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Cobalt-Catalyzed Selective Hydrogenation of Nitriles to Secondary Imines

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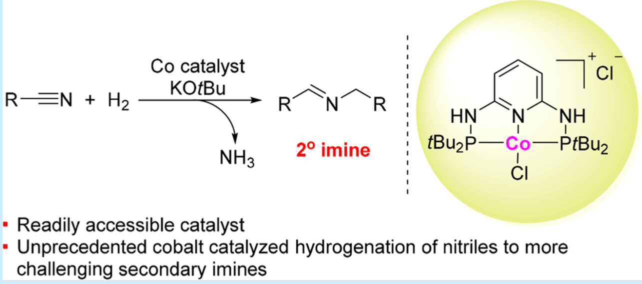
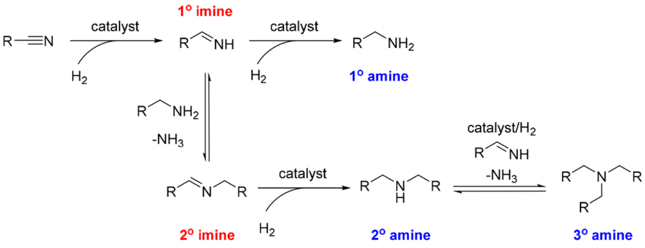
Supporting Information

ABSTRACT: The first example of cobalt-catalyzed selective hydrogenation of nitriles to secondary imines is reported. The results demonstrate the significantly different selectivity compared with the previously reported cobalt catalytic system during the nitrile hydrogenation. A variety of aromatic and aliphatic nitriles are hydrogenated to the corresponding secondary imines.



Catalytic hydrogenation of nitriles is a significant but challenging process in industry and academia.[1] The resulting product imines and amines are widely used as intermediates and precursors for pharmaceuticals and agrochemicals.[2] However, selectivity is a crucial issue in this methodology. Primary and secondary imines and a mixture of primary, secondary, and even tertiary amines are usually formed during the catalytic hydrogenation of nitriles (Scheme 1). The catalysts play a key role in selectivity,[1] and thus the development of a highly active and selective catalyst is desirable for the nitrile hydrogenation reactions.

Scheme 1. Possible Product Formation during Nitrile Hydrogenation



Traditionally, stoichiometric amounts of metal hydrides or hydrosilanes are used to reduce the nitriles.[3] However, these methods are not environmentally benign due to the generation of stoichiometric amounts of waste metal salts. In industry, the hydrogenation of nitriles is carried out by using heterogeneous catalysts typically based on Co, Ni, and Pd, but they often suffer from low selectivity and limited functional group tolerance.[4] To overcome these limitations, the homogeneous catalytic systems for the selective hydrogenation of nitriles to primary,[1,5] secondary,[6] or tertiary amines[7] have been explored. In addition, an attractive and challenging goal is the direct hydrogenation of nitriles to selectively produce secondary imines. In this respect, only a few catalytic systems have been developed. The first report of a homogeneous hydrogenation of nitriles to secondary imines was published by Garcia and co-workers using a nickel catalyst in 2009.[8] However, this methodology is operated at high temperatures (140−180 °C) and limited to mono- and dicyanobenzene derivatives. Berke and co-workers demonstrated the hydrogenation of nitriles to the corresponding secondary imines as major products catalyzed by molybdenum and tungsten pincer complexes, yielding a mixture of primary amine, primary imine, and secondary imine and requiring high temperature and pressure (140 °C, 60 bar of H_2).[9] Recently, Prechtl and co-workers reported the hydrogenation of nitriles to secondary imines catalyzed by a ruthenium pincer complex under mild conditions, while this method is limited to only a few substrates.[5c] In addition, Sabo-Etienne observed the formation of *N*-benzylidenebenzylamine during the hydrogenation of benzonitrile catalyzed by a ruthenium system.[10] Very recently, the selective hydrogenation of nitriles to secondary imines catalyzed by an iron pincer complex with a broad substrate scope was reported by Milstein and co-workers, but the drawbacks of this catalytic system are the multistep synthetic operations and the requirement of toxic carbon monoxide gas

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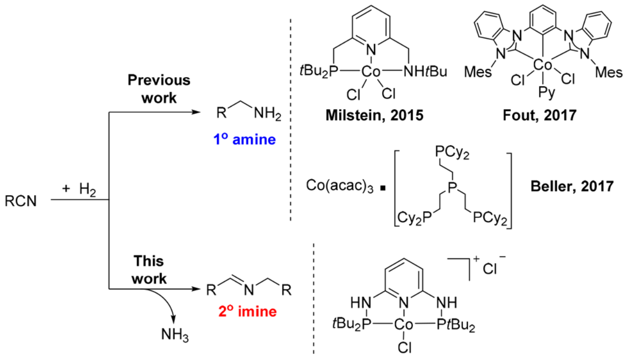
Org. Lett. XXXX, XXX, XXX−XXX

during the course of the preparation of the catalyst.[11] Hence, selective hydrogenation of nitriles to secondary imines under mild reaction conditions using well-defined, environmentally benign, and readily accessible catalysts remains challenging.

Owing to their sustainability, low cost, and earth abundance, efforts have been made toward the development of cobalt catalysts for homogeneous hydrogenation.[12] Nevertheless, catalytic hydrogenation of nitriles based on Co complexes are less developed. Milstein and co-workers reported the first homogeneous Co-catalyzed hydrogenation of nitriles to primary amines in 2015 (Scheme 2).[5e] Very recently, the groups of Fout and Beller developed nitrile hydrogenation reactions to afford primary amines, catalyzed by a cobalt bis(carbene) pincer complex and cobalt/tetradentate phosphine catalyst system, respectively (Scheme 2).[5k,l] To our knowledge, Co-catalyzed selective hydrogenation of nitriles to secondary imines has not been reported thus far.[13] As part of our ongoing interest in the PN^3-pincer complexes and their catalysis,[14] herein, we present the first selective hydrogenation of nitriles to secondary imines catalyzed by a well-defined and readily accessible PN^3P cobalt pincer complex (Scheme 2).

Scheme 2. Cobalt-Catalyzed Hydrogenation of Nitrile



Pyridine-based pincer complexes are of particular interest especially since the discovery of the new mode of metal−ligand cooperation involving the aromatization−dearomatization process of the ligands.[15] In this context, the straightforward synthesis of cobalt complexes **Co1**, **Co2**,[16] and **Co3** (Figure 1) could be achieved by the treatment of $CoCl_2$ with 1.1 equiv of the corresponding pincer ligand at room temperature in THF. These cobalt(II) complexes were crystallographically characterized (Figure 2). The X-ray structure of **Co1** shows a rare square-planar Co(II) complex with a noncoordinating chloride anion,[17] while the complexes **Co2**[18] and **Co3** adopt a distorted square-pyramidal structure with two chlorides coordinating to the cobalt center, probably because of the steric bulk of the four *tert*-butyl groups of the PN^3P ligand in **Co1**.

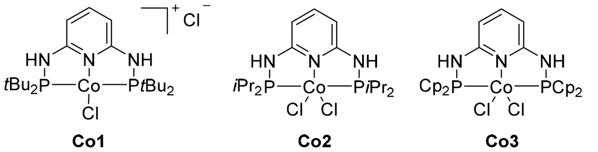


Figure 1. PN^3P Co pincer complexes **Co1**, **Co2**, and **Co3**.

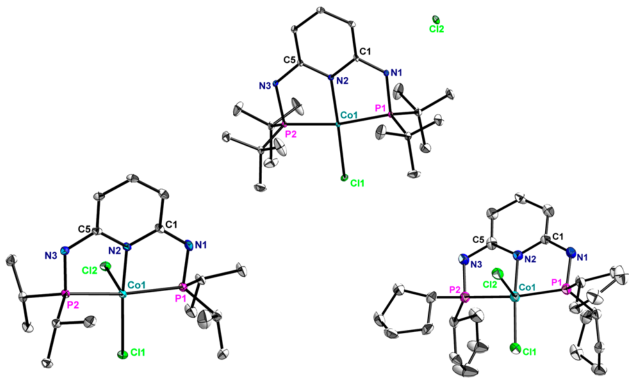
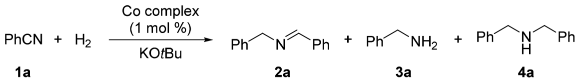


Figure 2. X-ray structures of complexes **Co1**, **Co2**, and **Co3** at 30% ellipsoid probability. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å). **Co1**: Co1−Cl1 2.1975(8), Co1−N2 1.925(2), Co1−P1 2.1250(7), Co1−P2 2.1131(7). **Co2**: Co1−Cl1 2.2501(7), Co1−Cl2 2.4439(7), Co1−N2 1.9654(18), Co1−P1 2.2279(8), Co1−P2 2.2174(7). **Co3**: Co1−Cl1 2.240(2), Co1−Cl2 2.423(2), Co1−N2 1.975(6), Co1−P1 2.210(2), Co1−P2 2.217(2). Selected bond angles (deg). **Co1**: Cl1−Co1−N2 178.24(7), P1−Co1−P2 169.21(3), Cl1−Co1−P1 96.26(3), Cl1−Co1−P2 94.54(3), N2−Co1−P1 85.51(7), N2−Co1−P2 83.70(7). **Co2**: Cl1−Co1−N2 161.91(6), P1−Co1−P2 166.46(3), Cl1−Co1−Cl2 103.13(2). **Co3**: Cl1−Co1−N2 165.51(18), P1−Co1−P2 167.47(9), Cl1−Co1−Cl2 99.08(8).

The hydrogenation of benzonitrile (**1a**) was chosen as the model reaction to test the activity of the cobalt complexes. The use of complex **Co1** (1 mol %) and KO*t*Bu (4 mol %) in toluene at 130 °C under 62 atm of H_2 for 24 h resulted in complete conversion of the **1a** with the formation of 85% *N*-benzylidenebenzylamine (**2a**) and 11% of benzylamine (**3a**) (Table 1, entry 1). Cobalt complex **Co2** or **Co3** could also be employed as catalyst for the selective hydrogenation of **1a** to secondary imines **2a**, albeit with lower yield and selectivity (Table 1, entries 2 and 3). It is noteworthy that these results are strikingly different from those of the analogous PNP cobalt complex **Co4** (having CH_2 rather than NH spacers) by Milstein and co-workers, enabling the catalytic hydrogenation of benzonitrile (**1a**) to benzylamine **3a** as a major product with the formation of a small amount of **2a** (Scheme 3).[5e] In addition, the X-ray structure of this PNP cobalt complex **Co4** exhibits a highly distorted square-pyramidal structure with two chlorides coordinating to the cobalt center (see the Supporting Information),[19] different from that of complex **Co1** in spite of only the small change on the spacers. These comparisons indicate the critical role of the ligand modification. We have previously demonstrated that the PN^3P−Ru complexes showed the significantly enhanced reactivities for the dehydrogenation of amines to imines compared to those of the Milstein PNPs.[20] Such unique catalytic performances prompted us to further optimize the conditions. A control experiment showed that no reaction occurred under these conditions in the absence of the catalyst (Table 1, entry 4). Without the base, a mixture of **2a** (36%), **3a** (13%), and *N*-benzylbenzylamine (**4a**, 47%) were obtained, which suggested the vital importance of base for the selectivity control during the catalytic hydrogenation of nitriles (Table 1, entry 5). In contrast to toluene, the use of THF as solvent favored the formation of primary amine **3a** as a major product (Table 1, entry 6). Benzene was found to give a similar yield of **2a**, along with the formation of a small amount of **3a** (Table 1, entry 7). Lowering the H_2 pressure to 41 atm under analogous reaction conditions led to lower selectivity toward **2a** (Table 1, entry 8). Significantly, only **2a** was detected by GC−MS at a lower temperature of 80 °C, despite the lower

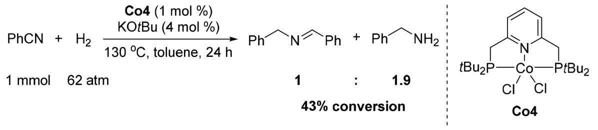
Table 1. Optimization Studies for the Hydrogenation of Benzonitrile[a]



entry	catalyst	solvent	ρ_{H2} (atm)	temp (° C)	t (h)	conv[b] (%)	yield[b] (%) 2a	3a	4a
1	**Co1**	toluene	62	130	24	>99	85	11	
2	**Co2**	toluene	62	130	24	>99	56	41	
3	**Co3**	toluene	62	130	24	>99	64	33	
4[c]		toluene	62	130	24	<1	trace	trace	
5[d]	**Co1**	toluene	62	130	24	>99	36	13	47
6	**Co1**	THF	62	130	24	>99	25	71	
7	**Co1**	benzene	62	130	24	>99	81	13	
8	**Co1**	toluene	41	130	24	>99	65	30	
9	**Co1**	toluene	62	80	24	63	63		
10	**Co1**	toluene	102	80	41	73	73		
11[e]	**Co1**	toluene	62	100	24	88	85		
12[e]	**Co1**	toluene	62	100	36	94	90		
13[e]	**Co1**	toluene	62	100	48	>99	97		
14	**Co1**	toluene	62	110	48	>99	91	6	

[a] Condition: [Co] complex (0.01 mmol), **1a** (1 mmol), KO*t*Bu (0.04 mmol), solvent (6.0 mL). [b] Conversions and yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using CH_2Br_2 as the internal standard or GC−MS using *m*-xylene as internal standard. [c] Without catalyst. [d] Without KO*t*Bu. [e] Benzaldimine formation was observed (<5%).

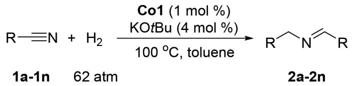
Scheme 3. Hydrogenation of Benzonitrile Catalyzed by Co4

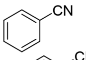
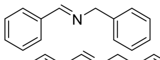
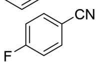
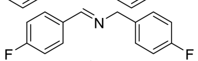
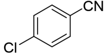
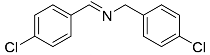
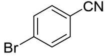
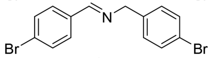
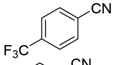
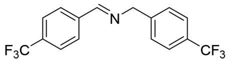
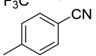
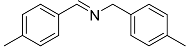
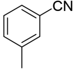
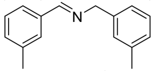
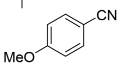
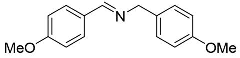
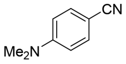
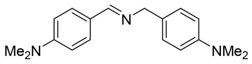
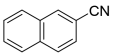
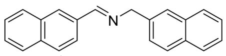
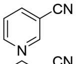
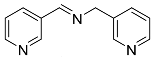
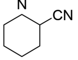
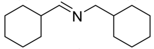
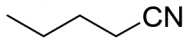
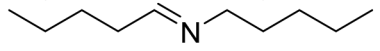
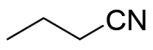
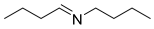


conversion of **1a** (Table 1, entry 9). Increasing the H_2 pressure to 102 atm did not significantly improve the conversion of **1a** (73%, Table 1, entry 10). Gratifyingly, the conversion could be improved considerably when the reaction temperature was increased from 80 to 100 °C (Table 1, entry 11). By extending the reaction time at 100 °C, the full conversion could be achieved with excellent selectivity to **2a** (Table 1, entries 12 and 13). The reaction is quite sensitive to the reaction temperature, and when the reaction was carried out at 110 °C, primary amine **3a** was formed (Table 1, entry 14).

Using entry 13 in Table 1 as the standard reaction conditions, the substrate scope of this cobalt-catalyzed hydrogenation of nitriles was explored. As shown in Table 2, various benzonitriles containing either electron-donating or -withdrawing substituents were hydrogenated in good yields. Hydrogenation of 4-fluorobenzonitrile (**1b**) afforded *N*-(4-fluorobenzylidene)-4-fluorobenzylaminein (**2b**) in excellent yield under the standard reaction conditions (Table 2, entry 2). In the cases of 4-chlorobenzonitrile (**1c**) and 4-bromobenzonitrile (**1d**), the corresponding secondary imines were formed in 82% and 84% yields, respectively, with the halide substituent being tolerated (Table 2, entries 3 and 4). Hydrogenation of 4-(trifluoromethyl)benzonitrile (**1e**) resulted in 93% conversion and 71% isolated yield of corresponding secondary imine at a slightly higher temperature, 110 °C (Table 2, entry 5). 4-Methylbenzonitrile (**1f**) and 3-methylbenzonitrile (**1g**) were hydrogenated to their corresponding secondary imines in excellent conversions with good selectivities (Table 2, entries 6 and 7). Further, the catalytic reactions of 4-methoxybenzonitrile (**1h**) and 4-*N*,*N*-dimethylbenzonitrile (**1i**) yielded the corresponding secondary

Table 2. Hydrogenation of Nitriles to Secondary Imines Catalyzed by Co1[a]



entry	substrate		product		conversion (%)[b]	yield (%)[b,c]
1		**1a**		**2a**	>99	97 (81)
2		**1b**		**2b**	>99	97 (81)
3		**1c**		**2c**	>99	95 (82)
4		**1d**		**2d**	>99	98 (84)
5		**1e**		**2e**	87 [93][d]	86 (69) [89 (71)][d]
6		**1f**		**2f**	>99	97 (81)
7		**1g**		**2g**	>99	94 (78)
8		**1h**		**2h**	>99	95 (83)
9		**1i**		**2i**	87 [96][e]	80 (69) [88 (76)][e]
10		**1j**		**2j**	>99	94 (81)
11		**1k**		**2k**	74	71 (49)
12		**1l**		**2l**	61	61
13		**1m**		**2m**	53	53
14		**1n**		**2n**	47	47

[a] Conditions: **Co1** (0.01 mmol), **1a** (1 mmol), KO*t*Bu (0.04 mmol), toluene (6.0 mL), 62 atm of H_2, 100 °C. [b] Conversions and yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using CH_2Br_2 as the internal standard or GC−MS using *m*-xylene as internal standard. [c] Yield of isolated product in parentheses. [d] 110 °C. [e] 130 °C.

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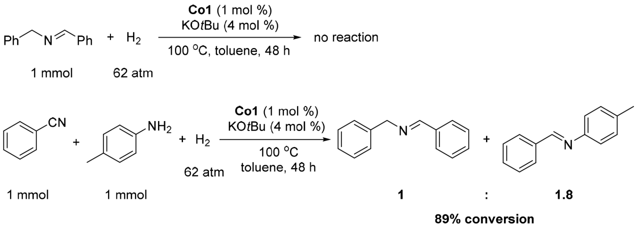
Org. Lett. XXXX, XXX, XXX−XXX

imines in good to moderate yields (Table 2, entries 8 and 9). Similarly, 2-naphthonitrile (**1j**) furnished 81% of the corresponding imine under the same hydrogenation conditions (Table 2, entry 10). Notably, heterocyclic nitrile 3-pyridinecarbonitrile (**1k**), which is usually regarded as a challenging substrate due to its chelating character, could also be hydrogenated, although in lower conversion (74%) and yield (49%) (Table 2, entry 11).[21] Aliphatic nitriles are usually considered to be more challenging substrates because of the possible base-induced condensation side reactions. When the aliphatic nitriles were subjected to the hydrogenation reaction, the reaction was found to be sluggish (Table 2, entries 12−14). Under the catalytic conditions, hydrogenation of secondary alkyl nitrile cyclohexylcarbonitrile gave the corresponding imine in only 61% yield detected by GC−MS (Table 2, entry 12). Under analogous reaction conditions, valeronitrile and butyronitrile produced 53% and 47% yields of the corresponding second imines (Table 2, entries 13 and 14).

To gain further understanding of the high selectivity toward secondary imines in this catalytic system, the control experiments were carried out (Scheme 4). When secondary imine **2a** was subjected to the standard hydrogenation conditions, further hydrogenation did not occur. This result is consistent with the high selectivity for the formation of secondary imines. When hydrogenation of **1a** was conducted in the presence of *p*-toluidine, besides the formation of **2a**, benzylidene-*p*-toluidine was also produced as a major product, suggesting that the intermediate primary imine was formed during the hydrogenation reaction. Considering these observations mentioned above, the reaction step to form intermediate primary imine might be rate-determining for the whole reaction (Scheme 1). Attempts to isolate the active catalyst during the reactions were not successful, but the plausible catalyst activation may involve a dearomatized cobalt complex formed via the deprotonation of one of the N−H arms of **Co1** under the reaction conditions, which can then react with H_2 to afford a cobalt hydride species for the hydrogenation of the nitriles.[14,22]

Scheme 4. Control Experiments



In conclusion, we have developed the first cobalt-catalyzed selective hydrogenation of nitriles to secondary imines under relatively mild conditions with generally high conversions and high selectivity. Importantly, the well-defined and readily accessible PN^3P cobalt pincer complex showed significantly different selectivity with the existing cobalt catalytic system during the nitriles hydrogenation, providing another case with respect to the crucial role that ligand modification may have. In light of the catalytic performance and the simple preparation, complex **Co1** holds promise as an economical catalyst for the selective hydrogenation of nitriles. Attempts to isolate the catalytically active species and theoretical investigations on this system are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02744.

Experimental details, and characterization data (PDF)

Accession Codes

CCDC 1858908, 1858909 and 1859265 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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