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Synthesis of hindered tertiary amines by a mild reductive amination procedure

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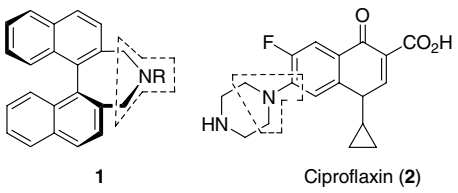
Abstract—An efficient metal-free procedure for the synthesis of tertiary amines by the reductive amination of carbonyl compounds is reported, which allows a convergent access to sterically hindered amines of the general formulas $NR(R')_2$ and $NRR'R''$. The mild and operationally simple protocol uses the Hantzsch ester for transfer hydrogenation and catalytic amounts of thiourea for imine activation.

Tertiary amines are key structural elements in synthetic reagents (e.g., **1**, Fig. 1)[1] and numerous biologically active natural products and pharmaceuticals like the clinically used antibiotic ciproflaxin (**2**),[2] which renders their synthesis an objective of high priority from the perspective of organic and medicinal chemistry. The direct reductive amination of carbonyls is widely recognized as one of the most convergent and simple procedures for the synthesis of amines and a number of procedures have been developed to carry out such a process in a one-pot fashion[3–5] While many applications for the preparation of primary and secondary amines have been reported, the synthesis of tertiary amines using such protocols is much less developed, due to increased steric hindrance. This is particularly true for the amination of alpha-branched carbonyls and preparation of aromatic amines.

Herein, we report an efficient direct reductive amination procedure for the synthesis of sterically demanding tertiary amines under mild and operationally simple conditions.

Based on an innovative biomimetic approach, we have recently developed an amination procedure of ketones and aldehydes for the synthesis of secondary aromatic amines.[5,6] This method uses the Hantzsch ester for transfer hydrogenation and proceeds in the presence of molecular sieves and catalytic amounts of thiourea for imine activation. The efficiency and wide applicability of this procedure to various substrates, including polyfunctional, as well as unreactive aldehydes and amines, prompted us to investigate whether this approach could also be extended to tertiary amines.

As a first target we studied the access to aromatic amines of the general type $NR(R')_2$ by the reaction of a primary amine (**3**) with two (or more) equivalents of a carbonyl fragment (**4**, Table 1). For this purpose, the preparation of tertiary amine **7a** by the condensation of *para*-anisidine (**3a**) with benzaldehyde (**4a**) in the presence of Hantzsch ester (**5**), 5 Å molecular sieves and catalytic amounts of thiourea (**6**) was evaluated. After developing reaction conditions, the desired synthesis of tertiary amine **7a** proceeded in an essentially quantitative manner. Optimum conditions included a slight excess of the aldehyde (2.2 equiv) and the Hantzsch ester



1 Ciproflaxin (**2**)

Figure 1. Tertiary amines: key structural elements in synthetic reagents such as **1** and bioactive structures (e.g., **2**).

Keywords: Organocatalysis; Synthetic methodology; Tertiary amines; Reductive amination; Hantzsch ester.
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† Recently renamed from Gesellschaft für Biotechnologische Forschung mbH.

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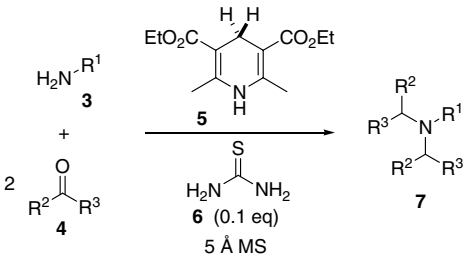
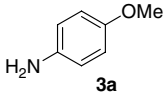
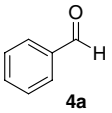
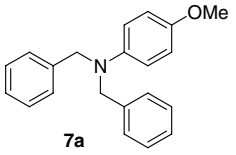
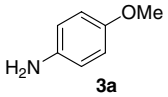
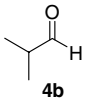
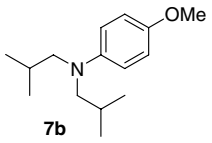
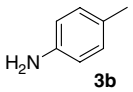
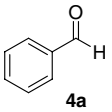
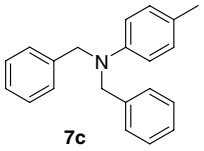
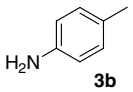
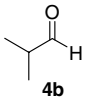
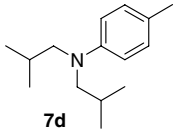
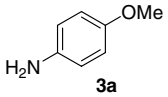
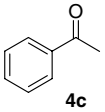
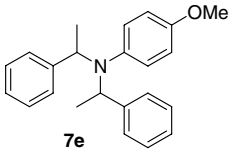
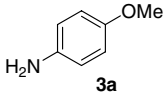
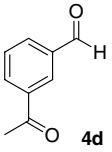
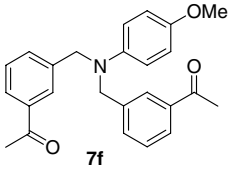
Table 1. Synthesis of tertiary amines of the type: $NR(R')_2$[a]



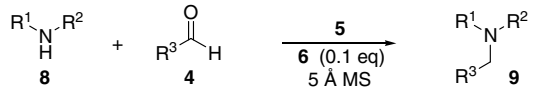
Entry	Amine **3**	Carbonyl **4**	Product amine **7**	Yield[c] (%)
1	 **3a**	 **4a**	 **7a**	90
2	 **3a**	 **4b**	 **7b**	73
3	 **3b**	 **4a**	 **7c**	82
4	 **3b**	 **4b**	 **7d**	64
5	 **3a**	 **4c**	 **7e**	<5[b]
6	 **3a**	 **4d**	 **7f**	63

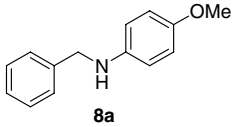
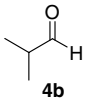
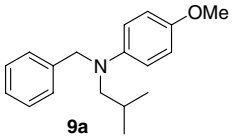
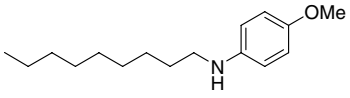
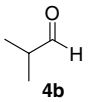
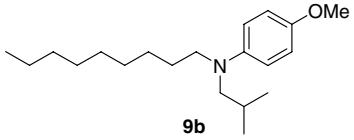
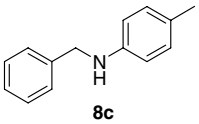
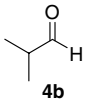
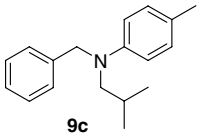
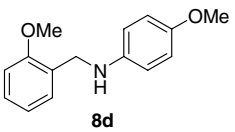
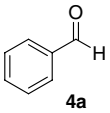
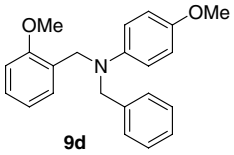
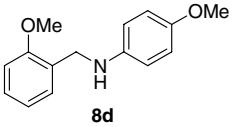
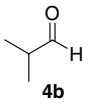
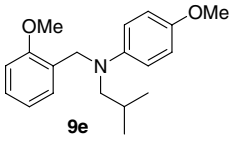
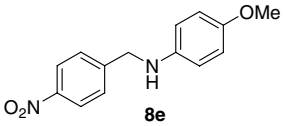
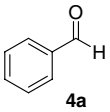
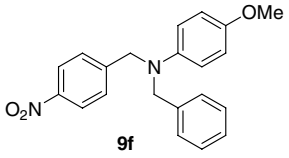
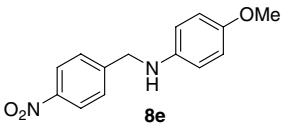
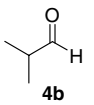
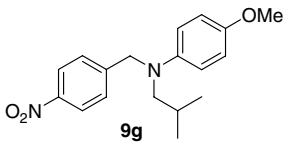
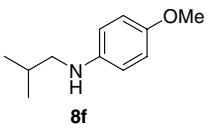
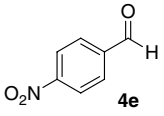
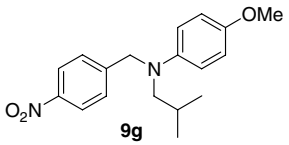
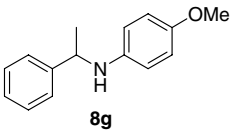
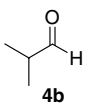
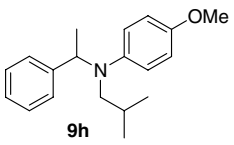
[a] Reaction conditions: 1 mmol amine, 2.2 mmol carbonyl compounds, 2.4 mmol Hantzsch ester, 0.1 mmol thiourea; toluene, 60 °C, 24–72 h.[6,10]
[b] Only monoalkylation was observed.
[c] Isolated yield after column chromatography.

(2.4 equiv) in toluene at 60 °C, which is slightly lower when compared to the previously devised conditions for the synthesis of secondary amines.[7–9] Under these conditions a complete conversion to the tertiary amine was observed. In particular, no trace of the intermediate secondary amine was detectable by NMR of the crude product.

Under these conditions a variety of amines and aldehydes may be converted, including aliphatic alpha-branched substrates (**4a**,**b**, e.g., entries 2 and 4) as well as electronically less rich amines (entries 3 and 4). In all examples, the desired tertiary amines (i.e., **5b–d**) were obtained in high yields.[10] The observation, that ketones could not be converted to the tertiary products (entry 5) under these conditions, leading only to monoalkylation, opened the possibility to selectively react mixed substrates, such as **4d** incorporating both an aldehyde as well as a ketone functionality (entry 6). This allowed access to the desired polysubstituted amine **7f** as the main

Table 2. Synthesis of tertiary amines of the type: NRR′R″[a]



Entry	Amine **8**	Aldehyde **4**	Product amine **9**	Yield[b] (%)
1	 **8a**	 **4b**	 **9a**	77
2	 **8b**	 **4b**	 **9b**	75
3	 **8c**	 **4b**	 **9c**	63
4	 **8d**	 **4a**	 **9d**	79
5	 **8d**	 **4b**	 **9e**	75
6	 **8e**	 **4a**	 **9f**	86
7	 **8e**	 **4b**	 **9g**	82
8	 **8f**	 **4e**	 **9g**	84
9	 **8g**	 **4b**	 **9h**	56

[a] Reaction conditions: 1 mmol amine, 1.2 mmol of carbonyl compound, 1.4 mmol Hantzsch ester, 0.1 mmol thiourea; toluene, 60 °C, 24–72 h.[10,11]
[b] Isolated yield after column chromatography.

product, which was obtained in preparatively useful yields. This demonstrates the general functional group tolerance of our method, which together with the mild conditions adds to the overall efficiency of our procedure.

With this method in hand, we then proceeded to further study and expand the applicability also for the synthesis of trisubstituted amines of the general type NRR′R″ by the reaction of a secondary amine (**8**)[11] with an additional aldehyde component under similar reductive conditions as developed above (Table 2). To obtain full conversion on a reasonable time scale, using 1.2 equiv of the aldehyde and 1.5 equiv of the reducing agent proved beneficial. In all cases, the desired trisubstituted amines (**9**) were obtained in good (entries 1–8) to useful (entry 9) yields.[12] Both aliphatic and aromatic aldehydes and amines are accepted as substrates (e.g., entries 1–3) and variations in the electronic and steric properties are tolerated (entries 4–8). The order of attaching the aldehyde component appears to have no influence on the isolated yield (entries 7 and 8). Notably, also alpha-branched amines such as **8g** (entry 9), which may be readily obtained by the reductive amination of the respective ketones as previously described,[5b] are alkylated under these conditions to give the desired products (**9h**). This demonstrates the usefulness of our method also to particularly sterically demanding tertiary amines.

In conclusion, we have developed an efficient procedure for the synthesis of structurally diverse tertiary amines of the general formulas $NR(R')_2$ and NRR′R″, including aromatic and sterically demanding amines. The operationally simple procedure uses the Hantzsch ester for transfer hydrogenation and proceeds in the presence of molecular sieves and thiourea. The mild conditions and chemoselectivity of this protocol should enable applications also to complex and/or acid-sensitive substrates. It is expected, that this method opens the venue for further exploring sterically hindered tertiary amines as synthons for preparative and medicinal chemistry.

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7. *General procedure*: A solution of the amine (**3a**–**b**, 1.00 mmol) and the carbonyl component (**4a**–**d**, 2.20 mmol) in toluene (5 mL) was treated with the Hantzsch ester (**3**, 760 mg, 2.40 mmol), thiourea (**4**, 7.6 mg, 0.100 mmol) and MS 5 Å (1.0 g) and the mixture was stirred under nitrogen at 60 °C until complete conversion (24–72 h). After filtration over Celite, the solvent is evaporated and the residue purified by flash chromatography on silica gel using mixtures of petroleum ether and ethyl acetate as eluants to give the product amines (**7a**–**f**) in a pure form.
8. The use of only 2 equiv of the carbonyl component leads to a decrease in the isolated yields, in particular when volatile aldehydes are used.
9. The second amination step is much slower due to steric reasons, which allows a selective amination for the synthesis of secondary amines, as previously reported: see Ref. 5. For optimum conversion also in the second amination step, thiourea is crucial.
10. All new compounds had spectroscopic data in support of the assigned structures. Examplary data: **7a**: ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.28 (m, 10H), 6.76 (d, $J = 9.2$ Hz, 2H), 6.69 (d, $J = 9.2$ Hz, 2H), 4.55 (s, 4H), 3.72 (s, 3H); ^{13}C NMR δ (75 MHz, $CDCl_3$): 151.9, 143.9, 139.1, 128.6, 127.0, 126.9, 114.8, 114.7, 55.8, 55.2; HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{21}NO$ $[M]^+$: 303.1623. Found: 303.1626. Compound **7c**: ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.26 (m, 10H), 6.97 (d, $J = 8.7$ Hz, 2H), 6.66 (d, $J = 8.7$ Hz, 2H), 4,61 (s, 4H), 2.22 (s, 3H); ^{13}C NMR δ (75 MHz, $CDCl_3$): 147.2, 139.0, 129.8, 128.6, 126.8, 126.1, 112.9, 54.5, 20.2; HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{21}N$ $[M]^+$: 287.1674. Found: 287.1674. Compound **9e**: ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.16 (m, 1H), 7.0 (m, 1H), 6.82 (m, 2H), 6.75 (d, $J = 9.2$ Hz, 2H), 6.54 (d, $J = 9.2$ Hz, 2H), 4.50 (s, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.15 (d, $J = 8$ Hz, 2H), 2.10 (dt, $J = 7.0$, 8.0 Hz, 1H), 0.96 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR δ (75 MHz, $CDCl_3$): 157.3, 150.9, 143.8, 127.6, 127.4, 126.7, 120.3, 114.8, 113.5, 109.9, 60.4, 55.8, 55.2, 50.9, 27.6, 20.6; HRMS (ESI): *m*/*z*: calcd for $C_{19}H_{25}NO_2$ $[M+H]^+$: 300.1964.

Found: 300.1962. Compound **9g**: ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.12 (d, $J = 8.7$ Hz, 2H), 7.36 (d, $J = 9.2$ Hz, 2H), 6.76 (d, $J = 9.2$ Hz, 2H), 6.62 (d, $J = 9.2$ Hz, 2H), 4.54 (s, 2H), 3.72 (s, 3H), 3.11 (d, $J = 7.1$ Hz, 2H), 2.04 (m, 1H), 0.94 (d, $J = 6.61$ Hz, 6H); ^{13}C NMR δ (75 MHz, $CDCl_3$): 152.1, 147.6, 147.1, 142.9, 127.7, 123.8, 115.3, 114.8, 61.1, 56.4, 55.7, 27.5, 20.8; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{22}N_2O_3$ $[M]^+$: 314.1630. Found: 314.1634.

11. For the synthesis of the secondary amines, see Ref. 5.

12. *General procedure*: A solution of the secondary amine (**8a**–**e**, 1 mmol) and the aldehyde (**4a**/**b**/**e** 1.2 mmol) in toluene (5 mL) was treated under nitrogen with the Hantzsch ester (**3**, 390 mg, 1.50 mmol), thiourea (**4**, 7.6 mg, 0.100 mmol) and MS 5 Å (1.0 g) and the mixture was stirred at 60 °C until completion of the reaction (24–72 h). After filtration over Celite, the solvent is evaporated and the residue purified by flash chromatography on silica gel using mixtures of petroleum ether and ethyl acetate as eluents to give product amines (**9a**–**h**) in a pure form.