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Catalytic C–H arylation of unactivated heteroaromatics with aryl halides by cobalt porphyrin

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ABSTRACT

Direct C–H arylation of unactivated heteroaromatics with aryl halides catalyzed by cobalt porphyrin is reported. The reaction is proposed to go through a homolytic aromatic substitution reaction. The aryl radical is electrophilic and a SOMO–HOMO interaction is predominant in the aryl radical addition process.

Heterobiaryls are very important structural motifs as they are commonly found in drugs, natural products, and optoelectronic materials.[1] 2-Acylhydrazino-5-arylpyrrole derivatives are used as antifungal reagents against *Candidae* (Fig. 1a).[2] The potential HIV-integrase inhibitor is constituted of an arylfuran moiety (Fig. 1b).[3] 2-Arylpyrrole is the precursor of a potential anti-inflammatory and analgesic agent 5-aryl-1,2-dihydro-1-pyrrolizinones.[4] Therefore, facile and convenient syntheses of heterobiaryls are attractive.

Transition metal catalysts have been widely used in cross-coupling reactions to construct heterobiaryls.[5–10] Heterobiaryls were first synthesized from heteroarylsilanes and aryl halides with a stoichiometric use of copper(I) salt.[5] 2- and 3-arylfurans have been prepared by the nickel-catalyzed cross-coupling of 2- and 3-halofurans with aryl Grignard reagents.[6] Later, heterobiaryls synthesized by the palladium-catalyzed Kumada,[7] Suzuki–Miyaura,[8] Stille[9,1d] and Hiyama[10] cross-couplings have also been reported. However, palladium catalysts and preactivation of heteroaromatics are required in most of the works.

Utilization of cheap and more abundant transition metal complex as a catalyst for the direct C–H arylation is attractive. Recently, 1st row transition metal catalysts have gained much attention in cross-coupling reactions. They are much cheaper and less toxic, such as Fe and Ni.[1a,c,5] On the other hand, the direct C–H arylation of heteroaromatics with aryl halides have been achieved in some heterocycles, such as oxazoles, 1,2,3-triazoles, and indoles.[11] Direct C–H arylation avoids preactivation of heteroaromatics, which is user-friendly and cost-effective. However, cobalt remains less-explored as a catalyst for the direct C–H arylation of heteroaromatics. Recently, we have reported the cobalt(II) porphyrin-catalyzed direct C–H arylation of unactivated arenes with aryl halides.[12] The reaction mechanism was proposed to proceed through a homolytic aromatic substitution followed by hydrogen atom abstraction to give the corresponding biaryls. However, the electronic influence on the homolytic aromatic substitution process remains unclear. This led us to turn our attention to both electron rich and poor heteroaromatics, for investigation of the electronic effect of aryl radical addition onto the heteroaromatics and the synthesis utility. Herein, we report the successful direct C–H arylation of heteroaromatics with aryl halides to give the heterobiaryls. Electron rich heteroaromatics reacted faster suggesting the importance of the electrophilic aryl radical in homolytic aromatic substitution.

Both π-excessive pyrrole and furan underwent successful direct C–H arylation with aryl halides (Table 1). In the presence of a catalytic amount of Co^{II}(tap) (tap = tetrakis-4-anisylporphyrinato dianion) (5 mol %), together with KOH (10 equiv) and ^{t}BuOH (10 equiv), 4-iodotoluene (1 equiv) was successfully coupled with pyrrole

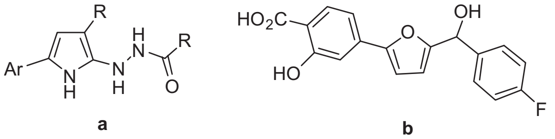

Figure 1. (a) Structure of 2-acylhydrazino-5-arylpyrrole derivatives; (b) structure of HIV-integrase inhibitor candidate.

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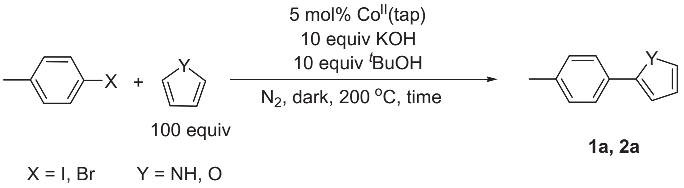
Table 1
Cobalt-catalyzed arylation of pyrrole and furan with 4-halotoluenes



1a, 2a

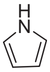
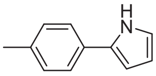
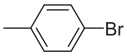
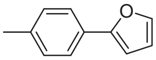
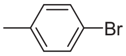
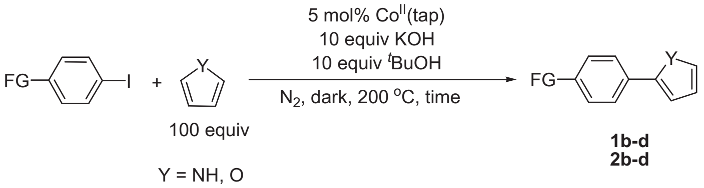
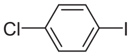
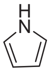
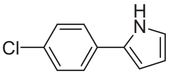
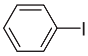
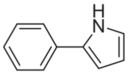
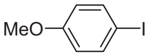
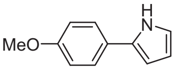
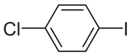
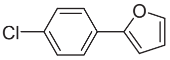
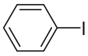
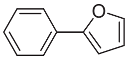
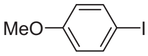
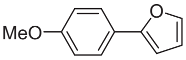
Entry	Aryl halide	Solvent	Time (min)	Product	Yield (%)
1			15	 **1a**	74
2			30		52
3			60	 **2a**	62
4			60		42

Table 2
Cobalt-catalyzed arylation of pyrrole and furan with aryl iodides



1b-d
2b-d

Entry	Aryl halide	Solvent	Time (min)	Product	Yield (%)
1			30	 **1b**	54
2			30	 **1c**	69
3			30	 **1d**	66
4			60	 **2b**	49
5			60	 **2c**	52
6			60	 **2d**	62

(100 equiv) at 200 °C under N$_2$ to give a 74% yield of 2-(4-methylphenyl)pyrrole **1a** in only 15 min (Table 1, entry 1). When furan was used instead of pyrrole, a longer reaction time of 1 h was required for completion (Table 1, entry 3).

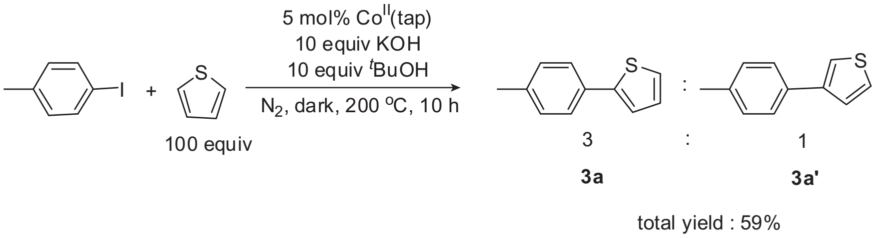
Arylbromides reacted slower than aryliodides (Table 1). 4-Bromotoluene reacted with pyrrole and furan to give the corresponding coupling products **1a** and **2a** in 52% and 42% yields, respectively. However, the reaction took longer time and gave lower yields of the products. The weaker carbon–iodine bond (65.0 kcal/mol)[13] of 4-iodotoluene compared with the carbon–bromine bond (80.4 kcal/mol)[13] in 4-bromotoluene accounts for the higher reactivity. The Ar–halogen bond cleavage is likely the rate-limiting step.

The direct C–H arylation is general for both electron rich and electron deficient aryl iodides. Pyrrole and furan reacted with electronically different 4-chloroiodobenzene, iodobenzene, and 4-iodoanisole to give the corresponding coupling products in good yields in similar time (Table 2, entries 1–6). Therefore, the electronic effect of aryl radicals is not significant in this reaction system. This agrees well with the orthogonal nature of the sp^2 radical orbital to the delocalized π system in an aryl radical rendering the inductive effect through σ-bond insignificant.

The direct C–H arylation of pyrrole and furan was highly regioselective to give 2-arylheteroaromatics and highly chemoselective as no N–H atom abstraction or N-arylation was observed.[14]

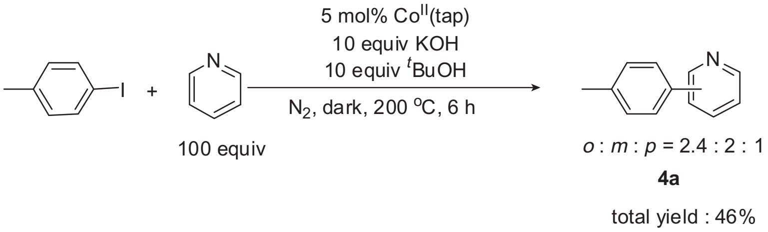
However, when π-excessive thiophene and π-deficient pyridine were examined, it is surprising that the arylation of thiophene and pyridine are not regioselective. For thiophene, both 2- and 3-arylated thiophene were obtained in a 3:1 ratio (Eq. (1)). While for pyridine, the *ortho*, *meta*, *para* selectivities follow closely with the statistical ratio (Eq. 2).[15]

The regioselectivity of the arylation can be rationalized using the stability of the 2- and 3-arylheterocyclic radical intermediates. There are more resonance structures associated with 2-arylheterocyclic radical intermediate than 3-arylheterocyclic one (Fig. 2). However, in the case of thiophene, the S atom expands the valance to d orbital. Thus both 2- and 3-arylthiophenium radical intermediates are stabilized by resonance without a large difference. Therefore, 3-arylthiophene is formed as well.



3a **3a'**

(1)



4a

(2)

In order to investigate the nature of the homolytic aromatic substitution, competition arylation reactions with an equimolar mixture of heteroaromatic and benzene were carried out (Table 3). The aryl radicals reacted faster with substrates electron richer than benzene. This suggests that the aryl radicals are electrophilic.

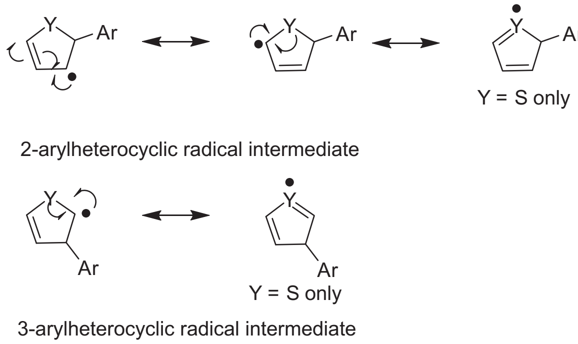


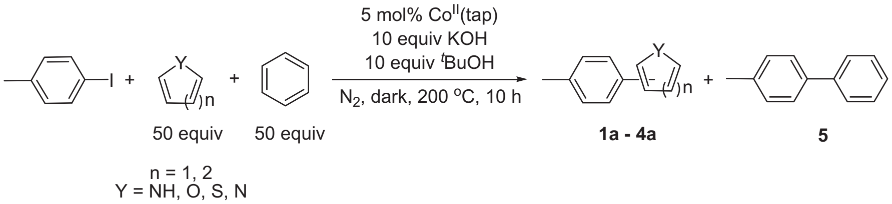
Figure 2. Resonance structures of 2- and 3-arylheterocyclic radical intermediates (Y = NH, O, S).

To gain a more quantitative understanding on the reactivities of heteroaromatics on heterobiaryl formation, the frontier molecular orbital interaction between phenyl radical and heteroaromatics is considered. For approximation, the ionization energy (I.E.) corresponds to the negative energy of the highest occupied molecular orbital (HOMO),[16] and the electron affinity (E.A.) corresponds to the negative energy of the lowest unoccupied molecular orbital (LUMO).[17] The energy of the singly occupied molecular orbital (SOMO) correlates with the I.E. of the phenyl radical. Table 4 shows the SOMO–HOMO energy level differences are much smaller than the SOMO–LUMO energy level differences. Thus the SOMO–HOMO interaction dominates the reactivity. The product ratio per C–H bond against the SOMO–HOMO energy level difference is shown in Figure 3. The linear correlation of increasing reactivity with the smaller SOMO–HOMO energy level difference further supports the SOMO–HOMO interaction in the aryl radical addition process, and the aryl radicals are therefore electrophilic.[20]

Based on the above data, the mechanism proposed for the direct C–H arylation of heteroaromatics is shown in Figure 4. First, the aryl radical is generated by a carbon halogen bond cleavage with Co^{II}(tap). The aryl radical then adds to the heteroaromatics to give the heteroaryl radical intermediate. The radical intermediate is then deprotonated with a *tert*-butoxide[21] or a hydroxide anion to give the heteroaryl radical anion. Then, intermolecular dissociative electron transfer from the heteroaryl radical anion to the starting aryl halide furnishes aromatization and completes the chain.[22] Curran and co-workers recently proposed that an oxygen molecule is a radical chain carrier for aromatization of the intermediate **A**.[23] However, this Co^{II}(tap)-catalyzed direct C–H arylation of heteroaromatics was much slower under air than under N$_2$ and required a longer reaction time of 1 h. Thus, oxygen did not facilitate the aromatization in this reaction system. Moreover, a base is essential for the reaction supporting the deprotonation step in the mechanism.[24] For the cobalt complex part, Co^{III}(tap)X undergoes ligand substitution with KOH to give Co^{III}(tap)OH, which rapidly regenerates Co^{II}(tap) and H_2O_2.[25] H_2O_2 then quickly decomposes to give water and oxygen by base.[26]

In summary, a convenient method of preparing heterobiaryls by direct C–H arylation of heteroaromatics with aryl halides catalyzed by cobalt(II) porphyrin was successfully demonstrated. The SOMO–HOMO interaction is dominant in the aryl radical addition process, which suggests that the aryl radicals are electrophilic.

Table 3
Competition reaction between heteroaromatics and benzene



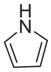
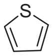
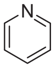
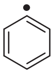
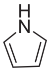
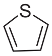
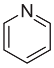
Entry	Heteroaromatics	Product ratio (**1a**–**4a**:**5**)	Product ratio per C–H bond	Total yield (%)
1		4.00:1.00	6.00	40
2		2.30:1.00	3.45	63
3		1.65:1.00	2.48	69
4		0.55:1.00	0.66	33

Table 4
SOMO–HOMO and SOMO–LUMO energy level differences between phenyl radical and heteroaromatics

Entry	Heteroaromatics	I.E. (eV)[18]	E.A. (eV)[19]	SOMO–HOMO energy level difference (eV)	SOMO–LUMO energy level difference (eV)
1		8.32	1.10	/	/
2		8.27	−2.38	0.05	10.61
3		8.81	−1.76	0.49	10.08
4		8.86	−1.17	0.54	9.49
5		9.26	−0.62	0.94	8.94

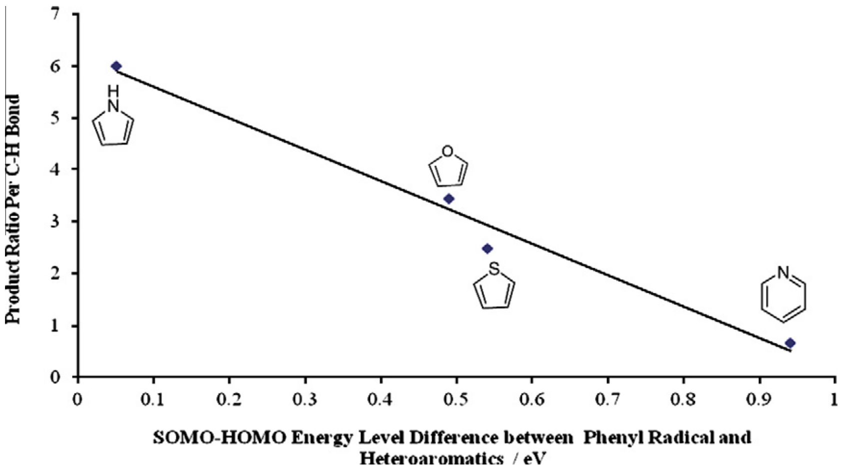


Figure 3. Product ratio per C–H bond against SOMO–HOMO energy level difference.

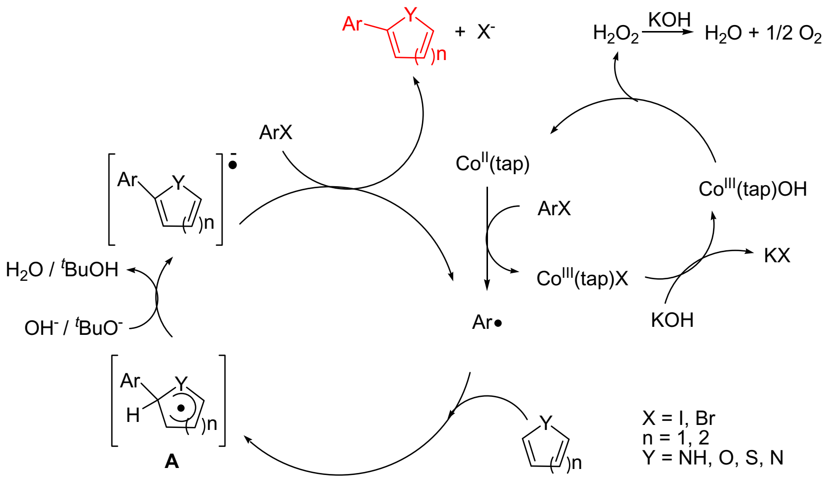


Figure 4. Proposed reaction mechanism.

Acknowledgment

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Supplementary data

Supplementary data (including experimental procedures, ^{1}H NMR spectra, characterization of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.051.

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