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ARTICLE TYPE

Rh(III)-Catalyzed Regioselective Hydroarylation of Alkynes via Directed C-H Functionalization of Pyridines

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Rh(III)-catalyzed C-3 selective alkenylation of pyridine derivatives via hydroarylation of alkynes has been developed. The reaction shows high regioselectivity, high yield and good functional group tolerance, providing a convenient strategy for the synthesis of trisubstituted (pyridin-3-yl)alkenes.

Since the pioneering work of Murai on carbonyl-directed alkenylation of aromatic ketones with alkynes catalyzed by $Ru(H)_2(CO)(PPh_3)_3$, chelation-assisted hydroarylation of internal alkynes has proven to be a valuable tool for the efficient synthesis of trisubstituted alkenes from readily available arenes and alkynes.[1,2] Mechanically, hydroarylation catalyzed by low-valent transition metal species generally proceeds via oxidative addition of transition metals into the *ortho* C-H bonds, which could then undergo hydrometallation of alkynes followed by reductive elimination to provide the alkenylated products.[3-5] Alternatively, the hydroarylation of alkynes catalyzed by high-valent transition metals generally involves the metalation-deprotonation of *ortho* C-H bonds, followed by migratory insertion of the metallacycle into alkynes and subsequently protodemetalation.[6-7] From a synthetic point of view, this protocol can be complementary to the oxidative olefination process because trisubstituted olefin products are generated, and no oxidant is needed.

Despite significant progress in hydroarylation of simple arenes, the hydroarylation of pyridines is still limited, likely due to the electron-deficiency of the ring and the strong coordination of the nitrogen atom.[8] Nakao and Hiyama demonstrated Ni(0)-catalyzed C-2 selective alkenylation of pyridine-*N*-oxides (Figure 1A).[4a] Shortly after, the same group reported C-2 alkenylation of pyridines by Ni(0)-Lewis acid cooperative catalysis.[4b] Ong, Nakao and Hiyama independently reported Ni(0)-Al(III) mediated C-4 selective alkenylation of pyridines using *N*-heterocyclic carbenes as ligands.[4c,d] Recently, Chang realized a bishydroarylation of alkynes with 2,2'-bipyridine under *in situ* generated Rh(I)-IMes catalyst (Figure 1A).[5] However, these examples are mechanically limited to low-valent transition metals via an oxidative addition pathway, which are usually not completely regio- and stereoselective. Herein, we report a Rh(III)-catalyzed hydroarylation of alkynes with pyridines in the presence of HOAc and $Cu(OAc)_2$, proceeding regio- and stereoselectively through a directed C−H cleavage to produce the corresponding alkenylated products (Figure 1B).[9]

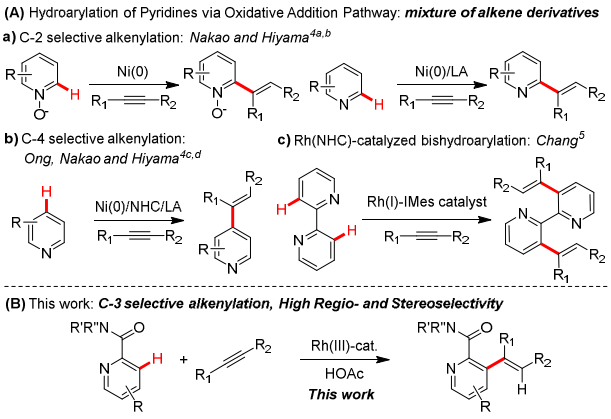


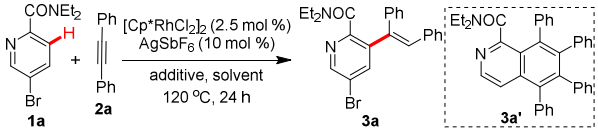
Figure 1 Transition-Metal-Catalyzed Hydroarylation of Alkynes with Pyridine Derivatives

We commenced our study by investigating the hydroarylation of **2a** with picolinamide **1a** under the conditions previously reported for oxidative olefination reaction and the desired product **3a** was obtained in 74% yield (Table 1, entry 1).[9e] Adding 4 equiv of HOAc improved the yield dramatically (entry 2, 92%). Control experiments showed that both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ were essential for this reaction (entries 5 and 6). It is surprising that the removal or the use of catalytic amount of $Cu(OAc)_2$ resulted in reduced yields (entries 7 and 8). To verify whether $Cu(OAc)_2$ was just as a source of acetate, $Cu(OAc)_2$ was replaced by CsOAc; however, only trace amount of product was obtained (entry 9).[10] Other Lewis acids, such as $CuSO_4$, $Mn(OAc)_2$ and $Co(OAc)_2{\cdot}4H_2O$, gave moderate to high yields (entries 10-12); while $CuBr_2$ failed to give any product (entry 13). Since this hydroarylation reaction is redox-neutral and no oxidant is needed, we hypothesized that $Cu(OAc)_2$ might act as a Lewis acid to coordinate competitively with the pyridine nitrogen.

With the optimized conditions in hand, we further explored the substrate scope of picolinamides to test the generality of this protocol (Table 2). A variety of picolinamides with valuable functional groups, such as chloro, fluoro, bromo, methoxycarbonyl, *p*-methoxyphenyl and acetoxyl, are compatible with this protocol, furnishing the desired products in moderate to high yields. Halogenated picolinamides such as bromide, chloride and fluoride, could react smoothly with alkynes under the standard or slightly modified conditions to

give good yields (entries 1-2, and 8-13). Picolinamides with electron-donating groups were somewhat less reactive than those with electron-withdrawing groups (entries 1-3 *vs* 4-5; entries 6-7 *vs* 9-10), together with the overall electron-deficient of pyridines, rendering an electronphilic reaction mechanism less likely. Interestingly, the *Z*-isomer was afforded in 37% yield while the electron-donating methoxy group appeared at the 6-position (entry 7). Additionally, this reaction was sensitive to steric hindrance; substrates bearing sterically demanding group at the 4-position were less reactive or failed under the reaction conditions (entries 11-15).

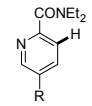
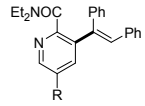
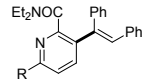
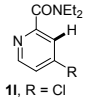
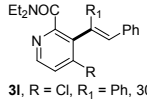
Table 1. Optimization of the Reaction Conditions[a]



Entry	Additive (equiv)	HOAc (equiv)	Solvent	Yield (%)
1	$Cu(OAc)_2$ (1.0)	–	DCE	74(15[b])
2	$Cu(OAc)_2$ (1.0)	4.0	DCE	92
3	$Cu(OAc)_2$ (1.0)	4.0	*t*-Amyl-OH	58
4	$Cu(OAc)_2$ (1.0)	4.0	1,4-dioxane	91
5[c]	$Cu(OAc)_2$ (1.0)	4.0	DCE	16
6[d]	$Cu(OAc)_2$ (1.0)	4.0	DCE	0
7	–	4.0	DCE	46
8	$Cu(OAc)_2$ (0.1)	4.0	DCE	45
9	CsOAc (1.0)	4.0	DCE	<10
10	$CuSO_4$ (1.0)	4.0	DCE	79
11	$Mn(OAc)_2$ (1.0)	4.0	DCE	90
12	$Co(OAc)_2$ (1.0)	4.0	DCE	89
13	$CuBr_2$ (1.0)	4.0	DCE	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), additive in 2 mL solvent at 120 °C for 24 h. Isolated yield. [b] Yield of isoquinoline (**3a'**). [c] Without $AgSbF_6$. [d] Without $[Cp^*RhCl_2]_2$.

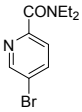
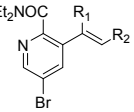
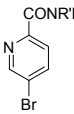
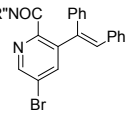
Table 2 Hydroarylation of Alkynes with Picolinamides

Entry	Picolinamide **1**	Alkyne **2**	Products **3**, Yield (%)
			
1	**1a**, R = Br	**2a**	**3a**, R = Br, 92
2	**1b**, R = Cl	**2a**	**3b**, R = Cl, 79
3[b]	**1c**, R = F	**2a**	**3c**, R = F, 81 (19[c])
4	**1d**, R = CO_2Me	**2a**	**3d**, R = CO_2Me, 91
5	**1e**, R = PMP	**2a**	**3e**, R = PMP, 56
6	**1f**, R = OAc	**2a**	**3f**, R = OAc, 57
			
7	**1g**, R = Me	**2a**	**3g**, R = Me, 82
8	**1k**, R = OMe	**2a**	**3k**, R = OMe, 63 (37[d])
9	**1h**, R = F	**2a**	**3h**, R = F, 99
10	**1i**, R = Cl	**2a**	**3i**, R = Cl, 99
11	**1j**, R = Br	**2a**	**3j**, R = Br, 90
			
12	**1l**, R = Cl	**2a**, R_1 = Ph	**3l**, R = Cl, R_1 = Ph, 30
13		**2b**, R_1 = Me	**3l**, R = Cl, R_1 = Me, 87
14	**1m**, R = Br	**2b**, R_1 = Me	**3m**, R = Br, 75
15	**1n**, R = OMe	**2b**, R_1 = Me	**3n**, R = OMe, 49
16	**1o**, R = Me	**2b**, R_1 = Me	NR

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (0.2 mmol), HOAc (0.8 mmol) in 2 mL DCE at 120 °C for 24 h. Isolated yield. [b] 0.1 mmol $Cu(OAc)_2$ and 1.6 mmol HOAc were added. [c] Isolated yield of isoquinoline (**3c'**) via oxidative annulation of **1c** with **2a**. [d] Isolated yield of *Z* isomer (**3k'**).

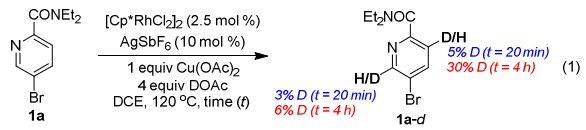
The scope of internal alkynes was also investigated, and the results are summarized in Table 3. A variety of Bis(*p*-substituted phenyl)acetylenes (**2c**-**2g**) underwent hydroarylation with **1a** to produce desired products in moderate to high yields (entries 1-5). Alkyne **2g** bearing an electron-donating methoxyl group in the phenyl ring reacted with **1a** to afford *Z*-isomer predominantly, which was consistent with the hydroarylation with **1h** (Table 3 entry 5 *vs* Table 2 entry 7). Symmetrical dialkyl alkyne, 4-octyne (**2h**), could also react with **1a** to give **3u** in excellent yield (entry 6). The reaction of unsymmetrical 1-phenyl-1-butyne (**2i**) and 1-phenyl-1-propyne (**2j**) with **1a** proceeded smoothly, affording the alkenylated products in excellent yields with the phenyl group distal to the amide group predominantly (entries 7-8). Other *N*,*N*-dialkyl substituted picolinamides reacted efficiently with diphenylacetylene **2a** under current conditions to give the alkenylated products in good yields (entries 9-11).

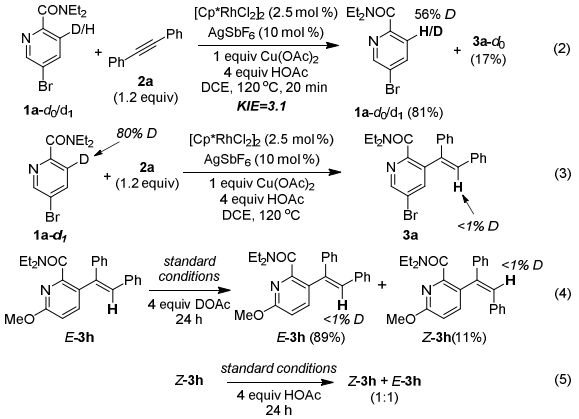
Table 3 Substrate Scope of Alkynes and Amides

Entry	Picolinamide **1**	Alkyne **2**	Product **3**, Yield (%)
			
1	**1a**	**2c**, R_1, R_2 = *p*-F-C_6H_4	**3p**, R_1, R_2 = *p*-F-C_6H_4, 85
2	**1a**	**2d**, R_1, R_2 = *p*-Cl-C_6H_4	**3q**, R_1, R_2 = *p*-Cl-C_6H_4, 99
3	**1a**	**2e**, R_1, R_2 = *p*-MeC_6H_4	**3r**, R_1, R_2 = *p*-Me-C_6H_4, 94
4	**1a**	**2f**, R_1, R_2 = *p*-^{t}Bu-C_6H_4	**3s**, R_1, R_2 = *p*-^{t}Bu-C_6H_4, 51
5	**1a**	**2g**, R_1, R_2 = *p*-OMe-C_6H_4	**3t**, R_1, R_2 = *p*-MeO-C_6H_4, 36 (62[b])
6	**1a**	**2h**, R_1, R_2 = ^{n}Pr	**3u**, R_1, R_2 = ^{n}Pr, 94
7	**1a**	**2i**, R_1 = Et, R_2 = Ph	**3v**, R_1 = Et, R_2 = Ph, 98 (9:1)[c]
8	**1a**	**2j**, R_1 = Me, R_2 = Ph	**3w**, R_1 = Me, R_2 = Ph, 100 (20:1)[c]
			
9	**1o**, R', R'' = $(CH_2)_5$	**2a**	**3x**, R', R'' = $(CH_2)_5$, 87
10	**1p**, R', R'' = Cy	**2a**	**3y**, R', R'' = Cy, 76
11	**1q**, R', R'' = Bn	**2a**	**3z**, R', R'' = Bn, 81

[a] Standard conditions. Isolated yield. [b] Isolated yield of *Z* isomer (*Z*-**3t**). [c] Ratios of regioisomers are given in parentheses, determined by ^1H NMR. Major isomers are shown.

To probe the mechanism of the hydroarylation reaction, further experiments were performed. When picolinamide 1a was subjected to the reaction conditions in the absence of alkyne for 20 min and 4 hours, 5% and 30% deuterium incorporation was observed at the 3-position of the recovered starting material **1a**, respectively (eqn (1)). These results suggest the reversibility of C-H activation under the reaction conditions. Interestingly, deuterium incorporation was also observed at the 6-position. Moreover, a primary KIE value (3.1) was obtained, indicating that C-H bond cleavage might occur during the rate-determining step (eqn (2)). Next, deuterated picolinamide **1a-*d*$_1$** was subjected to the reaction conditions, and no deuterium incorporation was observed in the olefinic position of the product (eqn (3)). This fact suggests that the oxidative addition of the *ortho* C-H bond under current conditions is improbable.





The possibility of alkyne activation via cationic catalysts was ruled out based on the exclusive formation of the *E*-isomers in most of the cases via *syn*-selective addition of the C-C triple bond, as well as on the high value of the KIE.[11] However, *Z*-isomers were obtained when electron-rich picolnamide **1h** or alkyne **2g** were used as coupling partners (Table 2, entry 7 and Table 3, entry 5). Alkene isomerization occurred when *E*-**3h** and *Z*-**3h** were exposed to the reaction conditions, respectively (eqn (4) and (5)). However, no deuterium incorporation in the olefinic position when *E*-**3h** was subjected to the hydroarylation conditions in DOAc(eqn (4)). These experiments ruled out the possibility of alkene isomerization via the resonance structure **III** (Figure S1, ESI†).[12] We rationalized that an *anti*-nucleometallation across the electron-rich alkenes followed by the *syn*-elimination pathway might account for the occurrence of *Z*-**3h** and *Z*-**3t**. Based on these experiments and literature precedent, a plausible mechanism is proposed to explain both the deuteration experiments and the observed alkene geometry (Figure S1, ESI†).[13]

In summary, we have developed a Rh(III)-catalyzed hydroarylation of a broad range of internal alkynes with picolinamides to afford trisubstituted (pyridin-3-yl)alkenes. Given that the oxidative olefination was limited to terminal activated olefins, such as styrenes and acrylates, that only give *E*-linear alkenes, current hydroarylation protocol offers a complementary approach to access the branched products.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Figure S1, Experimental procedures, characterization data, and copies of ^{1}H anf ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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