

Branch-Selective Hydroarylation: Iodoarene–Olefin Cross-Coupling

Samantha A. Green,[†] Jeishla L. M. Matos,[†] Akiko Yagi, and Ryan A. Shenvi*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

S Supporting Information

ABSTRACT: A combination of cobalt and nickel catalytic cycles enables a highly branch-selective (Markovnikov) olefin hydroarylation. Radical cyclization and ring scission experiments are consistent with hydrogen atom transfer (HAT) generation of a carbon-centered radical that leads to engagement of a nickel cycle.

Metal hydrides (MH) can react with unsaturated organic substrates to generate carbon-centered radicals through hydrogen atom transfer (HAT),¹ a mechanism elucidated during investigations into α -methylstyrene hydrogenation by HMn(CO)₅.² Recently, we proposed³ that a large body of olefin hydrofunctionalizations originally designed to mimic the reactions of metalloenzyme cofactors, typified by the Mukaiyama hydration,⁴ also proceed via MH HAT. Most if not all methods that trace back to Mukaiyama's alkene hydration with organosilanes and cobalt β -diketonates^{4b} use classical, stoichiometric radical traps to functionalize alkenes⁵ and are therefore limited in their breadth of coupling partners. We wondered if radical intermediates in MH HAT catalytic cycles (Figure 1) could instead intercept intermediates in nickel

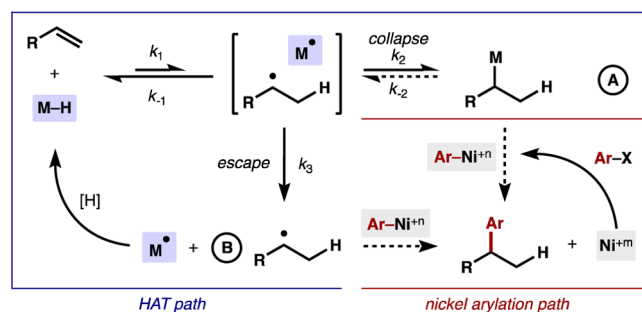


Figure 1. Hypothetical reaction that merges HAT with nickel arylation.

catalytic cycles⁶ and expand both areas into uncharted hydrofunctionalization territory.^{7,8} Here we report the first foray into this area: a highly branch-selective olefin hydroarylation.

In well-characterized MH HAT to alkenes, the initial radical cage pair² possesses an extremely short lifetime whereby internal return (k_{-1}) is rapid and collapse (k_2) or cage escape (k_3) is rate determining (Figure 1).¹ In our previous investigation into HAT isomerization^{3b} we observed collapse of secondary radicals at ambient temperature, which arrested the reactivity of the cobalt catalyst and limited turnovers. It was unclear whether such a Co(III) organometallic (A) could

undergo transmetalation, or alternatively if cage escape from cobalt would be fast enough to yield a radical (B) for arylnickel engagement. Nevertheless, the overall process would enable a branch-selective olefin hydroarylation (Figure 2) that is

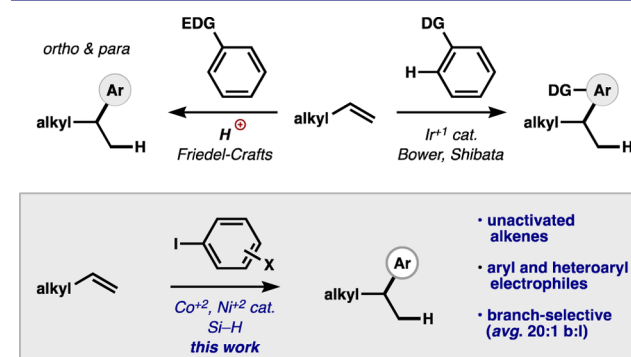


Figure 2. Precedent for branch-selective aliphatic olefin hydroarylation.

currently difficult to achieve. Aside from styrenyl alkenes, which can favor Markovnikov arylation,⁹ hydroarylation of unactivated alkenes to obtain branched products in preference to linear products is represented largely by Friedel–Crafts alkylation¹⁰ and branch-selective Murai-type hydroarylation using directing groups.^{11–13} In addition, we recently published an intramolecular hydroarylation¹⁴ based on an HAT/Smiles–Truce rearrangement;^{15a} Shigehisa reported an intramolecular arene annulation;^{15b} and Herzog reported an HAT/Minisci-type hydroarylation.^{15c} Here, we show that Co(Sal^{t-Bu,f-Bu})¹⁶ and (dtbbpy)NiBr₂¹⁷ cocatalyze a branch-selective hydroarylation of terminal aliphatic alkenes and iodoarenes.

To intercept arylnickel complexes with HAT-generated radicals, we initially explored the coupling of alkenes with nucleophiles such as arylzinc halides^{18a} or arylboronic acids.^{18b} However, these species reacted with the cobalt(III) complex or the stoichiometric silane faster than with Ni(II). Therefore, inspired by Weix's alkyl–aryl cross-electrophile coupling,¹⁷ we instead investigated aryl iodides in the presence of a stoichiometric reductant. While we thought this was an attractive approach, we were aware of—and experienced—many potential pitfalls, such as aryl iodide and alkene reduction by the silane, alkene hydrosilylation, alkene isomerization, and biaryl formation. Optimized conditions and instructive variations are shown in Table 1.

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Table 1. Effect of Reagents on Reaction Outcome^a

H_{17}C_8 + C_8H_{17}
 1 (1.3 equiv.) + 2 (1 equiv.)
 5 mol% (dtbbpy)NiBr₂
 20 mol% Co(Sal^{t-Bu, t-Bu})
 50 mol% 5
 2 equiv. Ph(*i*-Pr)SiH₂
 DMPU (0.3 M), 22 °C
 3 + 4

entry	variations from above	% 3	% 4
1	none	75	<5
2	3 equiv of Zn ⁰	59	<5
3	no 5	20	—
4	TBHP instead of 5	<5	—
5	PhSiH ₃ instead of Ph(<i>i</i> -Pr)SiH ₂	42	—
6	no (dtbbpy)NiBr ₂	—	—
7	no dtbbpy ligand	—	—
8	no Co(Sal ^{t-Bu, t-Bu})	<5	21
9	air instead of argon	<5	—
10	Co(acac) ₂ , Fe(acac) ₃ , or Mn(dpm) ₃	—	—

^aNMR yields average of two runs.

Whereas zinc metal was originally explored as a nickel reductant (entry 2),¹⁷ the silanes required for HAT catalysis reduced Ni(II) just as effectively. In particular, we found Ph(*i*-Pr)SiH₂ to be superior to PhSiH₃.¹⁹ We have previously used *tert*-butyl hydroperoxide (TBHP) to turnover the catalyst of our HAT hydrogenation,^{3a} but this oxidant led instead to hydrosilylation and decreased yields (see Supporting Information).¹⁹ Based on observations by Shigehisa that fluoropyridinium salts are compatible with silane reductants,²⁰ we utilized 5 as a stoichiometric oxidant to effect initial conversion of Co(II) to Co(III) and turnover the cobalt cycle, although at this point the role of reagent 5 is still speculative. Exclusion of either catalyst disfavored formation of 3; nickel by itself delivered the linear product 4.²¹ Other catalysts used in Mukaiyama-type hydrofunctionalizations were ineffective.

We also found that this HAT hydroarylation is limited to terminal alkenes, since 1,1-disubstituted alkenes isomerized preferentially to the internal position. More substituted alkenes were unreactive with catalysts such as Co(Sal^{t-Bu, t-Bu}) under these anaerobic conditions, as observed previously.^{3b} Although we probed the alkene scope with 4-trifluoromethyl-iodobenzene (Table 2), 4-cyanoiodobenzene proved to be a superior substrate (see Table 3). Among terminal alkenes, the scope is good: adjacent branching is well-tolerated (6–8), even vinylcyclohexane. Allylic functional groups are generally inferior to homoallylic groups, but still surprisingly competent. Among the more remarkable examples are thiophene 14 and sulfide 16, neither of which arrest catalysis, as well as organoboronate 15 and organohalides 17 and 18, for which competitive insertion does not predominate.²² Proximal alcohols or ethers are

Table 2. Scope of the Alkene^a

4-trifluoromethyl-iodobenzene (1 equiv.) + R-alkene (1.3 equiv.)
 5 mol% (dtbbpy)NiBr₂
 20 mol% Co(Sal^{t-Bu, t-Bu})
 50 mol% 5
 2 equiv. Ph(*i*-Pr)SiH₂
 DMPU (0.3 M), 22 °C
 Hydroarylated product

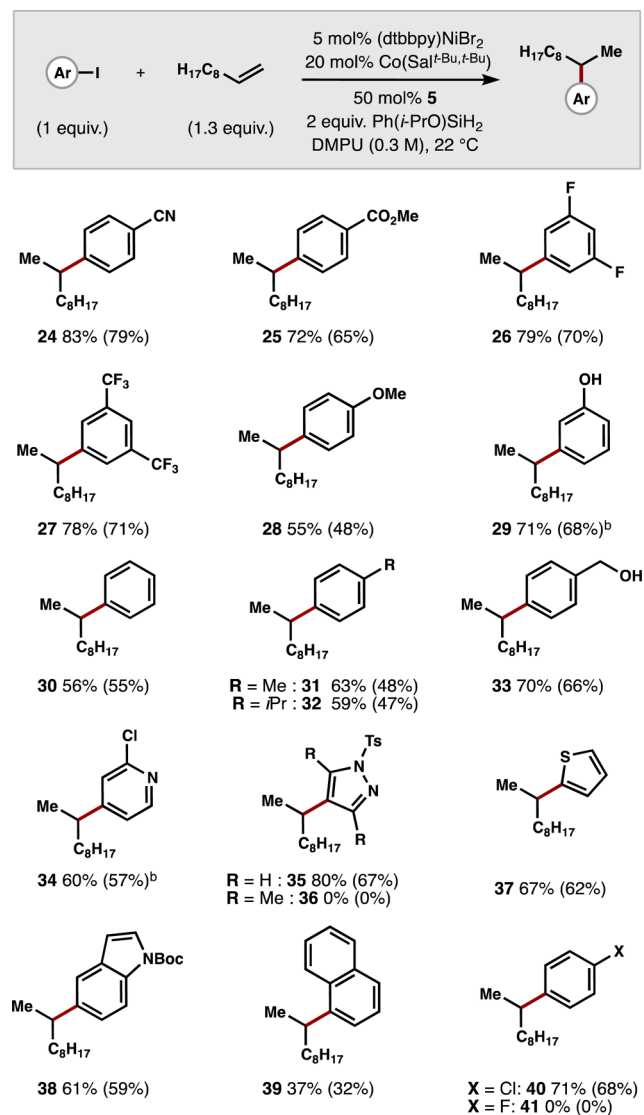
6 86% (79%)
 7 84% (78%)
 8 70% (61%)
 n = 1: 9 38% (31%)
 n = 2: 10 76% (75%)
 n = 1: 11 67%^c (66%)
 n = 2: 12 73% (70%)
 X = O: 13 72%^d (68%)
 X = S: 14 67% (65%)
 15 69%^b (33%)
 16 55%^b (42%)
 17 66%^e (66%)
 18 67% (67%)
 n = 1 19 45%^b (43%)
 n = 2 20 95%^b (86%)
 n = 3 21 37% (20%)
 n = 4 22 47%^f (36%)
 n = 5 23 60%^f (53%)

^aNMR yields isolated yield in parentheses; branched/linear ≥ 20 unless noted. ^b30 mol % [Co]. ^cb/l = 11. ^db/l = 9. ^e5% double arylation. ^fb/l = 7. Compound 8 (1:1 d.r.).

currently problematic, but increased distance from the alkene leads to increased yields.

While the yields seem to correlate to cobalt catalyst loading, arene electronics also play a significant role (Table 3) plausibly due to rates of nickel oxidative addition to the iodoarene. Electron-withdrawing groups generally increase yields of hydroarylation (24–27). While electron-rich aromatic rings show diminished yields, they are still competent in the reaction (28–33). Most importantly, variously substituted heterocycles can be used in the arylation (34–38), which differs starkly from the constraints of Minisci-type reactions with electron-poor sites on electron-deficient heterocycles. In general, *ortho*-substituted arenes give diminished yields (36, 39). Surprisingly, 1-fluoro-4-iodobenzene do not yield hydroarylated product, despite its utility in similar arylations and at alternative positions on the arene ring (e.g., 26).²³

The intermediacy and behavior of radicals²⁴ in this reaction²⁵ were probed with radical clocks 43 and 47 (Figure 3) whose

Table 3. Scope of the Iodoarene^a

^aNMR yields isolated yield in parentheses; branched/linear ≥ 20 unless noted. ^b*b/l* = 18.

unimolecular rate constants for cyclization and scission, respectively, are roughly 1×10^5 and 1×10^8 at 37 °C.²⁶ Observation of a 1.7:1.0 mixture of cyclized and uncyclized hydroarylation products **43** and **44** indicates that the step subsequent to radical formation occurs at rates comparable to radical cyclization (other isomers were produced in only trace amounts). On the other hand, no products of direct arylation of vinylcyclopropane **46** were observed, only the product of ring opening, **47**, a result of its higher rate constant. Without knowledge of catalytic intermediate concentrations, these data only suggest radical lifetimes, not rate constants for bimolecular reactions. But since radical collapse (k_2) appears to terminate our isomerization of terminal alkenes at room temperature, either these conditions decrease the rate of collapse and allow cage escape or cleavage of the collapsed organocobalt is rapid, possibly via oxidation by **5**. An alternative polar mechanism²⁷ for interception of arylnickel is possible, especially in light of recent work by Shigehisa and Hiroya.^{20,28} Suffice it to say, full elucidation of the mechanism will require some work; the sketch in Figure 1 is likely to be a gross oversimplification.²⁹

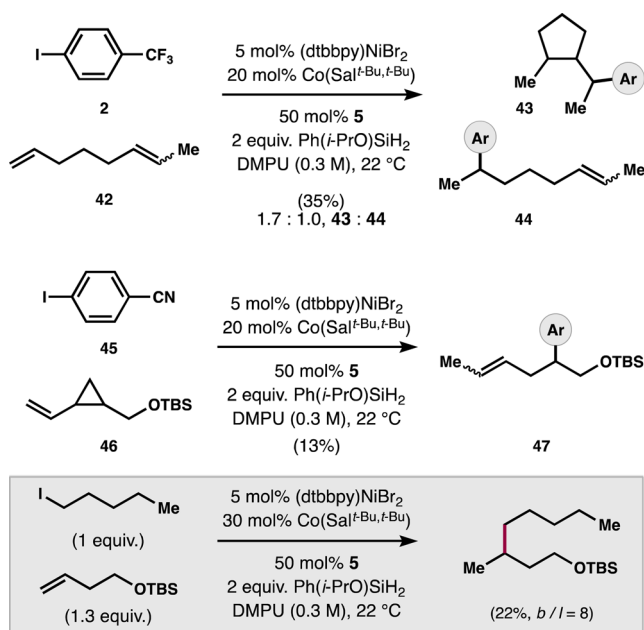


Figure 3. Observations and future directions.

Finally, this chemistry does not appear limited strictly to hydroarylation, but instead may be applicable to a broad array of cross-coupling partners. For example, replacement of aryl iodide with 1-iodopentane yields the branched hydroalkylated product,³⁰ albeit in low yield.

In summary, we report a method for branch-selective (Markovnikov) hydroarylation that relies on the union of cobalt MH HAT and nickel catalytic cycles. In contrast to prior work in nickel-catalyzed cross-coupling, the nucleophilic radical intermediate does not derive from an organohalide, carboxylate, boronate, or oxirane, but instead from a prochiral alkene, which complements this related work and may be advantageous in some circumstances, especially addition of chirality. To the best of our knowledge, this is the first example of HAT olefin hydrofunctionalization that intercepts an organometallic co-reactant.⁵ Consequently, this reaction engine advances MH HAT chemistry beyond classical radical traps and may allow a much greater breadth of coupling partners, as exemplified by iodoarenes and iodoalkanes. We aim to adapt this chemistry to a range of cross-coupling reactions that are capable of forging challenging bonds between complex subunits,³¹ which may help small molecule therapeutics 'escape from flatland.'³²

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08507.

Detailed experimental procedures (PDF)
Spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*rshenvi@scripps.edu

Author Contributions

[†]S.A.G. and J.L.M.M. contributed equally.

Notes

The authors declare no competing financial interest.

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