence, upon addition of excess of base (10 mol% $NaHCO_3$), the reaction was completely suppressed (entry 1). The same reaction in the presence of **5** gave no product (entry 2). In contrast, over 80% yield of product can be realized within 24 hours with 5 mol% or 10 mol% of **3** (entries 3 and 4). Other substituted aryl aldehydes gave poor to moderate yields.

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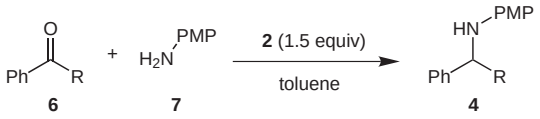
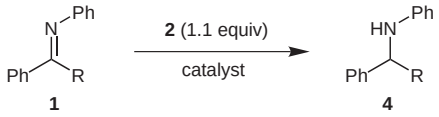
Table 1 Thiourea-Catalyzed Reductive Amination



Entry	R	Catalyst (mol%)	Temp (°C)	Conditions	Yield (%)[a]
1	H	–	r.t.	base,[b] 24 h	trace
2	H	**5** (10)	r.t.	base,[b] 24 h	trace
3	H	**3** (10)	r.t.	base,[b] 24 h	86
4	H	**3** (5)	r.t.	base,[b] 24 h	84
5	H	–	70	5 Å MS,[c] 24 h	91 (93[12])
6	Me	–	50	5 Å MS,[d] 48 h	<5
7	Me	**5** (10)	50	5 Å MS,[d] 48 h	<5 (88[11])
8	Me	**3** (10)	50	5 Å MS,[d] 48 h	<5
9	Me	–	50	5 Å MS,[c] 48 h	89 (<5[11])

[a] Yield of **4** after column chromatography.
[b] 10 mol% of $NaHCO_3$ was added.[13]
[c] Unactivated (Acros organics, pellets, 4–8 mesh, product number: 197285000).
[d] Activated.

Table 2 Imine Reduction with Thioureas

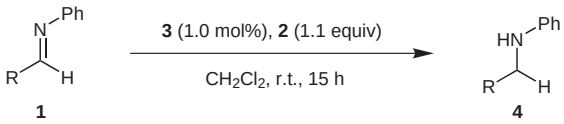


Entry	R	Catalyst (mol%)	Conditions	Yield (%)[a]
1	Me	–	toluene, 50 °C, 48 h	trace
2	Me	**5** (20)	toluene, 50 °C, 48 h	trace
3	Me	**3** (20)	toluene, 50 °C, 48 h	trace
4	H	–	CH_2Cl_2, r.t., 24 h	trace
5	H	**5** (10)	CH_2Cl_2, r.t., 24 h	trace
6	H	**3** (10)	CH_2Cl_2, r.t., 15 h	91
7	H	**3** (5)	CH_2Cl_2, r.t., 15 h	89
8	H	**3** (1)	CH_2Cl_2, r.t., 15 h	89
9	H	**3** (0.1)	CH_2Cl_2, r.t., 60 h	87

[a] Yield of **4** after column chromatography.

We therefore turned our attention to the reduction of isolated imines to further clarify the crucial step in the reported reductive amination. These were allowed to react with reductant **2** under thiourea catalysis (Table 2). While the ketimine derived from **6a** only gave traces of product, the aldimine **1b** produced the corresponding amine even at 1 mol% loading of **3** (entry 8), while **5** again had no catalytic effect (entries 2 and 5). Loadings as low as 0.1 mol% are also possible at the expense of longer reaction times (entry 9).

Table 3 Thiourea-Catalyzed Reduction of Aldimines



Entry	R	Yield (%)[a]
1	Ph	89
2	4-MeC_6H_4	92
3	4-$O_2NC_6H_4$	91
4	4-BrC_6H_4	93
5	3-HOC_6H_4	86
6	4-FC_6H_4	84
7	3-ClC_6H_4	90
8	2,6-$Cl_2C_6H_3$	86
9	3-$MeOC_6H_4$	84
10	*i*-Bu	80
11	*c*-Hex	87

[a] Yield of pure **4** after column chromatography.

Using dichloromethane as solvent and **3** (1 mol%) as catalyst we explored the scope of this acid- and metal-free transfer hydrogenation for the aldimines (Table 3).[14] In general, a variety of aromatic aldimines can be reduced, including electron-rich, electron-deficient, as well as *ortho*-, *meta*-, and *para*-substituted aryl aldehydes. In addition, aliphatic aldimines can also be reduced to give the respective amines with high yields (entries 10 and 11).

The present paper questions some of the published literature protocols[11,12] on the reductive amination of aldehydes and ketones. At the same time, we present a practical method for the thiourea-catalyzed reduction of aromatic as well as aliphatic aldimines with a Hantzsch ester as the hydrogen source.

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(13) Since it is difficult to avoid the formation of carboxylic acids generated from aldehydes during the reaction, 10 mol% of $NaHCO_3$ was added.

(14) **General Procedure for the Thiourea-Catalyzed Transfer Hydrogenation of Aldimines**
In a typical experiment the aldimine **1** (1.0 mmol), thiourea **3** (1 mol%) and Hantzsch dihydropyridine **2** (1.1 equiv) were suspended in anhyd CH_2Cl_2 (5 mL) in a flask. The resulting mixture was allowed to stir at r.t. for 15 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using mixtures of PE and Et_2O to afford the pure corresponding amine **4**. All compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS.
Compound **4a**: light yellow oil. IR (film): 3418, 1699, 1602, 1505, 1179, 1064 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (s, 2 H), 6.50–6.52 (d, 2 H, *J* = 8.71 Hz), 6.59–6.63 (t, 1 H, *J* = 7.41 Hz), 7.04–7.09 (t, 2 H, *J* = 7.40 Hz), 7.14–7.27 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.2, 112.8, 117.5, 127.1, 127.4, 128.5, 129.2, 139.4, 148.1. HRMS: *m/z* calcd for $C_{13}H_{13}N$: 183.10425; found: 183.10347.