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General and Regioselective Synthesis of Pyrroles via Ruthenium-Catalyzed Multicomponent Reactions

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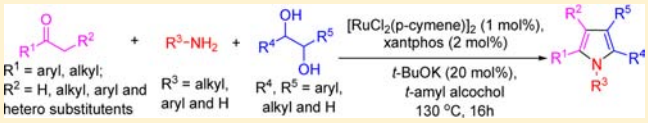
Supporting Information

ABSTRACT: A general and highly regioselective synthesis of pyrroles via ruthenium-catalyzed three-component reactions has been developed. A variety of ketones including less reactive aryl and alkyl substrates were efficiently converted in combination with different type of amines and vicinal diols into various substituted pyrroles in reasonable to excellent isolated yields. Additionally, α-functionalized ketones gave synthetically interesting amido-, alkoxy-, aryloxy-, and phosphate-substituted pyrroles in a straightforward manner. The synthetic protocol proceeds in the presence of a commercially available ruthenium catalyst system and catalytic amount of base. It proceeds with high atom-efficiency and shows a broad substrate scope and functional group tolerance, making it a highly practical approach for preparation of various pyrrole derivatives.



INTRODUCTION

The development of efficient catalytic systems to convert abundant feedstocks into valuable products is of high importance in modern synthetic chemistry.[1] During the past decade, the "hydrogen autotransfer" methodology has become a powerful tool for the benign construction of carbon−carbon (C−C) and carbon−nitrogen (C−N) bonds using sustainable and abundant alcohols as coupling reagents.[2,3] In principle, in these transformations only water is generated as byproduct, and more hazardous alkylating agents such as alkyl halides can be avoided. Generally, the dehydrogenation of the alcohol in the presence of suitable transition-metal catalysts and ligands is the key point for substrate activation. In this respect, in recent years, important advancements from the groups of Williams,[4] Fujita,[5] Bruneau,[6] Krische,[7] Kempe,[8] us,[9] and others[10] have been achieved. Notably, most of this work focused on the synthesis of alkyl amines and related C−C bond formations. However, the preparation of biologically interesting heterocycles by employing N−H alkylation or C−H alkylation is scarcely explored.

Because of the significant importance of pyrroles, which are not only applied in current pharmaceuticals[11] but also used as versatile intermediates in the preparation of agrochemicals, flavors, dyes, and functionalized materials,[12] recently we have established a new ruthenium-catalyzed three-component coupling reaction.[13] Parallel to our work, Kempe and co-workers described an elegant Ir-catalyzed reaction of β-aminoalcohols with alcohols to give pyrroles.[14,15]

As compared to other recently developed pyrrole syntheses,[16] the novel dehydrogenative protocols start from easily available substrates giving the heterocycle in an atom-efficient manner with only one single operation. Nevertheless, these methodologies are still somewhat limited. While using the Ir-catalyst, stoichiometric amount of base have to be used, the known ruthenium-catalyzed coupling protocol is restricted to the use of activated benzylic ketones with amines and sterically less-hindered vicinal diols. Hence, there is still a need for improved catalyst systems. In this respect, we report here a general and versatile method for the synthesis of various substituted pyrroles from less reactive but abundant aryl and alkyl ketones as well as α-functionalized and activated benzylic ones in the presence of a $[Ru(p\text{-cymene})Cl_2]_2$/Xantphos/*t*-BuOK catalyst system.

RESULTS AND DISCUSSION

To develop an improved catalytic system for a general synthesis of pyrroles, the formation of 3-methyl-1-phenethyl-2-phenyl-1*H*-pyrrole **4a** from propiophenone **1b**, 2-phenylethanamine **2a**, and ethylene glycol **3a** was chosen as a model reaction. Initially, the influence of different bases, catalyst precursors, and ligands on the reaction efficiency was determined. Applying our previously published catalytic systems based on $[Ru_3(CO)_{12}]$ in the presence of phosphine ligands and K_2CO_3 in the model reaction, only a trace amount of **4a** was formed (Table 1, entry 1). However, changing K_2CO_3 to stronger bases resulted in improved yields, and *t*-BuOK gave the best yield (Table 1, entries 2−4). Hence, we tested *t*-BuOK in combination with xantphos (L1) and several other common hydrogen autotransfer catalysts (Table 1, entries 5−8). Gratifyingly, cost-effective $[Ru(p\text{-cymene})Cl_2]_2$ gave the best yield (Table 1, entry 7). The use of this catalyst in the absence of base or ligand led to decreased product yields (Table 1, entries 9,10). Notably, under catalyst-free conditions, no desired product was obtained. This clearly indicates that base, ligand, and the ruthenium catalyst are crucial factors for the formation of the product (Table 1, entry 11). Furthermore, we tested $[Ru(p\text{-cymene})Cl_2]_2$ together with other ligands, which have proven

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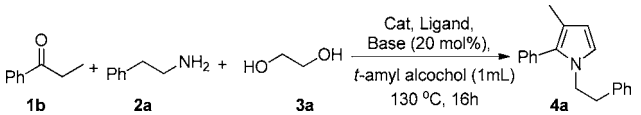
Table 1. Investigating the Model Reaction: Synthesis of 4a[a]



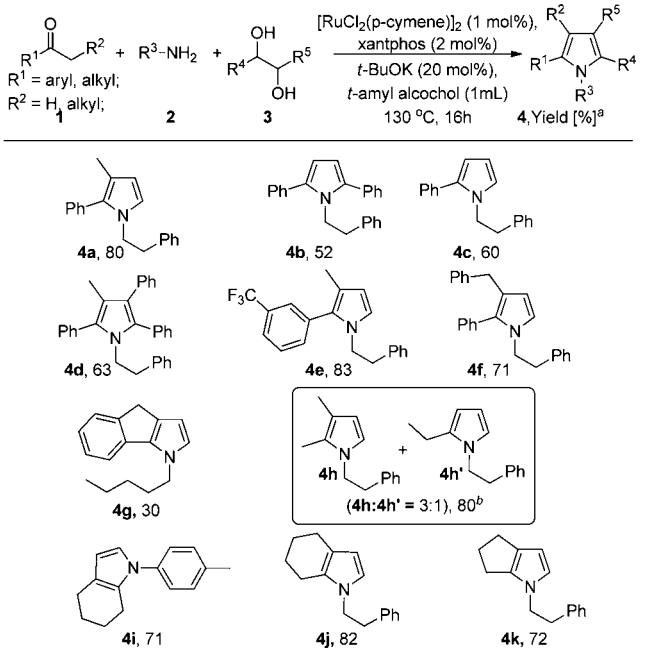
entry	catalyst	base	ligand[b]	4a yield %[c]
1	$Ru_3(CO)_{12}$[d]	K_2CO_3	L1	<5
2	$Ru_3(CO)_{12}$[d]	KOH	L1	40
3	$Ru_3(CO)_{12}$[d]	MeONa	L1	52
4	$Ru_3(CO)_{12}$[d]	*t*-BuOK	L1	56
5	$RuHCl(CO)(PPh_3)_3$[e]	*t*-BuOK	L1	52
6	$Rh(OAc)_3$[e]	*t*-BuOK	L1	16
7	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK	L1	87
8	$[Cp^*IrCl2]_2$	*t*-BuOK	L1	69
9	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK		56
10	$[Ru(p\text{-cymene})Cl_2]_2$		L1	32
11		*t*-BuOK	L1	
12	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK	L2	<10
13	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK	L3	<10
14	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK	L4	42
15	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK	L5	65
16	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK	L6	62
17	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-BuOK	L7	43

[a]Reation conditions: Unless otherwise specified, all reactions were carried out under argon protection with **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (1.1 mmol), catalyst (0.005 mmol), and ligand (0.02 mmol of monophosphine, 0.01 mmol of diphosphine) in *tert*-amyl alcohol (1 mL) at 130 °C for 16 h. [b]For ligand information, see Table S1 in the Supporting Information. [c]GC yield using hexadecane as an internal standard. [d]Catalyst loading (0.0034 mmol). [e]Catalyst loading (0.01 mmol).

successful in hydrogen autotransfer reactions,[7a,9a,b,d,e] in the presence of *t*-BuOK as the base. The results showed that these ligands are not as efficient as xantphos (L1) (Table 1, comparie entries 12−17 with 7). Thus, the optimal yield of **4a** was obtained at 130 °C and by using 1 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ catalyst, 2 mol % of Xantphos (L1), 20 mol % of *t*-BuOK, along with *t*-amyl alcohol as the solvent.

With the improved conditions in hand, we examined the generality and limitation of the modified ruthenium catalyst system. First, we focused on the three-component reaction using less-reactive aryl and alkyl ketones with different amines and vicinal diols. As shown in Scheme 1, all of the reactions proceeded smoothly and furnished the desired products in moderate to very good isolated yields (Scheme 1, see **4a**−**4k**). Interestingly, not only aryl ketones can be converted into 2-aryl pyrroles (Scheme 1, see **4a**−**4g**), but also abundant alkyl ketones afforded alkyl-substituted pyrroles in high yields (Scheme 1, see **4h**−**4k**). The reaction using butanone **1f** gave two regioisomers **4h** and **4h′** in a ratio of 3:1, and the C−C coupling mainly occurred at the methyl-substituted α-position. The reactions of 1-indanone **1e**, cyclohexanone **1g**, and cyclopentanone **1h** resulted in interesting tri- and bicyclic products **4g**, **4i**−**4k**, respectively. These examples demonstrate the potential of the methodology for the construction of various annulated heteroclycles. Noteworthy, not only 1,2-, 1,2,3-, and 1,2,4-substituted pyrroles can be conveniently prepared, even bulky 1,2-diphenylethane-1,2-diol **3c** can be utilized to form more complex fully substituted pyrrole derivative (Scheme 1, see **4d**).

Scheme 1. Synthesis of Substituted Pyrroles Using Less Reactive Aryl and Alkyl Ketones[a]



[a](a) Isolated yield. (b) Total yield of two regioisomers. Reaction conditions: See Table S2 in the Supporting Information.

Because of the interesting bioactivities and applications in medicinal chemistry of heteroatom-substituted pyrroles,[17] we subsequently tried to introduce heteroatom substituents into the pyrrole skeleton by using α-functionalized ketones. Hence, the coupling process of *N*-(2-oxo-2-phenylethyl)benzamide **1i** with less sterically hindered amine **2a** and diol **3a** was tested. Gratifyingly, the desired 3-benzamido-substituted pyrrole **5a** is afforded in almost quantitative yield (Scheme 2, see **5a**). Further investigations showed that **1i** in combinations with different vicinal diols and amines gave various substituted products in high yields upon isolation (Scheme 2, see **5b**−**5e**). Interestingly, α-alkoxy ketone **1j** and α-aryloxy ketone **1k** also proved to be efficient coupling partners, providing a variety of 3-alkoxy- and -aryloxy-pyrroles in moderate to high yields (Scheme 2, see **5f**−**5n**). Noteworthy, diethyl 2-oxo-2-phenylethyl-phosphonate **1l** was successfully converted into the corresponding product **5o** in a moderate yield upon isolation. This example demonstrates the potential for further preparation of pyrrole-based phosphonates and also phosphine ligands via chemoselective reduction of the phosphate groups.[18] In general, reactions of bulky 2,3-disubstituted diols (phenyl-substituted diols **3b**, **3c** and butane-2,3-diol **3d**) and weak nucleophiles, for example, aniline **2c**, gave the products in lower yields (Scheme 2, see **5b**, **5e**, **5h**−**5j**, **5l**, and **5m**), indicating that the steric effect and nucleophilicity of the amines are two major factors influencing the reaction efficiency.

Employing unsymmetrical vicinal diols such as **3b** and **3e** could result in two regioisomeric pyrroles. Gratifyingly, in all cases, either one product was obtained exclusively (Scheme 2, see **5m** and **5n**) or a high regioselectivity was observed (Scheme 2, **5d** and **5d′** in a ratio of 96:4). This selectivity can be rationalized as follows: Prior to the C−N bond-forming step, the C−C coupling occurs at the more reactive, sterically less hindered position of the vicinal diol.

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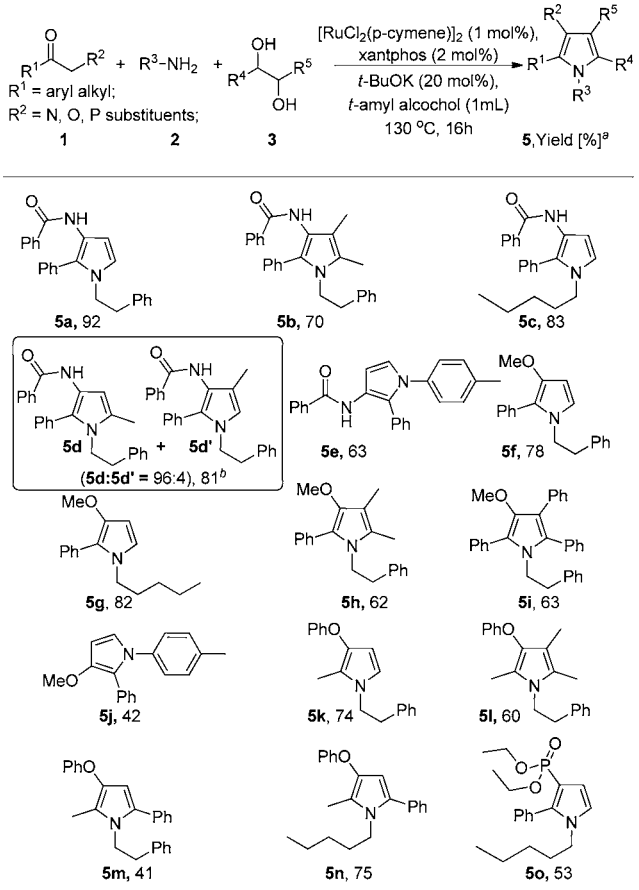
Scheme 2. Synthesis of Substituted Pyrroles Using α-Functionalized Ketones[a]

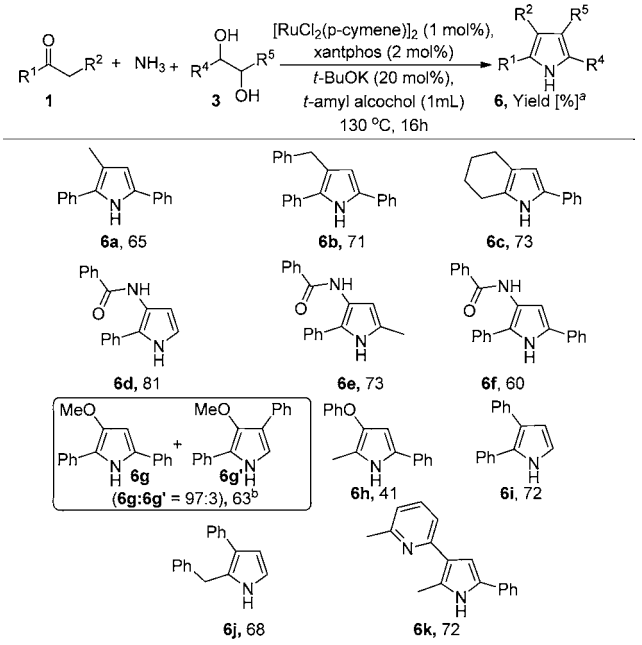


[a](a) Isolated yield. (b) Total yield of **5d** and **5d′**. Reaction conditions: sSee Table S3 in the Supporting Information.

Considering the importance of *N*-nonsubstituted pyrroles widely applied in industry and academic research,[19] we turned our attention to this class of compounds by using ammonia, which is a cheap but challenging amine coupling reagent.[20] As shown in Scheme 3, the reactions of various ketones including functionalized ones with different vicinal diols gave the corresponding products in moderate to high yields (Scheme 3, see **6a**−**6k**). Simple cyclohexanone **1g** was efficiently transformed into the biologically interesting tetrahydroindole skeleton in good yield (Scheme 3, see **6c**). Notably, even the pyridyl-substituted ketone afforded the desired product in good yield (Scheme 3, see **6k**). Similar to the results described in Scheme 2, unsymmetrical 1-phenylethane-1,2-diol **3b** and propane-1,2-diol **3e** gave the corresponding products in good yields with high regioselectivity (Scheme 3, see **6a**−**6c**, **6e**−**6h**, and **6k**).

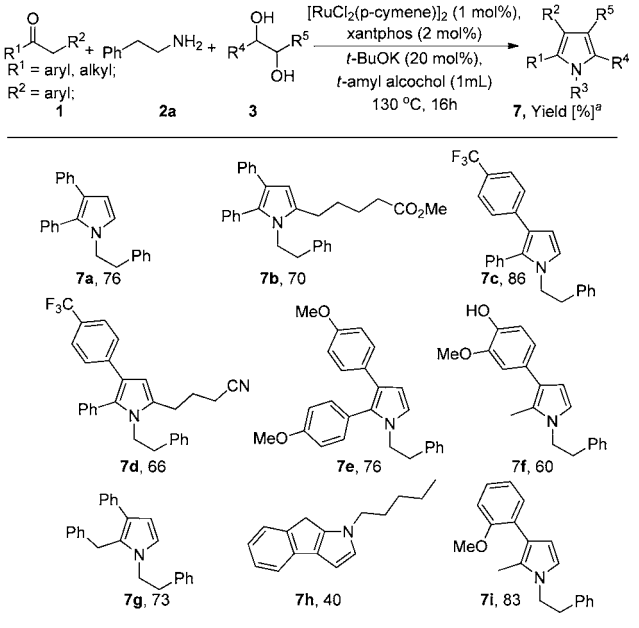
Finally, the generality of our synthetic protocol was further evaluated by testing a number of combinations of reactive benzylic ketones with vicinal diols and 2-phenylethylamine **2a**. As shown in Scheme 4, all of the reactions proceeded efficiently and afforded the substituted pyrroles in high yields upon isolation. It was found that the substituents possessing different electronic properties on benzylic ketones were tolerated and have little influence on the formation of products. In addition to 1-(4-hydroxy-3-methoxyphenyl)propan-2-one **1r**, also unsymmetrically functionalized vicinal diols with ester- and cyno-

Scheme 3. Synthesis of *N*-Nonsubstituted Pyrroles from Various Ketones and Ammonia[a]



[a](a) Isolated yield. (b) Total yield of **6g** and **6g′**. Reaction conditions: See Table S4 in the Supporting Information.

Scheme 4. Synthesis of Substituted Pyrroles Using Benzylic Ketones[a]



[a](a) Isolated yield. Reaction conditions: See Table S5 in the Supporting Information.

substituents were transformed into the desired products regioselectively in good yields (Scheme 4, **7b**, **7d**, and **7f**).

To gain insight into the possible mechanism of the three-component coupling reaction, deuterium-labeling experiments were carried out. Here, instead of *t*-amyl alcohol, toluene was used, and the reaction was interrupted after 3 h to observe intermediates. The reaction using hydroxyl-deuterated ethylene glycol **3a′** with 2-phenylacetophenone **1m** and 2-phenylethyl-

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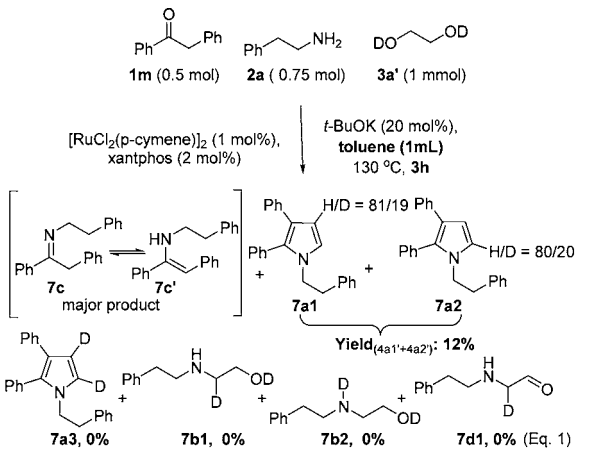
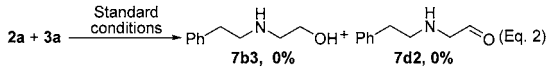
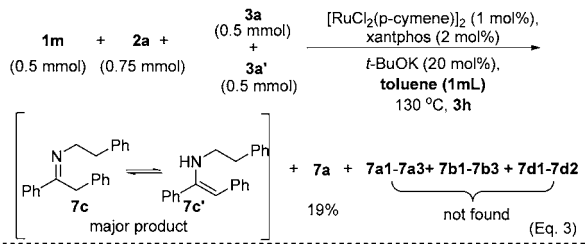
amine **2a** resulted in enamine **7c** (or imine **7c′**) as the major products. Two monodeuterated pyrroles (eq 1, see **7a1** and





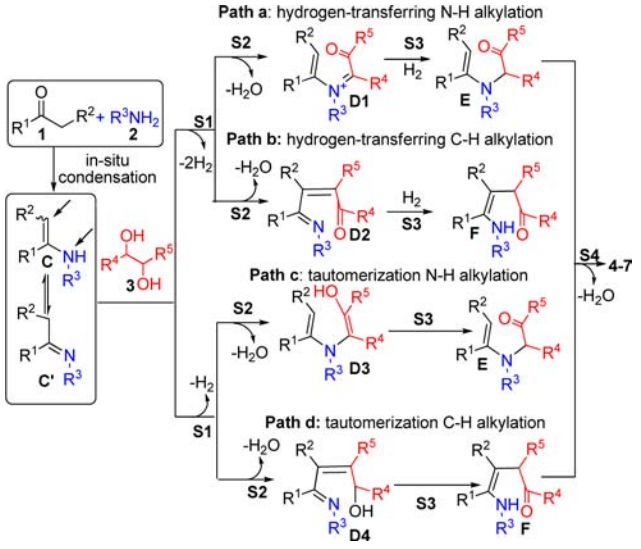


7a2) were observed as the minor products in 12% (combined yield) with a comparable H/D ratio at positions 4 and 5 (see eq 1: 81/19 and 80/20, respectively). These results prove that the hydrogen from dehydrogenation of the vicinal diol was transferred into the newly formed C−C and C−N bonds. However, bis-deuterated product **7a3** as well as deuterated amino alcohols and amino ketone (eq 1, see **7b1**−**7b2**, **7d1**) were not observed.

Moreover, the reaction between **2a** and **3a** also did not produce any amino alcohol **7b3** or amino ketone **7d2** under the standard conditions (see eq 2). Therefore, the reaction pathway involving an amino alcohol (or amino ketone) intermediate seems to be less favored. Interestingly, the competition reaction between equimolar amounts of **3a** and **3a′** with **1m** and **2a** did not give any deuterated product (see eq 3), which indicates that the dehydrogenation of the diol might be the rate-determining step in the whole reaction.

On the basis of the above-described findings, the possible reaction pathways of the three-component reactions are proposed in Scheme 5. Initially, enamine intermediate **C** (or its tautomer imine **C′**) is generated from in situ condensation of ketone **1** and amine **2**. It subsequently condenses with the carbonyl group arising from the metal-induced double or mono dehydrogenation of the diol. Depending on the position of the condensation reaction, in principle four intermediates **D1**, **D3** and **D2**, **D4** can be formed, respectively. The hydrogenation of the iminium group of **D1** or the alkene group of **D2** gives intermediates **E** and **F**, respectively (Scheme 5, see the

Scheme 5. Proposed Reaction Pathways



hydrogen-transferring alkylation pathways: **a** and **b**). Alternatively, the intramolecular tautomerization involving hydrogen-atom migratory processes could also generate **E** and **F** (Scheme 5, see paths **c** and **d**). Finally, the thermodynamic favorable dehydration of **E** and **F** releases the heterocyclic product. Concerning the highly regioselective pyrrole formation, at least for terminal diols pathways **b** and **d** in Scheme 5 seem to be favored.

■ SUMMARY

We present a general, highly regioselective and straightforward method for the synthesis of all kinds of substituted pyrroles. By employing the commercially available $[Ru(p\text{-cymene})Cl_2]_2$/Xantphos/*t*-BuOK catalyst system, a variety of abundant aryl and alkyl ketones as well as α-functionalized and activated benzylic ones were reacted with different type of amines (anilines, alkyl amines, and ammonia) and vicinal diols to give the corresponding heterocyclic products in reasonable to excellent isolated yields. Our synthetic protocol is straightforward, atom-efficient, and does not need stoichiometric amounts of additives or base. Because of the importance of pyrroles in biology, organic, and material chemistry, this practical synthetic strategy has the potential to be used frequently.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J. P.; White, W. *Chem. Rev.* **2006**, *106*, 3002.

(2) For reviews on borrowing-hydrogen methodology, see: (a) Crabtree, R. H. *Organometallics* **2011**, *30*, 17. (b) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753. (d) Lamb, G. W.; Williams, J. M. J. *Chim. Oggi* **2008**, *26*, 17. (e) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 155.

(3) (a) Guillena, G.; Ramyn, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611. (b) Guillena, G.; Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358.

(4) (a) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *J. Org. Chem.* **2011**, *76*, 2328. (b) Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635. (c) Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, *46*, 1541. (d) Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7375. (e) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766. (f) Lamb, G. W.; Watson, A. J. A.; Jolley, K. E.; Maxwell, A. C.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 3374. (g) Pridmore, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **2008**, *49*, 7413.

(5) (a) Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *Adv. Synth. Catal.* **2011**, *353*, 1161. (b) Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108. (c) Yamaguchi, R.; Mingwen, Z.; Kawagoe, S.; Asai, C.; Fujita, K.-i *Synthesis* **2009**, 1220. (d) Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K.-i. *Org. Lett.* **2008**, *10*, 181. (e) Fujita, K.-i.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943.

(6) (a) Yuan, K.; Jiang, F.; Sahli, Z.; Achard, M.; Roisnel, T.; Bruneau, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8876. (b) Zeyneb, S.; Sundararaju, B.; Achard, M.; Bruneau, C. *Org. Lett.* **2011**, *13*, 3964. (c) Sundararaju, B.; Achard, M.; Sharma, G. V. M; Bruneau, C. *J. Am. Chem. Soc.* **2011**, *133*, 10340.

(7) (a) Leung, J. C.; Geary, L. M.; Chen, T.-Y.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 15700. (b) Montgomery, T. P.; Hassan, A.; Park, B. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 11100. (c) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. (d) Geary, L. M.; Woo, S. K.; Leung, J. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2972. (e) Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 18618. (f) Leung, J. C.; Patman, R. L.; Sam, B.; Krische, M. J. *Chem.-Eur. J.* **2011**, *17*, 12437. (g) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582. (h) Zbieg, J. R.; McIntuff, E. L.; Leung, J. C.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 1141. (i) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. *Nat. Chem.* **2011**, *3*, 287.

(8) (a) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924. (b) Michlik, S.; Kempe, R. *Chem.-Eur. J.* **2010**, *16*, 13193. (c) Blank, B.; Michlik, S.; Kempe, R. *Chem.-Eur. J.* **2009**, *15*, 3790. (d) Blank, B.; Michlik, S.; Kempe, R. *Adv. Synth. Catal.* **2009**, *351*, 2903.

(9) (a) Imm, S.; Bahn, S.; Zhang, M.; Neubert, L.; Neumann, H.; Klasovsky, F.; Pfeffer, J.; Haas, T.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7599. (b) Zhang, M.; Imm, S.; Bahn, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11197. (c) Bahn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853. (d) Imm, S.; Bahn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8126. (e) Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian J.* **2007**, *2*, 403.

(10) (a) Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H. *Organometallics* **2011**, *30*, 4174. (b) Andrushko, N.; Andrushko, V.; Roose, P.; Moonen, K.; Börner, A. *ChemCatChem* **2010**, *2*, 640.

(11) (a) Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446. (b) Menichincheri, M.; Albanese, C.; Alli, C.; Ballinari, D.; Bargiotti, A.; Caldarelli, M.; Ciavolella, A.; Cirla, A.; Colombo, M.; Colotta, F.; Croci, V.; D'Alessio, R.; D'Anello, M.; Ermoli, A.; Fiorentini, F.; Forte, B.; Galvani, A.; Giordano, P.; Isacchi, A.; Martina, K.; Molinari, A.; Moll, J. K.; Montagnoli, A.; Orsini, P.; Orzi, F.; Pesenti, E.; Pillan, A.; Roletto, F.; Scolaro, A.; Tatò, M.; Tibolla, M.; Valsasina, B.; Varasi, M.; Vianello, P.; Volpi, D.; Santocanale, C.; Vanotti, E. *J. Med. Chem.* **2012**, *55*, 4446. (c) Thompson, R. B. *FASEB J.* **2001**, *15*, 1671.

(12) (a) Mason, M. E.; Johnson, B.; Hamming, M. *J. Agric. Food Chem.* **1966**, *14*, 454. (b) Lunak, S.; Vala, M.; Vynuchal, J.; Ouzzane, I.; Horakova, P.; Moziskova, P.; Elias, Z.; Weiter, M. *Dyes Pigm.* **2011**, *91*, 269. (c) Lunak, S.; Havel, L.; Vynuchal, J.; Horakova, P.; Kucerik, J.; Weiter, M.; Hrdina, R. *Dyes Pigm.* **2010**, *85*, 27. (d) Takase, M.; Yoshida, N.; Narita, T.; Fujio, T.; Nishinaga, T.; Iyoda, M. *RSC Adv.* **2011**, *2*, 3221. (e) Blangy, V.; Heiss, C.; Khlebnikov, V.; Letondor, C.; Evans, H. S.; Neier, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1688. (f) Wienk, M. M.; Turbiez, M.; Gilot, J.; Janssen, R. A. J. *Adv. Mater.* **2008**, *20*, 2556. (g) Wu, D.; Descalzo, A. B.; Weik, F.; Emmerling, F.; Shen, Z.; You, X. Z.; Rurack, K. *Angew. Chem., Int. Ed.* **2007**, *47*, 193.

(13) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597−601.

(14) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140−144.

(15) Srimani, D.; Ben-David, D.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012−4015.

(16) For selected recent examples on pyrrole syntheses, see: (a) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088. (b) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (c) Lourdusamy, E.; Yao, L.; Park, C. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7963. (d) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (e) Stuart, D. R.; Alsaben, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (f) Mizuno, A.; Kusama, H.; Iwasa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 8318. (g) Lu, Y. D.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5430. (h) Cyr, D. J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366. (i) Larionov, O. V.; Meijere, A. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (j) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (k) Xin, X.; Wang, D.; Li, X.; Wang, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693. (l) Jiang, Y.; Chan, W. C.; Park, C. M. *J. Am. Chem. Soc.* **2012**, *134*, 4104. (m) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002. (n) Kel'in, A. V.; Sromek, A. W.; Gevorgya, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.

(17) (a) Dydio, P.; Lichosyt, D.; Jurczak, J. *Chem. Soc. Rev.* **2011**, *40*, 2971. (b) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.

(18) Li, Y. −H.; Lu, L. Q.; Das, S.; Pisiewicz, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 18325−18329.

(19) (a) Thies, N.; Hrib, C. G.; Haak, E. *Chem.-Eur. J.* **2012**, *18*, 6302. (b) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (c) Ackermann, L.; Ligin, A. V. *Org. Lett.* **2011**, *13*, 3332. (d) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2836. (e) Ghosh, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1918.

(20) (a) Klinkenberg, J. L.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 86. (b) Pigen, D.; Muller, C.; Vogt, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8130.