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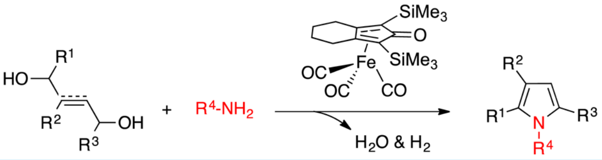
Iron-Catalyzed Sustainable Synthesis of Pyrrole

Balakumar Emayavaramban,[†] Malay Sen,[†] and Basker Sundararaju*,[†]

[†]Fine Chemical Laboratory, Department of Chemistry, Indian Institute of Technology—Kanpur, Kanpur 208016, India

Supporting Information

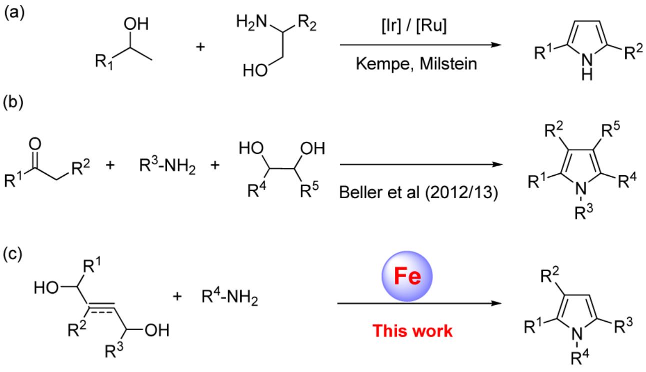
ABSTRACT: Efficient, sustainable, highly regiospecific substituted pyrroles were synthesized using a well-defined, air stable, molecular iron(0) complex. The developed methodology is broadly applicable and tolerates a variety of functional groups. C-2, C-3, and C-2 & C-4 substituted pyrroles were synthesized in good yield. Symmetrical bis-pyrroles were accessible for the first time using an iron catalyst. On the basis of the experimental observation, we propose that the reaction proceeds through a hydrogen autotransfer process followed by second oxidation/intramolecular dehydrative condensation to provide the pyrrole.



Hydrogen borrowing or hydrogen auto transfer (HA) reactions catalyzed by transition metals are considered to be one of the most environmentally benign transformations as the reactions do not produce any side product except water.[1] This well-established concept proceeds through initial activation of inert substrate (C−X) into reactive intermediate (C = X) via dehydrogenation assisted by the transition metal, followed by functional group transformation to produce second reactive intermediate (C = Y), which will be subsequently reduced to inert product (C−Y) by the in situ formed metal hydride to regenerate active catalytic species. Such transformations are currently possible with noble metals, especially Ru, Ir, and Pd. With advancement of green chemistry and sustainability, it is now imperative to develop catalysts derived from metals that are earth abundant, nontoxic, and environmental friendly for challenging C−N bond formation without any side products.[2] Pronounced efforts were witnessed very recently using first row transition metals for such catalytic transformations.[3] In this regard, the first report for C−N bond formation starting from alcohol via HA process using well-defined low valent iron (0) complex[4] was reported by Barta and Feringa[5a,d] followed by Wills[5b] and Zhao.[5c] Due to its inherent redox property, the iron(0)tricarbonyl complex is widely known to activate inert substrate via dehydrogenation/hydrogenation reactions that were reported earlier for C−C bond formation.[6]

The significance of polysubstituted pyrroles was exhibited in many different fields, including pharmaceuticals,[7a] natural products,[7d] dyes,[7c] and materials,[7b] which are often challenging synthetic targets. Although it is possible to synthesize pyrrole through traditional routes, it suffers from harsh reaction conditions, multistep synthesis, nonavailability of raw materials, poor functional group tolerance, and unpredictable regioselectivity.[8] To overcome these limitations, modern methods were developed by employing the hydrogen autotransfer process. Kempe[9] and Milstein[10] independently developed the [Ir]- and [Ru]-based catalytic system for pyrrole synthesis starting from amino alcohol and secondary alcohol (Scheme 1a).

Scheme 1. General Synthesis of Pyrroles via Hydrogen Autotransfer



At the same time, similar strategy was reported by Beller for [Ru]-catalyzed multicomponent catalytic pyrrole synthesis using the same (HA) process (Scheme 1b).[11] While the former method required a stoichiometric amount of base, the latter needed a catalytic amount of base to proceed the reaction toward the product. Tonks et al. first demonstrated a green synthetic route for the production of polysubstituted pyrroles through oxidative coupling of alkynes with diazenes via a Ti(II)/Ti(IV) redox process.[12] In our continuous effort on the development of catalysts based on base metals for sustainable transformations,[13] we envisioned the possibility of iron-catalyzed pyrrole synthesis starting from buten-1,4-diol and primary amine (Scheme 1c). We postulate that the initial allylic amination of buten-1,4-diol **1** with primary amine lead to intermediate **A** via HA process which then undergoes second oxidation of alcohol, leading to intermediate **B** followed by

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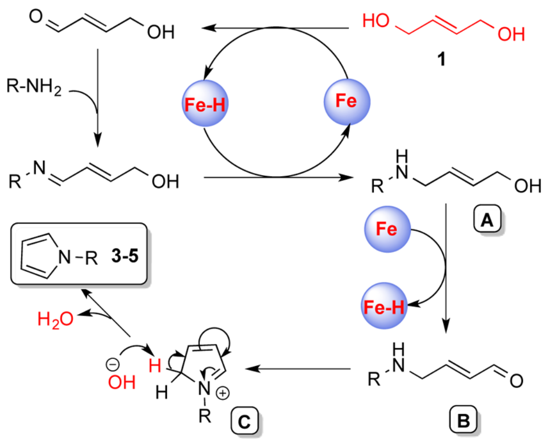
intramolecular condensation and dehydration to pyrroles 3−5, as shown in Scheme 2.

Scheme 2. Postulated Catalytic Cycle for Pyrrole Synthesis

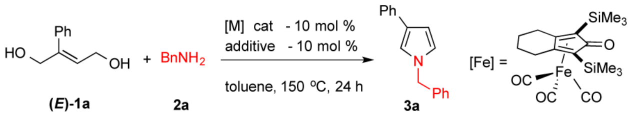


Murahashi did the pioneering work using Pd black, which proceeded through a Pd-catalyzed dehydrogenation/reduction pathway for allylic amination of (*Z*)-buten-1,4-diol followed by Pd-assisted intramolecular cyclization.[15] After nearly a decade, Watanabe reported the same reaction using [Ru] catalyst, albeit in low yield.[16] The catalyst utilized in this reaction is known for isomerization of double bonds; hence, it was proposed that the reaction proceeded through an isomerization pathway. Recently, Williams et al. reported the same reaction with Ru(II) catalyst to expand the scope of the reaction.[17] It is worth mentioning that the reported reactions are documented only for nonsubstituted pyrroles starting from commercially available *cis*-buten-1,4-diol/butyn-1,4-diol. Herein, we report a novel, efficient synthesis of pyrrole using an air stable, well-defined iron(0) catalyst.

We initiated our investigation to get access to C-3 substituted pyrrole using (*E*)-2-phenylbut-2-ene-1,4-diol and benzyl amine as a model substrate along with catalytic amount of [Fe]-catalyst and Me_3NO in 2 mL of toluene at 150 °C for 24 h, which were standard conditions that are established by us for allylic amination.[13] Under these reaction conditions, 79% of 3-phenyl-*N*-benzylpyrrole was isolated (Table 1, entry 1). Neither changing the concentration nor altering the substrate ratio improved the product formation (entries 2 and 3). Addition of molecular sieves has no effect on the reaction (entry 4). Brief screening of other solvents such as CPME and *m*-xylene gave similar yields as entry 1, while *α*,*α*,*α*-trifluorotoluene decreased the yield of **3a** (entries 5−7). Other iron precursors did not give any product formation (entries 8 and 9). We also compared the reactivity of some well-known HA catalysts, which are found to be less efficient under standard reaction conditions (entries 10−12). Moderate yield of **3a** was obtained when the reaction was performed without any additive (entry 13).

With best conditions in hand, we next examined scope and limitation of various amines and alcohols. At first, various amines were tested by keeping (*E*)-2-phenylbut-2-ene-1,4-diol as a coupling partner (Scheme 3). *o*- and *p*-Substituted benzyl amines gave expected pyrroles in good yield (**3b** and **c**). Pyridine-2-ylmethanamine, possessing a strong chelating group, reacted smoothly with moderate yield (**3d**).

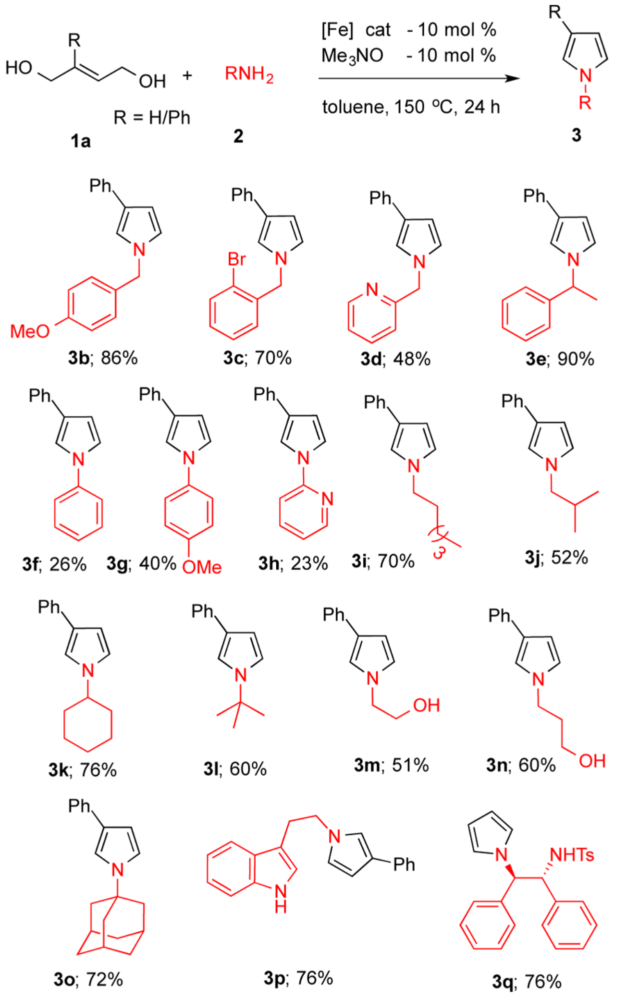
Table 1. Optimization of Reaction Parameters[a]



	[M]	additive	solvent	yield (%)[b]
1	[Fe]	Me_3NO	toluene	79
2	[Fe]	Me_3NO	toluene	52[c]
3	[Fe]	Me_3NO	toluene	52[c,d]
4	[Fe]	Me_3NO	toluene	71[c,e]
5	[Fe]	Me_3NO	CPME	77
6	[Fe]	Me_3NO	$C_6H_5CF_3$	44
7	[Fe]	Me_3NO	*m*-xylene	71
8	$Fe_2(CO)_9$		toluene	nr
9	$[CpFe(CO)_2]_2$		toluene	nr
10	$[Cp^*IrCl_2]_2$	^tBuOK	toluene	22
11	$[Ru(p\text{-}cym)Cl_2]_2$	Dppf + ^tBuOK	toluene	29
12	Pd/C		toluene	nr
13	[Fe]		toluene	53

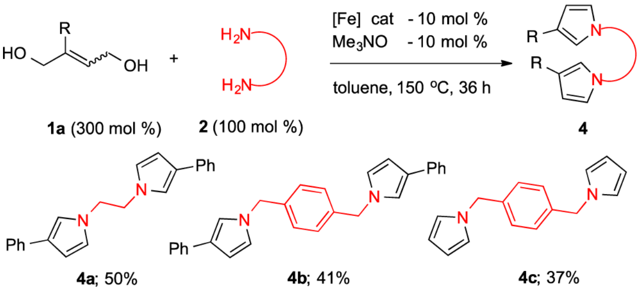
[a] All reactions were carried out in an argon atmosphere using **1a**/**2a**/[Fe]/additive in 0.3/0.45/0.03/0.03 mmol, respectively, in 2 mL of toluene at 150 °C (oil bath temperature) for 24 h. [b] Isolated yield. [c] One milliliter of toluene was used. [d] **1a**/**2a** (0.6/0.3 mmol) was used. [e] Fifty milligrams of 4 A° MS was added. CPME = cyclopentylmethyl ether

Scheme 3. Scope of Amines



Excellent product formation was observed when α-methylbenzylamine (**2e**) was used as the amine partner. The reaction was sluggish when aromatic amines including 2-aminopyridine were utilized, and moderate yield was obtained (**3f**–**h**). Aliphatic amines such as hexyl, isobutyl, cyclohexyl, and *tert*-butyl amines gave moderate to good yield under the standard conditions (**3i**–**l**). *β*- and *γ*-amino alcohols were tested as a primary amine source, and gratifyingly, both gave the corresponding pyrrole (**3m** and **3n**) selectively without any oxidation of primary alcohol. Sterically bulkier amine such as adamantyl amine, medicinally important tryptamine, and monoprotected 1,2-diphenylethylene diamine were successfully converted into pyrrole in respectable yield (**3o**–**q**). This extensive scope of amine demonstrates high functional group tolerance, which includes Br, alcohol, and amide. It is necessary to mention that, during the preparation of this manuscript, Barta et al. reported the analogous reaction using a catalytic amount of iron(0) tricarbonyl complex for nonsubstituted pyrrole starting from *cis*-buten-1,4-diol and butyn-1,4-diol.[18] We extended this methodology further to the synthesis of symmetrical bis-pyrrole starting from diamine with excess (*E*)/(*Z*)-diol through a one pot process in satisfactory yield (Scheme 4).

Scheme 4. Symmetrical Bis-pyrrole Synthesis



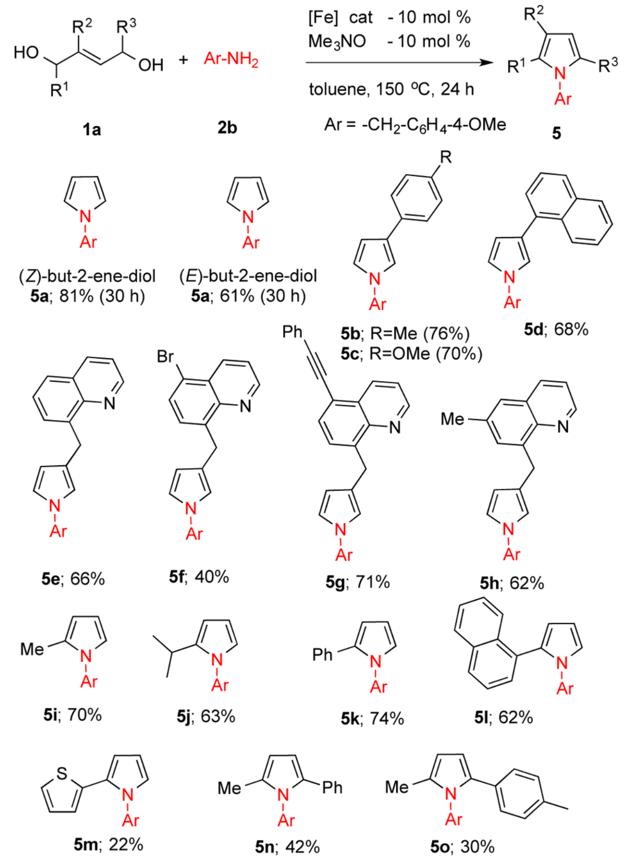
We next explored the scope of the various substituted diol **1**. We began our investigation by testing commercially available *cis*- and *trans*-buten-1,4-diol by keeping 4-OMe-benzylamine as a coupling partner (Scheme 5). Both *cis*- and *trans*-isomers gave the expected pyrroles in good yield, but there is a significant difference in reactivity, which depends on the stereoisomer of the starting diol.

For example, *cis*-buten-1,4-diol gave 81% yield, whereas the *trans*-isomer provided only 61% isolated yield of pyrrole **5a** after 30 h. C-3 functionalized pyrroles can be extended to other functional groups such as *p*-tolyl-, *p*-anisyl, and naphthyl under the standard conditions starting from the substituted *E*-diol (**5b**–**d**).

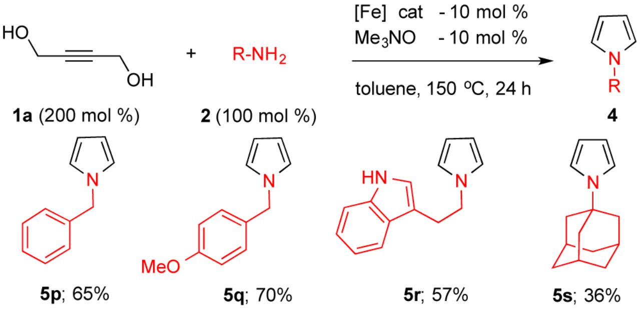
Quinoline and substituted quinoline, including bromo and alkyne groups on the backbone were tolerated to access to C-3 functionalized pyrroles in high yield (**5e**–**h**).

More pleasingly, C-2 substituted pyrroles were prepared using our established protocol in moderate to good yield (**5i**–**m**), which are difficult to dehydrogenate, as iron-catalyzed reactions using an iron–carbonyl complex are not well-established for amination of secondary alcohols. Further, to our delight, 2,4-disubstituted pyrroles were obtained in decent yield under optimized reaction conditions (**5n** and **o**). Then, we examined reactivity of butyn-1,4-diol with our established protocol to synthesize pyrrole similar to the previous report by Watanabe and Williams using ruthenium catalysts. Analogous reactivity was observed with buten-1,4-diol, and nonsubstituted pyrroles were obtained in decent yield (Scheme 6).

Scheme 5. Scope of Alcohols



Scheme 6. Synthesis of Pyrrole from Butyn-1,4-diol



To establish the proposed mechanism, intermediate A was isolated from the known procedure and exposed to standard reaction conditions that rendered **5t** in 59% yield.[19]

In conclusion, we demonstrated straightforward iron-catalyzed substituted pyrrole synthesis starting from *cis*/*trans*-buten-1,4-diol and their derivatives via a hydrogen autotransfer process. The wide scope of amine and alcohol implies that the reaction was indeed selective and tolerates a variety of functional groups. 1,4-Hydride addition of *α*,*β*-unsaturated imine is not possible with our presented iron catalyst, even with external hydrogen pressure.[14] Hence, we ruled out the possibility of an isomerization pathway, although it was proposed with ruthenium earlier. With the advent of this new protocol, more sustainable applications will be envisioned for pyrrole derivatives, especially via further C–H bond functionalization, which epitomizes use in materials, dyes, natural products, and biologically active intermediates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02819.

> Experimental methods, optimization of reaction conditions, and other supplementary data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: basker@iitk.ac.in

Notes

The authors declare no competing financial interest.

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