Homogeneous Catalysis

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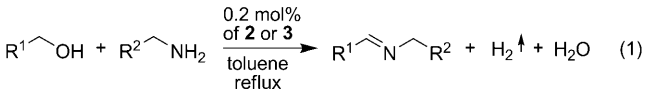
Direct Synthesis of Imines from Alcohols and Amines with Liberation of H_2**

*Boopathy Gnanaprakasam, Jing Zhang, and David Milstein**

Imines are important compounds because of their diverse reactivity, which has led to widespread applications in laboratory and industrial synthetic processes.[1] Traditionally, imines are synthesized from the reaction of ketones or aldehydes with amines in the presence of an acid catalyst. Imines have also been prepared by the self-condensation of amines upon oxidation[2] and by the oxidation of secondary amines.[2b,c,3] The catalytic N-alkylation of amines[4] and ammonia[5] with alcohols is thought to involve imines as transient intermediates that undergo rapid hydrogenation.

The development of an efficient, general method for the synthesis of imines from alcohols and amines is very desirable because of its potential versatility and wide scope. The formation of imines by coupling alcohols with amines in the presence of stoichiometric amounts of oxidants has been reported, but it is limited to activated alcohols and leads to the generation of stoichiometric amounts of waste.[6] Recently, interesting oxidative coupling reactions of alcohols with primary amines under O_2 were reported, but the reactions were also limited to activated (benzylic) alcohols, and a maximum turnover number of 50 was reported.[6,7]

We now report a general, efficient, and environmentally benign method for the direct synthesis of imines by the reaction of alcohols with amines. This reaction occurs with liberation of H_2 gas and water, high turnover numbers, and no waste products. Furthermore, the reaction proceeds under neutral conditions and no hydrogen acceptor is needed [Eq. (1)]. Remarkably, hydrogenation of the imine does not take place.



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[*] Dr. B. Gnanaprakasam, Dr. J. Zhang, Prof. D. Milstein
Department of Organic Chemistry
Weizmann Institute of Science, 76100 Rehovot (Israel)
Fax: (+972) 8-934-4142
E-mail: david.milstein@weizmann.ac.il
Homepage: http://www.weizmann.ac.il/Organic_Chemistry/milstein.shtml

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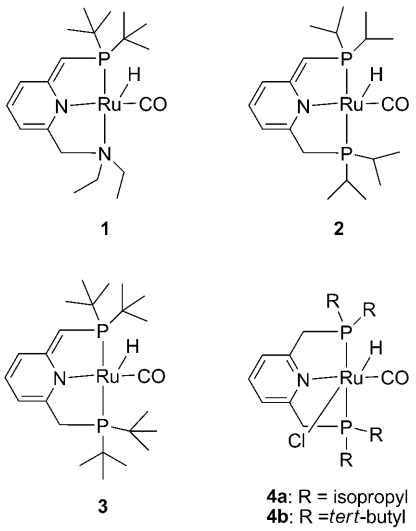
Supporting information for this article (general procedures for the dehydrogenative coupling of amines with alcohols, spectroscopic data for the product imines, and synthesis of complexes **2** and **4**) is available on the WWW under http://dx.doi.org/10.1002/anie.200907018.

We have previously reported the catalytic dehydrogenative coupling of primary alcohols to give esters,[8] the dehydrogenation of secondary alcohols to give ketones,[9] and the hydrogenation of esters to give alcohols.[10] These reactions are catalyzed by de-aromatized 2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine (PNN) and 2,6-bis(diisopropylphosphinomethyl)pyridine (PNP) pincer-type Ru^{II} complexes **1** and **2**, respectively (Scheme 1).



Scheme 1. PNN- and PNP-type ruthenium pincer complexes.

Complex **1** is also an excellent catalyst for the coupling of alcohols with amines to form amides with the liberation of H_2.[11] All these reactions are based on metal–ligand cooperation during the reversible deprotonation of a pyridinyl methylene group, in which de-aromatization/aromatization are key catalytic steps.[8,10–14] Surprisingly, when the PNP complex **3**, analogous to the PNN complex **1** (except for having a phosphine rather than an amine "arm"), was employed in the reaction of alcohols with amines, dehydrogenative coupling to form imines, rather than amides, took place [Eq. (1)]. Only minor amounts of amides were detected. It is noteworthy that hydrogenation of the imines to amines was not observed.

Complex **3** was prepared by reaction of the PNP ligand with $[RuHCl(CO)(PPh_3)_3]$ to form the hydridochloride complex **4b**, followed by deprotonation of the latter with KO*t*Bu, in analogy to the preparation of complex **2**[10] (see the Supporting Information).

Heating a solution containing equimolar amounts of benzyl alcohol and benzylamine in toluene at reflux in the

presence of 0.2 mol% **3** under argon resulted in the formation of water. After 56 h, GC analysis showed 94% conversion of benzyl alcohol (85% conversion after 22 h) to form the imine (87%) and a minor amount of the ester (3%). Analysis of the gas phase revealed the formation of dihydrogen. The solvent was evaporated and the residue was submitted to vacuum distillation to give pure *N*-benzylidene-1-phenylmethanamine in 79% yield (Table 1, entry 1). The NMR and GC-MS spectra of the isolated product are consistent with the reported data.[15]

A variety of alcohols and amines were examined to explore the scope of this reaction (Table 1). Heating a solution containing equimolar amounts of benzyl alcohol and 1-hexylamine with 0.2 mol% of **3** in toluene at reflux for 52 h resulted in 100% conversion (90% conversion after 20 h) of the starting compounds, and *N*-benzylidenehexan-1-amine was isolated in 82% yield after distillation. Only traces of amide and ester were detected. The water formed during the course of the reaction does not hinder the reaction, although we previously reported that the PNN complex **1** adds water reversibly, with aromatization, to form a hydrido-hydroxo complex.[13] Such a reaction probably also takes place with complex **3**, but considering the much larger concentration of the alcohol (as compared with water) in toluene, and the reversibility of water addition, the presence of water does not pose a problem.

A variety of substituted benzyl alcohols undergo efficient dehydrogenative coupling with amines containing either electron-donating or -withdrawing substituents. Thus, heating 4-methoxybenzyl alcohol with 1-hexylamine, or 3,4-dimethoxybenzyl alcohol with 2-phenylethylamine, in toluene at reflux for 48 h with 0.2 mol% of **3** resulted in the formation of the corresponding imines in 89 and 92% yields, respectively (Table 1, entries 3 and 4). The bicyclic amine (−)-*cis*-myrtanylamine reacts effectively with 4-methylbenzyl alcohol with 97% consumption of the alcohol, and the corresponding imine was isolated in 88% yield (entry 5). Complex **3** also catalyzes effectively the reaction of 4-fluorobenzyl alcohol with 4-fluorobenzylamine to afford the imine in 77% yield after distillation (entry 6). Substitution of the amine at the α position does not decrease the yield of the imine; for example, the reaction of 4-methoxybenzyl alcohol with 2-heptylamine generated the corresponding imine in good yield (entry 7). The reaction of 4-methoxybenzyl alcohol and benzylamine furnished *N*-(4-methoxybenzylidene)-1-phenylmethanamine in 90% yield (entry 8). Notably, all the aromatic primary alcohols gave the corresponding imines as the primary products.

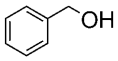
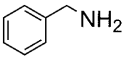
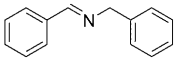
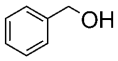
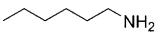
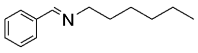
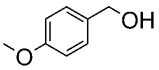
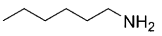
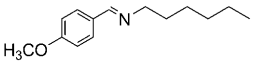
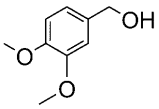
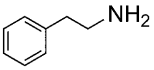
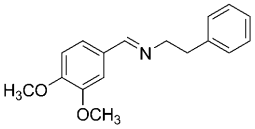
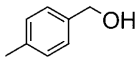
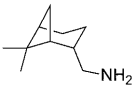
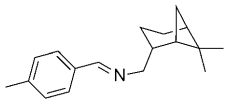
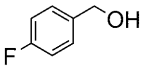
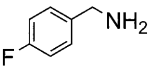
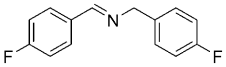
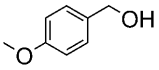
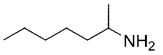
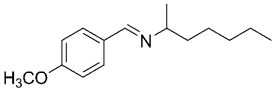
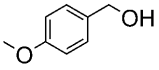
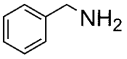
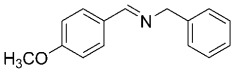
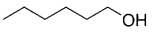
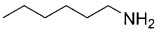
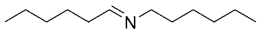
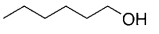
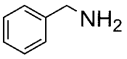
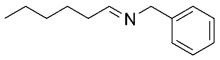
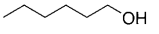
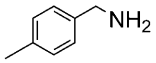
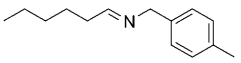
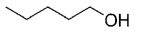
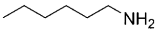
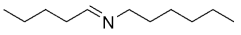
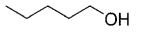
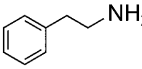
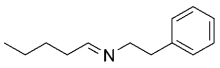
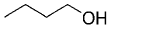
The synthesis of aliphatic imines is inherently more challenging because of their instability and difficult isolation. The possibility of expanding the scope of the new reaction to the synthesis of these versatile compounds was also explored: a solution of 1-hexanol and 1-hexylamine in toluene was heated at reflux for 48 h in the presence of 0.2 mol% of complex **3**. A 90% conversion of the alcohol was achieved, and the corresponding pure imine was isolated in 65% yield (entry 9). Minor amounts of the corresponding amide (10%) and ester (5%) were detected by GC analysis. The reactions of 1-hexanol with benzylamine and with 4-methylbenzylamine led to the corresponding imines in moderate yields. Surprisingly, 18% of the corresponding amide and 7% of the corresponding ester were formed in the reaction of 1-hexanol and benzylamine (entry 10). GC analysis showed that the reaction of 1-hexanol with 4-methylbenzylamine (entry 11) afforded imine (62%), amide (12%), and ester (7%). The imines were characterized by NMR spectroscopy and GC-MS analysis. When these reactions were carried out with 1-pentanol, the yield of the imine improved significantly. Thus, reaction of 1-pentanol with 1-hexylamine or 2-phenethylamine led to the corresponding imines in good yields (entries 12 and 13). However, 16% of the corresponding amide and 5% of the ester were also detected in the case of 1-hexylamine (entry 12). Monitoring the progress of the reaction by GC analysis revealed that 30% of the alcohol was consumed after 4 h, and the imine was formed as the sole product. Longer reaction times led also to the formation of minor amounts of the amide and ester. Interestingly, the reaction of 1-butanol with 2-heptylamine exhibited excellent selectivity for the formation of the imine, which was obtained as the sole product after evaporation of the solvent (as observed by NMR spectroscopy) and was isolated in 86% yield (entry 14). The reaction of 1-butanol with 4-methylbenzylamine resulted in greater than 98% conversion (entry 15) with formation of imine (63%), amide (14%), and ester (6%), as observed by GC analysis. Lower conversion was observed in the reaction of cyclohexylmethanol with 1-hexylamine, even after heating at reflux for four days, which led to the isolation of the imine in 57% yield (entry 16). The reaction can also be carried out with secondary alcohols, although it is slower. Thus, reaction of cyclohexanol and benzylamine in the presence of **3** resulted in only 20.5% conversion after 22 h at reflux, with the corresponding ketimine formed in 20% yield (entry 17).

The dehydrogenative reaction of alcohols and amines was also studied with the de-aromatized isopropyl-substituted PNP catalyst **2**. Thus, heating the solution of 4-methoxybenzyl alcohol, benzylamine, and 0.2 mol% of **2** in toluene at reflux for 48 h, followed by complete evaporation of the solvent and excess amine under high vacuum at 60°C (water bath) provided the *N*-(4-*m*ethoxybenzylidene)-1-phenylmethanamine in 92% yield. Similarly, the reaction of 1-butanol and 2-heptylamine catalyzed by complex **2** gave *N*-butylideneheptan-2-amine as the only product (76% conversion) after 52 h at reflux.

Conveniently, the new catalytic reaction can be carried out in air. Thus 4-methoxybenzyl alcohol, benzylamine, catalyst **3**, and toluene were placed into an open flask and heated at reflux for 24 h under air. The conversion of the alcohol was monitored by GC analysis, and after all the alcohol was consumed, the solvent and excess of amine were completely removed under high vacuum at 60°C (water bath). This led to an 89% yield of the respective imine as the sole product, in an almost pure state (Table 1, entry 18).

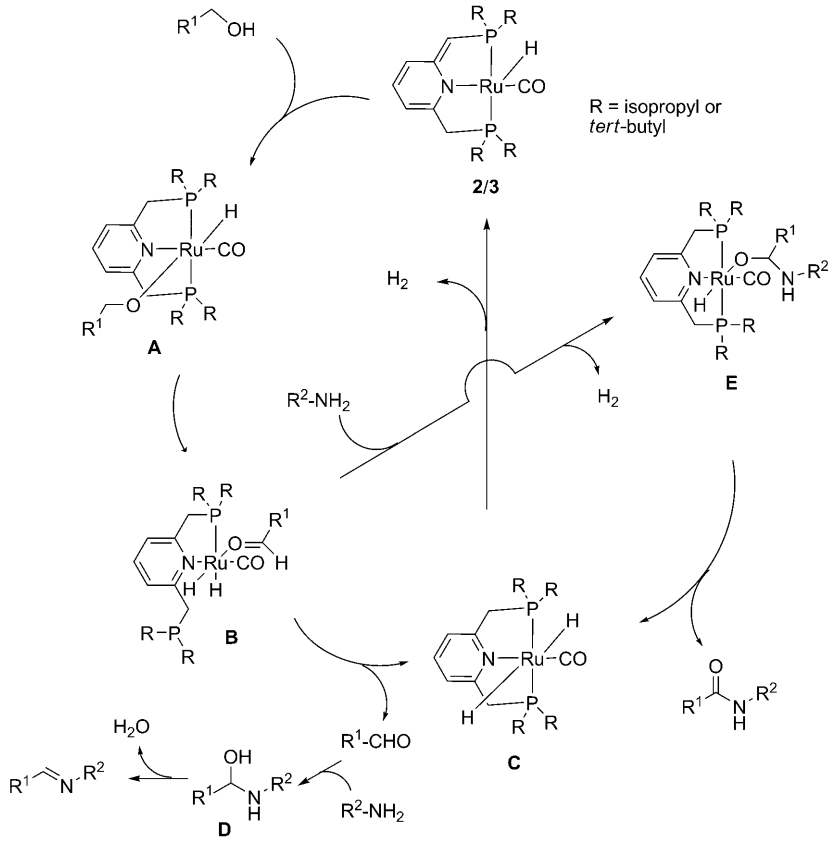
While insufficient mechanistic data exist at present, a likely mechanism for the direct imination of alcohols with amines catalyzed by complexes **2** and **3** which accounts for the strikingly different catalytic activity of these complexes compared with that of complex **1** is presented in Scheme 2.

Table 1: Direct synthesis of imines from alcohols and amines catalyzed by the dearomatized ruthenium complex **3**.[a]

Entry	R^1CH_2OH	R^2NH_2	*t* [h]	Conv. of alcohol	$R^1{=}N{-}R^2$	GC yield [%]	Yield of isolated product [%]
1			56	>94		87 imine, 3 ester	79
2[b]			52	100		–	82
3[b]			48	100		–	89
4[b]			48	100		–	92
5[b]			48	97		–	88
6[b]			56	90		–	77
7[b,c]			48	97		–	84
8[b,c]			48	100		–	90
9			48	90		67 imine, 10 amide, 5 ester	65
10[d]			56	96		63 imine, 18 amide, 7 ester	57 imine 16 amide
11[d]			56	94		62 imine, 12 amide, 7 ester	60 imine, 10 amide
12[c]			46	>96		69 imine, 16 amide, 5 ester	68
13			52	>94		78 imine, 6 amide, 4 ester	–
14[b,c]			56	–		–	86
15[d]			32	>98		63 imine, 14 amide, 6 ester	58 imine, 12 amide
16			56	72		traces of amide and ester	57
17[b]			22	20.5		20 imine and traces of ketone	–
18[e]			24	100		–	89

[a] Complex **3** (0.02 mmol), alcohol (10 mmol), amine (10.1 mmol), *m*-xylene (1 mmol, internal standard), and toluene (3 mL) were heated at reflux in a Schlenk tube. Conversion of alcohols and yields of products were determined by GC. [b] Only imine was observed by GC. [c] Crude yield, almost pure by NMR spectroscopy. [d] Amide was completely separated by precipitation upon addition of *n*-hexane to the crude reaction mixture. [e] Under air.

Activation of the O–H bond of the alcohol by complex **2** or **3** likely results in the aromatized intermediate **A**, which upon β-H elimination (perhaps involving "arm" opening) yields the coordinated aldehyde intermediate **B**. Dissociation of the aldehyde leads to the known dihydride **C** which liberates H_2 (formed from a hydride and a methylene proton) to



Scheme 2. Possible mechanism for imine (and amide) formation.

regenerate complex **2** or **3**. Reaction of the aldehyde with the amine generates an unstable hemiaminal **D** which loses water to produce the product imine. If nucleophilic attack on the coordinated aldehyde (in **B**) takes place, a hemiaminal intermediate **E** can be formed and undergo dehydrogenation to produce an amide. Apparently, in the case of the PNN complex **1**, which bears a hemilabile amine "arm", the coordinated aldehyde is attacked which leads to an amide,[11] while with the PNP complexes **2** or **3** closure of the phosphine "arm" results in rapid dissociation of the aldehyde. The fact that complexes **2** and **3** show similar catalytic activity indicates that steric factors are not responsible for directing the reaction towards imines rather than amide products. This study represents an unusual case in which structurally similar complexes lead to entirely different catalytic reactions.

In conclusion, a new reaction has been discovered in which imines are formed with high turnover from alcohols and amines. The reaction occurs under neutral conditions with liberation of molecular hydrogen. The reaction can be applied to a variety of alcohols and amines and offers an environmentally friendly, general method for the synthesis of imines. Mechanistic studies are in progress.

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[1] a) J. P. Adams, *J. Chem. Soc. Perkin Trans. 1* **2000**, 125 – 139; b) J. Gawronski, N. Wascinska, J. Gajewy, *Chem. Rev.* **2008**, *108*, 5227 – 5252.
[2] a) K. Orito, T. Hatakeyama, M. Takeo, S. Uchiito, M. Tokuda, H. Suginome, *Tetrahedron* **1998**, *54*, 8403 – 8410; b) A. H. Éll, J. S. M. Samec, C. Brasse, J.-E. Bäckvall, *Chem. Commun.* **2002**, 1144 – 1145; c) M. Largeron, A. Chiaroni, M.-B. Fleury, *Chem. Eur. J.* **2008**, *14*, 996 – 1003; d) C. S. Yi, D. W. Lee, *Organometallics* **2009**, *28*, 947 – 949.
[3] a) J. S. M. Samec, A. H. Éll, J.-E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327 – 2334; b) S.-I. Murahashi, Y. Okano, H. Sato, T. Nakae, N. Komiya, *Synlett* **2007**, 1675 – 1678; c) G. Jiang, J. Chen, J.-S. Huang, C.-M. Che, *Org. Lett.* **2009**, *11*, 4568 – 4571; d) X.-Q. Gu, W. Chen, D. Morales-Morales, C. M. Jensen, *J. Mol. Catal. A* **2002**, *189*, 119 – 124.
[4] For reviews, see a) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555 – 1575; b) T. D. Nixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans.* **2009**, 753 – 762; c) A. Tillack, D. Hollmann, D. Michalik, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8881 – 8885; d) K.-I. Fujita, Y. Enoki, R. Yamaguchi, *Tetrahedron* **2008**, *64*, 1943 – 1954, and references therein.
[5] C. Gunanathan, D. Milstein, *Angew. Chem.* **2008**, *120*, 8789 – 8792; *Angew. Chem. Int. Ed.* **2008**, *47*, 8661 – 8664.
[6] L. Blackburn, R. J. K. Taylor, *Org. Lett.* **2001**, *3*, 1637 – 1639.
[7] a) M. S. Kwon, S. Kim, S. Park, W. Bosco, R. K. Chidrala, J. Park, *J. Org. Chem.* **2009**, *74*, 2877 – 2879; b) J. W. Kim, J. He, K. Yamaguchi, N. Mizono, *Chem. Lett.* **2009**, *38*, 920 – 921.
[8] J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840 – 10841.
[9] a) J. Zhang, M. Gandelman, L. J. W. Shimon, D. Milstein, *Dalton Trans.* **2007**, 107 – 113; b) J. Zhang, M. Gandelman, L. J. W. Shimon, D. Milstein, *Organometallics* **2004**, *23*, 4026 – 4033; c) C. Gunanathan, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2009**, *131*, 3146 – 3147.
[10] J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem.* **2006**, *118*, 1131 – 1133; *Angew. Chem. Int. Ed.* **2006**, *45*, 1113 – 1115.
[11] C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790 – 792.
[12] Metal–ligand cooperation in the activation of C–H bonds and H_2 by PNP-Ir complexes: a) E. Ben-Ari, G. Leitus, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2006**, *128*, 15390 – 15391; b) M. A. Iron, E. Ben-Ari, R. Cohen, D. Milstein, *Dalton Trans.* **2009**, 9433 – 9439; c) G. Zeng, Y. Guo, S. Li, *Inorg. Chem.* **2009**, *48*, 10257 – 10263.
[13] Metal–ligand cooperation in consecutive light-induced splitting of water by complex **1**: S. W. Kohl, L. Weiner, L. Schwartsburd, L. Konstantinovski, L. J. W. Shimon, Y. Ben-David, M. A. Iron, D. Milstein, *Science* **2009**, *324*, 74 – 77.
[14] Dehydrogenative coupling of alcohols catalyzed by an acridine-based PNP-Ru complex to form acetals: C. Gunanathan, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2009**, *131*, 3146.
[15] P. G. M. Wuts, Y.-W. Jung, *J. Org. Chem.* **1991**, *56*, 365 – 372.

