

Communication

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Branch-Selective Hydroarylation: Iodoarene-Olefin Cross Coupling

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Supporting Information Placeholder

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 anthracene hydrogenation by $HCo(CO)_{4}$ 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 beta-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 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.



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

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) are rate determining (Figure 1).¹ In our previous

investigation into HAT isomerization^{3b} we observed collapse of secondary radicals at ambient temperature, which arrests the reactivity of the cobalt catalyst and limits turnovers. It was unclear whether such a Co(III) organometallic (A) could transmetallate, 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 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.^{11,12,13} In addition, we recently published an intramolecular hydroarylation¹⁴ based on an HAT/ Smiles-Truce rearrangement;^{15a} Shigehisa reported an intramolecular arene annula-tion;^{15b} and Herzon reported an HAT/ Minisci-type hydropyridylation.^{15c} Here, we show that Co(Sal^{t-Bu,t-Bu})¹⁶ and (dtbbpy)NiBr₂¹⁷ co-catalyze a branch-selective hydroarylation of terminal aliphatic alkenes and iodoarenes.



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

To intercept arylnickel complexes with HAT-generated radicals, we initially explored the coupling of alkenes with nucleophiles like 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 aryliodides 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 hydrosilation, alkene isomerization and biaryl formation. Final conditions and instructive variations are shown in **Table 1**.

Table 1. Effect of reagents on reaction outcome^a



^{*a*} NMR 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*-PrO)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 SI).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 disfavors formation of **3**; nickel by itself delivers 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 like Co(Sal^{tBu,tBu}) under these anaerobic conditions, as observed previously.³ Although we probed the alkene scope with 4trifluoromethyl-iodobenzene (Table 2), 4-cyanoiodobenzene proved 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 currently problematic, but increased distance from the alkene leads to increased yield.

Table 2. Scope of the alkene^a



^{*a*} NMR yields; isolated yield in parentheses; branched / linear ≥ 20 unless noted, ^{*b*} 30 mol% [Co], ^{*c*} *b* / *l* = 11, ^{*d*} *b* / *l* = 9, ^{*e*} 5% double arylation, ^{*f*} *b* / *l* = 7.



Table 3. Scope of the iodoarene.^a



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

While the yields seemed to correlate to cobalt catalyst loadings, arene electronics also play a significant role (**Table 3**) plausibly due to rates of nickel oxidative addition to the iodoarene. Electron-withdrawing groups generally increased yields of hydroarylation (**24–27**). While electronrich aromatic rings showed diminished yields, they were 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 electrondeficient heterocycles. In general, *ortho*-substituted arenes gave diminished yields (**36**, **39**). Surprisingly, 1-fluoro-4iodobenzene did not yield hydroarylated product, despite its utility in similar arylations and at alterative 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 unimolecular rate constants for cyclization and scission, respectively, are roughly $1 \ge 10^5$ and $1 \ge 10^8$ 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 (no other isomers were produced above 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 aryliodide 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 nucleo-philic radical intermediate does not derive from an organo-halide, 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

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58 59 60 **Supporting Information**. The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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