



Published in final edited form as:

J Am Chem Soc. 2018 September 12; 140(36): 11317–11324. doi:10.1021/jacs.8b05868.

Iron-Nickel Dual-Catalysis: A New Engine for Olefin Functionalization and the Formation of Quaternary Centers

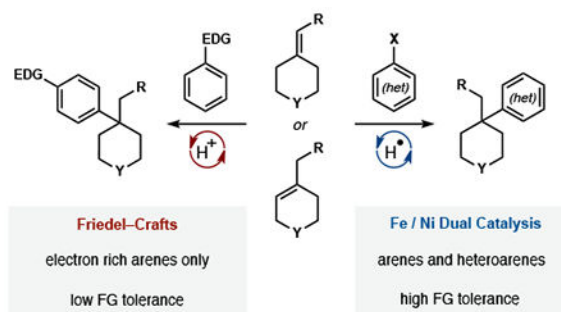
Samantha A. Green, Suhelen Vásquez-Céspedes, and Ryan A. Shenvi*

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

Abstract

Alkene hydroarylation forms carbon–carbon bonds between two foundational building blocks of organic chemistry: olefins and aromatic rings. In the absence of electronic bias or directing groups, only the Friedel–Crafts reaction can engage alkenes with Markovnikov selectivity to generate quaternary carbons. However, the intermediacy of carbocations precludes the use of electron-deficient arenes, including Lewis basic heterocycles. Here we report a highly Markovnikov-selective, dual-catalytic olefin hydroarylation that tolerates arenes and heteroarenes of any electronic character. Hydrogen atom transfer controls the formation of branched products and arene halogenation specifies attachment points on the aromatic ring. Mono-, di-, tri- and tetra-substituted alkenes yield Markovnikov products including quaternary carbons within non-strained rings.

Graphical Abstract



INTRODUCTION

Accelerating interest in high-fraction sp^3 (F_{sp^3}) scaffolds has highlighted two major gaps in chemical methodology.¹ First, few metal-catalyzed cross-coupling reactions are competent to generate quaternary ring carbons at a non-bridgehead position.² The products are three-

*Corresponding Author rshenvi@scripps.edu.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, compound characterization, and spectral data (PDF).

The authors declare no competing financial interest.

dimensional equivalents of biaryl motifs and represent chemical space that is sparsely populated by synthetic libraries and typically occupied by natural products.³ Second, although nickel complexes have recently reigned supreme as alkyl cross-coupling catalysts, reaction partners can suffer from a triple Achilles heel of low stability, low synthetic efficiency, and low atom economy (high formula weight loss).⁴ An ideal disconnection would obviate the need for pre-installation of a functional group and open access to a wide range of scaffolds or products inaccessible with other cross-coupling methods. Here we report a cross-coupling reaction with broad scope that forms quaternary carbons from a simple, abundant feedstock: the olefin.

Pioneering nickel-catalyzed arylation methods have used halides,⁵ organometaloids,⁶ carboxylic acids,⁷ and sulfones⁸ as alkyl radical precursors⁹ (Figure 1). Olefins offer orthogonal reactivity and the distinct advantage of relative inertness, allowing them to be carried through multistep syntheses. Furthermore, they are among the most prevalent functional groups in natural products and commercially available building blocks. Where Nature is not forthcoming, olefin synthesis or metathesis can merge two building blocks, and the nascent olefin itself can serve as the coupling point (Figure 2). Prior methods for arylative quaternary centers synthesis first form a functionalized tetrasubstituted carbon^{2a–c}, in itself a challenging task; yet the functional group is next ablated during the cross-coupling. A unique benefit of olefins is the ability to form a quaternary center without starting from a preformed tetrasubstituted carbon, circumventing the prefunctionalization step and improving the atom economy of the transformation.

Prior methods¹⁰ for the hydroarylation of olefins rely on the innate reactivity of arenes. Friedel–Crafts alkylation, a foundational reaction that adds a proton and arene across unbiased α -olefins with high Markovnikov regioselectivity, is generally limited to acid-stable, electron-rich aromatics, whereas electron-deficient and Lewis-basic heteroarenes are not tolerated.¹¹ Similarly, the Minisci reaction is confined to electron-deficient arenes and dependent on substrate bias for its innate regiocontrol.¹² In both methods, positional selectivity is controlled by ring electronics and mixtures often result. In contrast, cross-coupling takes advantage of the programmed reactivity of aryl halides, whereby a transition metal enables absolute regiocontrol and the ability to use the full spectrum of arene electronics.⁴

Here we demonstrate a Markovnikov-selective Fe/Ni dual-catalytic alkene hydroarylation of mono-, di-, tri-, and tetrasubstituted alkenes utilizing electronically diverse arenes and heteroarenes. Furthermore, this cross-coupling embeds quaternary carbons in oxetanes, pyrans, pyrrolidines, piperidines, and thianes in a single step from commercially available materials. Application of this dual catalytic system allowed for improved access to 3 drug leads and high-value building blocks for biomedical application.

RESULTS AND DISCUSSION

Recently we reported a proof-of-principle that olefins could engage in highly branch-selective hydroarylation by merging cobalt-catalyzed hydrogen atom transfer (HAT) and nickel catalysis.¹³ This reaction was limited to mono-substituted olefins, since substituted

olefins (**1a**) yielded exclusively an allylic isomer (**1a'**) (Figure 3). This limitation correlated with the tendency for terminal alkenes to form stable organocobalt complexes,¹⁴ implicating a transmetalation pathway. *Tert*-alkylcobalt species have never been observed¹⁵ and therefore their participation in this dual catalysis was deemed unlikely, if not mechanistically forbidden.

Early examples of HAT catalysis observed similar collapse to organometallics or rapidly reversible reactions that resulted in inverse kinetic isotope effects.^{16a} More recently, both Carreira^{16b} and Baran^{16c} observed non-inverse (normal) KIEs in reactions where HAT has been implicated, which indicates an irreversible atom transfer and cage escape. Successful engagement of a *tert*-alkyl radical with a low valent nickel might, therefore, occur with alternative catalyst systems, but would require a complete reconstruction of the dual catalytic cycles.

For the cycles to merge by unstabilized C-centered radical interception, the independent rates of each cycle must be similar. Whereas salen ligands cause rapid alkene consumption,¹⁴ alternative ligands decelerate the catalytic cycle.¹⁷ Mukaiyama's pioneering work in alkene radical hydrofunctionalization^{17,18} indicated that β -diketonate ligands significantly changed reaction rates, but subsequent interception of nickel catalytic cycles lacked precedent. Co(acac)₂ consumed the olefin within an hour through hydrogenation and hydration, but yielded none of our desired product (Table 1, entry 1). Mn(dpm)₃ similarly yielded only traces of the desired product, however there was little consumption of either starting material (entry 2) and a white heterogeneous slurry resulted. Iron, however, showed no promiscuity with Ni and delivered the first evidence of successful arylation, consistent with the initial cage escape hypothesis.^{16c,18c,19}

Investigation of olefin **3a** and aryl iodide **4** using Fe(acac)₃^{16c,18c,19a,b} (entry 3) yielded product **3b** with low catalyst turnover in the presence of metallic reductants. Whereas Mukaiyama observed no difference between sterically-differentiated complexes of Fe,^{18c} Baran and co-workers correlated increased bulk with reaction efficiency, which they proposed resulted from decreased catalyst decomposition.^{16c,19b} Accordingly, bench stable catalyst, Fe(dpm)₃, proved ideal. A brief survey of nickel ligands identified 4,4-di-*tert*-butylbipyridine (dtbbpy) as optimal, requiring only 2.5 mol% of Ni. The reaction was highly solvent dependent: 1,4-dioxane led to high yields and outperformed similar ethereal solvents (entry 4). Due to the limited solubility of Ni(II) precatalysts in 1,4-dioxane, we observed that precomplexed NiBr₂(dtbbpy) allowed for more reproducible yields. Use of Ph(*i*-PrO)SiH₂^{17,20} proved superior to a PhSiH₃/*i*-PrOH²¹ combination (entry 5) or PhSiH₃ alone. Finally, the presence of air was found to be critical for reactivity; no catalytic turnover occurred in its absence (entry 6).^{16c}

Optimal hydroarylation conditions transformed a variety of feedstock olefins—di-, tri- and tetra-substituted (**5a-19a**)—to branched aromatics (**5b-19b**) with exceptionally high regioselectivity.²² All olefins were coupled in >20:1 regioselectivity, except where noted. The reaction proved tolerant to many functional groups such as carbamates (**7b**), strained cyclobutanes (**8b**), redox-active esters (RAEs) (**16b**), amides (**17b**), vinyl thioethers (**18b**), vinyl boronates (**19b**), and nitriles (**5b-19b**). Ring size did not affect reactivity and the

arylated products (**9b-12b**) were obtained in high yield. Although this olefin cross-coupling can be viewed as complementary to decarboxylative or dehalogenative cross-electrophile coupling in some cases, in others there are no options: olefins **8a** and **13a** are unavailable as the corresponding carboxylate and unprecedented as the halide. Interestingly, [2.2.0]-bicyclohexene **8a**, an intermediate in Burns' scalable ladderane synthesis²³ could be hydroarylated in 70% yield where the strained cyclobutyl arene predominated (3:1) over the ring-opened product. Commercially available perfluorinated olefin **13a** and other fluorine-containing substrates (**14a**, **15a**) were successfully arylated, offering unique access to these perfluoroalkane and -arene derivatives in moderate to high yields. The propensity of RAEs to cross-couple with iodoarenes or reduce in the presence of silanes is established,²⁴ yet RAEs (**16b**) emerged unscathed from our reaction conditions: a 95:5 selectivity for cross-coupling *via* the olefin vs. the ester demonstrated the orthogonality of this coupling to prior work.

More challenging 1,1-disubstituted and trisubstituted olefins probed the capacity of this method to generate quaternary carbons and hindered attached ring motifs. Their reactivity required interception of nickel with a tertiary carbon radical, consistently a more difficult cross-coupling than *sec-alkyl* counterparts.^{2,4} Consequently, the conditions described above to couple secondary radicals for olefin **1a** and aryl iodide **2** yielded only arylation of the ethereal solvent (Table 3, entry 1).^{2c} An exhaustive ligand screen resulted in, at best, a 1:1 mixture of regioisomers. Instead, the "ligandless" nickel system developed by Fu provided superior results to traditional conditions.²⁵ NiBr₂(diglyme) in a mixture of THF/DMA produced the desired product **1b** with high regioselectivity (>20:1), although NMP (entry 2) eventually proved superior and 1,2-DCE increased Fe(dpm)₃ solubility. Even though air was still critical for reactivity, the addition of MnO₂ led to higher catalyst turnover (entry 3).

The significance of this reaction was illustrated by the ease with which quaternary carbons could be generated from simple alkenes, many of which (**20a-22a**, **24a-30a**, **32a-34a**) were in turn accessed via one-step olefination reactions from widely available ketones. We focused on cyclic coupling partners, which led to high Fsp³ scaffolds that extend along multiple vectors, yet are uncommon motifs in cross-coupling reactions.³ Embedded in these unsaturated substrates are Lewis basic functionality (**20a-29a**), carbamates (**26a-29a**), esters (**21a**, **30a**), silyl ethers (**1a**, **22a**, **32a**), phthalimides (**38a**), carbocycles (**30a-34a**) and acid sensitive ring motifs (**22a**, **26a-29a**, **32a**), all of which were tolerated and left the high branch selectivity largely unaffected (>20:1 regioselectivity except where noted).

Unsaturated heterocycles—oxetanes (**20a-22a**), tetrahydrofurans (**23a**), pyrans (**24a**), thianes (**25a**), pyrrolidines (**26a-28a**), and piperidines (**29a**)—all productively coupled. Of particular note, the compatibility of thianes with this method resulted in the first reported synthesis for this type of attached ring motif. Previously, placement of a quaternary center at C-3 of a pyrrolidine has required the intermediacy of either 2-pyrrolidinone or succinimide, resulting in a 3-4 step sequence that includes strong hydride reductants.²⁶ Fe/Ni dual-catalysis streamlined access via 3-pyrrolidinone olefination (to **26a-28a**) and high-yielding arylation (**26b-28b**). Olefination via ylides can generate a variety of pyrrolidines for which the corresponding tertiary bromides or boronic acids are unknown, making this method the only viable cross-coupling of these scaffolds.

Acyclic olefins have a greater potential to engage in background reductive Heck (anti-Markovnikov) reactivity than their more-hindered cyclic counterparts.^{2d} We nevertheless observed complete regioselectivity; no isomers were detected (**1b**, **35b–37b**, **39b**). Allylic substitution was well tolerated yielding branched diols (**37b**) and phthalimides (**38b**) in moderate to high yield. The increased steric bulk on tetrasubstituted olefins impedes accessibility by a metal catalyst, making them less reactive than disubstituted olefins.²⁷ Despite this, tetramethylethylene (**39b**) still served as a compatible olefin, albeit in modest yield. Notably, arylation of **1a** could be performed on gram scale without a significant deterioration in yield (52%).

Natural products and their derivatives (**40a–46a**) could also serve as successful coupling partners (Figure 2). Allyl glycine (**40a**) was arylated in high yield, opening the door to a range of unnatural amino acids. The terpenes caryophyllene oxide (**42a**) and β -pinene (**43a**) were arylated as their ring-opened products; however no evidence of epoxide opening was observed for **42b**, a demonstration of the mild, non-acidic conditions.

Although this method was compatible with a broad array of olefins, sterically hindered or unstable olefins (**46a–48a**) were low yielding and returned substantial starting materials.²⁸ Arylation of tropinone derivative **47a** offered access to a previously unexplored vector of phenyltropane derivatives, cocaine receptor ligands that have been pursued for the treatment of drug dependency, Parkinson's disease, and depression.²⁹ 1,3-diaxial interactions across the tropane ring significantly challenged the arylation and the product was obtained in low yield. Similarly, the highly congested core of tetrahydrocannabinoid derivative **48a** prevented significant engagement by the Fe catalyst and, while the product could be observed in low yield, the reaction yielded mostly unreacted olefin. For an additional list of less reactive substrates, see the SI.

In contrast to traditional Markovnikov-selective arylation reactions (Friedel-Crafts, Minisci), this dual-catalytic method was compatible with a range of arene electronics. Under the *sec-alkyl* conditions, the highest yields were obtained with electron-deficient arenes (Table 5A, **49**, **50**, **53–61**), however 4-iodoanisole (**52**) and an aryl boronate ester (**51**) were also successfully coupled. Heterocycles (**57–61**) served as effective coupling partners, although pyridines required substitution at C2.

Electron-deficient, -neutral, and -rich arenes successfully coupled in moderate to good yield, providing a library of C3-quaternary oxetanes (Table 5B, **62–75**). Iodopyridines (**68**, **69**) and bromopyrimidines (**70**, **71**) were successful coupling partners independent of electronic character, as was electron-rich 2-iodo-5-furan-dioxolane, which coupled in high yield with the acid-labile acetal fully intact. Other electron-rich heterocycles, such as benzothiophene proved to be more difficult, yet still were compatible—crucial for structure-activity interrogation campaigns. As proof-of-principle for the broader generality of this reaction engine, we found that a vinyl bromide could replace the haloarene and engage in cross-coupling with no subsequent hydrogenation of the styrene product (**75**). Interestingly, bromoarenes coupled effectively with *tert*-alkyl partners, but were significantly less efficient with *sec*-alkyl reactants (**62** vs Table 1, entry 7). The capacity of bromoarenes to cross-

couple offers a significant benefit due to their breadth of commercial availability compared to iodoarenes (ca. 78,000 (hetero)aryl bromides versus ca. 17,000 (hetero)aryl iodides).³⁰

During the assessment of the haloarene scope (Table 5), we focused on arenes in which Friedel–Crafts or Minisci reactions would be unsuccessful.^{11,12} The position of aryl halide substitution perfectly translated to alkylated product, whereas Friedel–Crafts alkylations (e.g. with anisole) generate mixtures of *o*- and *p*- regioisomers. Friedel–Crafts reactions are also unfavorable with electron-rich heterocycles such as furan and benzothiophene due to catalyst-induced polymerization or polyalkylation;³¹ dihydrofuran **6a** has never been reported in a Friedel–Crafts, presumably due to decomposition. Minisci-type reaction with 2-chloropyridine would yield a mixture of **58** and its C6 isomer. Furthermore, radical addition into C3 of pyridine and C5 of a pyrimidine is unfavorable, and products **57**, **59**, and **68–71** are not viable using Minisci chemistry.

A survey of compounds containing arylated quaternary centers identified the importance of oxetanes, a small ring that alters scaffold lipophilicity and acts as a ketone bioisostere with increased metabolic stability.³² Oxetanes may be prepared *via* transition metal-catalyzed conjugate addition, requiring extraneous functional groups (cyano, ester, sulfonates) that are often excised in the desired target.³² Alternatively, oxetanes can be prepared through ring closing dehydration that requires 3 or more steps and varies dramatically in yield (19–81%).³³ A Vertex patent detailing the use of small molecules for the modulation of ATP-binding cassette transporters investigated oxetane **80** (Figure 4),^{33c} whose aryl bromide precursor (**79**) has been employed in 9 patents^{33b–j} and one discovery article.^{33k} Oxetane **79** is commercially available at \$368/g³⁴ or can be prepared in 4 steps (8% overall yield) through Mitsunobu dehydration of the corresponding diol (**77**).^{33c}

Employment of our Fe/Ni dual catalysis allowed for the cross-coupling of olefin **20a** with 1,4-dibromobenzene, resulting in a 3 step synthesis of **79** from the inexpensive ketone **20'** in an overall yield of 27%. Furthermore, no dialkylation of the dihaloarene was observed. This method bypasses designer diol intermediates and cyclodehydration, and obviates the need for potentially explosive diazo reagents, providing a route that is more amenable to intermediate diversification.

A 2014 Allergan patent documented a library of *tert*-alkyl substituted arylthioethers for treatment of sphingosine-1 phosphate-related ocular diseases.³⁵ The patent identifies **82** as an intermediate en route to **84**, however there is no reported synthesis in the patent or elsewhere. Access may be attained through esterification of acid **83**, which is priced at \$3990/100 mg from the sole commercial vendor.³⁶ Alternatively, olefin hydroarylation simplifies access to **82** through oxetane olefination (Figure 4) and cross-coupling with 4-fluoriodobenzene (51% yield).

JDTic and its analogs (**87**) are potent *kappa*-opioid receptor antagonists that contain arylated quaternary carbons embedded in a piperidine.³⁷ Prior access to **86** required a 5-step sequence for the construction of the quaternary center.³⁷ Olefin cross-coupling, however, retrosynthetically signals the Wittig olefination of *N*-Boc 4-piperidone (**85b'**) followed by arylation/ deprotection to yield intermediate **86**, resulting in an 883% improvement in

overall yield (53% versus 6%) and a 40% reduction in step count compared to the prior route. As the olefin coupling partner is prepared by a Wittig olefination of *N*-Boc 4-piperidone, this sequence offers the ability to expansively derivatize similar heterocyclic ketones—oxetanones, piperidones, pyrrolidinones, pyranones—all of which are inexpensive.

Mechanistic analysis of this hydroarylation is complicated by the number of reaction components, but a thumbnail sketch is suggested in Figure 5A. A metal hydride formed from the iron precatalyst and silane has been proposed to undergo hydrogen atom transfer (HAT) with alkenes to generate carbon-centered radicals, consistent with the ring opening observed in **42b** and **43b**.^{16c,17} To further probe the intermediacy of a carbon-centered radical, a competition between our hydroarylation reaction and previously reported Fe-catalyzed Giese reaction (which has been postulated to occur via a radical mechanism)^{15c} was conducted (Figure 5B). In the absence of nickel, only Giese product was observed in a moderate yield. In the presence of nickel, our desired product and Giese product were formed in comparable yields. Additionally, in the presence of TEMPO, the reaction was completely inhibited and the TEMPO-adduct of the olefin starting material was isolated (Figure 5c).

Underscored by similarity in reaction conditions, coupling with *sec*-alkyl fragments may overlap in mechanism with Weix's reductive electrophile coupling, i.e. capture of the alkyl radical by an aryl—Ni(II) complex.^{5a} However, a 50% reduction in yield occurs when a bromoarene replaces an iodoarene under *sec*-alkyl coupling conditions, whereas *tert*-alkyl coupling conditions can use these haloarenes interchangeably with only slight variation in yield. Such insensitivity by the *tert*-alkyl conditions may indicate a reordering of steps, where an electron-rich alkyl Ni(I) species engages the haloarene, as suggested by Molander and Kozlowski.³⁸ Even though both *tert*- and *sec*-alkyl coupling reactions derive from identical transition metal nuclei, differences in optimal ligand, co-oxidant, solvent and rate indicate significant mechanistic disparities between both dual-catalytic cycles.

CONCLUSION

In conclusion, olefins may now be considered viable and broadly applicable cross-coupling partners for branch-selective hydroarylation, without the regioselectivity and chemoselectivity restrictions of Minisci and Friedel–Crafts reactions. Arylations of polysubstituted alkenes are enabled by iron-catalyzed hydrogen atom transfer and interception of traditional nickel catalytic cycles; two cycles that, to the best of our knowledge, have not been combined previously. These dual catalytic cycles enable cross-coupling of chemical feedstocks in a fundamentally new way, connecting unsaturated building blocks and arenes to generate privileged medicinal chemistry scaffolds and validated drug leads. Hydroarylation of partly saturated rings resembles an sp^3 equivalent of biaryl coupling, replacing one aromatic 'hub' with a high Fsp^3 motif. Such cross-couplings hasten synthetic, ideally combinatorial, approaches to natural product space and answer the call to escape from flatland.¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We would like to thank the following individuals for graciously providing the following starting materials: N. Z. Burns (**8a**), J. C. Lo (**29a**), R. M. Martinez (**33a**), and C. L. Obradors (**36a**). Generous support was provided by the National Science Foundation (GRFP to S. A. G) and the National Institutes of Health (R35 GM122606).

REFERENCES

- (1). Lovering F; Bikker J; Humblet C J. *Med. Chem.* 2009, 52, 6752. [PubMed: 19827778]
- (2). (a) Zultanski SL; Fu GC J. *Am. Chem. Soc.* 2013, 135, 624. [PubMed: 23281960] (b)Wang X; Wang S; Xue W; Gong HJ *Am. Chem. Soc.* 2015, 137, 11562.(c)Primer DN; Molander GA J. *Am. Chem. Soc.* 2017, 139, 9847. [PubMed: 28719197] (d)Mei T-S; Patel HH; Sigman MS *Nature* 2014, 508, 340. [PubMed: 24717439]
- (3). Brown DG; Bostrom JJ *Med. Chem.* 2016, 59, 4443.
- (4). Tasker SZ; Standley EA; Jamison TF *Nature* 2014, 509, 299. [PubMed: 24828188]
- (5). For selected examples see(a) Weix DJ, *Acc. Chem. Res.* 2015, 48, 1767. [PubMed: 26011466] (b)Zhou J; Fu GC J. *Am. Chem. Soc.* 2004, 126, 1340. [PubMed: 14759182] (c)Kadunce NT; Reisman SE J. *Am. Chem. Soc.* 2015, 137, 10480. [PubMed: 26256474]
- (6). For selected examples see(a) Tellis JC; Primer DN; Molander GA *Science* 2014, 345, 433. [PubMed: 24903560] (b)Jouffroy M; Primer DN; Molander GA J. *Am. Chem. Soc.* 2016, 138, 475. [PubMed: 26704168]
- (7). For selected examples see(a) Cornella J; Edwards JT; Qin T; Kawamura S; Wang J; Pan C-M; Gianatassio R; Schmidt M; Eastgate MD; Baran PS J. *Am. Chem. Soc.* 2016, 138, 2174. [PubMed: 26835704] (b)Zuo Z; Ahneman DT; Chu L; Terrett JA; Doyle AG; MacMillan DWC *Science* 2014, 345, 437. [PubMed: 24903563]
- (8). For selected examples see(a) Denmark SE; Cresswell AJ J. *Org. Chem.* 2013, 78, 12593. [PubMed: 24256193] (b)Ariki ZT; Maekawa Y; Nambo M; Crudden CM J. *Am. Chem. Soc.* 2018, 140, 78. [PubMed: 29215881] (c)Miao W; Zhao Y; Ni C; Gao B; Zhang W; Hu JJ *Am. Chem. Soc.* 2018, 140, 880.(d)Merchant RR; Edwards JT; Qin T; Kruszyk MM; Bi C; Che G; Bao D-H; Qiao W; Sun L; Collins MR; Fadeyi OO; Gallego GM; Mousseau JJ; Nuhant P; Baran PS *Science* 2018, 360, 75. [PubMed: 29456201]
- (9). Yan M; Lo JC; Edwards JT; Baran PS J. *Am. Chem. Soc.* 2016, 138, 12692. [PubMed: 27631602]
- (10). Nickel is known to participate in the hydroarylation of olefins via reductive heck reactions giving the anti-Markovnikov (or linear) product. For an example of such reactivity see Lu X; Xiao B; Zhang Z; Gong T; Su W; Yi J; Fu Y; Liu L *Nature Comm.* 2016, 7, article no. 11129.
- (11). Naredla RR; Klumpp DA *Chem. Rev.* 2013, 113, 6905. [PubMed: 23819438]
- (12). For selected examples see Ma X; Dang H; Rose JA; Rablen P; Herzon SB J. *Am. Chem. Soc.* 2017, 139, 5998. [PubMed: 28359149]
- (13). Green SA; Matos JLM; Yagi A; Shenvi RA J. *Am. Chem. Soc.* 2016, 138, 12779. [PubMed: 27623023]
- (14). Crossley SWM; Barabe F; Shenvi RA J. *Am. Chem. Soc.* 2014, 136, 16788. [PubMed: 25398144]
- (15). Puxeddu A; Costa G; Marsich NJ *Chem. Soc. Dalton Trans.* 1980, 9, 1489.
- (16). (a) Halpern J *Pure & Appl. Chem.* 1986, 58, 575.(b)Waser J; Gaspar B; Nambu H; Carreira EM J. *Am. Chem. Soc.* 2006, 128, 11693. [PubMed: 16939295] (c)Lo JC; Kim D; Pan C-M; Edwards JT; Yabe Y; Gui J; Qin T; Gutierrez S; Giacoboni J; Smith MW; Holland PL; Baran PS J. *Am. Chem. Soc.* 2017, 139, 2484. [PubMed: 28094980]
- (17). Crossley SWM; Obradors CL; Martinez RM; Shenvi RA *Chem. Rev.* 2016, 116, 8912. [PubMed: 27461578]
- (18). (a) Mukaiyama T; Isayama S; Inoki S; Kato K; Yamada T; Takai T *Chem. Lett.* 1989, 18, 449. (b)Inoki S; Kato K; Isayama S; Mukaiyama T *Chem. Lett.* 1990, 19, 1869.(c)Kato K; Mukaiyama T *Chem. Lett.* 1992, 21, 1137.

- (19). (a) Lo JC; Yabe Y; Baran PS *J. Am. Chem. Soc.* 2014, 136, 1304. [PubMed: 24428607] (b)Lo JC; Gui J; Yabe Y; Pan C-M; Baran PS *Nature* 2014, 516, 343. [PubMed: 25519131] (c)Leggans EK; Barker TJ; Duncan KK; Boger DL *Org. Lett.* 2012, 14, 1428. [PubMed: 22369097]
- (20). Obradors CL; Martinez RM; Shenvi RA *J. Am. Chem. Soc.* 2016, 138, 4962. [PubMed: 26984323]
- (21). PhSiH₃/EtOH at 60 °C is commonly employed in Fe-HAT reactions and has been proposed to form Ph(OEt)SiH₂ under the reaction conditions (ref 15c). In our reaction, this combination yields the product in 31% yield. Instead, PhSiH₃/i-PrOH could be used at room temperature to provide 41% of the desired coupling product (Table 1). A significant amount of protodehalogenation of the aryl iodide was seen with PhSiH₃/i-PrOH, which is likely the cause for the deterioration in yield. For a further discussion on silanes, please see the SI.
- (22). Reactions performed with styrene yielded product, albeit in low yield (< 20%).
- (23). Mercer JAM; Cohen CM; Shuken SR; Wagner AM; Smith MW; Moss FR; Smith MD; Vahala R; Gonzalez-Martinez A; Boxer SG; Burns NZ *J. Am. Chem. Soc.* 2016, 138, 15845. [PubMed: 27960308]
- (24). (a) Huihui KMM; Caputo JA; Melchor Z; Olivares AM; Spiewak AM; Johnson KA; DiBenedetto TA; Kim S; Ackerman LKG; Weix DJ *J. Am. Chem. Soc.* 2016, 138, 5016. [PubMed: 27029833] (b)Qin T; Malins LR; Edwards JT; Merchant RR; Novak AJE; Zhong JZ; Mills RB; Yan M; Yuan C; Eastgate MD; Baran PS *Angew. Chem. Int. Ed.* 2017, 56, 260.
- (25). Chu CK; Liang Y; Fu GC *J. Am. Chem. Soc.* 2016, 138, 6404. [PubMed: 27187869]
- (26). (a) Otani G; Yamada S *I Chem. Pharm. Bull.* 1973, 21, 2119. (b)Oda K; Meyers AI *Tetrahedron Lett.* 2000, 41, 8193.
- (27). Cui X; Burgess K *Chem. Rev.* 2005, 105, 3272. [PubMed: 16159153]
- (28). α -methyl styrene was found to give only traces of product with mostly dimerization of the α -methyl styrene observed.
- (29). Kuhar MJ; Carrol F; Boja JW; Lewin AH; Abraham P US Patent US20080153870A1.2008.
- (30). Number of commercially available compounds from Reaxys as of May 31st, 2018.
- (31). Joule JA; Mills K *Heterocyclic chemistry fifth edition* (Wiley, 2010).
- (32). (a) Bull JA; Croft RA; Davis OA; Doran R; Morgan KF *Chem. Rev.* 2016, 116, 12150. [PubMed: 27631342] (b)Wuitschik G; Carreira EM; Wagner B; Fischer H; Parrilla I; Schuler F; Rogers-Evans M; Muller KJ *Meet. Chem.* 2010, 53, 3227.
- (33). (a)Llona-Minguez S; Høglund A; Ghassemian A; Desroses M; Calderon-Montano JM; Moron EB; Valerie NCK; Wita E; Almløf I; Koolmeister T; Mateus A; Cazares-Korner C; Sanjiv K; Homan E; Loseva O; Baranczewski P; Darabi A; Mehdizadeh M; Fayezi S; Jemth A-S; Berglund UW; Sigmundsson K; Lundback T; Jensen AJ; Artursson P; Scobie M; Helleday T *J. Med. Chem.* 2017, 60, 4279. [PubMed: 28508636] (b)Brodney MA International patent WO2006106416A1. 2006. (c)Ruah SS, Miller MT; Bear B; McCartney J; Grootenhuis PD J. International patent WO2007087066A2. 2007. (d)Klar U; Schwede W; Moeller C; Rotgeri A; Bone W; International patent WO2011009534A2. 2011. (e)Apar JM; Srasappan A; Biftu T; Ping C; Danqing F; Guidry E; Hicks J; Kecec A; Wei L; Wilkeniing R; Wu Z International patent WO2014031515A1. 2014. (f)Scott JD; Stamford AW; Gilbert EJ; Cumming JN; Iserloh U; Wang L; Li W International patent WO2011044187A1. 2011 (g)Siegrist R; Heidmann B; Stamm S; Gatfield J; Bezencon O International patent WO2015186056A1. 2015. (h)Becker-Pelster EM; Buchgraber P; Buchmuller A; Engel K; Gnoth MJ; Himmel H; Kast R; Klar J; Knorr A; Lang D; Lindner N; Schmeck C; Schohe-Loop R; Tinel H; Trubel H; Wunder F; Keldenich J International patent WO2015091415A1. 2015. (i)Li B; Breinlinger E; Davis H; Hoemann M; Li B; Somal G; Van ES; Wang L International patent WO2014169473A1. 2014. (j)Bhagirath N; Dominique R; Kennedy-Smith J; Lopez-Tapia FJ; Mertz E; Qiao Q; So S-S. International patent WO2014064131A2. 2014. (k)Bezenjon O; Hedimann B; Siegrist R; Stamm S; Richard S; Pozzi D; Corminboeuf O; Roch C; Kessler M; Ertel EA; Reymond I; Pfeifer T; Kanter R; Toeroek-Schafroth M; Moccia LG; Mawet J; Moon R; Rey M; Capeleto B; Fournier EJ *Med. Chem.* 2017, 60, 9769.
- (34). The price of 3-(4-bromophenyl)-3-methyloxetane (79) is \$3680/10g from Pharmablock as of May 31st, 2018.

- (35). Nguyen PX; Cappiello JR; Heidelbaugh TM United States Patent US2014171393A1. 2014.
- (36). The price of 85 is from Aurora Fine Chemicals (\$3990/100 mg) as of May 31st, 2018.
- (37). (a) Carroll FI; Gichinga MG; Kormos CM; Maitra R; Runyon SP; Thomas JB; Mascarella SW; Decker AM; Navarro HA *Bioorg. Med. Chem.* 2015, 23, 6379. [PubMed: 26342544] (b) Nagai Y; Hino K; Uno H; Minami S *Chem. Pharm. Bull.* 1980, 28, 1387.
- (38). Gutierrez O; Tellis JC; Primer DN; Molander GA; Kozlowski MC *J. Am. Chem. Soc.* 2015, 137, 4896. [PubMed: 25836634]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Prior work: 3° sp³ substrates

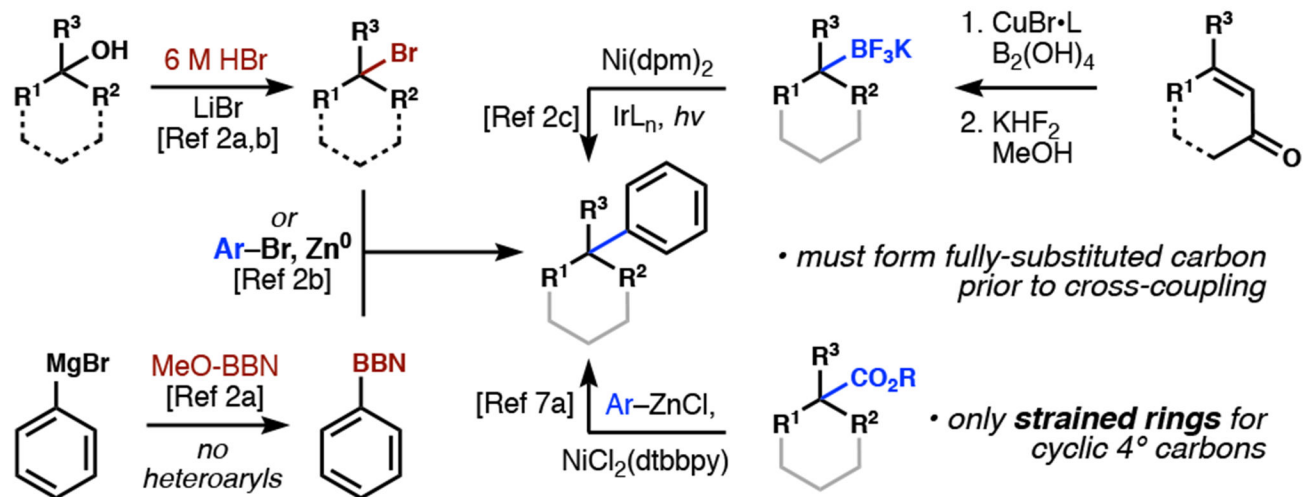


Figure 1.
Prior methods for the formation of arylated quaternary centers using Ni-catalysis.

This work: olefins

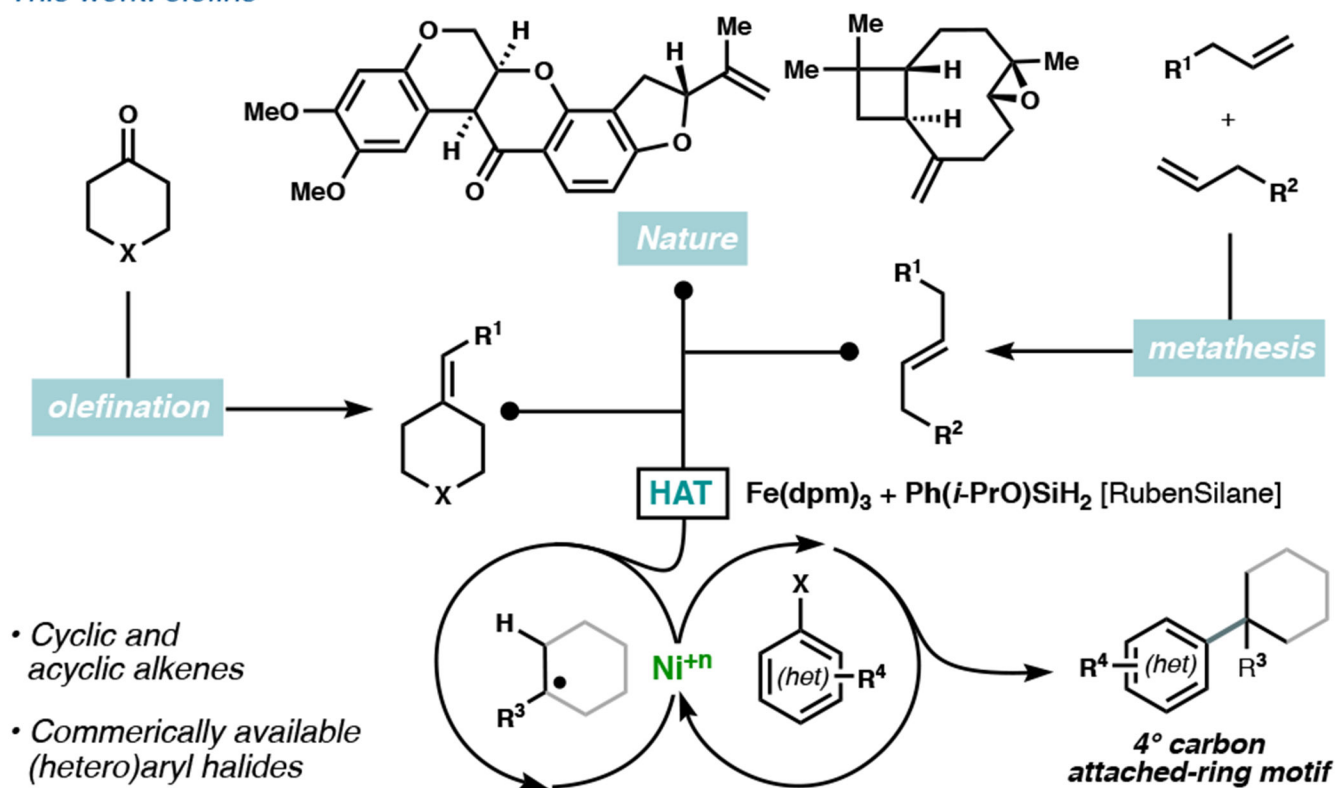
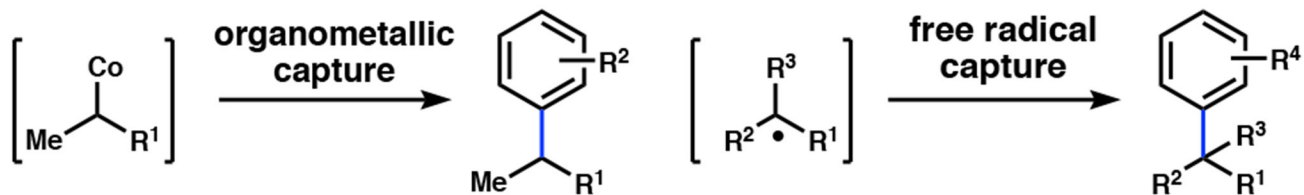


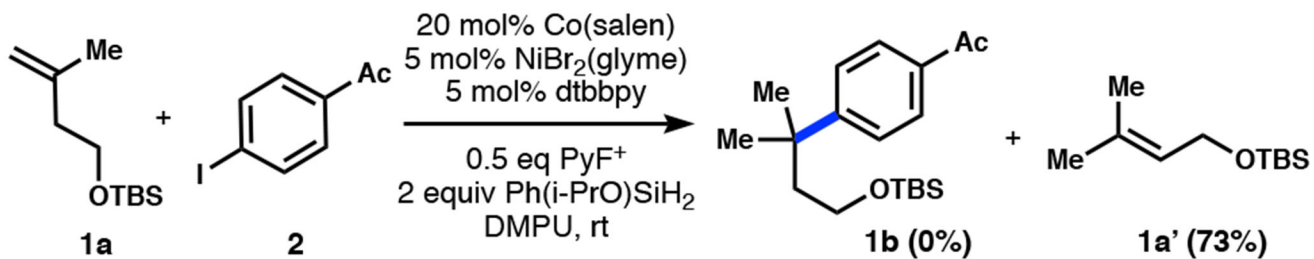
Figure 2.
Current work combining HAT and Ni catalysis.

Prior work: *Co(salen)*

This Work: *Fe(dpm)₃*



Prior Reaction Conditions



Current Reaction Conditions

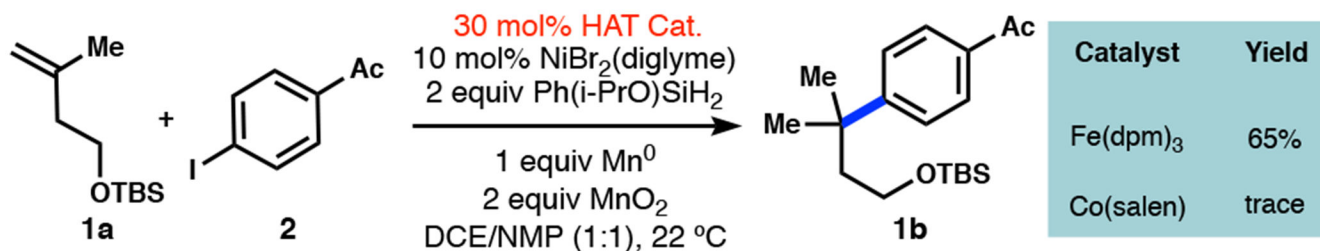


Figure 3. Comparison to our prior work with *Co(salen)* and our current work with *Fe(dpm)₃*: transmetalation vs free radical mechanism.

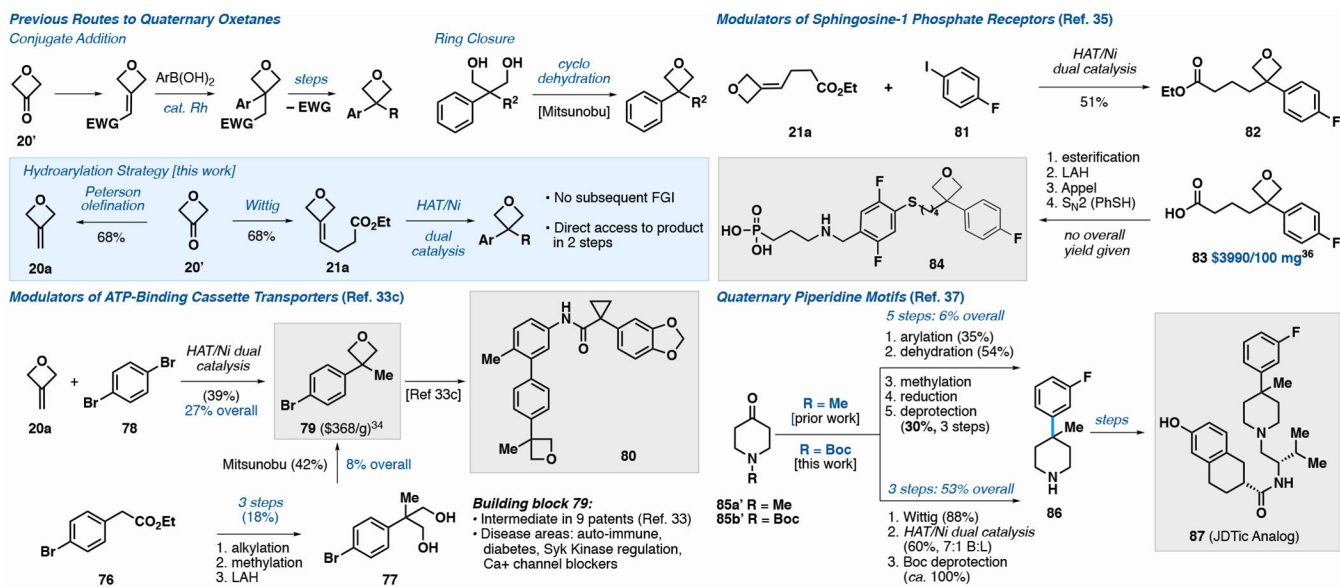
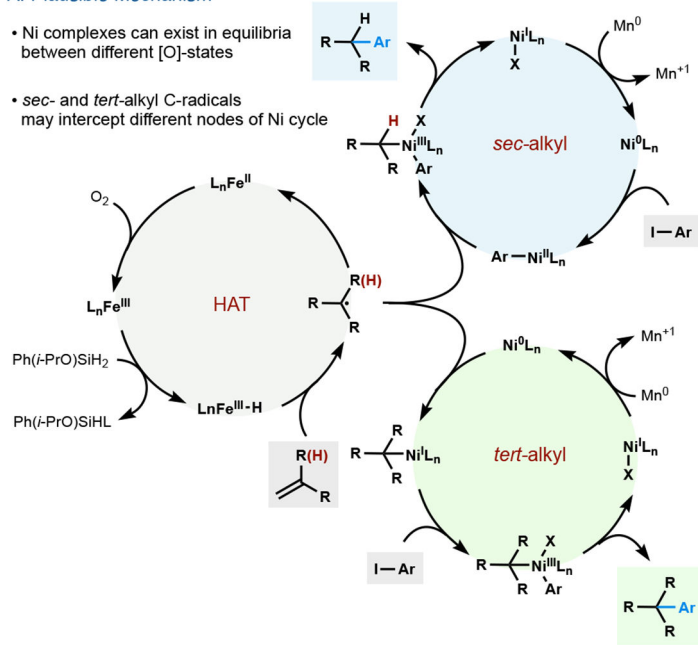


Figure 4. Application of Fe/Ni Dual catalysis to various biological intermediates containing oxetanes and piperidines.

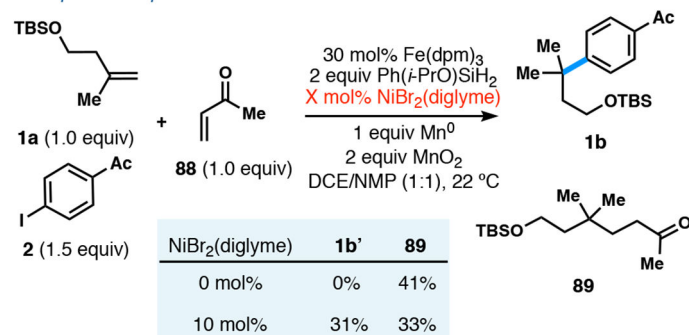
A. Plausible Mechanism

- Ni complexes can exist in equilibria between different [O]-states

- *sec*- and *tert*-alkyl C-radicals may intercept different nodes of Ni cycle



B. Competition Experiment with Giese Reaction



C. Radical Trapping with TEMPO

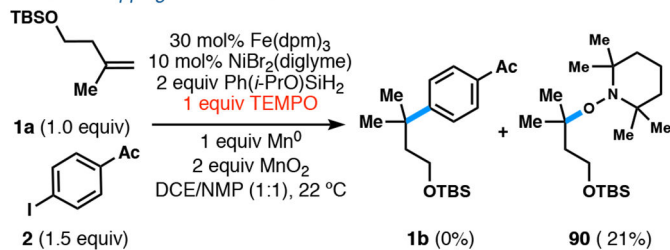
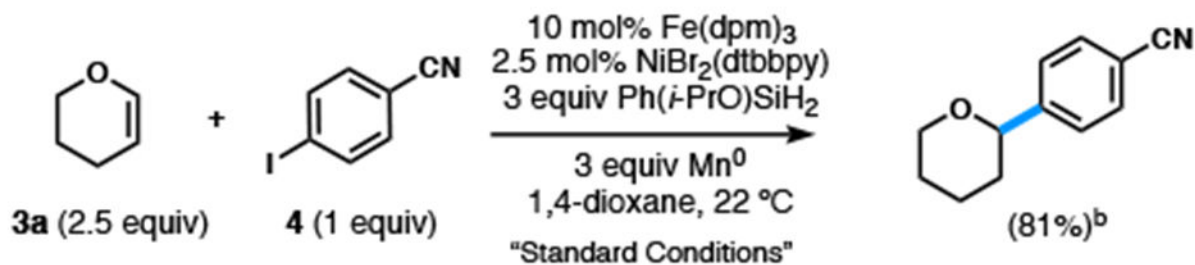


Figure 5.

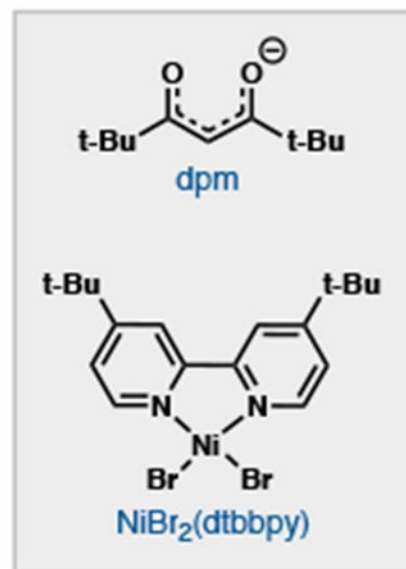
(A) Potential mechanism for *sec*- and *tert*-alkyl arylation. (B) Competition experiment to probe for intermediacy of radical reaction. (C) Radical trapping experiment with TEMPO.

Table 1.

Sec-alkyl Optimization



Entry	Deviation from "Standard Conditions"	Yield (%) ^a
1	Co(acac) ₂ instead of Fe(dpm) ₃	none
2	Mn(dpm) ₃ instead of Fe(dpm) ₃	<5
3	Fe(acac) ₃ instead of Fe(dpm) ₃	29
4	THF instead of 1,4-dioxane	24
5	PhSiH ₃ / <i>i</i> -PrOH	41 ^c
6	Under argon	9
7	ArBr instead of ArI	30
8	No NiBr ₂ (dtbbpy)	none
9	No Fe(dpm) ₃	none

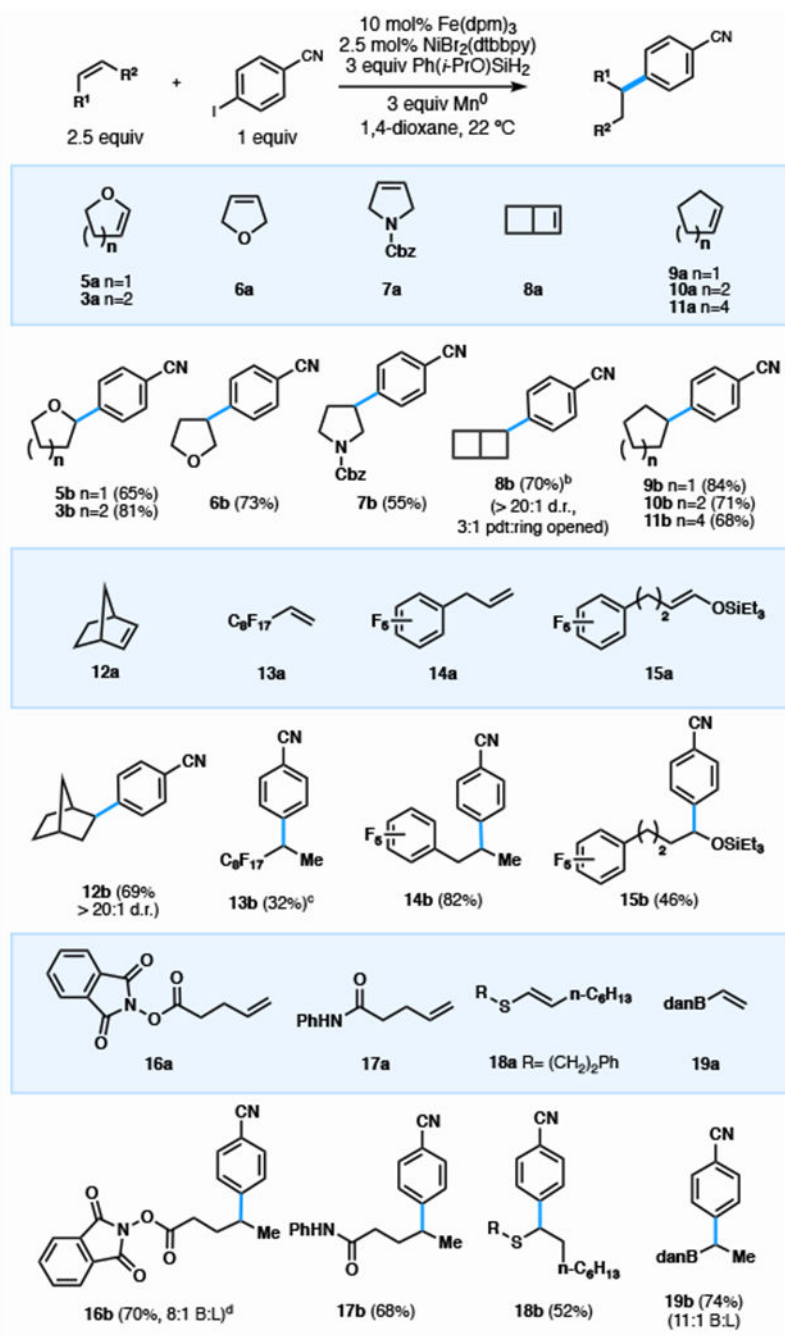


^a0.1 mmol scale, yield determined by FID using dodecane as an internal standard.

^b0.3 mmol scale, isolated yield.

^c3 equiv PhSiH₃, 6 equiv *i*-PrOH (anhydrous) instead of Ph(*i*-PrO)SiH₂.

Table 2.

Sec-alkyl Olefin Scope^a

^a0.3 mmol scale, isolated yield, reaction time: 12–48 h. 1 mL 1,4-dioxane, N₂ atmosphere for 2 h, then open to air. All substrates gave >20:1 branched:linear ratio except where noted

^bNMR yield.

^c 5 mol% NiBr₂(dtbbpy), 800 μL 1,4-dioxane.

^d 5 mol% NiBr₂(dtbbpy).

Author Manuscript

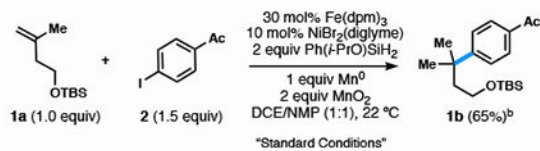
Author Manuscript

Author Manuscript

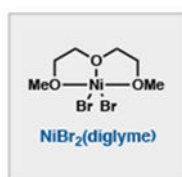
Author Manuscript

Table 3.

Formation of Quaternary Center Optimization



Entry	Deviation from "Standard Conditions"	Yield (%) ^a
1	10 mol% NiBr ₂ (dtbbpy)	none
2	No NMP	none
3	No MnO ₂	20
4	Under O ₂ instead of air	trace ^c
5	1 equiv H ₂ O	none
6	5 mol% NiBr ₂ (diglyme)	54
7	2 equiv Mn	43
8	1 equiv Ph(<i>i</i> -PrO)SiH ₂	28
9	No NiBr ₂ (diglyme)	none
10	No Fe(dpm) ₃	none

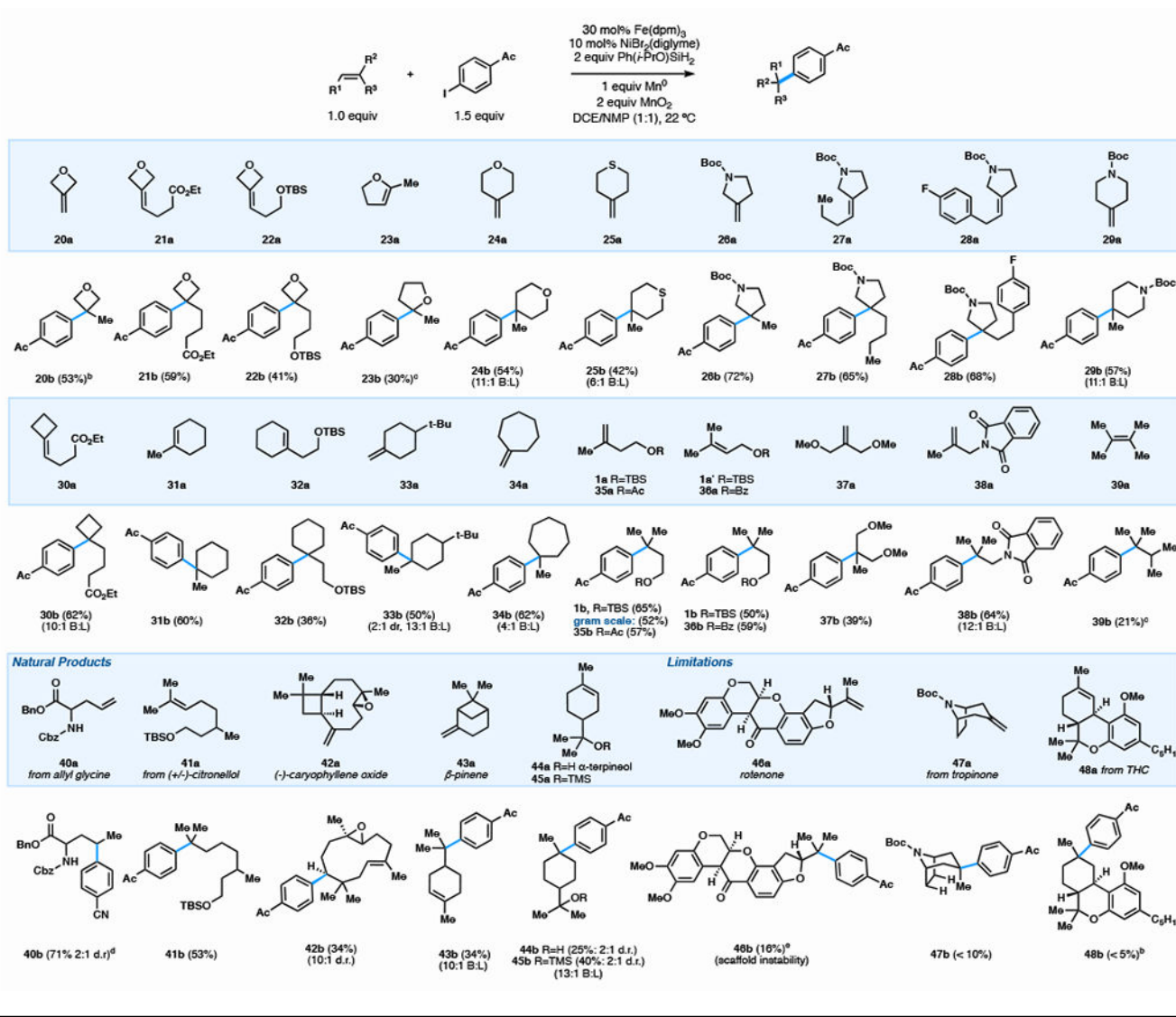


^a0.1 mmol scale, yield determined by FID using dodecane as an internal standard.

^b0.3 mmol scale, isolated yield.

^cUnder an O₂ balloon, the olefin was predominantly consumed to hydration via Drago—Mukaiyama Hydration.

Table 4.

Formation of Quaternary Centers: Olefin Scope^a

^a0.3 mmol scale, isolated yield, reaction time 16 h. 1.5 mL 1,2-DCE and 1.5 mL NMP. N₂ atmosphere for 1.5 h then open to air. All substrates gave >20:1 branched:linear (B:L) ratio except where notated

^b0.1 mmol scale, isolated yield.

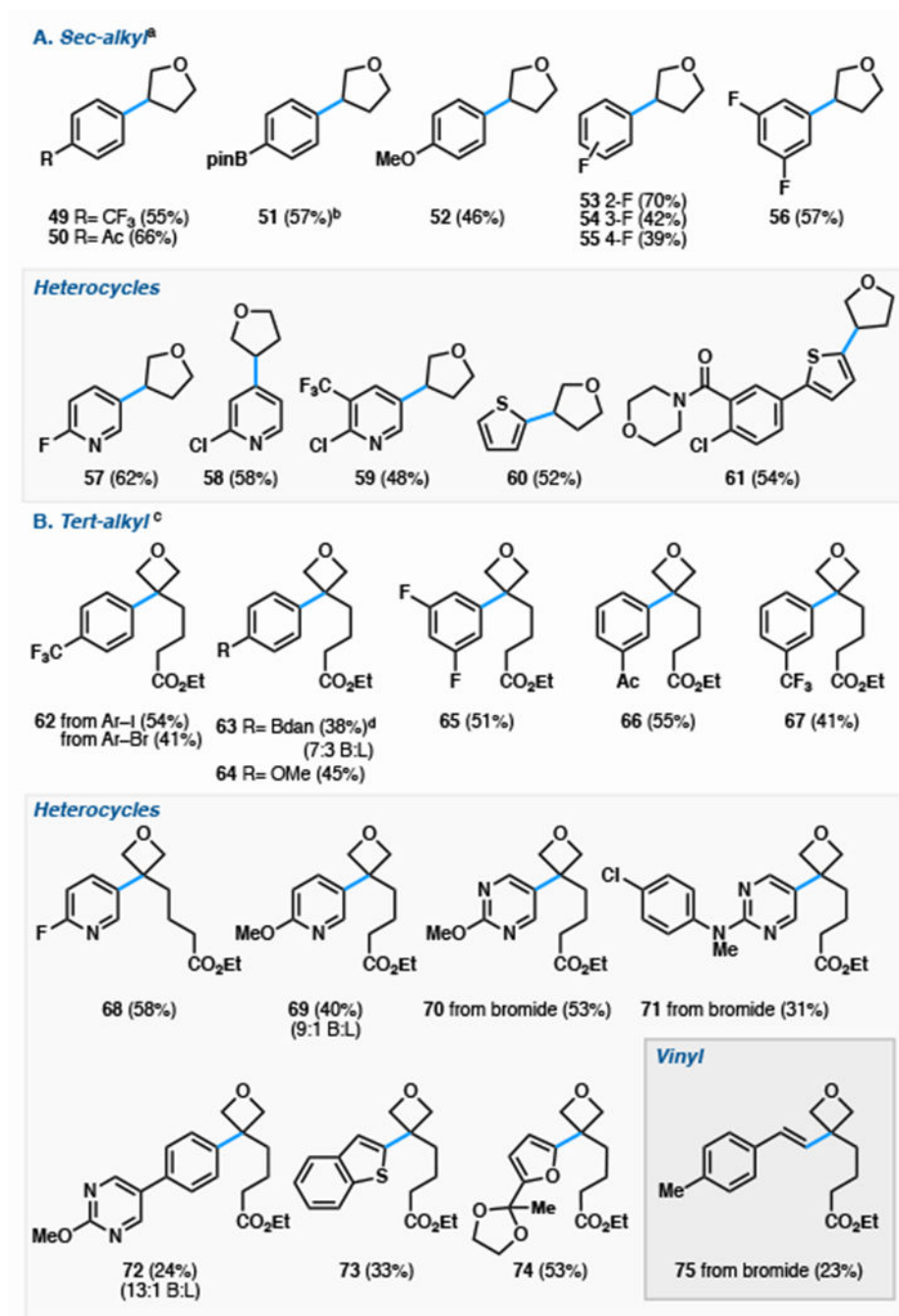
^crun under an air balloon.

^d0.3 mmol scale using reaction conditions from Table 2. Isolated yield.

^e0.1 mmol scale, Fe(dibm)₃ (50 mol%), NiBr₂(diglyme) (30 mol%), 2.5 h, NMR yield.

Table 5.

Aryl Halide Scope



A) Aryl halide scope for *sec*-alkyl conditions starting from olefin **6a**.

^a 0.3 mmol scale, isolated yield, reaction time: 12–48 h. 1 mL 1,4-dioxane, N₂ atmosphere for 2 h, then open to air. All substrates gave >20:1 branched:linear ratio except where noted

^b2:1 ratio of arylation at C3 vs C2.

(B) Aryl halide scope for *tert*-alkyl conditions using olefin **21a**.

^c0.3 mmol scale, isolated yield, reaction time 16 h. 1.5 mL 1,2-DCE and 1.5 mL NMP. N₂ atmosphere for 1.5 h then open to air.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript