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# Direct C−H Arylation of (Hetero)arenes with Aryl Iodides via Rhodium Catalysis

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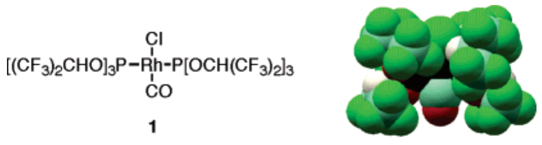
Organic molecules having (hetero)aryl−(hetero)aryl bonds represent privileged structural motifs frequently found in natural products or used in pharmaceuticals and functional organic materials. Therefore, the development of efficient methods for biaryl formation has been a topic of unparalleled importance in all aspects of pure and applied chemistry.[1] Although metal-catalyzed cross-coupling reactions of organometallics and organic halides have enjoyed widespread applications,[1] the direct C−H arylation of heteroarenes and arenes holds significant synthetic potential as it eliminates preactivation of coupling components.[2] During the last several years, impressive progress has been made for the direct C−H arylation methodology (mainly Pd catalysis),[3−5] but there still exists considerable room for further development. For example, a universal catalyst that can directly arylate all heteroarenes as well as simple arenes has not been forthcoming.

As a part of our program aimed at establishing programmable synthesis of (hetero)arene core functional molecules, we developed a rhodium complex **1** bearing a strongly $\pi$-accepting ligand, $P[OCH(CF_3)_2]_3$, as an efficient catalyst precursor for C−H arylation of (hetero)arenes with aryl iodides (Figure 1). The complex **1** can be prepared quantitatively by mixing $[RhCl(CO)_2]_2$ and $P[OCH(CF_3)_2]_3$ in toluene. A notable feature of this complex is its outstanding stability in air and moisture in the solid state. Virtually no decomposition of **1** has been detected after extended (>8 months) exposure to air. The X-ray crystal structure of **1** indicates that this may be due to the effective shielding of the rhodium atom by two bulky phosphite ligands (Figure 1).

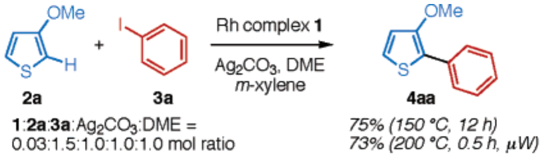


**1**

X-ray structure of **1**

***Figure 1.*** Rhodium complex **1** for catalytic direct C−H arylation.

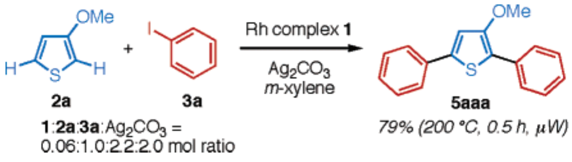
The following examples are typical (eqs 1 and 2). A mixture of 3-methoxythiophene (**2a**) and iodobenzene (**3a**) in *m*-xylene was stirred at 150 °C for 12 h in the presence of **1**, $Ag_2CO_3$, and 1,2-dimethoxyethane (DME) (**1**:**2a**:**3a**:$Ag_2CO_3$:DME = 0.03:1.5:1.0:1.0:1.0 molar ratio). A direct C−H arylation took place at the 2-position of **2a** to afford **4aa** in 75% yield with virtually complete regioselectivity (eq 1). When the reaction was conducted at 200 °C under microwave irradiation,[4c] the reaction was complete within 0.5 h to furnish **4aa** in 73% yield. The addition of DME suppressed the formation of diarylated product **5aaa**.[6] Selective double C−H arylation also was possible when an excess amount of **3a** (2.2 equiv to **2a**) was employed, yielding an interesting thiophene core $\pi$-system **5aaa** in 79% yield (eq 2).



(1)

**1**:**2a**:**3a**:$Ag_2CO_3$:DME = 0.03:1.5:1.0:1.0:1.0 mol ratio

*75% (150 °C, 12 h)*
*73% (200 °C, 0.5 h, µW)*



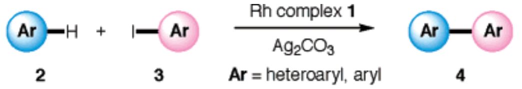
(2)

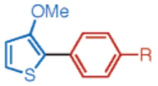
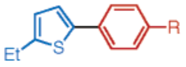
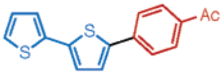
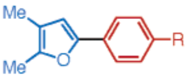
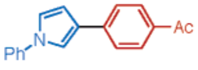
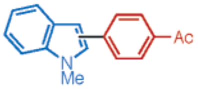
**1**:**2a**:**3a**:$Ag_2CO_3$ = 0.06:1.0:2.2:2.0 mol ratio

*79% (200 °C, 0.5 h, µW)*

A preliminary survey of substrates revealed that a range of five-membered heteroarenes, such as thiophenes, furans, pyrroles, and indoles, could be arylated through the present catalysis (Table 1). Although aryl bromides and triflates possessed poor reactivity, arylation proceeded efficiently with aryl and heteroaryl iodides.[7] While thiophenes (**2a**,**b**), bithiophene (**2c**), and 2,3-dimethylfuran (**2d**) were arylated selectively at carbons next to sulfur or oxygen, 1-phenylpyrrole (**2e**) was selectively arylated at the 3-position. The

***Table 1.*** Direct C−H Arylation of Heteroarenes Catalyzed by **1**[a]



| entry | **2**[b] | **3**[c] | product (**4**) | | yield (%)[d] |
|---|---|---|---|---|---|
| 1 | **2a** | **3a** |  | **4aa** (R = H) | 73 (80) |
| 2 | **2a** | **3b** | | **4ab** (R = Ac) | 94 (99) |
| 3 | **2a** | **3c** |  | **4ac** | 52 (58) |
| 4 | **2b** | **3a** |  | **4ba** (R = H) | 76 (99) |
| 5 | **2b** | **3b** | | **4bb** (R = Ac) | 79 (87) |
| 6 | **2b** | **3d** | | **4bd** (R = Me) | 50 (64) |
| 7 | **2c** | **3b** |  | **4cb** | 64 |
| 8 | **2d** | **3b** |  | **4db** (R = Ac) | 64 |
| 9 | **2d** | **3e** | | **4de** (R = CN) | 66 |
| 10 | **2e** | **3b** |  | **4eb** | 58 (86) |
| 11 | **2f** | **3b** |  | **4fb** (C-3)<br>**4fb'** (C-2) | 57<br>23 |

[a] Molar ratio: **1**:**2**:**3**:$Ag_2CO_3$:DME = 0.03:1.5:1.0:1.0:1.0. Conditions: 150−200 °C, 0.5 h (microwave) in *m*-xylene. [b] 3-Methoxythiophene (**2a**), 2-ethylthiophene (**2b**), 2,2′-bithiophene (**2c**), 2,3-dimethylfuran (**2d**), 1-phenylpyrrole (**2e**), 1-methylindole (**2f**). [c] Iodobenzene (**3a**), 4-iodoacetophenone (**3b**), 3-iodothiophene (**3c**), 4-iodotoluene (**3d**), 4-iodobenzonitrile (**3e**). [d] Isolated yield. The yield in parentheses is determined by NMR.

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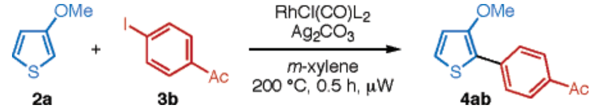
***Table 2.*** Effect of Ligand in Rh-Catalyzed C−H Arylation

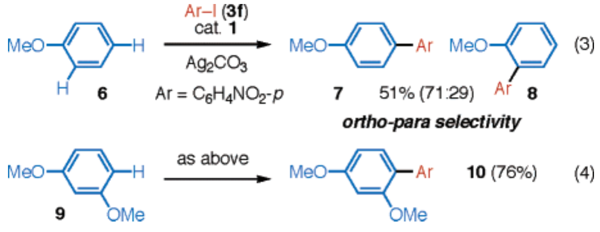


| ligand (L) | yield of **4ab** (%) | $\nu_{CO}$ in $RhCl(CO)L_2$ ($cm^{-1}$) |
|---|---|---|
| **$P[OCH(CF_3)_2]_3$** | **94** | **2070** |
| $P(C_6H_5)[OCH(CF_3)_2]_2$ | 31 | 2038 |
| $P(OC_6H_5)_3$ | 6 | 2018 |
| $P[OCH(CH_3)_2]_3$ | 9 | 2002 |
| $P(C_6H_5)_3$ | 0 | 1983 |

arylation of 1-methylindole (**2f**) also took place efficiently, but resulted in a 71:29 mixture of regioisomers.

The use of strongly $\pi$-accepting $P[OCH(CF_3)_2]_3$ as a ligand[8] is a key for the present catalysis. For example, when a less $\pi$-accepting ligand, such as $P(C_6H_5)[OCH(CF_3)_2]_2$, $P(OC_6H_5)_3$, $P[OCH(CH_3)_2]_3$, or $P(C_6H_5)_3$, was used in place of $P[OCH(CF_3)_2]_3$ for the reaction of **2a** and **3b**, the yield of arylation product **4ab** decreased from 94 to 31, 6, 9, and 0%, respectively (Table 2). There is a clear correlation between the arylation efficiency and the $\pi$-accepting ability of the ligand, judged by electronic parameters based on the carbonyl stretching frequency ($\nu_{CO}$) in *trans*-$RhCl(CO)L_2$ complexes.[9] Although the mechanism remains unknown, a possible mechanism could be a $Rh^I/Rh^{III}$ cycle with (i) oxidative addition of aryl iodides to $Rh^I$, (ii) electrophilic metalation[10] of heteroarenes, and (iii) reductive elimination of **4** with the regeneration of $Rh^I$ species.[11] The beneficial effect of strongly $\pi$-accepting $P[OCH(CF_3)_2]_3$ might be to render the rhodium center electron-deficient, thereby facilitating electrophilic metalation.

Finally, this protocol was applied to arenes[5] to evaluate its generalizability and to shed some light on the mechanism. Gratifyingly, direct C−H arylation did take place with benzene derivatives (eqs 3 and 4). For example, when anisole (**6**) was treated with *p*-nitrophenyl iodide (**3f**) under the influence of **1** and $Ag_2CO_3$ (**1**:**3f**:**6**:$Ag_2CO_3$ = 0.05:1.0:27:1.0 molar ratio), arylated anisoles were obtained as a mixture of regioisomers (51% yield; *o*:*m*:*p* = 29:0:71).[12] When 1,3-dimethoxybenzene (**9**) was used as a substrate, arylation occurred exclusively at the 4-position (eq 4). The manifestation of clear *ortho-para* selectivity in the arylation of alkoxybenzenes is consistent with an electrophilic metalation manifold but not with arylation through directed *ortho*-metalation and/or C−H oxidative addition.[2] A preliminary examination revealed that C−H arylation of alkylbenzenes also took place, albeit in low efficiency. Nevertheless, the successful arylation of arenes without catalyst directing groups is noteworthy.[5]



In summary, a new method for the catalytic C−H arylation of heteroarenes that manifests high activity paired with reasonably broad scope was developed. The successful C−H arylation of simple arenes speaks well for the potential of the present Rh catalysis for further development and applications. Elucidation of the reaction mechanism, development of more active catalysts, and applications of the direct arylation technology for materials science and pharmaceutical chemistry are currently underway.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) **5aaa** was obtained in 17% yield together with **4aa** (66%) when the reaction was conducted without DME under microwave irradiation.
(7) Although arylation proceeded well with electron-deficient and -neutral aryl iodides, the application of electron-rich aryl iodides often resulted in somewhat lower arylation efficiency under present conditions.
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(11) During the course of this study, we became aware of Rh-catalyzed arylation of indoles and pyrroles reported by Sames (ref 4b). Although they also proposed a mechanism based on electrophilic metalation, the regioselectivities were somewhat different with our catalysis. In addition, the arylation of thiophenes, furans, and simple arenes was not mentioned.
(12) The yield of arylation products (**7** and **8**) gradually decreased by decreasing the amount of anisole (**6**) employed: 51% (**3f**:**6** = 1:27), 48% (**3f**:**6** = 1:10), 42% (**3f**:**6**:*n*-octane = 1:5:6; *n*-octane was added as cosolvent), 25% (**3f**:**6**:*n*-octane = 1:2:6; *n*-octane was added as cosolvent).

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