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## COMMUNICATION

## Catalytic coupling of nitriles with amines to selectively form imines under mild hydrogen pressure<sup>†</sup>

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Imines are selectively formed by coupling of nitriles and amines under mild hydrogen pressure. The reaction is catalyzed by a bipyridine-based PNN Ru(n) pincer complex and proceeds under mild, neutral conditions at 4 bar of  $H_2$ .

The selective catalytic hydrogenation of nitriles to form imines is challenging.<sup>1</sup> Hydrogenation of nitriles generally results in mixtures of primary, secondary and tertiary amines as well as imines as side products.<sup>2</sup> The imines are key intermediates of this reaction, produced by the partial reduction of nitriles. The initially formed primary imine undergoes nucleophilic attack on the electron-deficient imine carbon by the product primary amine to produce a *gem*-diamine; the latter could undergo either direct hydrogenolysis or elimination of NH<sub>3</sub> (*via* dialkylated imines), followed by hydrogenation to form the corresponding secondary amine.<sup>21</sup> It was proposed that tertiary amines are formed by addition of the secondary amine to the imine and subsequent hydrogenolysis of the *gem*-diamine intermediate,<sup>2a,i</sup> or by first elimination of NH<sub>3</sub> from the *gem*-diamine to form an enamine intermediate that is subsequently hydrogenated to the tertiary amine (Scheme 1).<sup>2b,i</sup>

The composition of the products formed markedly depends on the nature of the catalysts, reaction temperature, hydrogen pressure and on the structure of the nitriles,<sup>3</sup> and examples of selective formation of primary amines<sup>4</sup> or secondary amines<sup>5</sup> were reported. Nitriles can also be hydrogenated in the presence of amines to give unsymmetrical amines.<sup>6</sup> Selective formation of an imine product by the hydrogenation of nitriles was reported in only one case.<sup>4d</sup> Sabo-Etienne et al. observed formation of N-benzylidene-1-phenylmethanamine during the hydrogenation of benzonitrile to benzylamine and were able to obtain it selectively when the reaction was performed in the absence of solvent; using a solvent (THF), a mixture of benzylamine and benzylidene-1-phenylmethanamine was obtained.<sup>4d</sup> We present here a new method for the synthesis of imines. It is based on crosshydrogenative coupling of nitriles with amines under mild hydrogen pressure. Imines have widespread applications in laboratory and industrial synthetic processes due to their diverse reactivity.<sup>7</sup> We believe that the selective formation of imines from readily available nitriles and amines has considerable synthetic potential.

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Scheme 1 Mechanism of the hydrogenation of nitriles to primary, secondary and tertiary amines, *via* imine intermediates.

We reported the efficient dehydrogenative coupling of alcohols with amines to give imines catalysed by a pyridine-based PNP Ru pincer complex.<sup>8h</sup> This reaction occurs with liberation of H<sub>2</sub> and water, with high turnover numbers, and no waste products are formed. Several other environmentally benign reactions catalyzed by tridentate PNN and PNP Ru(II) pincer complexes based on pyridine-<sup>8</sup> and acridine-<sup>9</sup> backbones were developed. Recently, the hydrogenation of amides to the corresponding alcohols and amines catalyzed by the bipyridine-based pincer complex **1** was reported.<sup>10</sup> This complex also catalyzes the hydrogenation of urea derivatives,<sup>11a</sup> organic carbonates, carbamates and formates<sup>11b</sup> and the hydrogenation of cyclic di-esters to 1,2-diols.<sup>11c</sup>

Here we report on the hydrogenation of nitriles in the presence or absence of added amine, catalyzed by complex **1** under mild, neutral conditions (Scheme 2).



Scheme 2 Hydrogenative coupling of nitriles with amines catalyzed by complex 1.

<sup>†</sup> Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/c2cc36639h

Reaction of benzonitrile with H<sub>2</sub> (10 bar) at 110 °C (bath temperature) in dry THF for 24 h catalyzed by 1 (1 mol%) resulted in complete conversion, yielding a mixture of benzylamine (65%) and dibenzylamine (30%). Significantly, upon lowering the temperature and pressure, selective imine formation took place. Thus, stirring benzonitrile (2 mmol) at 70 °C in 2 mL dry THF under 4 bar H<sub>2</sub> in the presence of 0.6 mol% catalyst 1 resulted after 16 h in formation of N-benzylidene-1-phenylmethanamine in 88% yield and no benzylamine or dibenzylamine was detected by GC-MS (entry 1). Apparently, the amine formed by the reduction of the nitrile attacks the intermediate imine and gives rise to a gemdiamine, which liberates ammonia to yield the desired imine. It is noteworthy that no hydrogenation of the product imine took place. Exploring further the scope with regard to different nitriles, reaction of 4-methyl benzonitrile and 4-methoxy benzonitrile under the same conditions resulted in N-(4-methylbenzylidene)-1-(p-tolyl)methanamine and N-(4-methoxybenzylidiene)-1-(4-ethoxyphenyl)methanamine, respectively, in excellent yields (81% and 92%, respectively; entries 2 and 3). Encouraged by these results we explored the possibility of coupling of amines with the intermediate imines produced by partial hydrogenation of nitriles, to obtain the cross-imines. Thus, upon 15 h stirring equimolar amounts of benzonitrile and hexylamine in THF under 4 bar of hydrogen at 70 °C in the presence of 0.6 mol% catalyst, complete conversion of the nitrile to form N-benzylidenehexan-1-amine in 85% yield took place (entry 4), in addition to a minor amount of the self-coupled product N-benzylidene-1-phenylmethanamine (12% yield). For comparison, reaction of benzonitrile with hexylamine under similar conditions as in entry 4 using 0.6 mol% of RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> did not result in any product formation. Increasing the reaction temperature to 110 °C, the H<sub>2</sub> pressure to 10 bars and the reaction time to 40 h resulted in the formation of a mixture of N-benzylhexan-1-amine (38% yield), N-benzylidenehexan-1amine (14% yield), dibenzylamine (18% yield), N-benzylidene-1phenylmethanamine (9% yield) and benzylamine (21% yield) (Table 1).

Studying the scope of this new reaction with regard to different nitriles and amines, the reaction of hexylamine with 4-methylbenzonitrile in the presence of 0.6 mol% catalyst 1 was carried out under 4 bar of hydrogen to give after 35 h N-(4-methylbenzylidene)hexan-1-amine in 84% yield and the selfcoupling product N-(4-methylbenzylidene)-1-(p-tolyl)methanamine in 10% yield (entry 5). Likewise the reaction between the electron poor nitrile 4-fluorobenzonitrile and hexylamine gave 55% conversion of the nitrile with 50% yield of N-(4-fluorobenzylidene)hexan-1-amine (entry 6). No self-coupling or reduction products of the imine were observed by GC-MS. Similarly, 90% yield of N-(4-methoxybenzylidene)hexan-1-amine was obtained after 23 h stirring of equimolar amounts of 4-methoxy benzonitrile and hexylamine under the same conditions (entry 7). N-(4-Methoxybenzylidiene)-1-(4-methoxyphenyl)methanamine was also obtained in 7% yield due to self-condensation. Exploring further the scope with regard to the amine, we studied also the reaction of nitriles with heptylamine under 4 bar of hydrogen. Thus, 27 h stirring of heptylamine with benzonitrile and 4-methoxybenzonitrile gave the corresponding cross products in 91% and 85% yields, respectively (entries 8 and 9), while only 14% and 4% yields, respectively, of N-benzylidene-1-phenylmethanamine and N-(4-methoxybenzylidene)-1-(4-methoxyphenyl)methanamine were

**Table 1** Hydrogenation of nitriles in the absence<sup>a</sup> or presence<sup>b</sup> of added amines

Entry	Nitrile	Amine	Product	Time (h)	Con- version (%)	Yield <sup>c</sup> (%)
1	CN	None		16	99	88
2	CN	None		49	85	81
3	MeO	N None	MeO	e48	99	92
4	C	H <sub>2</sub> N		15	99	85
5	<b>C</b> N	H <sub>2</sub> N	N~~~~	35	99	84
6	F	H <sub>2</sub> N	F	72	55	50
7	MeO	N <sub>H2</sub> N	MeO	23	99	90
8	CN	H <sub>2</sub> N		27	99	91
9	MeO	N H <sub>2</sub> N	MeO	27	99	85
10	€ CN	H <sub>2</sub> N		54	86	81 <sup>d</sup>
11	€ CN N CN	H <sub>2</sub> N		60	99	71 <sup>d</sup>
12		H <sub>2</sub> N		50	15 <sup>d</sup>	_
13	CN	H <sub>2</sub> N		27	99	80
14	≻cn	H <sub>2</sub> N	$\sum N $	20	99	74
15	∽∽_CN	H <sub>2</sub> N	~~~~N~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	20	99	69
16		None		70	55	30 <sup><i>d</i>,<i>e</i></sup>

<sup>*a*</sup> Complex **1** (0.6 mol%), nitrile (2 mmol),  $H_2$  (4 bar) and dry THF (2 mL) were heated in a 100 mL Fischer–Porter tube at 70 °C (bath temperature). <sup>*b*</sup> Complex **1** (0.6 mol%), nitrile (2 mmol), amine (2 mmol),  $H_2$  (4 bar) and dry THF (2 mL) were heated in a 100 mL Fischer–Porter tube at 70 °C (bath temperature). <sup>*c*</sup> Yields of the product and conversion of nitriles were determined by gas chromatography (GC) using toluene as an internal standard. <sup>*d*</sup> 0.8 mol% catalyst was used. <sup>*e*</sup> Isolated yield.

obtained, due to self-condensation of the corresponding nitriles. The optimized reaction conditions were applied also to heterocyclic nitriles. Thus, reaction of 3-cyanopyridine with hexylamine under 4 bar of hydrogen using 0.6 mol% catalyst was somewhat sluggish, yielding after 30 h 40% N-(pyridine-3ylmethylene)hexan-1-amine. The yield was improved to 81% (entry 10) by use of 0.8 mol% catalyst and a longer reaction time (54 h). No self-coupled product was observed. Similarly after 60 h stirring with heptylamine complete conversion of 3-cyanopyridine was observed, forming N-(pyridine-3-ylmethylene)heptan-1-amine in 71% yield (entry 11) with 20% yield of N-(pyridine-3-ylmethyl)heptan-1-amine as the reduced product of the corresponding imine. No self-coupled product was obtained in this case. Trying to couple 2-cyanopyridine with hexylamine using 0.8 mol% of 1 resulted in only 15% conversion to N-(pyridine-2-ylmethylene)hexan-1-amine (entry 12).



Scheme 3 Possible mechanism for cross coupling between nitriles and amines under mild  $H_2$  pressure catalyzed by complex 1.

This may be due to the chelating nature of 2-iminopyridine which might deactivate the catalyst.

Reaction of cyclohexylamine with benzonitrile led to 80% yield of *N*-benzylidenecyclohexanamine (entry 13) and 18% yield of *N*-benzylidene-1-phenylmethanamine as self-coupled products. The reaction of the alkyl nitriles isobutyronitrile or valeronitrile with hexylamine gave *N*-(2-methylpropylidene)-hexan-1-amine and *N*-pentylidenehexan-1-amine in 74% and 68% yields, respectively (entries 14 and 15). As an example of an intramolecular coupling reaction, we examined the reaction of 2-aminobenzyl cyanide at 0.8 mol% catalyst loading, leading to indole which was isolated after column (neutral alumina) chromatography in 30% yield (entry 16).

The mechanism illustrated in Scheme 3 might be possible, although other mechanisms cannot be excluded at this stage. Initially, coordination of the nitrile to the unsaturated complex 1 gives rise to the coordinatively saturated complex **A** which can undergo de-coordination of the bipyridine "arm" followed by addition of dihydrogen by metal–ligand cooperation to generate complex **B**. Subsequent hydride transfer to the nitrile group leads to the imine intermediate **C**. Nucleophilic attack by the amine on the coordinated imine can give intermediate **D**, which liberates a diamine with regeneration of the catalyst. NH<sub>3</sub> liberation from the diamine gives rise to the desired imine.

In conclusion, for the first time imines can be selectively formed by hydrogenative coupling of nitriles and amines. The reaction proceeds at relatively low temperature and under neutral, homogeneous conditions using the pincer catalyst **1**, under mild hydrogen pressure. This new, environmentally benign atom economical catalytic protocol exhibits a broad substrate scope, providing a variety of imines from amines and nitriles in good to excellent yields.

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