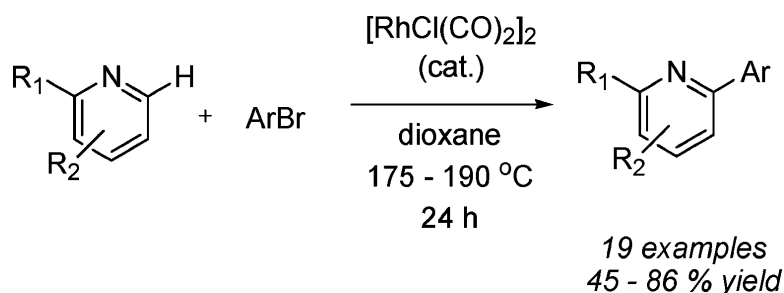Communication

Rh(I)-Catalyzed Direct Arylation of Pyridines and Quinolines

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19 examples
45 - 86 % yield

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Rh(I)-Catalyzed Direct Arylation of Pyridines and Quinolines

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Pyridine and quinoline nuclei are privileged scaffolds that occupy a central role in many medicinally relevant compounds.[1] Consequently, methods for their expeditious functionalization are of immediate interest. However, despite the immense importance of transition-metal-catalyzed cross-coupling for the functionalization of aromatic scaffolds, general solutions for coupling 2-pyridyl organometallics with aryl halides have only recently been presented.[2] Direct arylation at the *ortho* position of pyridine would constitute an even more efficient approach because it eliminates the need for the stoichiometric preparation and isolation of 2-pyridyl organometallics.[3,4] Progress toward this goal has been achieved by activation of the pyridine nucleus for arylation via conversion to the corresponding pyridine *N*-oxide[5] or *N*-iminopyridinium ylide.[6] However, this approach necessitates two additional steps: activation of the pyridine or quinoline starting material, and then unmasking the arylated product. The use of pyridines directly would clearly represent the ideal situation in terms of both cost and simplicity. We now wish to document our efforts in this vein, culminating in an operationally simple Rh(I)-catalyzed direct arylation of pyridines and quinolines.

We recently developed an electron-rich Rh(I) system for catalytic alkylation at the *ortho* position of pyridines and quinolines with alkenes.[7,8] Therefore, we initially focused our attention on the use of similarly electron-rich Rh(I) catalysts for the proposed direct arylation. After screening an array of electron-rich phosphine ligands and Rh(I) salts, only marginal yields (<20%) of the desired product were obtained. Much more efficient was an electron-poor Rh(I) system with [RhCl(CO)$_2$]$_2$ as precatalyst (Table 1).[9,10] For the direct

Table 1. Direct Arylation of 2-Methyl Pyridine
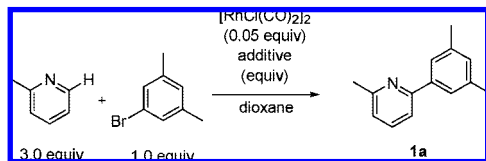
entry	additive (equiv)	concn (M)^a	temp (°C)	yield (%)^{b,c}
1	P(O^{i}Pr)$_3$ (0.30)	0.8	165	40
2	none	0.8	165	61
3	MgO (3.0)	0.8	165	33
4	N^{i}Pr$_2$^{i}Bu (3.0)	0.8	165	0
5	2,6-lutidine (3.0)	0.8	165	47
6	K$_2$CO$_3$ (3.0)	0.8	165	0
7	2,6-lut·HCl (0.25)	0.8	165	55
8	none	0.15	165	34
9	none	1.1	165	61
10	none	0.8	165	63^d
11	none	0.8	175	60^{d,e}
12	none	0.8	190	62^{d,e}

^{a} Refers to the absolute concentration in aryl bromide. ^{b} Determined by GC analysis with hexamethylbenzene as an internal standard. ^{c} The reaction time was 48 h unless otherwise indicated. ^{d} 6.0 equiv of 2-methylpyridine was employed. ^{e} The reaction time was 24 h.

Table 2. Investigation of Scope in Heterocycle
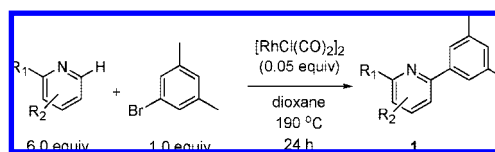
entry	heterocycle	product	% yield^a
1		1a	53
2		1b	51
3		1c	78
4		1d	70
5		1e	76
6		1f	67
7		1g	0
8		1h	86^b
9		1i	65^b

^{a} Isolated yield of analytically pure product; 0.4 mmol scale in ArBr; 0.8 M absolute concentration in ArBr. ^{b} Reaction run at 175 °C and 0.3 M absolute concentration in ArBr.

arylation of picoline with 3,5-dimethylbromobenzene, addition of P(O^{i}Pr)$_3$ afforded a promising 40% yield of the cross-coupled product **1a** (entry 1). The exclusion of phosphite additive proved even more effective, with the yield of **1a** improving to 61% (entry 2). Further enhancement in yield was not observed upon the inclusion of other additives such as MgO (entry 3), various organic bases (entries 4 and 5) and inorganic bases (entry 6), or a protic acid source (entry 7). Absolute concentration proved very important, with the best results being obtained at relatively high concentrations of the aryl bromide (compare entries 8 and 9). A marginal improvement was observed upon running the reaction with 6 equiv of 2-methylpyridine (entry 10).[11,12] The reaction temperature could also be increased to 175 or 190 °C while maintaining reaction yield, to enable the reaction time to be reduced to 24 h (entries 11 and 12).

With a set of optimized conditions in hand, we next set out to investigate the generality of the catalytic direct arylation with a variety of substituted pyridine derivatives (Table 2). Good arylation yields were observed for pyridine derivatives with straight-chain (entries 1 and 2), β-branched (entry 3), and α-branched (entry 4)

Table 3. Investigation of Scope in Aryl Bromide
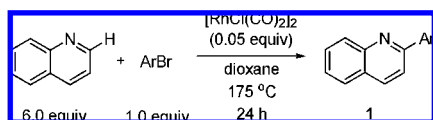
entry	ArBr	product	% yield[a]
1		**1h**	86
2		**1j**	74
3		**1k**	62
4		**1l**	70
5		**1m**	73
6		**1n**	77
7		**1o**	69
8		**1p**	68
9		**1q**	69
10		**1r**	70
11		**1s**	65
12		**1t**	45

[a] Isolated yield of analytically pure product; 0.4 mmol scale in ArBr; 0.3 M absolute concentration in ArBr.

substituents at the C-2 position. Tetrahydroquinoline also provided the arylated product in good yield (entry 5), as did 2,4-dimethylpyridine (entry 6). In contrast, when a substituent at the C-2 position is not present, arylation does not occur (entry 7). This result parallels our previous studies on Rh-catalyzed pyridine alkylation.[7,13] The steric interactions provided by a substituent at this position may reduce the energy difference between the *N*-bound complex and the C−H activation intermediate. Consistent with the requirement for C-2 substitution, quinoline is also a highly effective substrate for direct arylation (entry 8). As illustrated in entry 9, the compatibility of the reaction conditions with chloro substitution should enable efficient further elaboration of the arylation product by standard cross-coupling methods. However, no arylation was observed for 2-fluoropyridine or 2-chloropyridine.

The substrate scope in aryl bromide was also evaluated with quinoline as the coupling partner (Table 3). Both electron-rich and electron-poor aryl bromides are accommodated with equal efficiency (compare, for example, entries 4 and 11). A variety of useful functional groups are tolerated, including aryl and alkyl ethers (entries 3 and 4), chloride (entry 8), fluoride (entry 9), and ketone functionality (entry 10). While cross-coupling proceeds smoothly with *meta* substitution on the aryl bromide ring (see, for example, entry 1), attempted cross-coupling with 2-methylbromobenzene failed to afford product, with only unreacted starting material recovered.

Studies exploring reaction scope were conducted using 5 mol % of the Rh(I) catalyst. However, the reaction can be performed with comparable efficiency employing only 1 mol % of the catalyst. In this case, the reaction was run neat, resulting in complete consumption of the aryl bromide after 24 h and a 68% isolated yield of the arylated product **1e** (eq 1).
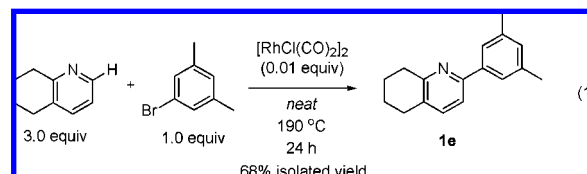
In summary, we have developed a Rh(I)-catalyzed strategy for the direct arylation of pyridines and quinolines. The heterocycle is used *without* the need for prefunctionalization, and all reaction components are inexpensive and readily available. The strategy represents an expeditious route to an important class of substituted heterocycles and should be of broad utility.[14]

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

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(12) Mass balance experiments indicate <10% unproductive loss of the heterocycle after complete consumption of the aryl bromide. For all of the aryl bromides investigated, neither hydrodehalogenation nor dimerization was observed.
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(14) For several mechanistic possibilities, please see the Supporting Information.

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