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Nickel-catalyzed reductive arylation of activated alkynes with aryl iodides

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Abstract

The direct, regioselective, and stereoselective arylation of activated alkynes with aryl iodides using a nickel catalyst and manganese reductant is described. The reaction conditions are mild (40 °C in MeOH, no acid or base) and an intermediate organomanganese reagent is unlikely. Functional groups tolerated include halides and pseudohalides, free and protected anilines, and a benzyl alcohol. Other activated alkynes including an amide and a ketone also reacted to form arylated products in good yields.

Keywords

reductive; arylation; alkyne; nickel; catalyzed

Tri-substituted alkenoates are important building blocks for the synthesis of natural products,¹ and thus a variety of methods have been developed for their synthesis. These methods include olefination,² cross-coupling,^{3,4} Heck reactions of alkenes,⁵ reductive Heck reactions of alkynes,⁶ C-H activation,⁷ and the addition of organometallic reagents across alkynes.^{8,9,10} Of these approaches, the Heck reaction and the addition of organometallic reagents across alkynes are the most well developed. Reductive arylation combines attractive elements of these two approaches, the use of organic halides and addition across simple alkynes, but a simple β -selective reaction is unknown.

The reductive arylation of alkynes is less well developed than addition reactions to alkenes. Although palladium-catalyzed reactions tend to give products of multiple alkyne insertions¹¹ and favor α -addition of alkynones and alkynoates,¹² broadly useful approaches to vinyl

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Supplementary Material

Detailed experimental procedures, data on optimization and deuteration experiments, product characterization, and copies of NMR spectra are available online.

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arenes and heterocycles have been developed.⁶ Cheng has reported nickel-catalyzed annulations of alkynes to form lactones¹³ and quinolines,¹⁴ including a single example of β -selective arylation.¹⁵ Although it was unclear if stereochemical control and high chemical yield would be possible without a cyclization event, our own studies on reductive-Heck like reactions prompted us to investigate this process.¹⁶

After some initial exploration of reactivity, we found that methyl octynoate could be coupled with iodobenzene in the presence of a nickel(II) source, a bidentate amine ligand, and manganese reductant. While reasonable yields could be obtained in a variety of solvents, the best results were obtained in methanol. In contrast to Cheng's work, we found nitrogen donor ligands, especially phenanthroline (**L1**, entry 1), to be superior to dppe (**L2**, entry 8). Control reactions demonstrated that nickel and ligand were both necessary for the reaction (Table 1, entries 2 and 3).

A variety of activated alkynes participated in the arylation reaction and provided primarily the products of *syn* addition across the alkyne, yielding the (*E*)-isomer **3**, as well as minor amounts of the (*Z*)-isomer (Scheme 1). The exception was a reaction run with ethyl phenylpropiolate which formed α -aryl alkenoate **4ca** and only a trace amount of the β -arylation product. In addition, product **4ca** was found to be a methyl ester instead of an ethyl ester due to competitive transesterification. Transesterification was not observed in reactions with a *tert*-butyl ester and a dimethyl amide (see products **3ba** and **3db**).

The chemistry tolerated aryl iodides with a wide range of functional groups (Scheme 2). The selective functionalization of the carbon-iodine bond over other carbon-halogen/pseudohalogen/boron bonds was observed, providing products that could be further functionalized using a variety of methods. Aryl iodides with a variety of other functional groups, including anilines and a benzyl alcohol, as well as a vinyl iodide also provided trisubstituted alkenoates **3aj**, **3ak**, **3al**, **3an** and **3ao** in good yields.

Both sterics and electronics of the aryl iodide affected the selectivity of the arylation. Aryl iodides with *ortho*-substitution resulted in better selectivity for the (*E*) product (Scheme 2, **3ab** vs. **3ah**), as did reactions with electron-rich aryl iodides (Scheme 2, **3ab** and **3aj** vs. **3aa** in Scheme 1). In contrast, π -withdrawing substituents on aryl iodides provided significant amounts of the α -addition products in addition to the major (*E*)- β -aryl alkenoate (Scheme 3).

For some of the low-yielding substrates, byproducts including biaryl, hydrodehalogenation, and alkyne-dimer were observed. Specifically, with 2-iodotrifluorotoluene, there was an equal amount of hydrodehalogenated, hydroarylated, and bisarylated products, as well as a small amount of alkyne dimer observed. For *ortho*-iodotoluene, there was a significant amount of iodoarene remaining, and some bisarylated product. Efforts to minimize bisarylated product using protic additives were not successful.

Mechanistic experiments support a reductive Heck mechanism, as suggested by Cheng (Scheme 4).^{13,14} An organomanganese intermediate is not likely because 1) acidic functional groups are tolerated (benzyl alcohol, primary aniline), 2) the reaction is run in an alcohol solvent, and 3) stoichiometric reactions without added manganese produce product with similar yield and selectivity (Table 2). Additionally, the synthesis of arylmanganese reagents

requires the use of additives (indium) or highly activated manganese.¹⁷ We also confirmed that the α -vinyl proton in the product is derived from the methanol solvent by running the reaction in deuterated methanol (see SI for details).

Further evidence in support of a reductive Heck mechanism is the stoichiometric reaction of (phenanthroline)Ni^{II}(aryl)I complex **6** with an alkynoate to form the expected addition product **3ar** (Table 2). Arylnickel **6** was synthesized in analogy to our published method¹⁸ and characterized by ¹H NMR and elemental analysis. Stoichiometric reactions of **6** with alkynoate **1a** formed expected product **3ar** under a variety of conditions in less than one hour (entries 2–5). Intermediate reduction of **6** is not required to form product because reactions run both with and without added Mn⁰ provided similar yields of **3ar** (entries 2–5). Finally, **6** was a competent precatalyst, with similar initial rates to a reaction with a pre-formed catalyst (entries 1 and 6), although the final yield with **6** was slightly lower.

A proposed catalytic cycle, accounting for both product and byproduct formation, is shown in Scheme 4. The nickel(II) pre-catalyst is reduced to nickel(0) before sequential oxidative addition and migratory insertion. Protolysis liberates the product, completing the catalytic cycle.

In conclusion, a simple, nickel-catalyzed method for the synthesis of β -aryl alkenoates from alkynoates and aryl iodides has been developed. This method has broad functional-group compatibility, does not use a large excess of either reagent, and reactions can be set up on the benchtop with unpurified methanol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1. Alkyne scope^a

^a Reactions conducted as in Table 1, footnote a. Yields reported are of isolated yields of *E* olefin (major isomer). *E/Z* and α/β ratios determined by GC analysis. Ar = Ph unless noted. ^b Alkynoate used was ethyl 3-phenylpropiolate. ^c Reaction was run at 60 °C.

Scheme 2. Aryl halide scope^a

^a Reactions conducted as in Table 1, footnote a. Yields reported are of isolated yields of *E* olefin **3** (major isomer). *E/Z* ratio determined by GC analysis. ^b Yield reported is of combined *E* and *Z* isomers.

Scheme 3. Aryl iodides that yielded α-arylation product **4**^a^a Reactions conducted as in Table 1, footnote a. Yields reported are of isolated yields. β/α ratio determined by GC analysis.

Scheme 4.
Proposed catalytic cycle

Table 1Reductive arylation of methyl octynoate with iodobenzene^a

entry	deviation from entry 1	yield ^b	<i>E/Z</i> ratio ^c
1	none	92	8:1
2	no nickel	6	5:1
3	no phenanthroline (L1)	0	NA
4	5 mol% $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$	95	13:1
5	5 mol% L1	72	14:1
6	no Mn^0 powder	0	NA
7	1 mol% catalyst	56	10:1
8	dppe (L2) instead of L1	1	NA

^aStandard reaction conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), 2 mL methanol, heated in a reaction block at 40 °C for 20-24 h.^bYield reported is corrected GC yield of combined isomers with respect to decane.^c*E/Z* ratio determined by GC analysis.

Table 2Stoichiometric studies of an arylnickel(II) complex^a

entry	equiv ArI	equiv Mn ⁰	equiv alkyne	yield ^b
1 ^c	Catalytic reaction with NiCl ₂ •2H ₂ O and L1			78
2	0	0	1.0	83
3	0	2	1.0	68
4	0	0	50	62
5	0	2	50	81
6 ^c	40	80	40	63

^a Reactions conducted as in Table 1, footnote a.^b Yield reported is corrected GC yield calculated with respect to an internal standard.^c ArI remaining after 24 h.