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Hydroheteroarylation

A Versatile Rhodium(I) Catalyst System for the Addition of Heteroarenes to both Alkenes and Alkynes by a C–H Bond Activation**

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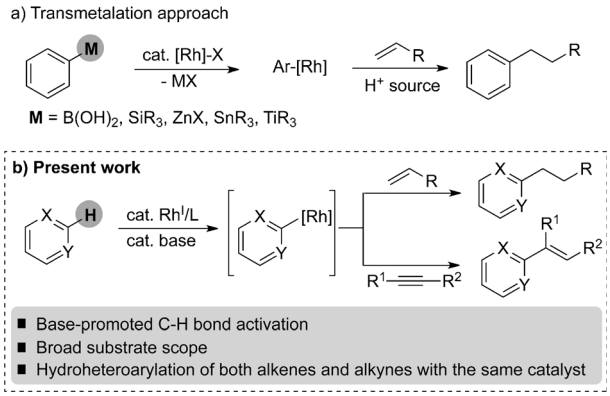
The transmetalation of organometallic reagents that are employed in reactions with unsaturated C–C bonds has become a well-established method since the development of highly efficient and selective catalytic systems. Indeed, a wide range of organometallic reagents, including boron, silicon, zinc, and titanium species, were introduced for rhodium-catalyzed arylation reactions (Scheme 1 a).[1] On the other hand, the direct addition of (hetero)arenes across alkenes and alkynes through metal-mediated C–H bond activation has



Scheme 1.

emerged as an attractive alternative to the conventional approach because it offers a more straightforward and economical route to alkyl or alkenyl (hetero)arenes.[2] In fact, the direct C–H bond functionalization method does not require preactivation of (hetero)arenes, thus avoiding the generation of stoichiometric amounts of byproducts. However, the ability to selectively activate a single C–H bond in the presence of electronically or sterically similar C–H bonds is crucial to make this functionalization method more reliable. In this respect, the introduction of directing groups is highly effective in facilitating selective activation at the *ortho* position through the in situ formation of chelating metallic intermediates.[3,4]

The hydroheteroarylation of multiple C–C bonds to directly afford functionalized heteroarenes is an important reaction of high synthetic utility. Representatively, Ellman, Bergman, and co-workers reported the alkylation of heterocycles with alkenes using a catalytic system composed of a Rh^I complex bearing a monodentate phosphine, and an acid.[2c,d] The reaction was found to proceed via substrate-based Rh/N-heterocyclic carbene intermediates, which were generated by an isomerization-initiated C–H bond activation. Hiyama and co-workers developed a Ni/Lewis acid binary catalyst system for the reaction of heteroarenes with alkenes and alkynes.[5] Although other catalytic systems and reaction conditions have also been developed for the hydroarylation of double and triple bonds,[6] there is still room for improvement, especially with respect to selectivity, reaction conditions, and substrate scope. We present herein the first example of a rhodium catalyst system that enables the facile addition of heteroarenes to both alkenes and alkynes (Scheme 1 b). Furthermore, the presence of a base was important and its role is discussed in the context of mechanism.

In our continuing efforts to develop metal-catalyzed reactions,[7] we found that certain well-defined rhodium-based catalytic systems displayed excellent selectivity and reactivity in the C–H bond activation of heteroarenes.[8] In this context, we envisioned the use of a highly selective *ortho* activation of heterocycles for the hydroarylation of unsaturated compounds.

Initially, we investigated various combinations of rhodium species, ligands, and bases for the reaction of 4-phenylpyridine *N*-oxide (**1a**, 2.5 equivalents) with *tert*-butyl acrylate (**2a**).[9] The desired hydroarylation reaction was observed, albeit in low yield (Table 1, entry 1), when the dimeric species $[\{Rh(cod)Cl\}_2]$ (2 mol%) was used, in the presence of PCy_3 ligand (5 mol%) and CsOAc (25 mol%). When the bidentate ligand **L2** was used, the yield of the monoaddition product **3a** was dramatically increased, although a trace amount of bishydroarylation compound **4a** was observed (entry 2). No conversion was observed without base and its nature was crucial to the reaction efficiency (entries 2–5). The absence of ligand led to low yield (entry 6) and the highest selectivity and yield was observed with 1,2-bis-(diphenylphosphino)ethane (**L4**, entry 8), although the use of other ligands, including N-heterocyclic carbene, gave poor yields (entries 7 and 9).

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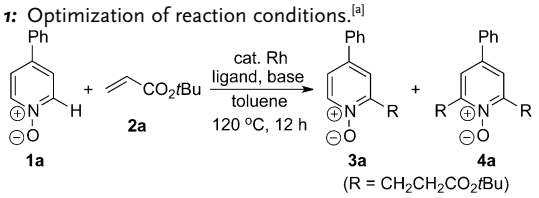
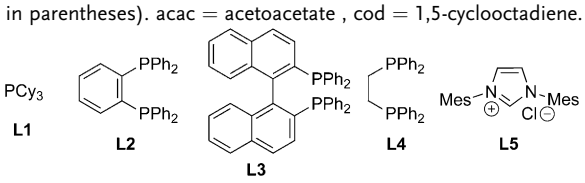
Table 1: Optimization of reaction conditions.[a]



Entry	Rh catalyst	Ligand	Base	Yield [%][b] 3a	4a
1	[{Rh(cod)Cl}$_2$]	**L1**	CsOAc	11	–
2	[{Rh(cod)Cl}$_2$]	**L2**	CsOAc	90 (84)	4
3	[{Rh(cod)Cl}$_2$]	**L2**	none	<1	
4	[{Rh(cod)Cl}$_2$]	**L2**	*t*BuONa	29	–
5	[{Rh(cod)Cl}$_2$]	**L2**	K_2CO_3	24	–
6	[{Rh(cod)Cl}$_2$]	none	CsOAc	5	–
7	[{Rh(cod)Cl}$_2$]	**L3**	CsOAc	7	–
8	[{Rh(cod)Cl}$_2$]	**L4**	CsOAc	95 (90)	3
9	[{Rh(cod)Cl}$_2$]	**L5**	CsOAc	<1	–
10	Rh(acac)$_3$	**L4**	CsOAc	<1	–
11	[Rh(cod)$_2$(BF$_4$)]	**L4**	CsOAc	<1	–

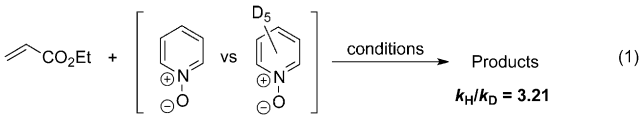
[a] Reaction conditions: **1a** (0.625 mmol), **2a** (0.25 mmol), Rh catalyst (2 mol%), ligand (5 mol%) and base (25 mol%) in toluene (0.5 mL). [b] Yield as determined by NMR spectroscopy (yield of isolated product in parentheses). acac = acetoacetate , cod = 1,5-cyclooctadiene.



Alternative rhodium precursors to [{Rh(cod)Cl}$_2$] afforded poorer results (entries 10 and 11).

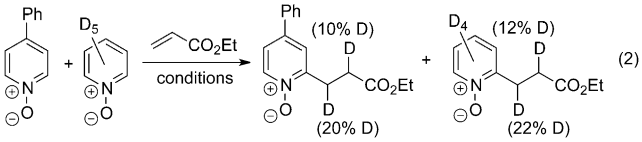
To gain mechanistic insight, the role of the base was investigated by means of a H/D exchange experiment.[10] A significant level of deuterium incorporation (61%) was observed at the *ortho* position of 4-phenylpyridine *N*-oxide (**1a**) when the reaction mixture was treated with D_2O following its subjection to the optimized conditions in the absence of olefin (Figure 1A).[11] In contrast, negligible exchange was observed when the base was excluded (Figure 1B) and in the case where the rhodium precursor and ligand were excluded (Figure 1C). This observation is consistent with the postulate that *ortho* C–H bond cleavage of substrate **1a** proceeds through a base-assisted proton abstraction with the help of metal coordination.[12] In fact, several research groups,[13] including our own,[8a–b] validated this mechanistic proposal through experimental and theoretical studies.

A competition experiment between pyridine *N*-oxide and its deuterated analogue revealed a significant kinetic isotope effect (KIE), $k_H/k_D = 3.21$, thus suggesting that the C–H bond cleavage step is rate-limiting [Eq. (1)]. In addition when the



(1)

cross-over experiment of 4-phenylpyridine *N*-oxide and [D_5]pyridine *N*-oxide was carried out under the optimal conditions a similar ratio of intermolecular deuterium scrambling was observed in each isolated product [Eq. (2)], thus implying that the reaction does not proceed through inner-sphere 1,4-conjugate addition.



(2)

On the basis of the above observations, a mechanistic proposal, involving a generalized heterocyclic structure, is presented in Scheme 2. We assume that the [{Rh(cod)Cl}$_2$] precursor and cesium acetate undergo ligand exchange to give **I**,[14] which is presumed sufficiently active to facilitate a key base-promoted proton abstraction and metalation step to generate the Rh/heteroaryl species **II**.[15] Subsequent olefin insertion into the rhodium–aryl bond would result in the desired C–C bond, thus leading to a Rh/alkyl intermediate **III** or its enolate species (not shown). Although protonolysis of

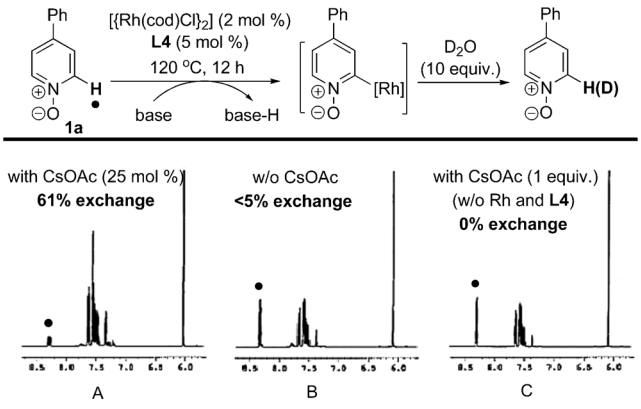
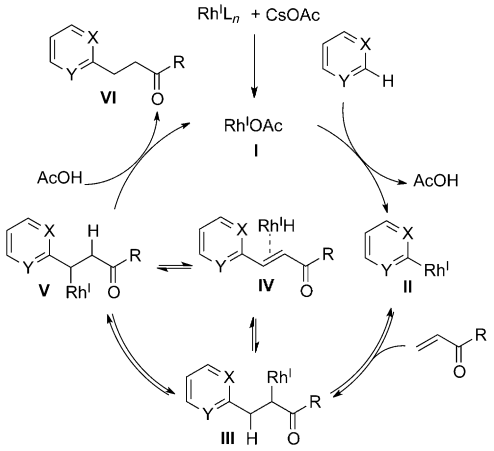


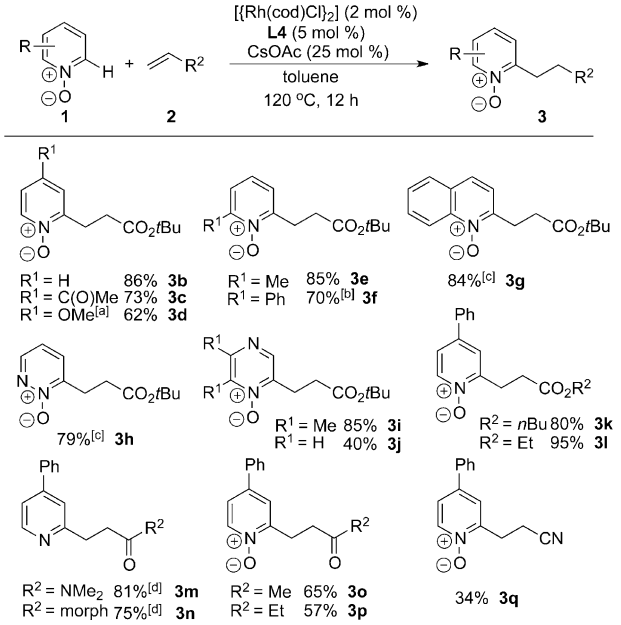
Figure 1. Rhodium/base-mediated H/D exchange experiments. w/o = without.



Scheme 2. A plausible mechanism for the present reaction.

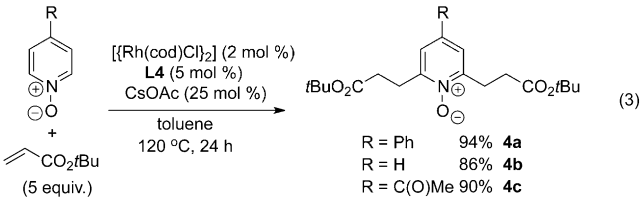
III may occur to deliver the desired product **VI**, the result of the aforementioned cross-over experiment led us to presume that the final protonation step occurs predominantly from isomeric intermediate **V**, which can be generated from **III** through a β-hydride elimination and re-insertion process.[16] In fact, an alkenyl derivative **IV** was isolated as a byproduct (5%) when 2-methylpyridine *N*-oxide was treated with an increased amount of *tert*-butyl acrylate (**2a**, 3.0 equivalents).[4d,17]

We next investigated the substrate scope of both the *N*-oxide and the alkene substrate (Scheme 3). Variation of the electronics of the pyridine *N*-oxide through substitution at the 4-position did not have a significant effect on reaction efficiency (**3b**–**3d**). Reactions with *ortho*-substituted pyridine *N*-oxides took place smoothly (**3e** and **3f**). Other types of *N*-oxides, such as those derived from quinoline, pyrazine, and pyridazine, were also viable in the hydroarylation of *tert*-butyl acrylate (**3g**–**3j**). Notably, the reaction was highly regioselective and occurred only at the position *ortho* to the *N*-oxide group, even in the presence of additional heterocyclic nitrogen atoms (**3h**–**3j**). Other *O*-alkylated conjugated esters also participated in the reaction with similar yields (**3k** and **3l**). Notably, although the hydroarylation of conjugated amides (**3m** and **3n**) and ketones (**3o** and **3p**) was highly efficient, that of acrylonitrile was not (**3q**). Internal electron-rich alkenes were unreactive under the reaction conditions.[18] Deoxygenation of the initially produced *N*-oxide products was successfully performed in a one-pot sequence by treatment of the crude reaction mixture with PCl_3, thus delivering the corresponding pyridine derivatives in high yields (**3m** and **3n**).[10]



Scheme 3. Hydroarylation of alkenes with *N*-oxides. Reaction conditions: **1** (0.625 mmol), **2** (0.25 mmol), Rh catalyst (2 mol%), **L4** (5 mol%), and base (25 mol%) in toluene (0.5 mL). [a] For 24 h in 1,4-dioxane (0.5 M). [b] **1**/**2** = 1:4. [c] **1**/**2** = 1:2.5. [d] Yield over two steps after deoxygenation using PCl_3 in toluene at 25 °C. morph = morpholine.

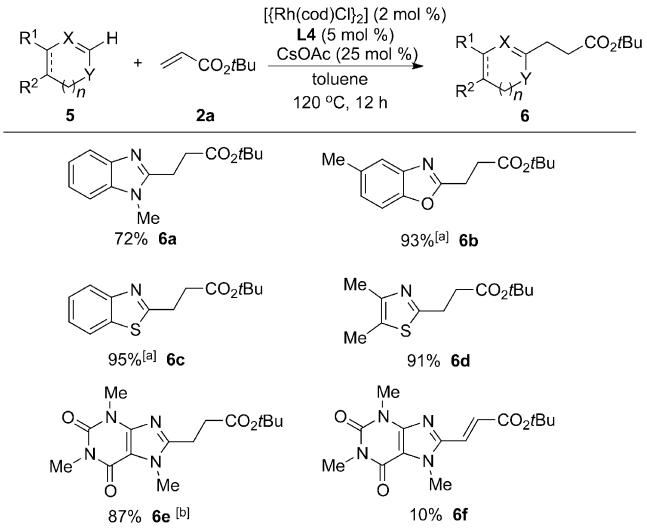
In the present hydroarylation protocol double addition of the alkene substrate could readily be enforced simply by reversing the stoichiometric ratio between the *N*-oxide and alkene substrate. Therefore, the use of an excess of alkene together with a prolonged reaction time gave dialkylated products in excellent yield [Eq. (3)].



(3)

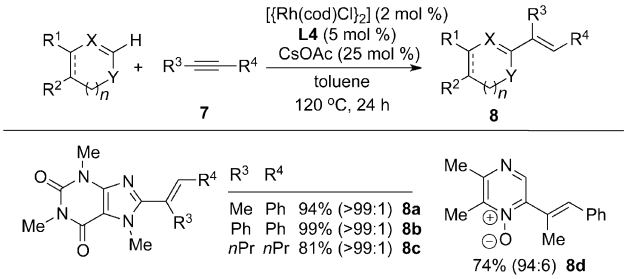
After the successful application of electron-deficient *N*-oxides, we were interested in whether our catalytic system could also be effective when electron-rich heterocycles were used. We were pleased to observe that various types of azoles, including benzimidazole, benzoxazole, benzthiazole, and thiazole, readily reacted with *tert*-butyl acrylate under the slightly altered reaction conditions where an excess of the olefin (2 equivalents) relative to the heteroarene was employed (Scheme 4). The desired alkylated heteroarenes were obtained in excellent yields in all cases examined. The isolation of olefinated byproduct **6f** from the reaction of caffeine reinforces our proposed mechanism, specifically the involvement of a β-hydride elimination process (Scheme 2; between **III** and **V** via **IV**).

As part of these studies, we preliminarly investigated the viability of an addition reaction across triple bonds using the same catalytic system. To our delight, we found that the hydroheteroarylation of disubstituted alkynes was very facile,



Scheme 4. Hydroarylation of alkenes with azoles. Reaction conditions: **5** (0.25 mmol), **2a** (0.5 mmol), Rh catalyst (2 mol%), ligand (5 mol%), and base (25 mol%) in toluene (0.5 mL).[a] 3.0 Equiv. of alkene was used for 24 h. [b] A byproduct (**6f**) was also obtained from this reaction.

thus affording alkenylated heteroarenes with excellent regio- and stereoselectivity (Scheme 5).



Scheme 5. Hydroarylation of alkynes with N-heterocycles. Reaction conditions: heteroarene (0.25 mmol), **7** (0.5 mmol), Rh catalyst (2 mol%), ligand (5 mol%), and base (25 mol%). Yield of isolated product and *E*/*Z* ratio, as determined by ^{1}H NMR spectroscopy, in parentheses.

The C–C bond formation of the addition reaction of caffeine to the unsymmetrical triple bond of 1-phenyl-1-propyne occurs exclusively at the methyl-substituted acetylenic carbon center presumably because of steric reasons, thus affording **8a** in high yield. The newly generated double bond was *E* configured, as determined by NOE analysis, thus suggesting that the addition step proceeds in a *syn* manner. The structure of **8a** was unambiguously confirmed by X-ray crystallographic analysis.[10] Analogous results were obtained with symmetric alkynes such as diphenylacetylene and 4-octyne, the addition of which was completely stereoselective (products **8b** and **8c**, respectively). Notably, the newly generated double bond of alkenylated heteroarenes did not isomerize under the present reaction conditions as was reported to occur in the system developed by Hiyama and co-workers.[5d] The alkyne hydroarylation procedure was also readily applied to electron-deficient *N*-oxides. For example, the reaction of 1-phenyl-1-propyne with pyrazine *N*-oxide proceeded with complete regioselectivity, although the stereoselectivity was slightly decreased with the *E* isomer **8d** being still favored. Additionally, we observed that the Rh-catalyzed hydroarylation of alkenes (*tert*-butyl acrylate) proceeded faster than that of alkynes (4-octyne) under identical reaction conditions (see the Supporting Information for details).

In summary, we have developed a highly efficient and convenient rhodium catalyst system for the direct hydroheteroarylation of unsaturated compounds with heteroarenes. A base co-catalyst was found to be crucial for the hetereoarene C–H bond-activation step. Substrate scope was very broad, including both electron-deficient pyridine *N*-oxides and electron-rich azoles. The identical catalytic system was applicable to the hydroheteroarylation of both alkenes and alkynes with excellent regio- and stereoselectivity. Detailed mechanistic studies and synthetic applications of this reaction are now underway.

Experimental Section

General procedure: A mixture of [{Rh(cod)Cl}$_2$] (2.5 mg, 2 mol%), 1,2-bis(diphenylphosphino)ethane (DPPE, 5.0 mg, 5 mol%), CsOAc (12 mg, 25 mol%) and 4-phenylpyridine *N*-oxide (107 mg, 0.63 mmol) was weighed into a 1 mL screw-capped vial equipped with a spinvane triangular-shaped Teflon stirbar. Toluene (0.5 mL) was added followed by *tert*-butyl acrylate (37 μL, 0.25 mmol). The vial was sealed with a Teflon-lined cap and the reaction mixture was stirred at 120 °C for 12 h in an oil bath. The reaction mixture was cooled to room temperature, filtered through a plug of Celite, and then washed with EtOAc (30 mL). The filtrate was concentrated, and evaporated to dryness under high vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2/acetone 10:1) to give 2-(3-*tert*-butoxy-3-oxopropyl)-4-phenylpyridine *N*-oxide in 90% yield.

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