Dehydrogenative Coupling Hot Paper

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Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes

*Prosenjit Daw+, Subrata Chakraborty+, Jai Anand Garg, Yehoshoa Ben-David, and David Milstein**

Abstract: *Herein, the first example of base-metal-catalyzed dehydrogenative coupling of diols and amines to selectively form functionalized 1,2,5-substituted pyrroles liberating water and hydrogen gas as the sole by-products is presented. The reaction is catalyzed by pincer complexes of earth-abundant cobalt.*

Pyrroles and their derivatives are valuable intermediates in the synthesis of numerous natural products, agrochemicals, flavors, dyes, and functional materials.[1] They also have antibacterial, antitumor, anti-inflammatory, and antifungal properties.[2] Polypyrroles are conducting polymers and used in solar cells[3] and batteries;[4] they can also be used as antioxidants and gas sensors.[5] The classical methods for pyrrole synthesis involve the Knorr,[6] Paal–Knorr[7] and Hantzsch[8] reactions. Lately, metal-catalyzed cyclization[9] and multicomponent coupling reactions[10] have been developed for the synthesis of functionalized pyrroles. Although these protocols are effective, most of them suffer from several shortcomings, such as poor availability of starting materials, multi-step synthetic operations, and copious waste generation.

In terms of sustainable synthesis, an environmentally benign route to pyrroles from renewable resources would be highly desirable. In this respect direct access to substituted pyrroles from readily available feedstocks like alcohols and polyols is attractive since alcohols are either industrial products or can be derived from lignocellulosic biomass.[11] Indeed, notable progress has been made in recent years in sustainable pyrrole synthesis based on the acceptorless dehydrogenation of alcohols[12] using complexes based on the noble metals Ir and Ru.[13] Kempe and Michlik first reported the efficient synthesis of pyrroles by reaction of amino alcohols with secondary alcohols catalyzed by triazine–iridium complexes,[14] and we reported in the same year that PNN–ruthenium pincer complexes are efficient catalysts for this reaction.[15] Attractive synthesis of various substituted pyrroles catalyzed by $[Ru_3(CO)_{12}]$/Xantphos and $[RuCl_2(p\text{-cymene})]_2$/Xantphos systems using ketones, vicinal diols, amines, and base was demonstrated by Beller et al.[16] An interesting dehydrogenative coupling of 2,5-hexanediol and amines to form pyrroles, albeit in modest yields (45–48 %), catalyzed by a ruthenium complex in the presence of sodium formate, was developed by Crabtree et al.[17]

However, despite the importance of such elegant methods for the synthesis of pyrroles employing noble metals, the development of nonprecious base-metal catalysts would be a significant advance from the perspective of abundance, cost, and sustainability.[18] Moreover, precious metals are often toxic, and potential contamination by particles of these metals is a significant issue in the pharmaceutical industry. Remarkable progress has been made in recent years regarding catalysis by complexes of first-row base metals (Fe, Mn, Ni, Co).[19–21] For example, several homogeneous cobalt catalysts were discovered to be effective in the hydrogenation of olefins,[21a,f] imines,[21a] ketones,[21b] and CO_2.[21h,i] Recently, we reported the first ester hydrogenation[22a] and nitrile hydrogenation[22b] reactions catalyzed by a pyridine-based PNNH–Co pincer complex. Homogeneous cobalt catalysts have also been exploited for dehydrogenation and dehydrogenative coupling reactions. Hanson and Zhang first reported dehydrogenation of secondary alcohols and dehydrogenative coupling of alcohols and amines to form imines, catalyzed by a cationic PNP–Co pincer complex (Figure 1 a).[21b] Jones et al. described the acceptorless dehydrogenation and hydrogenation of N-heterocycles using the same catalyst.[23] Very recently the groups of Kempe,[24a] Zhang,[24b] and Kirchner[24c] independently reported cobalt-catalyzed amine alkylation reactions by alcohols (Figure 1 a).

Herein, we report a pyrrole synthesis catalyzed for the first time by a base-metal complex. It involves acceptorless dehydrogenative coupling of 1,4-substituted 1,4-butanediols and various amines using a cobalt pincer complex to generate 1,2,5-substituted pyrroles with extrusion of water and H_2 as the only by-products.

Initially, we explored the possibility of pyrrole formation from diols and amines using our most promising PNNH–Co precatalyst **1**[22a] (Figure 1 b). To generate the active species, the use of one equiv of $NaHBEt_3$ and *t*BuOK as hydride source and base, respectively, was envisioned as observed in our earlier work on PNNH–Co-catalyzed ester and nitrile hydrogenations.[22]

Reaction of 2,5-hexanediol with n-heptylamine using $NaHBEt_3$, *t*BuOK, and complex **1** in toluene in a closed system in the presence of 4 Å molecular sieves resulted in the formation of *N*-heptyl-2,5-dimethylpyrrole in 74 % yield at 120 °C and in 92 % yield at 150 °C after 24 h (Table 1, entries 1 and 2). Analysis of the gas phase by gas chromatography

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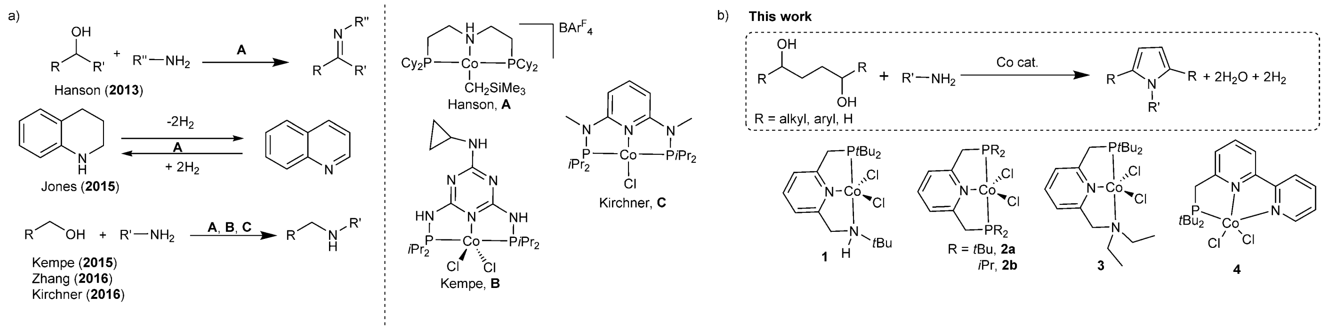
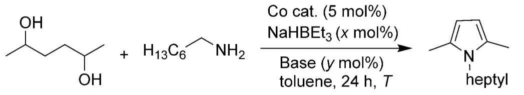


Figure 1. a) Known Co-catalyzed dehydrogenation and dehydrogenative coupling reactions. b) Co pincer complexes explored in this study for pyrrole synthesis.

Table 1: Optimization of the reaction conditions for the dehydrogenative coupling of 2,5-hexanediol and heptylamine.



Entry[a]	Cat.	x	Base (y)	T [°C]	Conv[b] [%]	Yield[b] [%]
1	**1**	5	*t*BuOK (5)	120	99	74
2	**1**	5	*t*BuOK (5)	150	99	92[c]
3[d]	**1**	5	*t*BuOK (5)	reflux	99	71
4[e]	**1**	5	*t*BuOK (5)	150	99	40
5	**2a**	5	*t*BuOK (5)	150	0	0
6	**2b**	5	*t*BuOK (5)	150	82	21
7	**3**	5	*t*BuOK (5)	150	99	77[c]
8	**4**	5	*t*BuOK (5)	150	66	4
9	**1**	5	KHMDS (5)	150	99	85[c]
10	**1**	5	NaOEt (5)	150	99	79[c]
11	**1**	5	KH (5)	150	99	90[c]
12	**1**	–	*t*BuOK (5)	120	0	0
13	**1**	5	–	120	99	16
14	**1**	–	–	120	0	0
15	**1**	10	*t*BuOK (5)	120	99	72
16	**1**	5	*t*BuOK (10)	120	99	70
17[f]	**1**	5	*t*BuOK(5)	120	99	71

[a] Conditions: 2,5-hexanediol (0.5 mmol), heptylamine (0.5 mmol), and dry toluene (2 mL) heated in a closed Teflon Schlenk tube at 120 or 150 °C bath temperature in the presence of 4 Å molecular sieves. [b] Yields and conversions determined by GC and conversion based on 2,5-hexanediol consumption. [c] Yield of isolated product. [d] The reaction was carried out in an open system under N_2 atmosphere while refluxing. [e] The reaction was carried out in the absence of molecular sieves. [f] The reaction was carried out using 1,4-dioxane as the solvent.

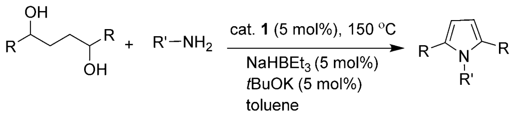
(GC) revealed the formation of H_2. A reaction carried out in an open system in refluxing toluene in the presence of molecular sieves generated 71 % of the pyrrole product (entry 3) indicating that the reaction is not affected significantly by the presence of hydrogen in the closed system. However, in the absence of molecular sieves in the closed system, a lower yield of pyrrole (40 %) was obtained under otherwise similar condition (entry 4).

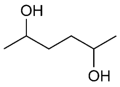
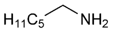
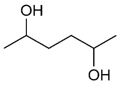
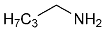
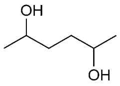
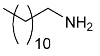
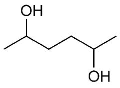
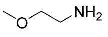
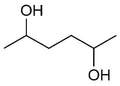
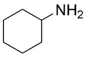
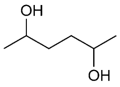
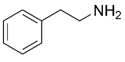
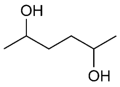
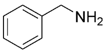
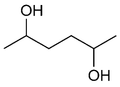
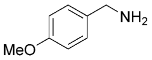
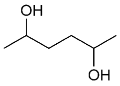
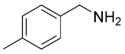
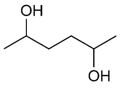
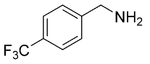
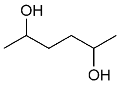
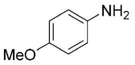
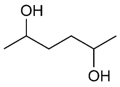
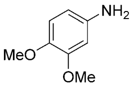
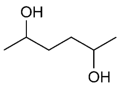
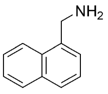
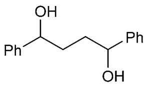
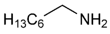
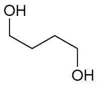
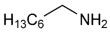
Our previously reported PNP– and PNN–Co dihalo complexes **2**,[25] **3**,[22a] and **4**[26] (Figure 1 b) were then screened. Surprisingly, *t*Bu-substituted complex **2a** did not show any formation of pyrrole at 150 °C (Table 1, entry 5), probably due to steric effects, whereas isopropyl-substituted catalyst **2b** produced 21 % of *N*-heptyl-2,5-dimethylpyrrole (entry 6) and complex **3** yielded 77 % of the pyrrole (entry 7). However, the yield of pyrrole was only 4 % when the bipyridine-based complex **4** was used (entry 8). Therefore the best-performing complex **1** was chosen for further optimization studies.

Exploring the effect of various bases, KHMDS, NaOEt, and KH were employed under similar reaction conditions giving decent yields of pyrroles (entries 9–11). Further testing revealed that in the absence of $NaHBEt_3$, using 5 mol % of pre-catalyst **1** and 5 mol % *t*BuOK at 120 °C, no conversion was observed (entry 12), in the absence of base, using 5 mol % $NaHBEt_3$ and 5 mol % of **1**, only 16 % of *N*-heptyl-2,5-dimethylpyrrole were obtained (entry 13), and in the absence of both *t*BuOK and $NaHBEt_3$, no reaction took place (entry 14). The aforementioned experiments indicate that both $NaHBEt_3$ and *t*BuOK play crucial roles in generating the catalytically active species. However, higher loading of either of them (*t*BuOK or $NaHBEt_3$) (to 10 mol %) under otherwise identical conditions did not significantly improve the yield of pyrrole (entries 15 and 16). Changing the solvent to 1,4-dioxane instead of toluene at 120 °C did not have a significant effect (entry 17). It is worth mentioning at this point that the difference in 2,5-hexanediol conversion and yield of pyrrole as observed in Table 1 indicates formation of a mixture of unindentified products resulting from 2,5-hexanediol. Also formation of small amounts of *N*-heptylidene-1-heptylamine and *N*-heptyl-1-heptylamine was detected by GC-MS, most likely as a result of dehydrogenative coupling of unreacted heptylamine catalyzed by Co.[27] The formation of *N*-heptylidene-1-heptylamine was further confirmed by performing a separate reaction of heptylamine in the absence of 2,5-hexanediol using 5 mol % of complex **1**, 5 mol % $NaHBEt_3$, and 5 mol % *t*BuOK giving 45 % of *N*-heptylidene-1-heptylamine after 24 h at 150 °C. However, the diamine *N*-heptyl-1-heptylamine was not observed in this case.

Using the optimized reaction conditions, the scope of this base-metal-catalyzed dehydrogenative coupling reaction was probed with 2,5-dihydroxyhexane and different amines. As shown in Table 2, various linear primary alkyl amines coupled with dehydrogenated 2,5-hexanediol to yield the corresponding 1,2,5-substituted pyrroles in excellent yields (Table 2, entries 1–4).

Table 2: Dehydrogenative coupling of diols and various amines catalyzed by complex **1**.



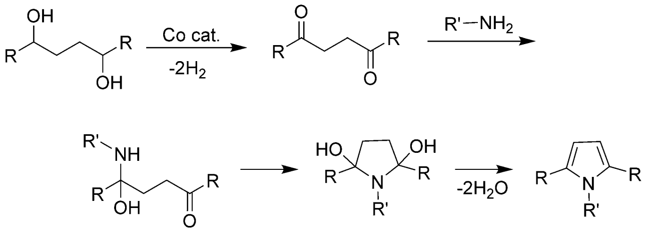
Entry[a]	Diol	Amine (RNH_2)	t [h]	Yield of pyrrole [%]
1			24	88[b]
2			24	93[b]
3			24	86[b]
4			24	90[b]
5			24	70[b]
6			24	62[b]
7			24	89[b]
8			36	68[b]
9			24	87[b]
10			24	60[b]
11			36	25[c]
12			36	22[c]
13			36	78[b]
14			36	56[c]
15			24	58[c]

[a] Conditions: diol (0.5 mmol), amine (0.5 mmol), toluene (2 mL), and 4 Å molecular sieves heated in an closed Schlenk tube for the specified time. [b] Yield of isolated product. [c] Yield determined by GC.

The reaction between 2,5-hexanediol and cyclohexylamine gave 70% yield of 1-cyclohexyl-2,5-dimethylpyrrole (entry 5). Similarly, 62% yield of *N*-phenethyl-2,5-dimethylpyrrole was obtained from 2,5-hexanediol and 2-phenethylamine (entry 6). Exploring the scope further, reactions of 2,5-hexanediol with various benzylamines were studied, resulting in moderate to good yields (entries 7–9). On the other hand dehydrogenative coupling of less basic 4-trifluoromethylbenzylamine with 2,5-hexanediol resulted in an only moderate 60% yield of the pyrrole (entry 10). Reaction of the less nucleophilic anilines with 2,5-hexanediol resulted in low yields (entries 11 and 12).

However, 2,5-hexanediol dehydrogenatively coupled with (1-naphthylmethyl)amine to yield the corresponding 1,2,5-substituted pyrrole in 78% yield (entry 13). The catalytic performance of **1** in the dehydrogenative coupling of 1,4-diphenyl-1,4-butanediol and heptylamine was also checked, producing a moderate 56% yield of 1-heptyl-2,5-diphenylpyrrole (entry 14). Dehydrogenative coupling of primary 1,4-butanediol with heptylamine resulted in 1-heptylpyrrole in 58% yield as observed by GC-MS (entry 15) along with other as yet unidentified products.[17]

Regarding the nature of the active cobalt catalyst, we previously reported that treatment of complex **1** with one equiv of $NaHBEt_3$ at room temperature gave the paramagnetic complex (PNNH)$Co^{I}Cl$, characterized by X-ray crystallography.[22a] This Co^{I} complex was prepared and isolated separately and tested in the dehydrogenative coupling of 2,5-hexanediol and heptylamine. Using 5 mol% of (PNNH)$Co^{I}Cl$ and 5 mol% *t*BuOK at 150 °C yielded 86% of *N*-heptyl-2,5-dimethylpyrrole after 24 h, which is comparable to the results obtained when using Co^{II} complex **1** in the presence of $NaHBEt_3$ and *t*BuOK (Table 1, entry 2). This suggests that the actual catalyst is a Co^{I} complex. However, attempts to isolate the active Co^{I} catalyst by treating (PNNH)$Co^{I}Cl$ with one equiv of *t*BuOK failed. We also could not isolate an in situ generated intermediate in the reactions. Nevertheless, we believe that under the reaction conditions, a mono-deprotonated Co^{I} complex is formed by dehydrohalogention via either the N−H or the methylene proton of the N-arm of the pincer ligand. The unique feature of the metal complexes developed with the PNNH ligand is that they have the potential for metal–ligand cooperation by both amine–amide and aromatization–dearomatization ligand transformations.[28] The possibly generated highly unsaturated Co^{I} complex is anticipated to be stabilized by potential binding with alcohol giving an alkoxy– Co^{I} complex, which could undergo dehydrogenation under the catalytic conditions to give the ketone, liberating H_2. The ketone subsequently could couple with the present amine and form the N-substituted pyrrole and water in a Paal–Knorr condensation (Scheme 1). This step was confirmed by a separate experiment starting from 2,5-hexanedione with heptylamine at 150 °C in the absence of catalyst, quantitatively yielding the corresponding *N*-heptyl-2,5-dimethylpyrrole. However, dehydrogenation of 2,5-hexanediol in the absence of an amine resulted in a mixture of unidentified products, not including 2,5-hexanedione. Nevertheless, the ability of catalyst **1** in the dehydrogenation of a secondary alcohol was demonstrated



Scheme 1. Plausible scheme for pyrrole synthesis from diols and amines catalyzed by Co.

by dehydrogenation of 1-phenylethanol using 5 mol % **1**, NaHBEt$_3$, and *t*BuOK (5 mol %), yielding acetophenone in 65 % yield at 120 °C after 24 h.

In conclusion, dehydrogenative coupling of diols and amines to form N-substituted pyrroles, catalyzed for the first time by a complex of an earth-abundant metal, was discovered. The reaction, catalyzed by Co pincer complexes, is applicable to a wide range of primary alkyl amines, benzylic amines, and aromatic amines, and to primary and secondary diols. Further investigation regarding the mechanism of this reaction is underway.

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Keywords: cobalt · dehydrogenative coupling · pincer complexes · pyrroles

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