Aminations

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Mild and Selective Cobalt-Catalyzed Chemodivergent Transfer Hydrogenation of Nitriles

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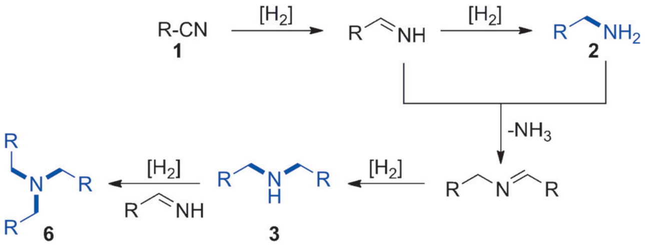
Abstract: *Herein, we describe a selective cobalt-catalyzed chemodivergent transfer hydrogenation of nitriles to synthesize primary, secondary, and tertiary amines. The solvent effect plays a key role for the selectivity control. The general applicability of this procedure was highlighted by the synthesis of more than 70 amine products bearing various functional groups in high chemoselectivity. Moreover, this mild system achieved >2000 TONs (turnover numbers) for the transfer hydrogenation of nitriles.*

The catalytic reduction of nitriles represents an efficient and green one-step synthesis of valuable amine products.[1] However, there is a crucial selectivity problem for this reaction owing to the formation of mixtures of primary amines, secondary amines, imines,[2] and even tertiary amines (Scheme 1). Within these possibilities, the selective synthesis of a certain amine product constitutes a particular challenge, especially for secondary and tertiary amines. This is because at least four steps are involved in the reaction sequence for the generation of secondary or tertiary amines via nitrile reduction. Consequently, a high degree of selectivity control is required for these reactions. Considering the intricate selectivity control, a direct synthesis of secondary[3] or tertiary amines[4] via catalytic reduction of nitriles has been much less explored, and noble metal catalysts are requisite for the known examples. To date, a general chemodivergent synthesis of primary and secondary amines via selective hydrogenation of nitriles has not been established, which is a significant but challenging goal in organic synthesis.



Scheme 1. Possible reaction pathways for the hydrogenation of nitriles.

Nitriles are conventionally reduced using stoichiometric amounts of sensitive metal hydrides, which suffers from low atom-efficiency and functional group tolerance. Clearly, the catalytic hydrogenation of nitriles is a more sustainable synthetic route. Direct hydrogenation with H_2 gas and transfer hydrogenation are two parallel strategies for hydrogenation reactions. Although heterogeneous catalysts are commonly used for the direct hydrogenation of nitriles with H_2 to produce primary amines in industry,[5] homogeneous catalysts can be more selective and milder. However, these reactions are almost limited to the precious metals (mainly based on ruthenium).[6] Very recently, noteworthy progress has been made by Beller's and Milstein's groups in this respect. They independently developed molecular-defined iron,[7] manganese,[8] and cobalt[9] catalysts for the direct hydrogenation of nitriles to primary amines under over 30 bar H_2 pressure and 100 °C. Complementary to the direct hydrogenation, the transfer hydrogenation could allow for reductions under ambient conditions without the need for hazardous pressurized H_2 gas nor elaborate experimental setups.[10] Nevertheless, very limited studies on the transfer hydrogenation of nitriles have been reported, which are all restricted to the use of noble metal catalysts.[11]

Herein, we describe the first cobalt-catalyzed transfer hydrogenation of nitriles for a chemodivergent synthesis of primary and secondary amines.[9,12] The selectivity control was achieved by using different solvents and cobalt catalysts. Moreover, a reductive amination of nitriles has been also realized in the presence of various amine substrates to produce unsymmetric secondary and tertiary amines (Scheme 2). Based on this strategy, over 70 amine products were synthesized selectively with well-defined cobalt catalysts and ammonia borane (NH_3-BH_3, AB) as a practical hydrogen donor.[13] These reactions could proceed under mild conditions without any additives.[14]

Following our interests for the development of new cobalt catalysts,[15] this investigation began with the preparation of a series of well-defined NNP[16] and PNP pincer cobalt catalysts **I–VIII**. After having these catalysts in hand, we studied their reactivity in transfer hydrogenation of benzonitrile **1a** using AB as the hydrogen donor in methanol (Table S1). The use of NNP pincer catalysts **I** and **II** afforded the best yields and selectivity for the formation of benzylamine **2a** and dibenzylamine **3a**, respectively. However, the

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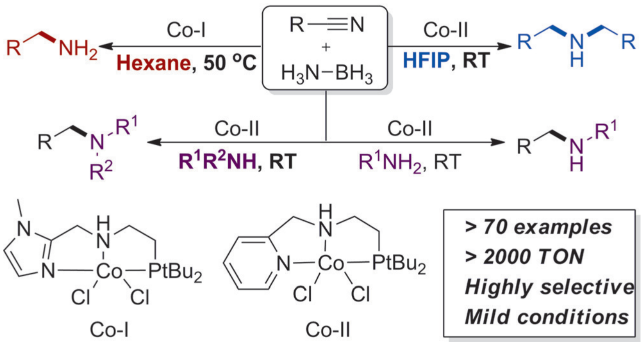
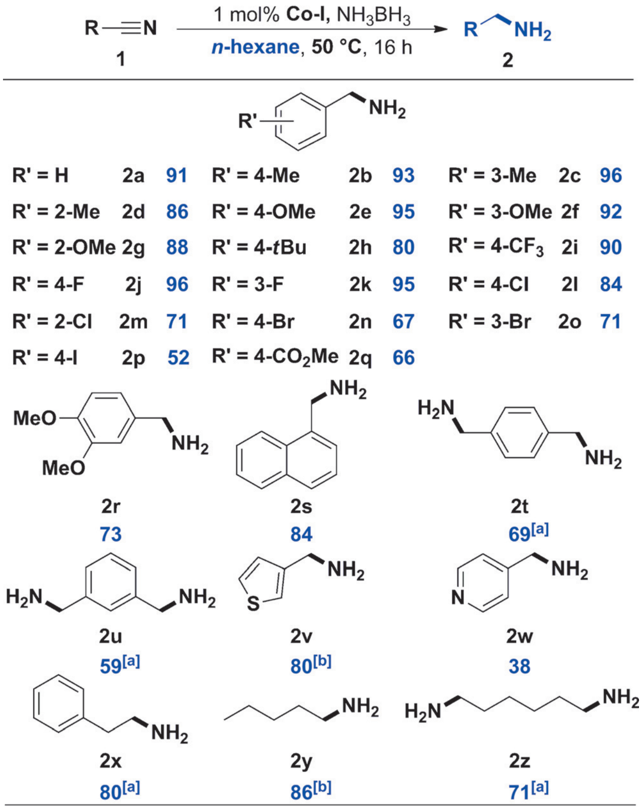


Scheme 2. This work: cobalt-catalyzed chemodivergent transfer hydrogenation of nitriles.



R' = H	2a	91	R' = 4-Me	2b	93	R' = 3-Me	2c	96
R' = 2-Me	2d	86	R' = 4-OMe	2e	95	R' = 3-OMe	2f	92
R' = 2-OMe	2g	88	R' = 4-*t*Bu	2h	80	R' = 4-CF$_3$	2i	90
R' = 4-F	2j	96	R' = 3-F	2k	95	R' = 4-Cl	2l	84
R' = 2-Cl	2m	71	R' = 4-Br	2n	67	R' = 3-Br	2o	71
R' = 4-I	2p	52	R' = 4-CO$_2$Me	2q	66			

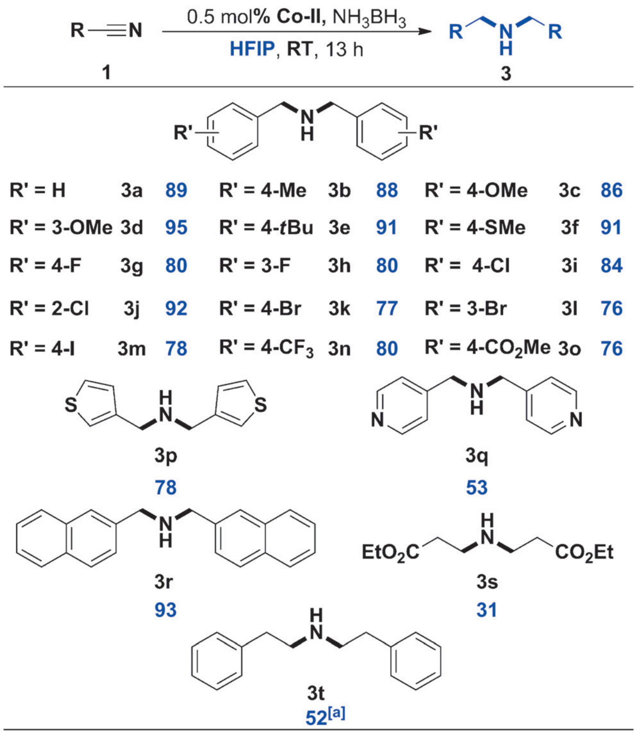
Scheme 3. Cobalt-catalyzed transfer hydrogenation of nitriles to primary amines. Reaction conditions: **1** (0.5 mmol), AB (0.8 mmol) in 1 mL of *n*-hexane, GC yield (%) were shown using biphenyl as the internal standard. [a] The reaction temperature was 100 °C. [b] The reaction temperature was 120 °C.

related PNP pincer catalysts **VI–VIII** led to much lower conversions, highlighting the beneficial effect of the N-coordinated side-arms among these NNP ligands. Based on these results, a more detailed optimization of other critical parameters, such as solvent, ratio of **1a** and AB, temperature, and catalyst loadings, was performed using cobalt catalysts **I** and **II** (Tables S2–S4). Interestingly, a strong influence of the solvent was observed (Table S5). The production of primary amine **2a** was most efficient in hexane utilizing catalyst **I** (1 mol %) and AB (1.6 equiv) at 50 °C, which enabled the production of **2a** in 91 % yield without the observation of secondary and tertiary amines. In the presence of cobalt catalyst **II** and hexafluoroisopropanol (HFIP) as the solvent, benzonitrile **1a** was converted into secondary amine **3a** in 89 % yield with only trace amount of benzylamine **2a** produced (4 % yield).

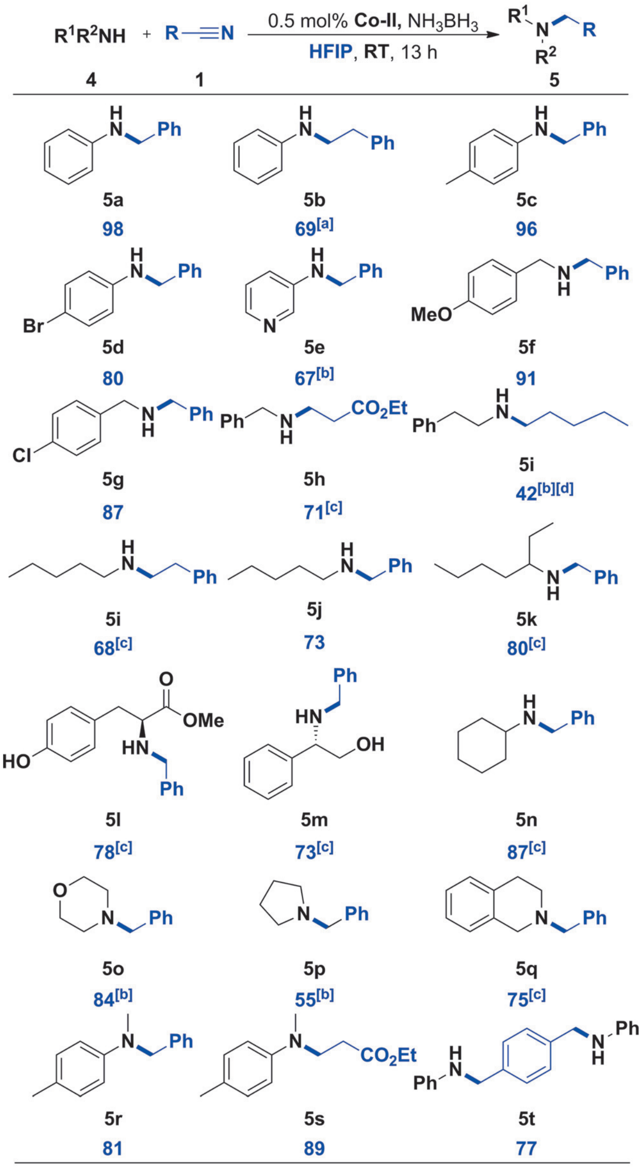
After establishing the optimized reaction conditions for the chemodivergent transfer hydrogenation of **1a**, the generality of this transformation was studied. In Scheme 3, we have summarized the transfer hydrogenation of various nitriles to primary amines **2** using Co catalyst **I** and hexane as the solvent. A total of 26 substrates with different steric and electronic natures were converted to the corresponding primary amine products **2** in good yields, indicating the general applicability of this procedure. Specifically, functional groups such as methoxyl, trifluoromethyl, fluoro, chloro, bromo, iodo, ester, as well as sulphur- and nitrogen-containing heterocycles were all well tolerated. Besides the (hetero)aromatic and aliphatic nitriles, the industrially relevant dinitriles were also hydrogenated successfully under these mild conditions to give valuable diamine products, such as 1,3-benzenedimethylamine **2u** and 1,6-hexamethylenediamine **2z**.

As mentioned above, the selective synthesis of secondary amines via nitrile reduction is more challenging. A survey of the substrate scope was performed to demonstrate the versatility of this cobalt-catalyzed transfer hydrogenation of nitriles to produce secondary amines **3**. This transformation proceeded smoothly in the presence of catalyst **II** (Scheme 4) and the solvent of HFIP at room temperature. The desired secondary amine products were obtained selectively in yields up to 95 %. A wide range of electron-donating as well as electron-withdrawing substituents were also well tolerated. Moreover, catalyst **II** was found to be also reactive for the transfer hydrogenation of alkyl nitriles to secondary aliphatic amines, albeit lower yields were obtained (**3s** and **3t**, Scheme 2).

Inspired by the high chemoselectivity of this reaction for the generation of symmetric secondary amines, we continued to examine the feasibility of this catalytic system for the preparation of unsymmetric secondary and tertiary amines by conducting the reaction in the presence of an additional amine substrate. A fast condensation of the added amine substrate with the primary imine intermediate would be critical to the success of this transformation. It could avoid the further reduction of the imine intermediate to give the corresponding primary amine as another strong nucleophile in this reaction system. Based on this consideration, the reductive amination of nitriles with a range of amines for the synthesis of unsymmetric amines was explored (Scheme 5). The present system could be effectively applied to a variety of aromatic and aliphatic primary amines affording the corresponding mono-N-alkylation products in good to excellent yields for most tested substrates. Notably, a selective N-alkylation of amino group in the presence of a hydroxy group could be realized under these mild conditions (**5l** and **5m**, Scheme 5).



Scheme 4. Cobalt-catalyzed transfer hydrogenation of nitriles to symmetric secondary amines. Reaction conditions: **1** (0.5 mmol), AB (0.8 mmol) in 2 mL of HFIP. Isolated yields (%) are shown. [a] The reaction temperature was 50 °C. HFIP = Hexafluoroisopropanol.



Scheme 5. Cobalt-catalyzed reductive amination of nitriles to unsymmetric secondary and tertiary amines. Reaction conditions: **1** (0.6 mmol), **4** (0.5 mmol), AB (0.8 mmol) in 2 mL of HFIP. Isolated yields (%) are shown. [a] **1** (0.5 mmol), **4** (0.6 mmol). [b] **1** (0.5 mmol), **4** (2 mmol). [c] **1** (0.5 mmol), **4** (1 mmol). [d] The reaction was carried out in 2 mL of *n*-hexane at 100 °C.

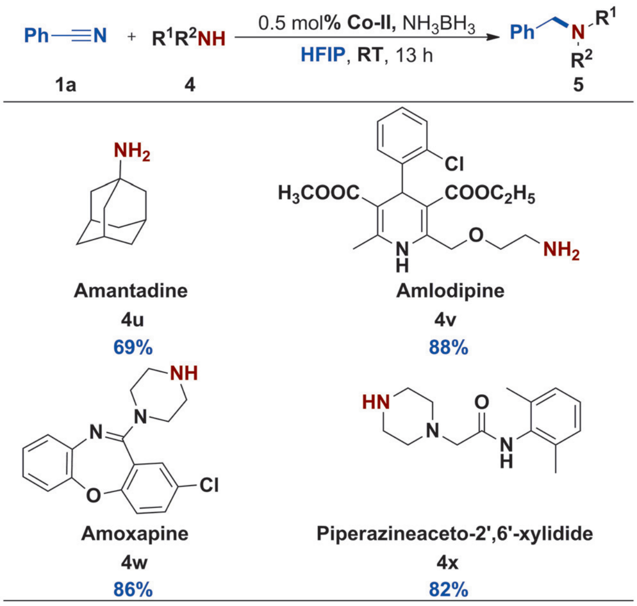
Furthermore, the tertiary amine products could be prepared in 55–89 % isolated yields using secondary amines as the substrates (**5o**–**5s**, Scheme 5). This transformation is indeed more difficult due to the weaker nucleophilicity of secondary amines compared to primary amines.[17] Interestingly, a facile synthesis of β-amino ester was also achieved via the reductive amination of ethyl cyanoacetate (**5h** and **5s**, Scheme 5).

In an effort to further demonstrate the synthetic utility of this procedure, it was further applied into the direct functionalization of pharmaceutical molecules (Scheme 6). Specifically, amantadine **4u** is an antiviral and antiparkinsonian drug, while amlodipine **4v** is a medication to lower blood pressure. The mono-N-benzylation of these two drug molecules bearing primary amine moieties was performed selectively via this reductive amination reaction with **1a**. The reactions of the secondary amines, **4w** as an antidepressant and the pharmaceutical intermediate **4x**, gave rise to the corresponding N-benzylated tertiary amines in 86 % and 82 % yields, respectively. Particularly, a variety of reducible functional groups, including ester, amide, C−Cl, dihydropyridine, and oxazepine, were well tolerated under these mild conditions. To the best of our knowledge, this is the first example of reductive amination of nitriles[18] catalyzed by a non-precious metal catalyst.

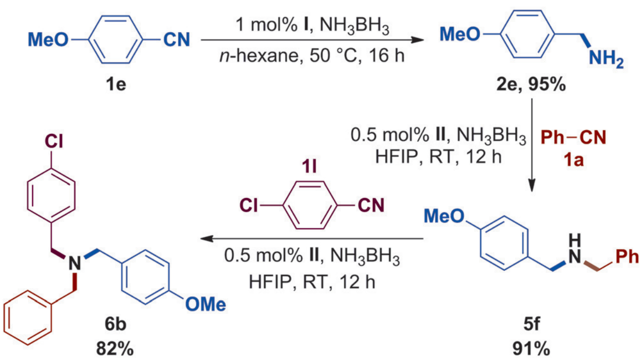
More interestingly, we established an efficient approach to access the tertiary amine product **6b** bearing three different substituents via sequential cobalt-catalyzed transfer hydrogenation of three aromatic nitrile substrates **1e**, **1a**, and **1l** (Scheme 7). This synthetic application further demonstrated the utility of this cobalt catalysis system.

The catalyst activity was also evaluated using 0.025 mol % catalyst loading for the transfer hydrogenation and reductive amination of benzonitrile **1a** (Scheme 8). To our delight, the desired secondary amine products **3a** and **5a** were acquired in 56 % and 59 % yield, respectively. Here, the corresponding turnover numbers are over 2000, which illustrate the high stability and efficiency of this cobalt catalyst in these reactions.

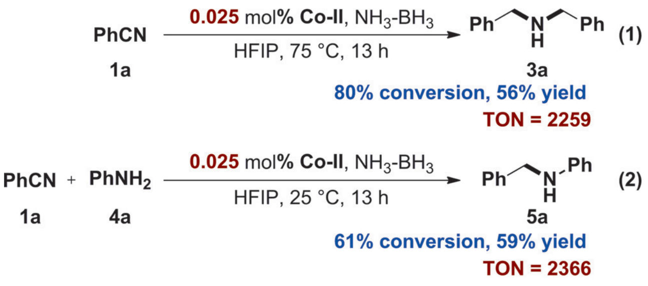
To gain more mechanistic insights, poisoning experiments were performed in the presence of substoichiometric amounts of PMe_3, PPh_3 with respect to cobalt catalysts and a drop of



Scheme 6. Direct functionalization of pharmaceutical molecules by cobalt-catalyzed reductive amination of nitriles.

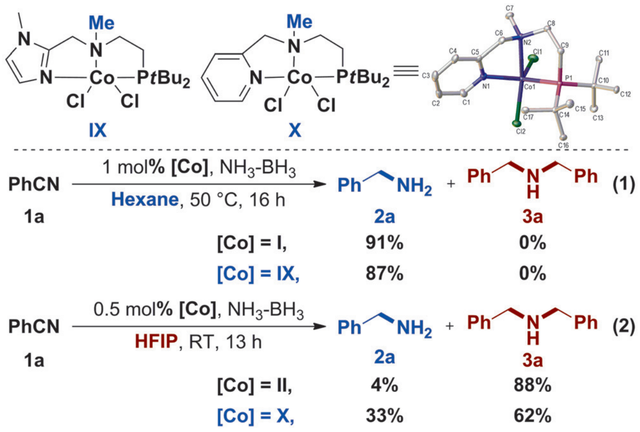


Scheme 7. A facile synthesis of tertiary amine from three different nitriles.



Scheme 8. The efficiency of the cobalt catalyst.

mercury (Tables S6 and S7). No significant inhibition effect was observed in all of these cases, which indicates the homogeneous nature of these cobalt catalysis systems. Furthermore, the N-methyl-substituted cobalt catalysts **IX** and **X** were synthesized to study the reaction mechanism of the hydrogen transfer process (Scheme 9). The comparable catalytic activities observed with cobalt precatalysts **I** and **IX** for the transfer hydrogenation of **1a** to primary amine product are consistent with an inner-sphere mechanism without the metal–ligand cooperativity. Moreover, high reaction conversion and yields were also achieved in the presence of N-methyl-substituted cobalt catalyst **X** for the production of secondary amine from **1a**, albeit with a lower chemoselectivity. These results demonstrated that the outer-sphere hydrogen transfer mechanism was not the major reaction pathway and the N−H groups of catalysts **I** and **II** were not indispensable in these transformations.



Scheme 9. Transfer hydrogenation of **1a** with N-methyl cobalt catalysts.

In summary, we have demonstrated the first general chemodivergent transfer hydrogenation reaction of nitriles to produce a variety of useful primary and secondary amines. The solvent effect is very crucial to determine the selectivity. These reactions proceed under mild conditions using the well-defined cobalt catalysts and ammonia borane as a practical hydrogen source. Interestingly, a related cobalt-catalyzed reductive amination of nitriles has been also realized in the presence of a wide range of amine substrates for the synthesis of unsymmetric secondary and tertiary amines. This convenient method could be applied into the direct functionalization of pharmaceutical molecules bearing other reducible functional groups.

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Keywords: amines · cobalt · nitriles · reductive amination · transfer hydrogenation

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