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Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes

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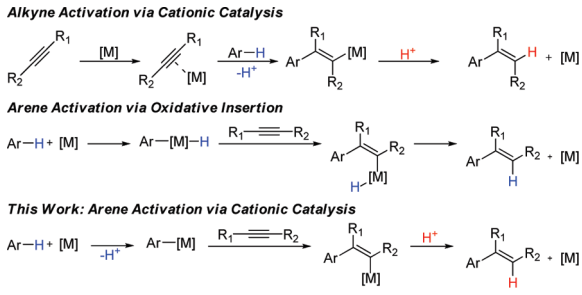
Transition-metal-catalyzed direct transformations of aromatic C−H bonds represent a burgeoning field in organic chemistry because it enables inherently efficient construction of organic building blocks.[1] Of these processes, alkyne hydroarylation has received much attention in recent years because it allows for the atom-economical synthesis of functionalized alkenes directly from simple arenes and alkynes.[2] Hydroarylation of alkynes typically occurs by two pathways (Scheme 1). The first proceeds through activation of the alkyne by a cationic metal complex.[2,3] The second proceeds via activation of the arene by oxidative insertion of a nucleophilic metal into a C−H bond.[2,4] Although many intra- and intermolecular examples have been reported, these pathways have limited scope and utility since they usually necessitate the use of electron-rich arenes, electron-deficient alkynes, or synthetically restricted directing groups. Moreover, the products are often obtained as regio- or stereoisomeric mixtures.

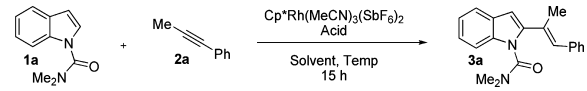
Scheme 1. Intermolecular Hydroarylation of Alkynes



An alternative pathway is the activation of the arene with an electrophilic metal, which could then undergo migratory insertion of the alkyne followed by protodemetalation (Scheme 1). Although this pathway holds promise for overcoming some of the limitations of hydroarylation, only Pd(II) catalysis has shown efficacy with intramolecular examples.[5] In an elegant example, Gevorgyan reported the hydroarylation of *o*-alkynyl biaryls.[6] Li reported the hydroarylation of *N*-arylpropiolamides under similar conditions.[7] Although these examples represent important advances, the development of novel catalysts is still necessary to achieve elusive intermolecular reactivity. Herein we report the Rh(III)-catalyzed intermolecular hydroarylation of alkynes. Preliminary mechanistic investigations suggest that the reaction proceeds through arene activation by the cationic metal catalyst. This relatively unexplored pathway allows intermolecular hydroarylation to proceed in high yields for a range of arenes and internal alkynes and is highly regio- and stereoselective.

We recently reported Rh(III)-catalyzed transformations at aromatic C−H bonds.[8] Since indoles represent an important motif in medicinal chemistry, this motif was selected along with $Cp^*Rh(MeCN)_3(SbF_6)_2$ and 1-phenyl-1-propyne (**2a**) for reaction development (Table 1). The

Table 1. Optimization of Hydroarylation Conditions[a]



entry	solvent	acid	temp (°C)	% yield[b]
1	PhMe	none	100	5
2	PhMe	AcOH	100	76
3	PhMe	PivOH	100	90
4	PhMe	PivOH	100	0[c]
5	*i*PrOAc	PivOH	100	93
6	***i*PrOAc**	**PivOH**	**90**	**99 (99)**

[a] Conditions: indole (1 equiv), alkyne (1.1 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (5 mol %), and acid (5 equiv) were dissolved in the solvent and heated at the indicated temperature for 15 h. [b] ^1H NMR yield of the major product using 1,3,5-trimethoxybenzene as an internal standard. An isolated yield is given in parentheses. [c] Using $[Cp^*RhCl_2]_2$ as the catalyst.

choice of the protecting group on indole was found to be crucial, with *N*,*N*-dimethylcarbamoyl being optimal.[9] We were pleased to find that heating the coupling partners in toluene with the catalyst afforded the desired product, albeit without catalyst turnover (entry 1). Superior catalytic efficiency was obtained when 5 equiv of acetic acid were added to the reaction mixture (entry 2) and again upon the use of pivalic acid (entry 3). Use of a related non-cationic catalyst, $[Cp^*RhCl_2]_2$,[10] led to no reactivity (entry 4). A screen of solvents revealed isopropyl acetate to be superior to toluene (entry 5). Finally, lowering the temperature to 90 °C gave **3a** in near quantitative yield (entry 6).

Table 2 outlines the scope of the hydroarylation under our optimized reaction conditions. Both electron-donating (**3b**) and electron-withdrawing (**3c**, **3d**) groups on the indole are tolerated, as is a chloro-substituted substrate (**3e**). This catalyst system also allows for the use of other heterocycles (**3f**−**h**), a range of different types of directing groups (**3h**−**k**), and electron-rich (**3i**, **3j**)[11] and electron-poor (**3k**) simply substituted benzenes in hydroarylation. A range of alkynes are also compatible with the reaction, including diaryl- (**3g,k**), electron-rich arene- (**3l**), alkenyl- (**3m**), cyclopropyl- (**3n**), heterocyclic- (**3o**), and trimethylsilyl-substituted (**3p**) alkynes as well as alkynes with ester (**3q**) and protected-alcohol (**3r**) moieties.[12] The dimethylcarbamoyl group can be easily removed using KOH in $EtOH/H_2O$ at 90 °C.[13]

To probe the reaction mechanism, C2-deuterated **1a** was subjected to the reaction conditions (eq 1). At low conversion, no deuterium incorporation in the product was observed.[14] This excludes the possibility of arene activation by oxidative insertion, which should retain deuterium incorporation (Scheme 1). Also, a decrease in deuterium incorporation in the starting material was observed, suggesting an arene metalation/protodemetalation equilibrium prior to reaction with the alkyne.[15] Futhermore, the requisite use of excess acid (Table 1, entry 1) suggests a protonation event

† Deceased November 11, 2009.

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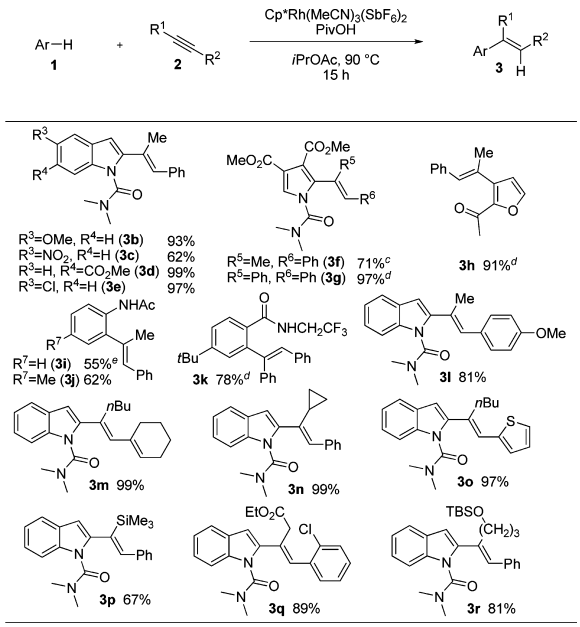
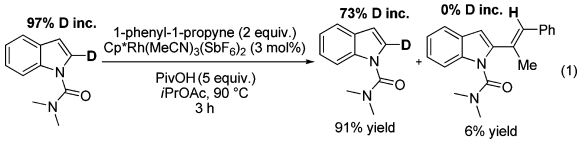
Table 2. Scope of the Rhodium-Catalyzed Hydroarylation[a,b]



[a] Conditions: arene (1 equiv), alkyne (1.1 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (5 mol %), and pivalic acid (5 equiv) in *i*PrOAc (0.4 M) at 90 °C for 15 h. [b] Isolated yields. [c] In 1,2-dichloroethane for 24 h. [d] Using 2 equiv of arene and 1 equiv of alkyne. [e] Using 2.5 mol % $Cp^*Rh(MeCN)_3(SbF_6)_2$ in *t*AmOH (0.2 M) at 70 °C.

in the catalytic cycle, and the arene scope highlights the importance of the presence of a directing group.



The high selectivity for syn addition renders the possibility of alkyne activation improbable (Scheme 1).[3,16] However, it is conceivable that syn addition arises from isomerization of the trans addition product. A control experiment in which a 1:2.2 mixture of *E* and *Z* isomers was exposed to the standard hydroarylation conditions showed no alkene isomerization, ruling out the possibility of alkene isomerization under these reaction conditions.

A proposed catalytic cycle that would explain both the decrease in deuterium incorporation and the observed alkene geometry is shown in Figure 1. First, reversible directed metalation with the rhodium(III) catalyst occurs, with concomitant loss of a proton.[17] The alkyne can then coordinate to the rhodium center, after which migratory insertion occurs. Finally, protonolysis yields the product and regenerates the catalyst.

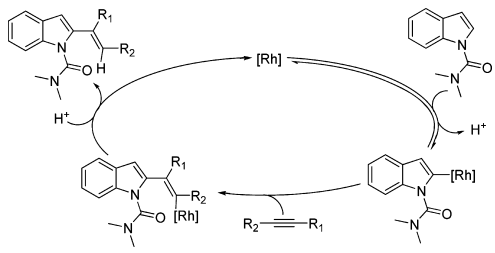


Figure 1. Proposed catalytic cycle.

In conclusion, we have developed an intermolecular rhodium(III)-catalyzed hydroarylation of alkynes. The reaction is applicable across a range of both arenes and alkynes. Consequently, this reaction should be useful for rapid, atom-economical preparation of organic building blocks. Furthermore, this novel reactivity for the intermolecular hydroarylation of alkynes should have broader implications for the development of related transformations.

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Supporting Information Available: Detailed 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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(11) Use of the dimethylcarbamoyl protecting group in this case led to poor conversion to product.

(12) Under the standard reaction conditions, terminal and dialkyl alkynes afforded only trace amounts of product.

(13) See the Supporting Information for details.

(14) Under the same reaction conditions, using **1a** and PivOD resulted in deuterium incorporation at the alkene position. A control experiment revealed no H/D exchange at the alkene of **3a** under the reaction conditions.

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