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Direct synthesis of pyridines and quinolines by coupling of γ-amino-alcohols with secondary alcohols liberating H_2 catalyzed by ruthenium pincer complexes†

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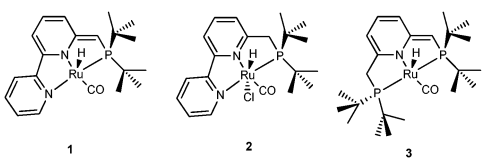
A novel, one-step synthesis of substituted pyridine- and quinoline-derivatives was achieved by acceptorless dehydrogenative coupling of γ-aminoalcohols with secondary alcohols. The reaction involves consecutive C–N and C–C bond formation, catalyzed by a bipyridyl-based ruthenium pincer complex with a base.

The synthesis of N-heterocycles has attracted much attention because of their prevalence in natural products and drugs.[1] Of the N-heterocycles, substituted pyridines are among the most important components of biologically active molecules and they are extensively used in pharmaceuticals, agrochemicals, and functional materials.[2] Substantial progress has been achieved in derivatizing pre-existing pyridine frameworks using metal-catalyzed cross-coupling protocols.[3] However, the most useful and flexible approach involves the development of *de novo* construction of the pyridine moiety. Thus, not surprisingly, much effort has been devoted to the synthesis of substituted pyridines[4,5] using a variety of protocols. Still, stitching together pyridines in a one-step reaction using readily available starting materials remains challenging.

Recently we have developed the Ru–bipyridine-based pincer complexes **1** and **2**[6] (Scheme 1) which efficiently catalyze several environmentally benign reactions, including the hydrogenation of amides,[6a] cyclic diesters,[6b] urea derivatives,[6c] organic carbonates, carbamates and formates;[6d] the dehydrogenative transformation of alcohols to carboxylic acid salts using water;[6e] dehydrogenative cross-esterification involving primary and secondary alcohols;[6f] catalytic coupling of nitriles with amines to selectively form imines under mild hydrogen pressure.[6g] Very recently, we have reported the direct synthesis of pyrroles by dehydrogenative coupling of β-aminoalcohols with secondary alcohols.[6h] Here we present an efficient, one-step synthesis of pyridines based on dehydrogenative coupling of γ-aminoalcohols with secondary alcohols, catalyzed by **1** and **2**.



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

We envisioned that alcohol dehydrogenation followed by consecutive C–N and C–C bond formation can eventually lead to dihydropyridines, which might undergo *in situ* dehydrogenation to the corresponding pyridines, based on the excellent catalytic dehydrogenation ability of complex **1** and its precursor complex **2** (Scheme 1). Bergman and Ellman *et al.* presented a two step synthesis of pyridines *via* dihydropyridines;[7] the procedure first involves the synthesis of dihydropyridines from imines and alkynes by rhodium-catalyzed C–H activation and electrocyclization, and then Pd/C-catalyzed air-oxidation, in acetic acid. It would be interesting to find a single catalyst that can form a dihydropyridine intermediate and dehydrogenate it to the desired pyridine in one reaction.

Initially, the reaction of γ-aminopropanol with 1-phenylethanol was chosen as a model system for dehydrogenative cross-coupling to form pyridines. Thus, refluxing an equimolar amount of γ-aminopropanol (2 mmol), 1-phenylethanol (2 mmol) and KO^{t}Bu (1 mmol, 0.5 eq. with respect to 1-phenylethanol) in 2 mL toluene for 24 h in the presence of 0.5 mol% complex **2** gave 45% yield of 2-phenylpyridine (Table 1, entry 1). Increasing the reaction time to 40 h, or the catalyst loading to 1 mol%, did not improve the yield of the product (Table 1, entries 2 and 3). Increasing the ratio of γ-aminopropanol : 1-phenylethanol to 1 : 2 enhanced the yield of the desired pyridine to 62% (Table 1, entry 4).

Varying the solvent volume had a minor effect. Thus, heating γ-aminopropanol (2 mmol) and 1-phenylethanol (4 mmol) in 0.5 mL toluene in the presence of 0.5 mol% complex **2** gave 2-phenylpyridine in 53% yield after 24 h, while under the same conditions using 4 mL solvent resulted in 58% yield of the product (Table 1, entries 5 and 6).

The solvent effect on the reaction was also examined. Thus, the yield of 2-phenylpyridine in a mixture of toluene (2 mL) and THF (0.5 mL) (68%) was higher than in toluene (62%) or THF

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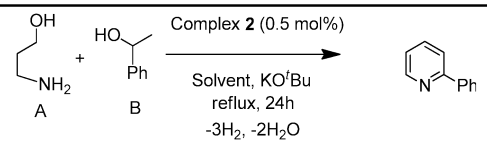
Table 1 Optimization of reaction conditions for the synthesis of 2-phenylpyridine[a]



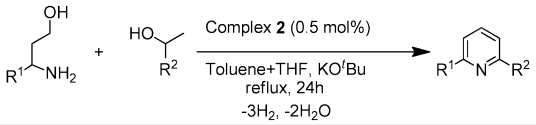
Entry	A : B	Solvent	Time (h)	Yield[b] (%)
1	1 : 1	Toluene (2 mL)	24	45
2	1 : 1	Toluene (2 mL)	40	47
3	1 : 1	Toluene (2 mL)	24	46[c]
4	1 : 2	Toluene (2 mL)	24	62
5	1 : 2	Toluene (0.5 mL)	24	53
6	1 : 2	Toluene (4 mL)	24	58
7	1 : 2	Benzene (2 mL)	24	48
8	1 : 2	THF (2 mL)	24	25
9	1 : 2	Toluene + THF (2 mL + 0.5 mL)	24	68
10	1 : 2	Toluene (4 mL)	24	52[d]

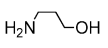
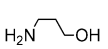
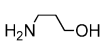
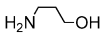
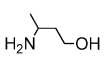
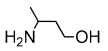
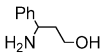
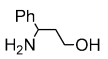
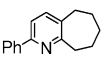
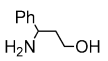
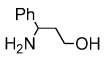
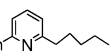
[a] γ-Aminopropanol (2 mmol), 1-phenylethanol (2 mmol or 4 mmol), KO^{t}Bu (0.5 eq. with respect to 1-phenylethanol) and complex **2** (0.5 mol%) were heated at reflux under argon. [b] Yields of the products were determined by gas chromatographic analysis of the crude reaction mixture using *m*-xylene as an internal standard. [c] 1 mol% catalyst was used. [d] Complex **3** was used.

(25%) alone, or in benzene (48%) (Table 1, entries 7–9). Actually, the de-aromatized complex **1** can be readily formed *in situ* by deprotonation of the air-stable complex **2** under basic reaction conditions.[6] The reaction in the presence of catalyst **3** led to a lower yield (52%) of the desired pyridine (Table 1, entry 10).

Using the favourable reaction conditions we set out to test the reactivity of various γ-aminoalcohols with secondary alcohols. A toluene–THF solution containing γ-aminopropan-1-ol (2 mmol), cycloheptanol (4 mmol), KO^{t}Bu (2 mmol) and catalyst **2** (0.01 mmol) was heated to reflux for 24 h and then cooled to room temperature. The reaction mixture was then extracted with dichloromethane and filtered through Celite. Evaporation of the solvent gave a crude mixture which was further purified by column chromatography using silica gel to obtain 70% isolated yield of 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (Table 2, entry 2). Expanding the scope of the reaction to other cyclic alcohols, the reaction of γ-aminopropan-1-ol with cyclohexanol in the presence of 0.5 mol% of **2** resulting in the formation of 5,6,7,8-tetrahydroquinoline in 53% yield after 24 h reflux (Table 2, entry 3) was studied. Reaction of γ-aminopropan-1-ol with cyclopentanol under the same conditions gave 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine in only 24% isolated yield (Table 2, entry 4). Expanding the scope of the reaction to other 3-amino-alcohols, we studied the reaction of γ-aminobutan-1-ol and 3-amino-3-phenylpropan-1-ol with various secondary alcohols. A toluene–THF solution containing γ-aminobutan-1-ol (2 mmol), cycloheptanol (4 mmol), KO^{t}Bu (2 mmol) and catalyst **2** (0.01 mmol) was heated to reflux for 24 h, resulting in the formation of 2-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine in good isolated yield (80%) after purification (Table 2, entry 5). Under similar reaction conditions, dehydrogenative coupling of γ-aminobutan-1-ol with cyclohexanol yielded 2-methyl-5,6,7,8-tetrahydroquinoline in 55% isolated yield (Table 2, entry 6). Reaction of 3-amino-3-phenyl-propan-1-ol with the alcohols 1-phenylethanol, cycloheptanol and cyclohexanol under the same reaction conditions resulted in the corresponding desired pyridines, 2,6-diphenylpyridine

Table 2 Synthesis of pyridines and quinolines using various amino alcohols and secondary alcohols catalyzed by the Ru pincer complex **2**[a]

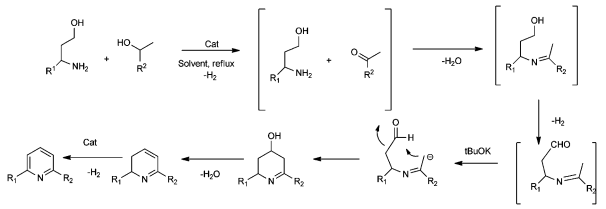


Entry	Amino alcohol	Alcohol	Product	Isolated yield[b] (%)
1				62
2				70
3				53
4				24
5				80
6				55
7				48
8				67
9				55
10				50
11				62
12				55
13				71
14				45

[a] γ-Aminoalcohol (2 mmol), secondary alcohol (4 mmol), KO^{t}Bu (2 mmol), catalyst (0.5 mol%) were heated in 2 mL toluene + 0.5 mL THF mixture at reflux for 24 h. [b] Yield of pure isolated product after column chromatography.

(48%), 2-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (67%), and 2-phenyl-5,6,7,8-tetrahydroquinoline (55%) in moderate to good isolated yields (Table 2, entries 7–9).

Next, the scope with regard to the acylic secondary alcohol was studied. In the case of 2-heptanol, two regioisomers can be formed by the abstraction of a proton bound to the primary or the secondary aliphatic carbon atom. Deprotonation at the less hindered side gave 2-pentyl-6-phenylpyridine as the major product in 50% isolated yield (Table 2, entry 10). GC-MS analysis indicated that together with the product pyridine, 10–20% of the corresponding tetrahydropyridine was also obtained. In the case of the reaction between 3-amino-3-phenylpropan-1-ol and 2-heptanol, the product 6-pentyl-2-phenyl-2,3,4,5-tetrahydropyridine was isolated in



Scheme 2 Plausible mechanism of formation of pyridine derivatives *via* a sequence of dehydrogenation and condensation reactions.

20% yield. This is not very surprising, since the bipyridyl-based Ru catalyst **1** (formed *in situ* from **2**) is an excellent hydrogenation catalyst. Thus, during the dehydrogenative coupling of secondary alcohols with aminoalcohols the H_2 formed can reduce the *in situ* formed dihydropyridine to tetrahydropyridine. On the other hand, we have shown that imines are not readily hydrogenated by the bipyridyl-based pincer catalyst.[6g]

Encouraged by the results of the new pyridine formation reaction, we were interested in applying the new methodology to the synthesis of quinolines. The quinoline moiety is present in many bioactive natural products, and various quinoline derivatives are known to display a broad range of pharmacological properties, which enable them to be used as anti-cancer,[8a] anti-HIV,[8b] anti-hypertensive,[8c] anti-tuberculosis,[8d] and anti-Alzheimer[8e] agents. Exploring the potential for the synthesis of quinolines, we studied the reaction of 2-aminobenzyl alcohol with different secondary alcohols, including 1-phenylethanol, cyclohexanol, cycloheptanol and cyclododecyl alcohol to obtain 2-phenylquinoline, 1,2,3,4-tetrahydroacridine, 7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoline, 6,7,8,9,10,11,12,13,14,15-decacyclododeca[*b*]quinoline, in moderate to good isolated yields (Table 1, entries 11–14). After the dehydrogenation of γ-aminoalcohols with secondary alcohols, the condensation to quinolines can proceed *via* a Friedländer pathway.[9]

Mechanistically, we suggest that O–H activation of the secondary alcohol by complex **1** results in aromatization of the pincer complex, followed by H_2 liberation from the resulting alkoxo complex to form a ketone. A sequence involving nucleophilic attack by the amine group of a γ-aminoalcohol molecule on the ketone can produce an imine intermediate, followed by dehydrogenation of the resulting imine–alcohol intermediate and C–C bond formation by condensation under basic reaction conditions, eventually leading to a dihydropyridine derivative which is further catalytically dehydrogenated to the desired pyridine by the ruthenium pincer complex (see Scheme 2 for the organic transformations).

In summary, a concise synthesis of substituted pyridines was achieved by selective and successive C–N and C–C bond formation catalyzed by 0.5 mol% of the bipyridyl based ruthenium PNN complex **1**, which is formed *in situ* using the air-stable complex **2** and a base. We believe that this one step, efficient coupling protocol which generates hydrogen gas is attractive for the preparation of a diverse range of pyridine and quinoline derivatives.

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Notes and references

1 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell, Oxford, UK, 4th edn, 2000.
2 (*a*) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043; (*b*) P. A. Keller, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, UK, 2008, vol. 7, pp. 217–308; (*c*) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627.
3 (*a*) I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036; (*b*) S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9254; (*c*) J. J. Mousseau, J. A. Bull and A. B. Charette, *Angew. Chem., Int. Ed.*, 2010, **49**, 1115.
4 (*a*) J. Varela and C. Saa, *Chem. Rev.*, 2003, **103**, 3787; (*b*) G. Zeni and R. L. Larock, *Chem. Rev.*, 2006, **106**, 4644.
5 (*a*) M. Movassaghi, M. D. Hill and O. K. Ahmad, *J. Am. Chem. Soc.*, 2007, **129**, 10096; (*b*) Y. Wei and N. Yoshikai, *J. Am. Chem. Soc.*, 2013, **135**, 3756; (*c*) C.-H. Lei, D. Wang, L. Zhao, J. Zhu and M.-X. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 4708; (*d*) T. J. Donohoe, J. A. Basutto, J. F. Bower and A. Rathi, *Org. Lett.*, 2011, **13**, 1036; (*e*) J. Chen, Q. Song, C. Wang and Z. Xi, *J. Am. Chem. Soc.*, 2002, **124**, 6238; (*f*) D. Suzuki, Y. Nobe, Y. Watai, R. Tanaka, Y. Takayama, F. Sato and H. Urabe, *J. Am. Chem. Soc.*, 2005, **127**, 7474; (*g*) M. Movassaghi and M. D. Hill, *J. Am. Chem. Soc.*, 2006, **128**, 4592; (*h*) J. R. Manning and H. M. L. Davies, *J. Am. Chem. Soc.*, 2008, **130**, 8602.
6 (*a*) E. Balaraman, B. Gnanaprakasam, L. J. W. Shimon and D. Milstein, *J. Am. Chem. Soc.*, 2010, **132**, 16756; (*b*) E. Balaraman, E. Fogler and D. Milstein, *Chem. Commun.*, 2012, **48**, 1111; (*c*) E. Balaraman, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2011, **50**, 11702; (*d*) E. Balaraman, C. Gunanathan, J. Zhang, L. J. W. Shimon and D. Milstein, *Nat. Chem.*, 2011, **3**, 609; (*e*) E. Balaraman, E. Khaskin, G. Leitus and D. Milstein, *Nat. Chem.*, 2013, **5**, 122; (*f*) D. Srimani, E. Balaraman, B. Ganaprakasam, Y. Ben-David and D. Milstein, *Adv. Synth. Catal.*, 2012, **354**, 2403; (*g*) D. Srimani, M. Feller, Y. Ben-David and D. Milstein, *Chem. Commun.*, 2012, **48**, 11853; (*h*) D. Srimani, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2013, **52**, 4012.
7 D. A. Colby, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 3645.
8 (*a*) A. Tsotinis, M. Vlachou, S. Zouroudis, A. Jeney, F. Timar, D. E. Thruston and C. Roussakis, *Lett. Drug Des. Discovery*, 2005, **2**, 189; (*b*) X. Franck, A. Fournet, E. Prina, R. Mahieux, R. Hocquemiller and B. Figadere, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3635; (*c*) N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran and J. T. Leonard, *Biol. Pharm. Bull.*, 2004, **27**, 1683; (*d*) A. Nayyar, A. Malde, R. Jain and E. Coutinho, *Bioorg. Med. Chem.*, 2006, **14**, 847; (*e*) P. Camps, E. Gomez, D. Munoz-Torrero, A. Badia, N. M. Vivas, X. Barril, M. Orozco and F. J. Luque, *J. Med. Chem.*, 2001, **44**, 4733.
9 J. M. Contelles, E. Perez-Mayoral, A. Samadi, M. C. Carreiras and E. Soriano, *Chem. Rev.*, 2009, **109**, 2652.

