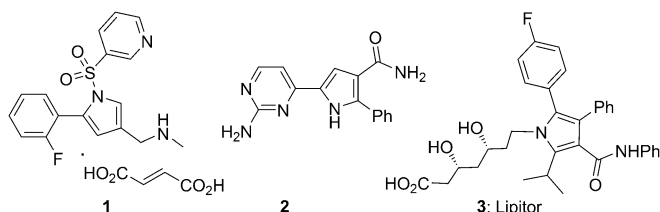


Selective Ruthenium-Catalyzed Three-Component Synthesis of Pyrroles**

Min Zhang, Helfried Neumann, and Matthias Beller*

Pyrroles represent interesting heterocycles that exhibit diverse biological and therapeutic activities. As shown in Scheme 1, notable pharmaceuticals such as the antitumor



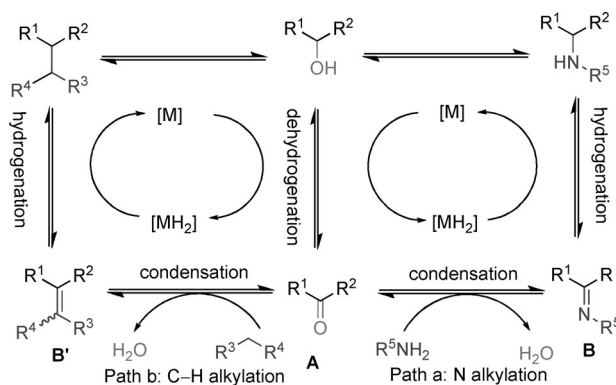
Scheme 1. Selected examples of pyrrole-based bioactive and pharmaceutical compounds.

agent **1**,^[1a] a potent blocker for potassium-competitive acid (**2**),^[1b] and the leading cholesterol-lowering drug Lipitor (**3**)^[1c] constitute multiple substituted pyrroles. In addition, pyrrole-based derivatives serve as valuable intermediates in preparation of agrochemicals, flavor components,^[2a] dyes,^[2b,c] and functionalized materials.^[3]

Traditionally, pyrroles are prepared by classical Paal-Knorr^[4] and Hantzsch^[5] syntheses. More recently, also metal-catalyzed inter-^[6] and intramolecular^[7] cyclization reactions have provided elegant approaches for their syntheses. Nevertheless, many of these synthetic protocols either need multiple steps and prefunctionalized substrates, or make use of reagents which generate halide wastes. In this respect, the development of atom-economic methodologies starting from inexpensive and easily available substrates remains a demanding goal.

During the past decade, transition-metal-catalyzed “borrowing-hydrogen”^[8] or the so-called “hydrogen autotransfer”^[9] reactions have evolved as powerful tools for the more benign amination and alkylation of alcohols. In both cases,

water is the only by-product and less environmentally benign alkylating agents such as alkyl halides are avoided. Mechanistic investigations showed that these processes proceed by the following tandem sequences: Metal-induced in situ dehydrogenation of the alcohol to generate the corresponding ketone **A**. Subsequent condensation of **A** with an amine (Scheme 2, Path a) or activated methylene compounds



Scheme 2. Direct amination and alkylation reactions of alcohols.

(Scheme 2, Path b) gives the imine **B** and alkene **B'**, respectively. Finally, hydrogenation of either **B** or **B'** releases the aminated or alkylated products. Interestingly, the hydrogen required for the final hydrogenation step comes from the first dehydrogenation step of the alcohol.

While significant improvements on alkylation of amines and activated methylene substrates have been reported in recent years by the groups of Williams,^[10] Fujita,^[11] Kempe,^[12] Beller,^[13] and others,^[14] the related transformations of enamines (or its tautomer imines) have been little explored.

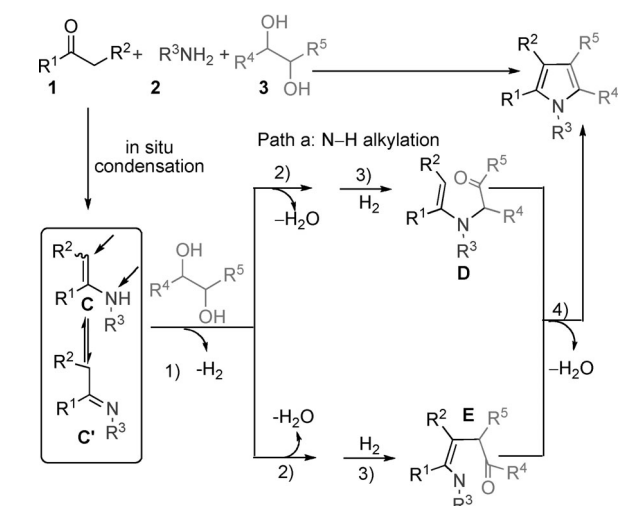
Based on our previous work in this area, we decided to combine both the ruthenium-catalyzed amination of alcohols and alkylations (Scheme 2) into one process. To the best of our knowledge such a tandem reaction has not been reported yet. However as shown in Scheme 3, this should be possible by the reaction of 1,2-diols with enamines or imines. After the sequential inter- and intramolecular ruthenium-catalyzed dehydrogenation and alkylation steps^[15] (Scheme 3, Paths a and b, steps 1–3), the thermodynamically favorable dehydration should result in substituted pyrroles (Paths a and b, step 4). One of the problems associated with the envisioned process is the control of regioselectivity because the enamine **C** (or imine **C'**) can competitively undergo initial alkylation at the NH or CH position, which should lead to different regioisomers. Furthermore, the starting materials are known to undergo aldol-type side reactions. To overcome the latter

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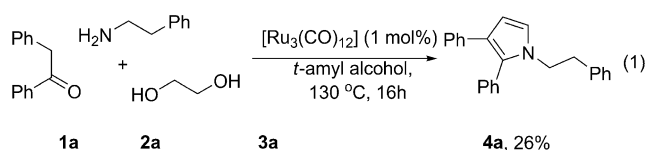
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Scheme 3. New three-component coupling to access pyrroles. Path a: C–H alkylation.

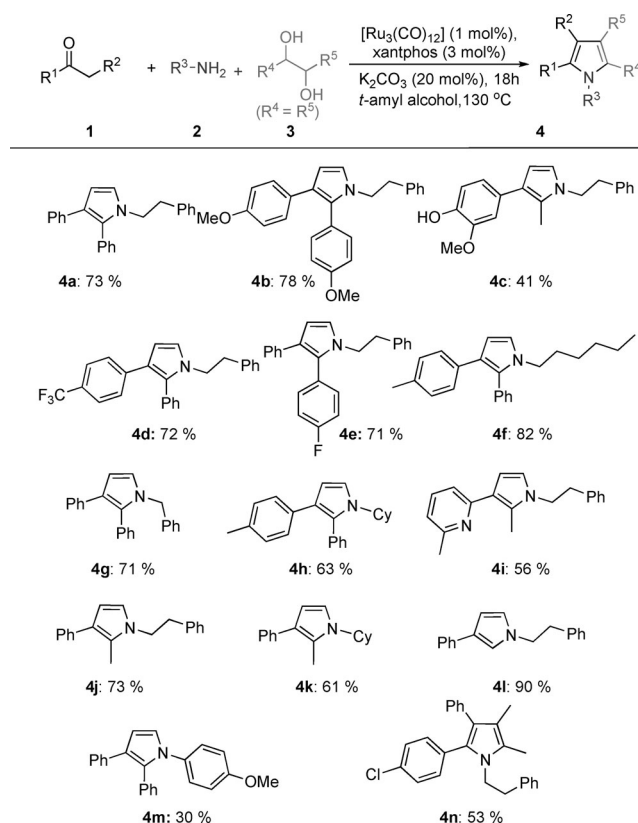
problem, we thought we could generate the required enamines in situ from ketones and amines (see Scheme S2 in the Supporting Information). With this hypothesis in mind, we initiated a study by testing the reaction of 1,2-diphenylethanone (**1a**), 2-phenylethanamine (**2a**), and ethylene glycol (**3a**). By performing the three component reaction in the presence of 1 mol % of $[\text{Ru}_3(\text{CO})_{12}]$ as the catalyst and *tert*-amyl alcohol at 130 °C for 16 hours, the desired pyrrole **4a** was observed in a 26 % yield [Eq. (1)].



Although this yield seems low, it should be noted that the overall sequence consists of six consecutive reaction steps involving two C–N and one C–C bond formations, two dehydration steps, as well as one catalytic dehydrogenation reaction, all of which proceed in only one operation.

Next, representative catalyst precursors, phosphine ligands, temperatures, and solvents were examined to improve the efficiency for the synthesis 1-phenethyl-2,3-diphenyl-1H-pyrrole (**4a**; see Table S1 in the Supporting Information). An optimal yield of 82 % for **4a** was obtained at 130 °C using 1 mol % of $[\text{Ru}_3(\text{CO})_{12}]$, 3 mol % of Xantphos (Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene), 20 mol % of K_2CO_3 , and *tert*-amyl alcohol as the solvent.

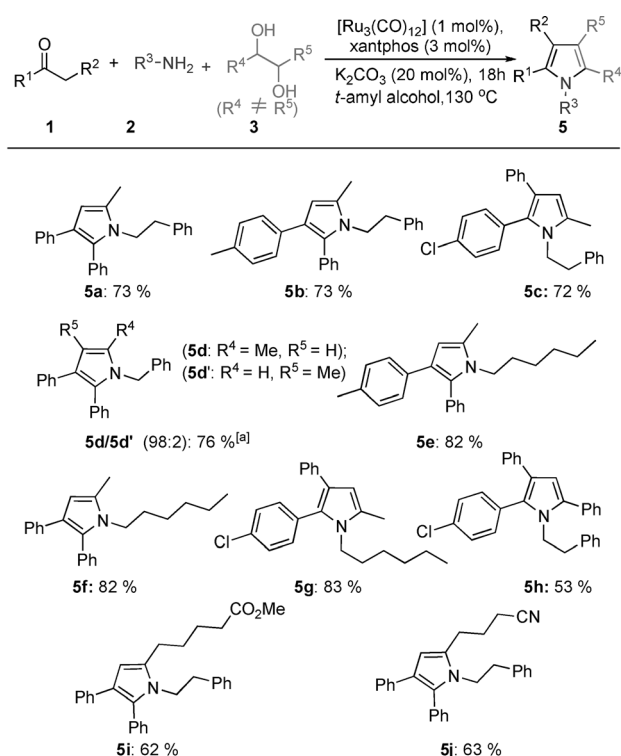
With optimized reaction conditions in hand, we examined the scope and limitations of our novel synthetic process. Initially, ethylene glycol (**3a**) was employed in combination with various benzylic ketones including functional and heterocyclic ones and primary amines, to synthesize 1,2,3-trisubstituted pyrroles. As shown in Scheme 4, all the reactions proceeded smoothly and gave the desired products in moderate to excellent yields upon isolation (**4a–4k** and



Scheme 4. Synthesis of substituted pyrroles using symmetrical vicinal diols. For reaction conditions and substrate information see Table S2 and Scheme S1 in the Supporting Information, respectively. Yield is that of the isolated product. Cy = cyclohexyl.

4m). The reaction using less sterically hindered 2-phenylacetaldehyde (**1i**) and the amine **3a** yielded the 1,3-disubstituted product in almost quantitative yield (**4l**). Notably, not just 1,3- and 1,2,3-substituted pyrroles can be conveniently prepared, but even more complex 1,2,3,4,5-pentasubstituted derivatives are directly accessible. Hence, butane-2,3-diol (**3b**) was converted into the fully substituted pyrrole **4n** in 53 % yield. Gratifyingly, anisidine (**2e**) was successfully employed for the three-component coupling reaction in spite of its limited nucleophilicity. And the N-arylated product **4m** was obtained, without further optimization, in lower yield. However, reactions using weak nucleophiles such as 4-methylbenzenesulfonamide or 1,1,1-trifluoro-3-phenylpropan-2-one failed to give the desired products. Apparently, in these cases the nucleophilicity of the corresponding enamine intermediates is insufficient for the cyclization process, and is in agreement with the proposed mechanism described in Scheme 3.

Next, the more challenging unsymmetrical vicinal diols **3e–h** were tested as substrates. Clearly, two regioisomeric pyrroles can result from these reactions, thus lowering the synthetic usefulness of the protocol. Gratifyingly, in all cases either one product was obtained exclusively (**5a–5c** and **5e–5j**; Scheme 5) or a very high regioselectivity was observed (**5d** and **5d'**). This observation also sheds some light on the origin of the reaction sequence: Prior to the C–N bond-forming step the C–H alkylation occurs at the more reactive, sterically less

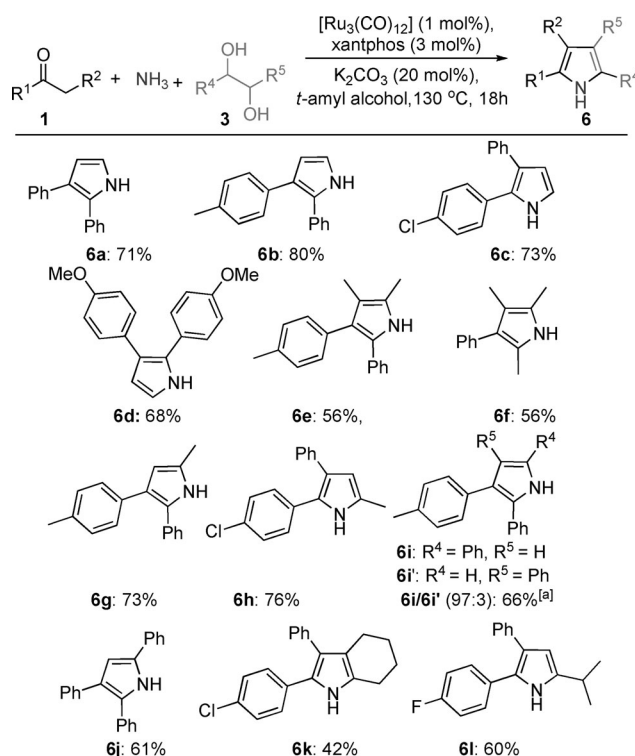


Scheme 5. Synthesis of substituted pyrroles using unsymmetrical vicinal diols. For reaction conditions and substrate information see Table S3 and Scheme S1 in the Supporting Information, respectively. Yield is that of isolated product. [a] Total yield of two isomers.

hindered position of the vicinal diols. Thus, at least for terminal diols Path b (Scheme 3) seems to be favored for the formation of pyrroles. It should be noted that the resulting 1,3-, 1,2,3-, and 1,2,3,5-substituted pyrroles (Schemes 4 and 5) can be easily and selectively additionally elaborated by direct C–H bond functionalization reactions.^[16]

Considering the importance of N-nonsubstituted pyrroles as versatile intermediates for industrial organic syntheses and academic research,^[15a,f,17] we finally focused our attention on the reaction of benzylic ketones and diols with ammonia, which is the most challenging amine coupling partner.^[13,18] We were pleased to find that in all cases examined the catalytic three-component reactions proceeded smoothly and furnished the corresponding products in moderate to good yields. Similar to the reactions described in Schemes 4 and 5, sterically less hindered vicinal diols gave the products (**6a–6d**, **6g–6h**; Scheme 6) in higher yields than when using the bulkier **3b** (see **6e–6f**) and **3f** (1-phenylethane-1,2-diol) (see **6i–6j**). In addition, the even less reactive cyclohexane-1,2-diol (**3g**) was well tolerated and gave the tetrahydroindole derivative **6k** in a reasonable yield. This example shows the potential of the methodology for the synthesis of a variety of annulated heterocycles. Interestingly, a Lipitor precursor can also be efficiently prepared by employing our synthetic protocol (**6l**; Scheme 4).

In summary, we have developed a straightforward ruthenium-catalyzed, three-component synthesis of pyrroles. This methodology allows preparation of various classes of multiply



Scheme 6. Synthesis of N-nonsubstituted pyrroles using ammonia. For reaction conditions and substrate information see Table S4 and Scheme S1 in the Supporting Information, respectively. Yield is that of isolated products. [a] Total yield of two isomers.

substituted pyrroles (1,3- and 2,3-disubstituted, 2,3,5- and 1,2,3-trisubstituted, 1,2,3,5- and 2,3,4,5-tetrasubstituted, as well as pentasubstituted derivatives) starting from easily available benzylic ketones, vicinal diols, and amines including primary anilines and alkyl amines as well as ammonia. Notably, the atom-efficient synthetic protocol proceeds efficiently in the presence of a commercially available [Ru₃(CO)₁₂]/Xantphos catalyst system without special glassware. We are convinced that our procedure has a significant value for the preparation of novel and known pyrrole derivatives, which represent important intermediates in biological, organic, and materials chemistry.

Experimental Section

Typical procedure for the preparation of **4a**: [Ru₃(CO)₁₂] (3.2 mg, 0.005 mmol), Xantphos (8.7 mg, 0.015 mmol), K₂CO₃ (13.8 mg, 0.1 mmol), and 1,2-diphenylethanone (**1a**; 98 mg, 0.5 mmol) were added successively to a glass pressure tube (25 mL) equipped with a magnetic stirrer bar, and the pressure tube was then purged. Under an argon atmosphere 2-phenylethylamine (**2a**; 91 mg, 0.75 mmol), ethylene glycol (62 mg, 1 mmol), and *tert*-amyl alcohol (1 mL) were added. The pressure tube was closed with a Teflon cap and the resulting mixture was stirred at 130 °C for 18 h under argon. After cooling to room temperature, the solvent was removed under vacuum. The residue was directly purified by flash chromatography on silica gel (eluent: heptane/ethyl acetate = 50:1) to give 1-phenethyl-2,3-diphenyl-1H-pyrrole (**4a**) as a white solid (118 mg, 73 %).

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