

Multiple Deprotonations and Deaminations of Phenethylamines to Synthesize Pyrroles

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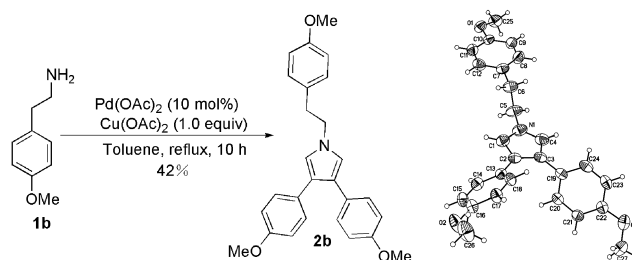
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The development of catalytic systems for direct functionalization of sp^3 C–H bonds provides extremely important tools for contemporary chemistry. The success of such processes would provide potentially economic and clean methods for constructing many chemicals directly from hydrocarbons and their simple derivatives. Currently, transition metal complexes have been widely tested to activate sp^3 C–H bonds for generation of new C–X bonds (X = C, O, B, etc.).^{1,2} However, simultaneous activation of two different sp^3 C–H bonds in a one-pot process has been rarely reported.³ Herein we present a process in which two different sp^3 C–H bonds were selectively activated under the same conditions to construct a useful core structure.

The sp^3 C–H bonds adjacent to amines are relatively activated and can be functionalized with different reagents under special conditions.^{3a,4} Li et al. demonstrated that Cu-based catalysts can perform such functions.^{3a,4a,b} They can also be activated by low valent Ir complexes to form fused rings, as reported by Sames et al. very recently.^{4c} It is also well-known that the benzylic sp^3 C–H bond is more reactive than general sp^3 C–H's in alkanes and can be activated through several different pathways.⁵ We attempted to activate the two different sp^3 C–H bonds in phenethylamine **1**. Previously, Kindler and Murahashi have reported that diphenethylamine can be produced by deamination of phenethylamine.⁶ The imine was assumed to be a key intermediate in the deamination of phenethylamine **1a** through C–H bond activation at the α -position of the amino group. Surprisingly, during our screening efforts to test different reaction conditions, we discovered a mysterious product with a very simple ¹H NMR spectrum. This product was produced when phenethylamine **1a** was treated with a stoichiometric amount $Cu(OAc)_2$ in the presence of a catalytic amount of $Pd(OAc)_2$. High-resolution mass spectroscopy indicated that the molecular weight of this product was 323.16720, which fits the formula of $C_{24}H_{21}N$ well. The IR spectrum implied that the compound contained a pyrrole ring as a core structure.

To further confirm the structure of the product, *p*-methoxyphenethylamine **1b** was employed as the starting material instead of phenethylamine **1a**, and a similar solid product **2b** was produced in a moderate isolated yield (Scheme 1). Single crystals of **2b** were easily obtained by recrystallization in diethyl ether and petroleum ether. The X-ray structure of **2b** was determined (Scheme 1), which indicated that the hypothesized structure of pyrrole product **2b** was correct. According to an extensive literature search, pyrrole is not only a common structural unit in many materials⁷ but also one of the more important structural motifs in numerous natural products⁸ and bioactive molecules.⁹ For example, 1-phenethyl-3,4-diaryl pyrrole **2** is the key scaffold of lamellarin, a bioactive marine natural product isolated from *prosobranch mollusc lamellarin* sp.¹⁰ The

Scheme 1



discovered transformation here may offer the most straightforward route to synthesize aryl-substituted pyrroles.

After the discovery of this method to access aryl-substituted pyrroles from commercially available phenethylamine, we systematically tested different reaction conditions (Table 1). We found that (i) this transformation could take place in the presence of $Cu(OAc)_2$ with lower efficiency (entries 1 and 2); (ii) $Pd(II)$ catalysts other than $Pd(OAc)_2$ can also promote this process in the presence of $Cu(OAc)_2$, while $PdCl_2$ had the highest efficiency. However, $Pd(0)$ species, such as $Pd_2(dba)_3$, decreased the efficiency of this reaction. It is noteworthy that this transformation could not run smoothly only in the presence of either a catalytic or stoichiometric amount of $Pd(II)$ species (entries 8 and 9); (iii) other metal salts, such as $FeCl_2$, $NiCl_2$, $PtCl_2$, etc., could not be employed as promoters to replace the $Pd(II)$ species (Supporting Information Table 1); (iv) in the presence of $PdCl_2$, other common inorganic oxidants, such as $K_2Cr_2O_7$, $FeCl_3$, etc., were not beneficial to the reaction, and no product **2a** was observed under these conditions (Supporting Information Table 1). When 1.0 equiv of $Cu(OAc)_2$ and 5 mol % of $PdCl_2$ were used, the reaction proceeded in good yield (42%) of **2a** from **1a** (entry 6). Increasing the quantity of $Cu(OAc)_2$ did not affect the efficiency of this transformation; in contrast, the yield of pyrrole decreased slightly with the decrease of the amount of $Cu(OAc)_2$. Moreover, the yield did not change much in the presence of either 5 or 10 mol % of $PdCl_2$. Finally, when the temperature was increased to 155 °C with xylene as the solvent, the reaction ran much faster and the efficiency of this transformation increased slightly. However, longer reaction times decreased the efficiency perhaps due to the decomposition of product under these harsh conditions (entry 10).

To explore the application of this method, the scope of the substrates was evaluated with a variety of substituted phenethylamines (Table 2). Electron-donating groups increased the efficiency of this transformation (entries 2–7, Table 2). In contrast, electron-withdrawing groups decreased the yields (entries 8–10, Table 2), indicating that the reactivity of the sp^3 C–H at the benzylic position was affected by electronic effects from the substituents on the phenyl ring. It was important to note that the sp^3 C–H bond of the

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Table 1. Deprotonation/Deamination of **1a** under Different Conditions^a

1a entry		[Pd] (mol%)	Cu salt (equiv)	2a (%) ^b
1	-	-	Cu(OAc) ₂ (1.0)	22
2	-	-	Cu(OAc) ₂ (2.0)	18
3	Pd(OAc) ₂ (5)	-	Cu(OAc) ₂ (1.0)	34
4	Pd(dba) ₂ (2.5)	-	Cu(OAc) ₂ (1.0)	16
5	Pd(CH ₃ CN) ₂ Cl ₂ (5)	-	Cu(OAc) ₂ (1.0)	38
6	Pd(PhCN) ₂ Cl ₂ (5)	-	Cu(OAc) ₂ (1.0)	37
7	PdCl ₂ (5)	-	Cu(OAc) ₂ (1.0)	42
8	PdCl ₂ (5 or 100)	-	-	<5
9	Pd(OAc) ₂ (100)	-	-	11
10	PdCl ₂ (5)	-	Cu(OAc) ₂ (0.5)	38
11	PdCl ₂ (5)	-	Cu(OAc) ₂ (2.0)	41
12 ^c	PdCl ₂ (5)	-	Cu(OAc) ₂ (1.0)	46

^a All reactions were carried out in the scale of 1.0 mmol in 4 mL of toluene unless otherwise noted. ^b Isolated yield. ^c The reaction was carried out in xylenes at 155 °C for 4 h.

Table 2. Syntheses of Pyrroles from Commercially Available Phenethylamines^a

1 entry		1	Ar	2	yield (%) ^b
1 ^c	1a	C ₆ H ₅	2a	46	
2 ^d	1b	<i>p</i> -CH ₃ OC ₆ H ₄	2b	51	
3 ^d	1c	<i>o</i> -CH ₃ OC ₆ H ₄	2c	64	
4 ^d	1d	<i>p</i> -CH ₃ C ₆ H ₄	2d	48	
5 ^d	1e	<i>m</i> -CH ₃ C ₆ H ₄	2e	45	
6 ^d	1f	<i>o</i> -CH ₃ C ₆ H ₄	2f	62	
7 ^d	1g	2,5-(CH ₃) ₂ C ₆ H ₃	2g	71	
8 ^c	1h	<i>p</i> -FC ₆ H ₄	2h	41	
9 ^c	1i	<i>m</i> -FC ₆ H ₄	2i	31	
10 ^c	1j	<i>m</i> -CF ₃ C ₆ H ₄	2j	40	
11 ^{c,e}	1a	C ₆ H ₅	2a	38	

^a All reactions were carried out in the scale of 1.0 mmol in 5.0 mol % of PdCl₂ and 1.0 equiv of Cu(OAc)₂ in 4 mL of toluene unless otherwise noted, and starting material was completely consumed. Products **2** were accompanied by varying amounts of highly polar byproducts. ^b Isolated yield. ^c The reaction was carried out in xylenes at 155 °C for 4 h. ^d The reactions were carried out in toluene at 115 °C for 16 h. ^e This reaction was carried out in the scale of 10.0 mmol.

benzylic methyl group was not activated under these conditions (entries 4–7, Table 2). Furthermore, fluoro-substituted phenethylamines (**1h** and **1i**) were also employed as substrates, and products were isolated with the original C–F bond on the phenyl ring untouched (entries 8 and 9, Table 2). The lower yields in these reactions may be due to the electron-withdrawing effect of the fluoro substituent. It is noteworthy that steric effects from the ortho substituents on the phenethylamine did not play an important role, and the corresponding products were obtained in moderate to good yields (entries 3, 6, and 7, Table 2). Moreover, high temperature increased the efficiency of this transformation slightly when phenethylamines, which contained electron-deficient groups on the phenyl ring, were used as the starting materials. In contrast, lower efficiency was observed with electron-rich phenethylamines as substrates at higher temperature (Supporting Information Table 2).

During this process, small amounts of benzyl nitrile and phenethyl *N*-acetamide were observed as byproducts. However, neither of these compounds could serve as substrates for this transformation. Thus, they were excluded as intermediates during

this process. Furthermore, starting from 2-(4-methoxyphenyl)-*N*-(2-phenylethylidene)ethanamine and *p*-methoxyphenethylamine, the desired pyrrole products were observed, in which both phenyl and methoxyphenyl groups were introduced into the product. Therefore, we hypothesized that an imine might be a key intermediate for this transformation, which was produced through dehydrogenation and deamination from phenethylamine based on a previous report.⁶

In summary, we have discovered a unique method to construct polysubstituted pyrroles from commercially available phenethylamines. During this transformation, twelve protons and two nitrogen atoms were removed. In addition, at least twelve bonds, including two types of sp³ C–H and C–N bonds, were cleaved and five new bonds (two C–N bond, two C–C double bonds, and one C–C single bond) were constructed in one pot. Further efforts to clearly understand the reaction mechanism and explore the synthetic utility of the reaction are underway.

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Supporting Information Available: A brief experimental details, X-ray structure, and other spectra data for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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