Palladium-Catalyzed Denitrative Mizoroki–Heck Reaction

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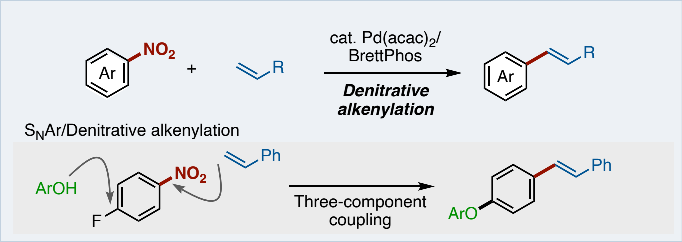
Supporting Information Placeholder

ABSTRACT: We have developed a Mizoroki–Heck reaction of nitroarenes with alkenes under palladium catalysis. The use of a Pd/BrettPhos catalyst promoted the alkenylation, whereas other catalysts led to a decrease in the product yield. In addition to nitroarenes, nitroheteroarenes were also applicable to the present reaction. Combination of a nucleophilic aromatic substitution (S_NAr) with the denitrative alkenylation produced a multi-functionalized arene in a one-pot operation.



The Mizoroki–Heck reaction is a powerful catalytic method for carbon–carbon (C–C) bond formation in synthetic organic chemistry (Figure 1A).[1] Typically, aryl halides (C–halogen bond) are coupled with alkenes in the presence of a palladium catalyst.[2] Over the past decade, oxidative Mizoroki–Heck reactions (C–H alkenylations), which utilized simple arenes (C–H bond) instead of aryl halides, have been reported as state-of-the-art methods of alkenylation.[3] Although these reactions can be applied to complex molecules as well, the regioselective installation of alkenes has some drawbacks. These reactions require the use of a directing group on the arene, or otherwise an adjustment of the electronic or steric nature of the arene, to gain both reactivity and regioselectivity. To address this issue, the use of a regioselectivity "anchor" such as the C–halogen bond is still necessary. Hence, various aryl electrophiles that operate under palladium catalysis instead of aryl halides have been developed. Currently, C–O bond-containing groups such as triflates, tosylates, and nonaflates are the most popular alternative aryl electrophiles.[4,5] Other aryl electrophiles such as diazonium salts (C–N bond),[6] sulfonyl chlorides, thiazolium salts (C–S bond),[7] acyl chlorides, acid anhydrides, esters, amides (C–C bond)[8] and telluronium salts[9] have been used as "anchors" for the Mizoroki–Heck reaction.

Meanwhile, Nakao and coworkers successfully developed palladium-catalyzed denitrative cross-coupling reactions between nitroarenes and nucleophiles, giving rise to arylation, amination (aliphatic amines), and hydrogenation (Figure 1B).[10] Other groups followed these pioneering results, thereby developing methods for alkylation, amination (aromatic amines), and alkynylation.[11] In collaboration with the Nakao group, our group also reported a denitrative intramolecular C–H coupling.[12] The use of a Pd/Brettphos catalyst is effective for these transformations. Recently, the groups of Nakao and Hu independently reported that an NHC ligand, {5-(2,4,6-triisopropylphenyl) imidazolylidene [1,5-a] pyridines}, is more effective than the Pd/Brettphos catalytic system for denitrative transformations.[11a,11b,13] However, there are no instances of denitrative alkenylation reported thus far. Herein, the first Mizoroki–Heck-type alkenylation of nitroarenes under palladium catalysis is described (Figure 1C).

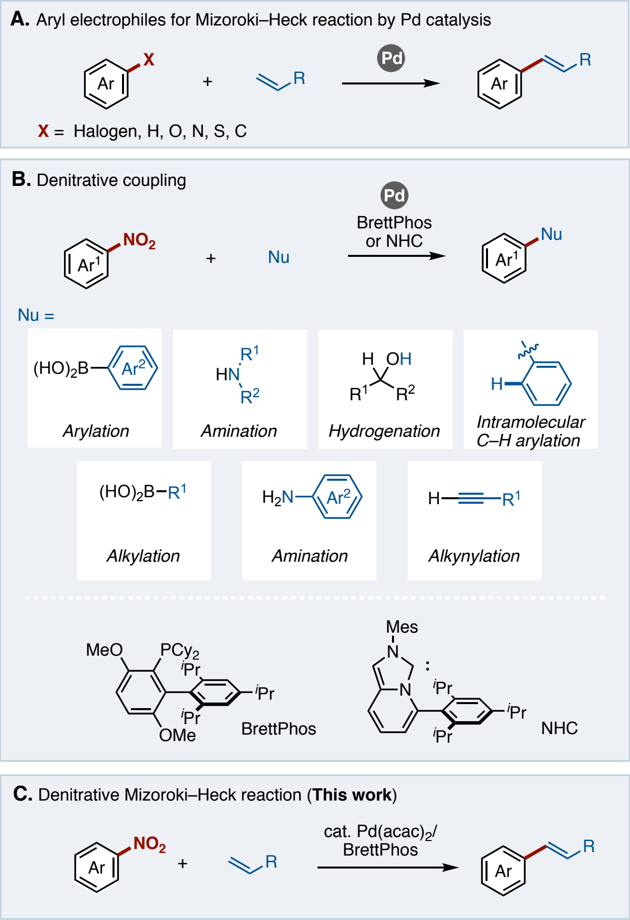
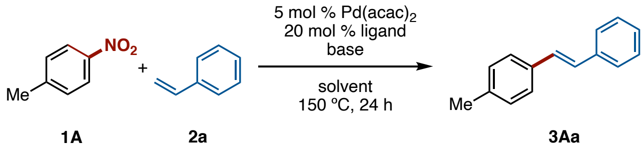


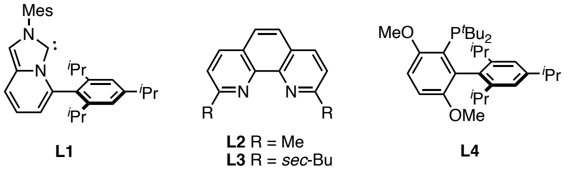
Figure 1. (A) Aryl electrophiles for the Mizoroki–Heck reaction. (B) Denitrative coupling. (C) Denitrative Mizoroki–Heck reaction.

To commence the screening of reaction conditions for the denitrative Mizoroki–Heck reaction, we selected 4-nitrotoluene (**1A**) and styrene (**2a**) as model substrates (Table 1). First, using 5 mol % Pd(acac)$_2$/BrettPhos as the catalyst (which has been effective for all denitrative couplings thus far), bases (3.0 equiv) and solvents were examined. All reactions were conducted at 150 °C for 24 h. CsF in 1,4-dioxane, which was one of the best combinations for denitrative Suzuki–Miyaura coupling,[10a] successfully afforded the desired coupling product **3Aa** in 8% yield (Table 1, entry 1). When the solvent was changed to higher boiling point solvents such as toluene, *m*-xylene, anisole, and benzotrifluoride (PhCF$_3$), the yields of **3Aa** increased to 20–53% (Table 1, entries 2–5). Using PhCF$_3$ as the solvent, we next examined the bases. K$_3$PO$_4$, which was the best base for the intramolecular denitrative C–H arylation,[12] did not work well (Table 1, entry 6). Interestingly, when carbonate bases were screened, the use of Rb$_2$CO$_3$ dramatically increased the yield of **3Aa** (80% yield, Table 1, entries 7–9). Next, a variety of ligands were investigated. NHC **L1** was not effective for this alkenylation (Table 1, entry 10). Electron-rich phosphines such as PCy$_3$ and dcype completely shut down this reaction (Table 1, entries 11 and 12).

Table 1. Screening of Reaction Conditions[a]



entry	ligand	base	solvent	**3Aa**/%
1[b]	BrettPhos	CsF	dioxane	8
2	BrettPhos	CsF	toluene	20
3	BrettPhos	CsF	*m*-xylene	52
4	BrettPhos	CsF	anisole	40
5	BrettPhos	CsF	PhCF$_3$	53
6	BrettPhos	K$_3$PO$_4$	PhCF$_3$	4
7	BrettPhos	K$_2$CO$_3$	PhCF$_3$	40
8	BrettPhos	Cs$_2$CO$_3$	PhCF$_3$	3
9	BrettPhos	Rb$_2$CO$_3$	PhCF$_3$	80
10	**L1**	Rb$_2$CO$_3$	PhCF$_3$	0
11	dcype	Rb$_2$CO$_3$	PhCF$_3$	0
12[c]	PCy$_3$	Rb$_2$CO$_3$	PhCF$_3$	0
13	**L2**	Rb$_2$CO$_3$	PhCF$_3$	12
14	**L3**	Rb$_2$CO$_3$	PhCF$_3$	10
15	XPhos	Rb$_2$CO$_3$	PhCF$_3$	21
16	SPhos	Rb$_2$CO$_3$	PhCF$_3$	7
17	RuPhos	Rb$_2$CO$_3$	PhCF$_3$	7
18	**L4**	Rb$_2$CO$_3$	PhCF$_3$	59

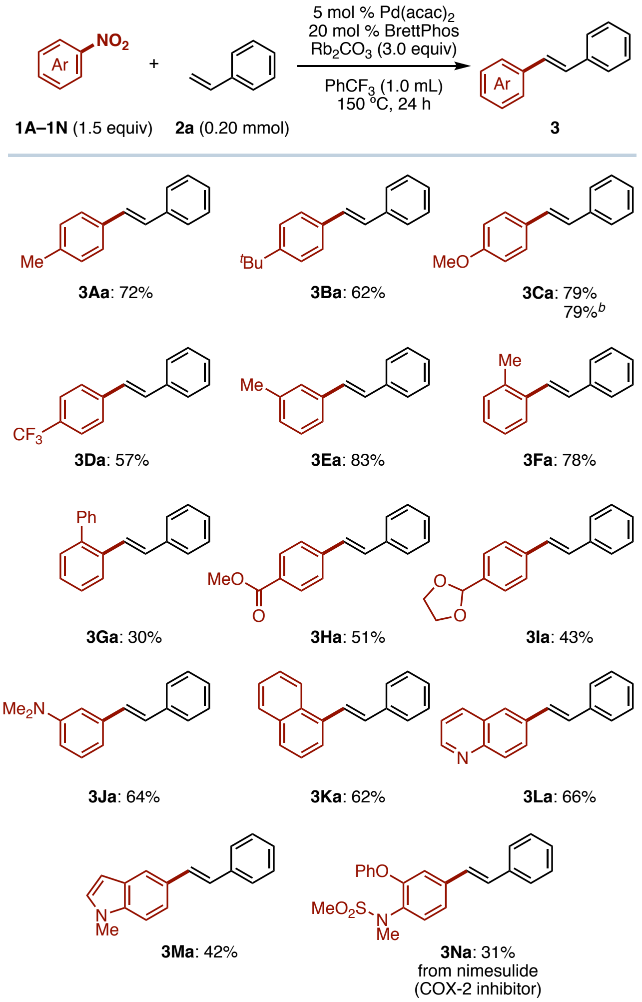


[a] Conditions: **1A** (1.5 equiv), **2a** (0.20 mmol), Pd(acac)$_2$ (5 mol %), ligand (20 mol %), base (3.0 equiv), solvent (1.0 mL), 150 °C, 24 h. [b] GC yields: ^{n}decane was used as an internal standard. Yields were determined based on the amount of **2a**. [c] Ligand (40 mol %) was used.

When phenanthroline-type ligands were used (such as **L2** and **L3**), the desired product **3Aa** was obtained, albeit in lower yields (Table 1, entries 13 and 14). Other Buchwald ligands such as XPhos, SPhos, and RuPhos worked, but the yields of **3Aa** were lower (Table 1, entries 15–17). *t*-BuBrettPhos (**L4**) was effective, but the yield was inferior to BrettPhos (Table 1, entry 18 vs entry 10). It should be noted that this reaction worked in the presence of H$_2$O (10 equiv), but did not work without bases.[14]

With optimal conditions in hand, the substrate scope regarding the nitroarene component was examined (Scheme 1). Electron-rich nitroarenes such as *t*-butyl- or methoxy-substituted nitrobenzenes worked well to give the corresponding alkenes **3Ba** and **3Ca** in good yields, even at 1 mmol scale. To test electron-deficient nitroarenes, 4-trifluoronitrobenzene was subjected to the reaction conditions, giving **3Da** in moderate yield. *meta*-Methyl and *ortho*-methyl nitrobenzene afforded the corresponding products **3Da** and **3Ea**, while an *ortho*-phenyl group decreased the yield significantly (**3Ga**). Methyl ester, acetal, and amines were tolerated under these reaction conditions to furnish the desired products **3Ha**–**3Ja** in moderate yields. Nitronaphthalene also gave the product **3Ka** in moderate yield. Not only nitroarenes, but also nitroheteroarenes can be used in this reaction. Indeed, nitroquinoline and nitroindole can be coupled with **2a** to furnish

Scheme 1. Substrate scope for nitroarenes.

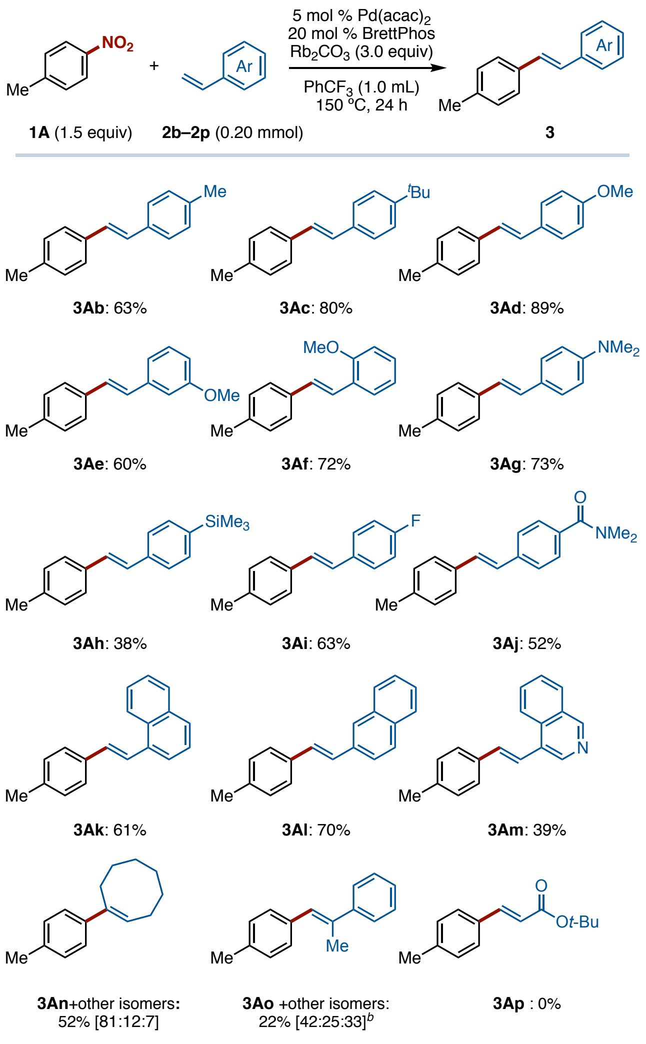


[a] Conditions: **1A**–**1N** (1.5 equiv), **2a** (0.20 mmol), Pd(acac)$_2$ (5 mol %), BrettPhos (20 mol %), Rb$_2$CO$_3$ (3.0 equiv), PhCF$_3$ (1.0 mL), 150 °C, 24 h. [b] 1.0 mmol scale

the products **3La** and **3Ma**. Nimesulide, which is a well-known NSAID, can also be coupled with **2a** to give alkene **3Na** in 31% yield.

Next, the alkene partner was investigated (Scheme 2). Styrene derivatives with an electron-donating substituent such as methyl, *t*-butyl, and methoxy on the C4-position of the phenyl group gave the corresponding coupling products **3Ab**–**3Ad** in good yields. Changing the *para*-methoxy group to the *meta*- and *ortho*-positions on the phenyl group did not affect the yield (**3Ae** and **3Af**). Functional groups such as amine (**3Ag**), silyl (**3Ah**), fluoro (**3Ai**), and amide (**3Aj**) are tolerated under these reaction conditions. Not only substituted styrene derivatives, but also vinylnaphthalenes (**3Ak** and **3Al**) and vinylisoquinoline (**3Am**) can be applied to this reaction to afford the corresponding coupling products in moderate to good yields. Cyclooctene worked as the alkenylating agent to give the coupling product **3An** as a mixture of isomers in 52% yield. However, the current limitation of this denitrative alkenylation is that disubstituted linear alkenes (**3Ao**) and α,β-unsaturated alkenes (**3Ap**) do not work well under the present reaction conditions.

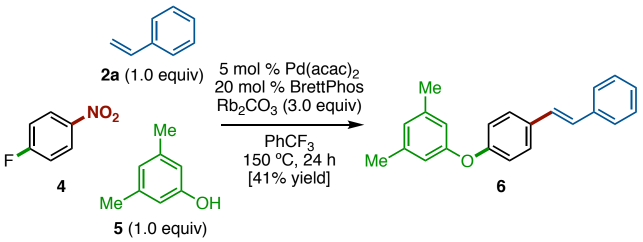
Scheme 2. Substrate scope for alkenes.



^{a}Conditions: **1A** (1.5 equiv), **2b**–**2p** (0.20 mmol), Pd(acac)$_2$ (5 mol %), BrettPhos (20 mol %), Rb_2CO_3 (3.0 equiv), $PhCF_3$ (1.0 mL), 150 °C, 24 h. ^{b}0.80 mmol scale.

Fluoronitroarenes can be readily substituted by a nucleophilic aromatic substitution (S_NAr). Taking advantage of this feature, a nucleophile was added to the denitrative alkenylation (Scheme 3). To this end, treating a mixture of 4-fluoronitrobenzene (**4**), 3,5-dimethylphenol (**5**) and styrene (**2a**) with the Pd/BrettPhos catalyst smoothly allowed for the three-component reaction to proceed, giving the coupling product **6** in 41% yield. Various disubstituted benzenes would be readily synthesized by changing the nucleophile.

Scheme 3. Three-component coupling by S_NAr/denitrative alkenylation.



In summary, we successfully developed a Mizoroki–Heck reaction of nitroarenes with styrene derivatives. Pd/BrettPhos was the most effective catalyst for this reaction, leading to stilbene derivatives with various functional groups. Expanding the range of applicable alkenes and developing more efficient catalysts are current objectives in our laboratory.

ASSOCIATED CONTENT

Experimental procedures and spectroscopic data for compounds including ^{1}H, ^{13}C NMR spectra (PDF)

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Notes

No competing financial interests have been declared.

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(14) For other conditions, see the Supporting Information for details.