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Intermolecular Hydropyridylation of Unactivated Alkenes

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Supporting Information

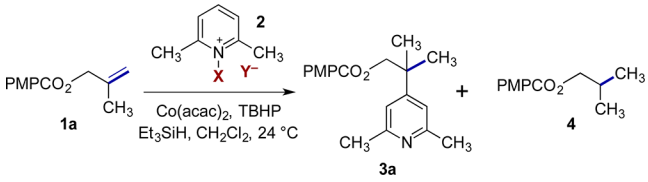
ABSTRACT: A general method for the hydropyridylation of unactivated alkenes is described. The transformation connects metal-mediated hydrogen atom transfer to alkenes and Minisci addition reactions. The reaction proceeds under mild conditions with high site-selectivities and allows for the construction of tertiary and quaternary centers from simple alkene starting materials.

Unactivated alkenes are inexpensive starting materials for synthesis. Hydroarylation, the direct or formal addition of arene C−H bonds across an alkene π-bond, is a useful method to functionalize alkenes. Most reported hydroarylation protocols are initiated by metal-mediated cleavage of an aryl C−H bond.[1] In many instances isomeric mixtures of products are formed, and the scope of the alkene is limited.[1b,d] We report a mechanistically distinct hydropyridylation reaction that is initiated by hydrogen atom transfer (HAT) to alkenes. The reaction occurs under mild conditions, is compatible with 1−4 carbogenic substituents on the alkene, and leverages the selectivity of HAT to achieve regiocontrol.

Advances in HAT to alkenes[2] have unlocked new methods for hydrogenation[3] and regiocontrolled hydrofunctionalization (H−X addition, X = O,[4] I,[3c] Br,[3c] Se,[3c] S,[4d,5] Cl,[4d,6] F,[7] and N[4d,8]).[9] To a large extent, the product selectivities are controlled by the stability of the alkyl radical intermediate. Selected examples of HAT-mediated C−C bond-forming processes include the reductive coupling of unactivated[10] and functionalized[11] alkenes with unsaturated carbonyls, the formal hydromethylation of alkenes,[12] the cycloisomerization of alkenyl arenes,[13] the cycloisomerization or cyclofunctionalization of dienes,[4d,13,14] alkene hydrocyanation,[4d,15] and alkene hydrooximation.[16] While an intramolecular alkene hydroarylation was recently reported,[17] the intermolecular coupling of alkenes and arenes by HAT is, to our knowledge, unknown.[2c]

Electron-rich alkyl radicals are typically unreactive toward electron-rich and -neutral arenes in intermolecular additions. However, recent advances in the addition of carbon-centered radicals to heteroaromatics[18] motivated us to examine the coupling of alkenes and pyridine derivatives under HAT conditions.[19] Initial attempts to couple 2-methylallyl 4-methoxybenzoate (**1a**) with 2,6-lutidinium *p*-toluenesulfonate[20] under HAT conditions[3b,c] were unsuccessful, and the starting alkene remained unreacted (entry 1, Table 1). Activation of 2,6-lutidine with boron trifluoride provided similar results (entry 2). When 2,6-lutidine *N*-oxide[21] was utilized as the heterocycle source, the conversion of **1a** was quantitative, and 23% of the Mukaiyama hydration product[4a] (not shown) was obtained.

Table 1. Optimization of the Hydropyridylation[a]



entry	X	Y⁻	conv **1a**	yield **3a**[b]	yield **4**
1	H	TsO^-	<5%	<5%	<5%
2	BF_3^-	—	<5%	<5%	<5%
3	O^-	—	>95%	<5%	<5%
4	OAc	Cl^-	30%	<5%	<5%
5	OCH_3	BF_4^-	>95%	(21%)	<5%
6	OCH_3	I^-	23%	<5%	<5%
7	OCH_3	TfO^-	>95%	40%	53%
8[c]	*OCH_3*	*$CH_3OSO_3^-$* (**2a**)	*>95%*	*(81%)*	*10%*

[a]General reaction conditions: **1a** (100 μmol), $Co(acac)_2$ (1.00 equiv), TBHP (1.00 equiv), lutidine derivative (5.00 equiv), Et_3SiH (5.00 equiv), CH_2Cl_2 (0.2 M), 24 °C, 16 h. Conversions and yields were determined by ^1H NMR spectroscopy using mesitylene as an internal standard. [b]Yields in parentheses are isolated yields after purification by flash-column chromatography. [c]Reaction employed 250 μmol of **1a**.

However, the desired product **3a** was not detected (entry 3). Attempts to activate 2,6-lutidine *N*-oxide by acetylation[22] resulted in 30% conversion of **1a** without formation of the desired product (entry 4). After extensive investigations, we found that *N*-methoxypyridinium tetrafluoroborate[23] was a competent coupling partner that could be transformed to the product **3a** in 21% isolated yield as a single isomer (entry 5). The variable conversion in entries 1−4 suggested the nature of the pyridinium counterion may impact HAT efficiency. Consequently, a series of *N*-methoxy-2,6-dimethylpyridinium salts were prepared. *N*-Methoxy-2,6-dimethylpyridinium iodide afforded 23% conversion of **1a** and <5% product (entry 6). *N*-Methoxy-2,6-dimethylpyridinium triflate generated >95% conversion of **1a**, 40% of the product **3a**, and 53% of the reduction product **4** (entry 7). Ultimately, we found that *N*-methoxy-2,6-dimethylpyridinium methylsulfate provided optimal yields and selectivities; using this reagent, the product **3a** was obtained in 81% isolated yield, and only 10% of the reduction product **4** was produced (entry 8). We suggest that the counterion alters the coordination sphere of the cobalt, leading to less efficient HAT and/or coupling of the alkyl radical. Reductions in the amounts of reagents or changes to the solvent or temperature lead to

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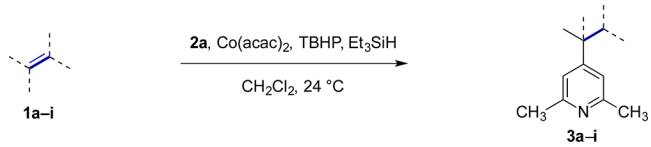
decreased yields (Table S1). A brief survey of nickel catalysts and aryl halide electrophiles[24] as coupling partners did not lead to the formation of any detectable addition products (data not shown).

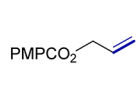
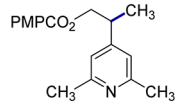
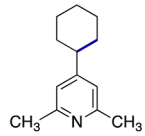
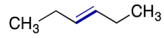
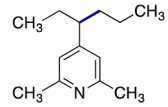
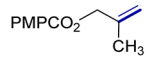
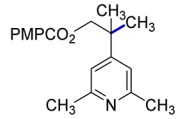
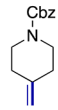
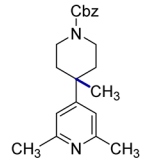
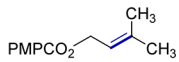
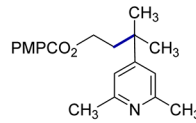
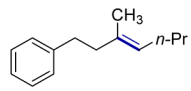
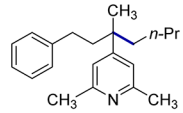
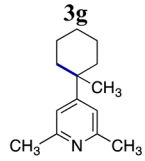
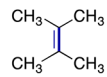
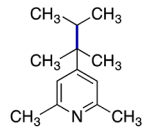
We then investigated the scope of the alkene reagent (Table 2). Using the α-olefin allyl *p*-methoxybenzoate (**1b**), the reductive coupling product **3b** was obtained in 63% yield (entry 1). Hydropyridylation of cyclohexene (**1c**) and *trans*-3-hexene (**1d**) proceeded in 71% and 47% yields (entries 2 and 3, respectively), demonstrating that *cis*- and *trans*-1,2-disubstituted alkenes are viable substrates. Hydropyridylation of the 2,2-disubstituted alkenes 2-methylallyl 4-methoxybenzoate (**1a**) and benzyl 4-methylenepiperidine-1-carboxylate (**1e**) proceeded in 81% and 71% yields (entries 4 and 5, respectively). Trisubstituted alkenes such as prenyl *p*-methoxybenzoate (**1f**), (*E*)-(3-methylhept-3-en-1-yl)benzene (**1g**), and 1-methylcyclohexene (**1h**) also transformed efficiently (72%, 81%, and 72% yields, entries 6–8, respectively). Notably, alternative isomers arising from carbon–carbon bond formation to the less-hindered position of the alkene were not detected by ^{1}H NMR analysis. The tetrasubstituted alkene 2,3-dimethyl-but-2-ene (**1i**) underwent hydropyridylation in 60% yield (entry 9).

A series of substituted *N*-methoxypyridinium salts were prepared to probe substituent effects on the arene, and additional alkenes were employed to further investigate scope and functional group compatibility (Table 3). Owing to line broadening in the NMR spectra of the unpurified products, isomer ratios were determined by LC/MS analysis or isolation (see Supporting Information (SI)). The monosubstituted pyridine **3j** was obtained in 59% yield and with 4.7:1 C-4:C-2 selectivity by addition of 2-methylallyl 4-methoxybenzoate (**1a**) to *N*-methoxypyridinium methylsulfate. The 4-picoline derivative **3k** was formed in 69% yield by addition of allyl *p*-methoxybenzyl ether to *N*-methoxy-4-methylpyridinium methylsulfate. The 2-picoline derivative **3l** was formed in 79% yield and with 78:1 C-4:C-2 selectivity by addition of methylenecyclobutane to *N*-methoxy-2-methylpyridinium methylsulfate. The 4-benzyloxypyridine derivatives **3m** and **3n** were formed in 85% and 79% yields, respectively, by addition of α-olefins containing Weinreb amide and ester substituents to *N*-methoxy-4-benzyloxypyridinium methylsulfate. The 4-cyanopyridine derivative **3o** was obtained in 53% yield by addition of a trisubstituted chloroalkene to *N*-methoxy-4-cyanopyridinium methylsulfate. The 4-phenylpyridine derivative **3p** was generated in 51% yield by the addition of 10-fluorodecene to *N*-methoxy-4-phenylpyridinium methylsulfate. The 4-chloropyridine derivatives **3q** and **3r** were produced in 63% and 37% yields, respectively, by the addition of alkenes bearing ester and alkyl bromide substituents to *N*-methoxy-4-chloropyridinium methylsulfate. For reasons that are not apparent, 3-substituted pyridinium salts are not efficient coupling partners. Thus, the addition of prenyl *p*-methoxybenzoate to *N*-methoxy-3-methylpyridinium methylsulfate or *N*-methoxy-3-bromopyridinium methylsulfate proceeded in low yield (23% and 12% yields, respectively, of the products **3s** and **3t**) and substantial amounts of unreacted alkene were recovered (52% and 78%, respectively).

Noteworthy aspects of this transformation include the ability to engage simple hydrocarbon feedstocks (e.g., alkenes **1c**, **1d**, **1h**, **1i**) and high functional group compatibility (e.g., esters, carbamates, benzyl ethers, amides, alkyl bromides, alkyl chlorides, and alkyl fluorides, among others). The requirment for an excess of the pyridinium salt is currently a disadvantage of the reaction, however the transformations are readily scaled to at least 1 mmol (Figure 1). Many of the pyridinium salts we utilized

Table 2. Preliminary Scope of the Alkene Reagent[a]



entry	alkene	product	yield[b]
1	 **1b**	 **3b**	*63%*
2	 **1c**	 **3c**	*71%*
3	 **1d**	 **3d**	*47%*
4	 **1a**	 **3a**	*81%*
5	 **1e**	 **3e**	*71%*
6	 **1f**	 **3f**	*72%*
7	 **1g**	 **3g**	*81%*
8	 **1h**	 **3h**	*72%*
9	 **1i**	 **3i**	*60%*

[a]General reaction conditions: **1a–i** (250 μmol), $Co(acac)_2$ (1.00 equiv), TBHP (1.00 equiv), **2a** (5.00 equiv), Et_3SiH (5.00 equiv), CH_2Cl_2 (0.2 M), 24 °C, 16 h. [b]Isolated yields after purification by flash-column chromatography.

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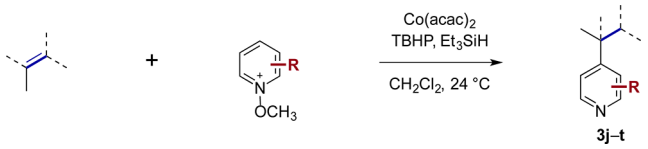
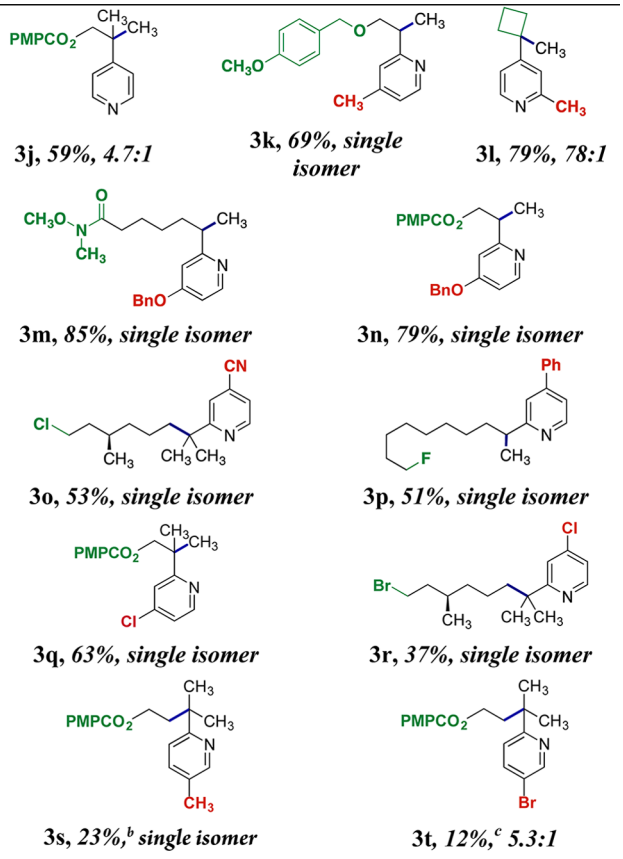
Table 3. Preliminary Scope of the Pyridine Coupling Partner[a]





[a]General reaction conditions: alkene (250 μmol), $Co(acac)_2$ (1.00 equiv), TBHP (1.00 equiv), pyridinium salt (5.00 equiv), Et_3SiH (5.00 equiv), CH_2Cl_2 (0.2 M), 24 °C, 16 h. In all instances, the pyridinium counterion = $CH_3OSO_3^-$. Yields reported were obtained by isolation. Due to line broadening, product isomer ratios could not be determined by ^1H NMR. "Single isomer" denotes instances wherein one product was observed by LC/MS analysis of the unpurified product mixture. See SI for isomer ratio determination of **3j**, **3l**, and **3t**. [b]52% alkene recovered. [c]78% alkene recovered.

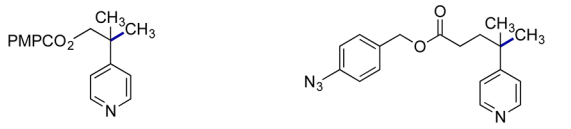
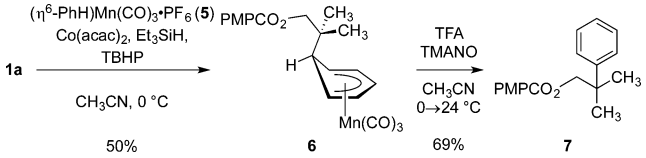


Figure 1. Yields of products on 1 mmol scale.

have not been reported before. They are easily prepared in one step and high yield (73–99%) in multigram quantities and are bench-stable solids, though they are hydroscopic (see SI).

With the successful application of HAT in the intermolecular hydropyridylation of unfunctionalized alkenes, we sought to extend the methodology to hydroarylation. The intermolecular hydroarylation reaction is challenging due to the difficulties in balancing the electronic properties of the arylation reagent with those of the electron-rich alkylradical intermediates. Among many arylation reagents examined, (η^6-benzene)manganese tricarbonyl hexafluorophosphate (**5**) was singularly successful and provided the desired reductive coupling product **6** in 50% yield under HAT conditions (Scheme 1). Upon oxidation, the formal hydroarylation product **7** was obtained in 35% yield over two steps.

Scheme 1. Formation of Cyclohexadienyl Manganese(I) Tricarbonyl Complex 6 and Oxidative Rearomatization



In summary, we have shown that the cobalt-mediated HAT protocol[3b,c] can be successfully applied to the reductive intermolecular cross-coupling of unfunctionalized alkenes and *N*-methoxypyridinium derivatives. This methodology provides a simple method for alkene hydropyridylation that connects metal-mediated HAT to alkenes and Minisci addition reactions. The method demonstrates excellent functional group compatibility and scope in both the alkene and the pyridine coupling partners. Efforts to extend this chemistry to the coupling of other heteroaromatic and benzene derivatives are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05271.

Detailed experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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