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Rhodium(III)-Catalyzed Arylation of Boc-Imines via C−H Bond Functionalization

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Supporting Information

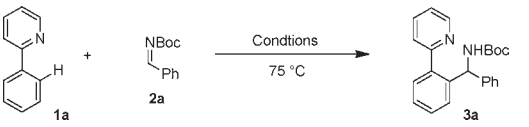
ABSTRACT: The first rhodium-catalyzed arylation of imines proceeding via C−H bond functionalization is reported. Use of a non-coordinating halide abstractor is important to obtain reactivity. Aryl-branched *N*-Boc-amines are formed, and a wide range of functionality is compatible with the reaction.

In the area of C−H bond functionalization, arylations of alkenes and alkynes have been well explored.[1] In contrast, analogous additions across C−O[2] or C−N[3−5] multiple bonds are rare. Due to the prevalence of α-branched amines in drugs and natural products,[6] we sought a method for the arylation of imines via C−H bond functionalization. The most closely related transformations are Pd-catalyzed additions to *N*-tosyl imines that rely on the functionalization of acidic C−H bonds.[5] Herein, we report the high-yielding 2-pyridyl-directed arylation of a wide range of aromatic *N*-Boc-imines with a Rh(III) catalyst.

Our investigations focused on additions to *N*-Boc-imines due to the convenience and ease of removal of the exceedingly popular Boc protecting group. As the test substrate for arylation, we chose 2-phenylpyridine (**1a**) because of the pyridyl directing group's high chemical stability and rich history in C−H functionalization with a variety of transition metals.[1d,1e,7]

We began our reaction exploration with Rh(III) catalysts. This type of catalyst has been proposed to activate C−H bonds via an electrophilic deprotonation mechanism to generate an aryl-Rh(III) species.[8] However, upon heating 10 mol % $[Cp^*RhCl_2]_2$ (Cp* = pentamethyl cyclopentadienyl) with 2-phenylpyridine and *N*-Boc-benzaldimine in CH_2Cl_2, no product was observed (entry 1, Table 1). Theorizing that the lack of reactivity may be due to the chloride ligands on the metal, which could prevent coordination of the *N*-Boc-imine, $AgSbF_6$ was added as a halide abstractor and provided the desired product **3a** in 55% yield (entry 2).[9] Utilizing coordinating solvents such as THF (entry 3) and DMF (entry 4) resulted in lower activity, while solvents such as benzene failed due to insolubility of the catalyst system (entry 5). Analogous iridium- (entry 6) and ruthenium-based (entry 7) complexes were found to be inactive for this transformation. Variable substrate stoichiometries were also explored (entries 8 and 9), with the highest yield being achieved by employing 2 equiv of the least expensive component, 2-phenylpyridine (entry 9). Under these conditions, the excess 2-phenylpyridine was recovered. Unreacted *N*-Boc-imine was not observed, and only small amounts of the hydrolyzed aldehyde product were detected. Other halide abstractors were also explored (entries 10−14), but $AgSbF_6$ proved to be optimal (entry 9).

Table 1. Screening of Reaction Conditions[a]



entry	catalyst	additive	solvent	% yield[b]
1	$[Cp^*RhCl_2]_2$	none	CH_2Cl_2	0
2	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_2Cl_2	55
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$	THF	30
4	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DMF	0
5	$[Cp^*RhCl_2]_2$	$AgSbF_6$	C_6H_6	0
6	$[Cp^*IrCl_2]_2$	$AgSbF_6$	CH_2Cl_2	0
7	$[Cp^*RuCl_2]_n$	$AgSbF_6$	CH_2Cl_2	0
8[c]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_2Cl_2	60
9[d]	**$[Cp^*RhCl_2]_2$**	**$AgSbF_6$**	**CH_2Cl_2**	**87**
10[d]	$[Cp^*RhCl_2]_2$	AgOAc	CH_2Cl_2	trace
11[d]	$[Cp^*RhCl_2]_2$	AgOTs	CH_2Cl_2	30
12[d]	$[Cp^*RhCl_2]_2$	$AgBF_4$	CH_2Cl_2	77
13[d]	$[Cp^*RhCl_2]_2$	$AgClO_4$	CH_2Cl_2	69
14[d]	$[Cp^*RhCl_2]_2$	$NaBPh_4$	CH_2Cl_2	0

[a] All reactions were performed by employing 0.05 mmol of 2-phenylpyridine and 0.05 mmol of imine in 0.5 mL of solvent with 10 mol % catalyst and 40 mol % additive. [b] Yields are based on NMR using 2, 6-dimethoxytoluene as an internal standard. [c] 0.1 mmol of imine. [d] 0.1 mmol of 2-phenylpyridine.

Evaluation of substituted 2-arylpyridines established that both electron-poor and -rich derivatives are effective arylation substrates and that the reaction is compatible with chloro, keto, and acetanilido functional groups (Scheme 1). For 2-(3-methylphenyl)pyridine, functionalization occurred solely *para* to the methyl group to provide **3f**. Multicyclic pyridine derivatives also serve as effective directing groups, with the bicyclic quinoline and tricyclic benzo[*h*]quinoline both providing the expected products **3g** and **3h**, respectively, in good yields. Notably, for all of

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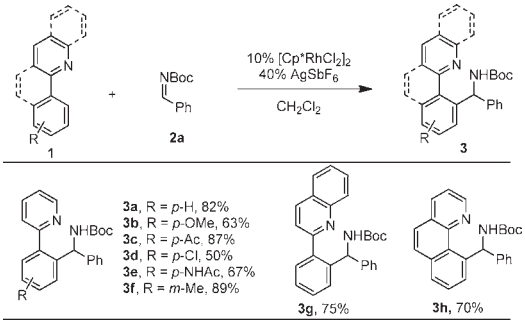
Scheme 1. Arylpyridine Substrate Scope[a]



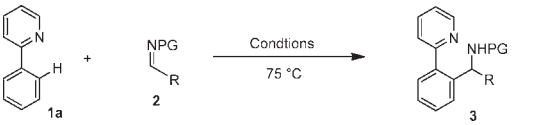
[a] All reactions were performed by heating 2-phenylpyridine (2 equiv), imine (1 equiv), $[Cp^*RhCl_2]_2$ (10 mol %), $AgSbF_6$ (40 mol %), and CH_2Cl_2 (0.1 M) in a sealed tube for 20 h at 75 °C. Isolated yields are reported.

the 2-arylpyridine substrates, products resulting from bis-arylation were not detected.

The substrate scope was further extended to a broad variety of substituted aromatic *N*-Boc-imines (Table 2, entries 1−12). Both electron-poor (entries 3, 5, 8, and 11) and electron-rich (entry 7) aromatic imines provided branched amine products in high yields. Substitutions at the *ortho* (entries 9 and 10), *meta* (entry 11), and *para* (entries 2−8) positions were all well tolerated. Moreover, the reaction showed excellent functional group compatibility, with *N*-Boc-imines substituted with chloro (entries 2 and 9), nitro (entry 3), methoxy (entry 7), ester (entry 8), and even the electrophilic carboxaldehyde (entry 11) functionality all providing branched amine products in high yields. In addition, the 2-thienyl-substituted branched amine product **3s** was obtained by addition to a heteroaromatic imine substrate (entry 12). Of the functionalities evaluated, only the nitrile group (entry 4) gave a low yield, likely due to competitive coordination of the CN group to the Rh(III) center. In support of this explanation, a dramatic reduction in yield was observed upon addition of benzonitrile to a previously successful substrate combination (see entry 13 versus 6). While a 1:4 ratio of $[Cp^*RhCl_2]_2$ to $AgSbF_6$ gave consistently good results, we found that ratio could be decreased to 1:2 for most substrates with no effect on rates or yields (see entries 7, 9, 10, and 12). However, the reaction failed to work when the ratio was below 1:2. For more reactive imines, good yields may be obtained with 5 mol % $[Cp^*RhCl_2]_2$ (entry 5). This lower catalyst loading provided a moderate reduction in yields when applied to less reactive substrates as a result of competitive imine decomposition pathways (entries 1, 2, and 7). Further decreasing the catalyst loading to 2.5 mol % $[Cp^*RhCl_2]_2$ resulted in low yields.

Alkyl *N*-Boc-imines were not effective substrates for this transformation as a result of self-condensation via imine-to-enamine tautomerization. We therefore explored other protecting groups for alkyl imine substrates. While *N*-diphenylphosphinoyl-pentaldimine proved to be unreactive (entry 14), addition to the corresponding *N*-tosyl-imine proceeded in good yield (entry 15). This result prompted us to also evaluate the reactivity of an aromatic *N*-tosyl-imine substrate, but *N*-tosyl-benzaldimine reacted with poor conversion to give the branched amine **3v** in only 40% yield (entry 16). We considered that the moderate yield observed might possibly be attributed to the reversibility of arylation of **3v**. This reversibility was demonstrated by subjecting purified **3v** to the reaction conditions,

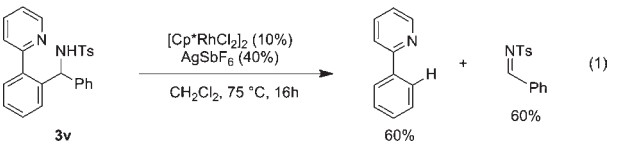
Table 2. Substrate Scope of Substituted Imines[a]



entry	R	protecting group	product	% yield[b]
1	C_6H_5	Boc	**3a**	82 (70)[c]
2	4-ClC_6H_4	Boc	**3i**	77 (64)[c]
3	4-$NO_2C_6H_4$	Boc	**3j**	77
4	4-CNC_6H_4	Boc	**3k**	50
5	4-$CF_3C_6H_4$	Boc	**3l**	95 (81)[c]
6	4-MeC_6H_4	Boc	**3m**	70
7[d]	4-$MeOC_6H_4$	Boc	**3n**	70 (51)[c]
8	4-$CO_2MeC_6H_4$	Boc	**3o**	70
9[d]	2-ClC_6H_4	Boc	**3p**	76
10[d]	2-MeC_6H_4	Boc	**3q**	92
11	3-$CHOC_6H_4$	Boc	**3r**	81
12[d]	2-thiophene	Boc	**3s**	71
13[e]	4-MeC_6H_4	Boc	**3m**	27
14[f]	*n*Bu	$P(O)Ph_2$	**3t**	0
15[f]	*n*Bu	Ts	**3u**	72
16	C_6H_5	Ts	**3v**	40
17	C_6H_5	Ns	**3w**	51

[a] All reactions were performed by heating 2-phenylpyridine (2 equiv), imine (1 equiv), $[Cp^*RhCl_2]_2$ (10 mol %), $AgSbF_6$ (40 mol %), and CH_2Cl_2 (0.1 M) in a sealed tube for 20 h at 75 °C. [b] Isolated yield. [c] Values in parentheses correspond to isolated yields after 40 h at 75 °C using $[Cp^*RhCl_2]_2$ (5 mol %) $AgSbF_6$ (20 mol %). [d] $AgSbF_6$ (20 mol %). [e] PhCN (1 equiv) added. [f] 2-Phenylpyridine (1 equiv).

which resulted in an equilibrium mixture of **3v**, 2-phenylpyridine, and *N*-tosyl-benzaldimine (eq 1),



consistent with the distribution observed in the arylation reaction (Table 2, entry 16). Significantly, while β-aryl elimination from aryl carbinols has been reported,[10] to our knowledge, the corresponding transformation for branched amines has not previously been described. The mechanisms of β-aryl elimination for both the previously reported carbinols and **3v** are likely to be similar, but further studies are needed. The reversibility of the reaction could be slightly shifted toward product by replacing the *N*-tosyl with the more electronegative *N*-nosyl[11] group (entry 17). Reversibility was not observed for the arylation products of aromatic *N*-Boc-imines or aliphatic *N*-tosyl-pentanaldimine.

A mechanism for the arylation reaction could involve initial electrophilic deprotonation of the *o*-phenyl C−H bond of 2-phenylpyridine to form an Ar−Rh(III) intermediate (Scheme 2).[8] Coordination of the *N*-Boc-imine would then activate the imine for addition, followed by protonolysis to regenerate the catalyst. Alternatively, rhodium could serve as a Lewis acid to activate the imine for electrophilic aromatic substitution (EAS).[12] However,

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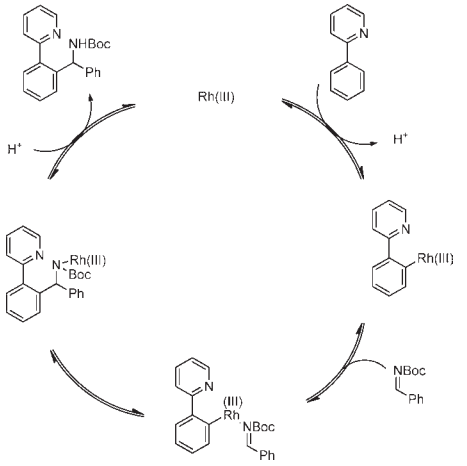
Scheme 2. Proposed Catalytic Cycle



this latter pathway is unlikely, given that only the electronically deactivated *ortho* position is functionalized on the electron-deficient 2-phenylpyridine. Furthermore, the observation that the reaction is more efficient for electron-poor 2-arylpyridines (see Scheme 1, **3b** vs **3c**) is inconsistent with an EAS pathway but supports an electrophilic deprotonation mechanism.

In summary, $[Cp^*RhCl_2]_2/AgSbF_6$ catalyzes the addition of 2-arylpyridines to *N*-Boc- and *N*-sulfonyl-imines via C−H bond functionalization to give branched amine products. Many commonly encountered functional groups, such as ketone, aldehyde, ester, halide, trifluoromethyl, amide, and nitro groups, are compatible with the method. Mechanistic studies and the investigation of alternative directing groups will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental details and spectral data for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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