Fe-Catalyzed Conjunctive Cross-Couplings of Unactivated Alkenes with Grignard Reagents

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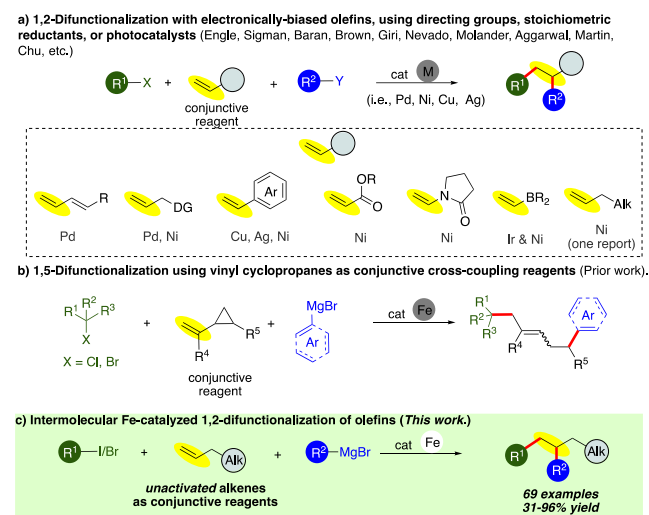
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ABSTRACT: A highly chemoselective iron-catalyzed three-component cross-coupling of unactivated olefins with alkyl halides (iodides and bromides) and sp2-hybridized Grignard reagents is reported. The reaction operates under fast turnover frequency and tolerates a diverse range of sp2-hybridized nucleophiles (electron-rich and electron-deficient (hetero)aryl, and alkenyl Grignard reagents), alkyl halides (tertiary alkyl iodides and bromides, and perfluorinated bromides), and unactivated olefins bearing diverse functional groups including tether alkenes, ethers, protected alcohols, aldehydes, and amines to yield the desired 1,2-alkylarylated products with high regiocontrol. Further, we demonstrate that this protocol is amenable for the synthesis of new (hetero)carbocycles including tetrahydrofurans and pyrrolidines via a three-component radical cascade cyclization/arylation that forges three new C-C bonds.

Olefins are ubiquitous in natural products and bioactive compounds and serve as versatile commodity feedstocks. 1,2-difunctionalization of olefins represents one of the most widely used strategies to build synthetic complexity in organic synthesis and serves as platform to introduce concepts of chemo-, regio-, and stereoselectivity.[1] Recently, there has been a surge in the development of three-component transition metal-catalyzed (TM) cross-couplings that employ olefins as conjunctive reagents because of their potential to rapidly increase diversity in a single step (**Scheme 1a**).[2, 3,4] However, selective transition metal-catalyzed three-component dicarbofunctionalization of *unactivated* alkenes is rare.[5] Moreover, despite the inherent attractive features of iron as a catalyst (Earth abundant, less toxic, inexpensive, and environmentally benign in comparison to Pd or Ni) in pharmaceutical settings,[6] *there are no general methods for iron-catalyzed three-component 1,2-dicarbofunctionalization of olefins*.[6,7,8,9,10,11,12,13] Recently, our group reported the use of strained *vinyl cyclopropanes* as conjunctive reagents protocol to promote a three-component Fe-catalyzed reaction using leading to *1,5-alkylarylation products* (**Scheme 1b**).[14,15] Unfortunately, despite numerous attempts, the 1,2-difunctionalization products were not observed, presumably due to much more rapid ring-opening of the incipient alkyl radical followed C-C bond formation. Herein, we report the first iron-catalyzed 3-component cross-coupling of *unactivated* alkenes with *both alkyl iodides and bromides* with sp2-hybridized Grignard nucleophiles leading to 1,2-dicarbofunctionalization of alkenes with broad scope and excellent regio- and chemoselectivity (**Scheme 1c**). Further, we applied this concept to develop a three-component radical alkylation/cyclization/arylation cascade leading to diverse (hetero)cyclic compounds. We anticipate that this report will lead to greater application of Fe as catalysts in three-component difunctionalization of olefins.

Scheme 1. Transition metal-catalyzed three-component difunctionalization of olefins

a) 1,2-Difunctionalization with electronically-biased olefins, using directing groups, stoichiometric reductants, or photocatalysts (Engle, Sigman, Baran, Brown, Giri, Nevado, Molander, Aggarwal, Martin, Chu, etc.).

b) 1,5-Difunctionalization using vinyl cyclopropanes as conjunctive cross-coupling reagents (Prior work).

c) Intermolecular Fe-catalyzed 1,2-difunctionalization of olefins (*This work*.)

*69 examples
31-96% yield*

As shown in Scheme 2, we hypothesize that alkyl halide **1** would engage with Fe species **A** to form the alkyl radical **int-1** and **B**.[12,13] Due to the high barrier associated for sterically hindered alkyl radicals and aryl iron **B** to undergo direct cross-coupling, we anticipate that the tertiary radical **int-1** would favor regioselective Giese addition to olefin **2** to form, in the absence of cyclopropyl groups, a transient secondary alkyl radical **int-2**.[16] Then the longer lived (persistent) aryl iron species can trap the less sterically hindered *2º alkyl radical* **int-2**, and undergo reductive elimination from **B'** to form the desired 1,2-difunctionalized conjunctive cross-coupled product and **C**. Finally, facile transmetallation with aryl Grignard **3** restarts the catalytic cycle.[17]

Recognizing that the success of the 3-component conjunctive cross-coupling hinges on driving the equilibrium towards **B'**, presumably by disfavoring the formation of **B** from tertiary alkyl radical addition of **int-1** to aryl iron **B**, we initiated our

studies under solvent-free conditions and at high concentration of

Scheme 2. Proposed pathway to access 1,2-dicarbofunctionalization of alkenes using iron catalysis.
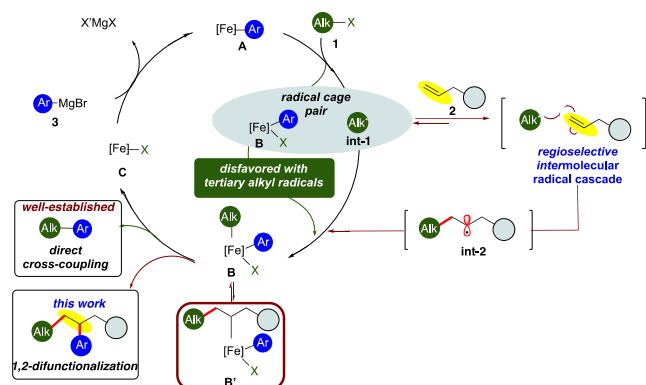
alkene. The challenge remains whether (a) we can drive the kinetics towards the Giese addition to **2**, (2) **int-2** is sufficiently long-lived to be intercepted by the persistent iron species **B**, and (c) **B'** will undergo reductive elimination to form the desired 1,2-difunctionalization product.

Table 1. Evaluation of Reaction Conditions[a]

| Entry	Deviations from above	Yield [%][b]
1	none	86
2	**L2** (20 mol %)	0
3	**L3** (20 mol %)	0
4	**L4** (20 mol %)	2
5	**L5** (20 mol %)	14
6	using Fe(OAc)$_2$ (5 mol %)	< 5
7	using FeBr$_2$ (5 mol %)	80
8	using Fe(OTf)$_2$ (5 mol %)	41
9[c]	in THF (0.2 mL)	83
10[c,d]	using Fe(acac)$_3$ (3 mol %) and **L1** (12 mol %)	90 (85)
11[c]	no **L1**	< 5
12[c]	no Fe(acac)$_3$ and no **L1**	0

[a]The reaction was performed with *tert*-butyl iodide **1** (0.1 mmol, 1.0 equiv), 4-phenyl-1-butene **2** (14 equiv; 1-1.3 equiv based on recovered starting material; See Supporting Information) and *meta*-methoxy phenyl Grignard **3** (1.4 equiv). Aryl Grignard **3** was added dropwise via syringe pump over 1 h. [b]The yield was determined by ^{1}H NMR using dibromomethane as internal standard. In parenthesis, isolated yield after column chromatography. [c]1.5 equiv of **3**. [d]0.20 mmol scale.

Initially, we elected to use *tert*-butyl iodide **1**, 4-phenyl-1-butene **2**, and *meta*-methoxy phenyl Grignard **3** as model substrates (**Table 1**). Gratifyingly, under our modified conditions for radical cross-coupling with vinyl cyclopropanes (i.e., using Fe(acac)$_3$ as precatalyst and 1,2-bis(dicyclohexylphosphino)ethane as ligand),[14a] we observed the formation of the desired 1,2-alkylaryl conjunctive cross-coupled product **4** in 86% yield and complete regioselectivity

with unactivated olefin **2** (Table 1, entry 1). Notably, other bisphosphine ligands commonly employed in direct Fe-catalyzed cross-coupling reactions with alkyl halides[10] significantly decrease the yield of the conjunctive cross-coupling (entries 2-5). Further, the use of iron precatalyst bearing strongly coordinating ligands inhibit the reaction (entry 6) while other precatalysts were less efficient (entries 7-8). Moreover, the use of THF as solvent had a minor effect on the overall efficiency of the conjunctive cross-coupling (entry 9). Finally, we could also perform the reaction in high yield under lower catalytic loading by increasing the amount of nucleophile (entry 10). Control experiments show that the Fe and ligand are both critical for the reaction (entries 11-12). For full details of reaction optimization and screening conditions, see Supporting Information.

With a set of optimized reaction conditions at hand, an exploration of the reaction scope and limitations of this bisphosphine iron-catalyzed 3-component cross-coupling was undertaken. As shown in Scheme 3, the reaction tolerated a wide range of electron-rich (e.g., **4**, **6**, **7**, **9**, **12**, **13**, **15**, **16**) and electron-deficient aryl Grignard nucleophiles (e.g., **5**, **8**, **11**, **14**, **17**) forming the desired 1,2-alkylaryl conjunctive cross-coupled products in high yield, typically. Further, various substituent patterns about the aryl nucleophile were tolerated including *meta* and *para* mono- and disubstituted aryl Grignard nucleophiles afforded the desired product in good yields. Importantly, vinyl Grignard reagents are also competent nucleophilic partners forming the regioselective 1,2-alkylvinyl product **18** in 41% yield. This represents the first example of transition-metal catalyzed 1,2-alkylvinyl functionalization of unactivated olefins. Unfortunately, sterically hindered Grignard reagents are not compatible reagents in this transformation presuemly due to the high energy to undergo inner-sphere reductive elimination.[11,12]

Scheme 3. Scope of Grignard Nucleophile on the 3-Component Conjunctive Cross-Coupling with Unactivated Alkenes[a]
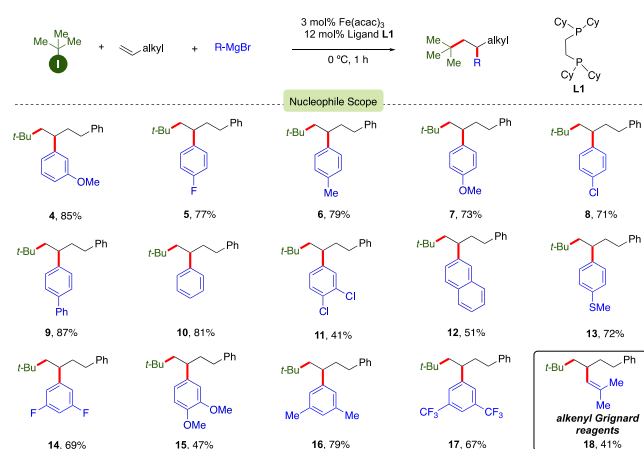
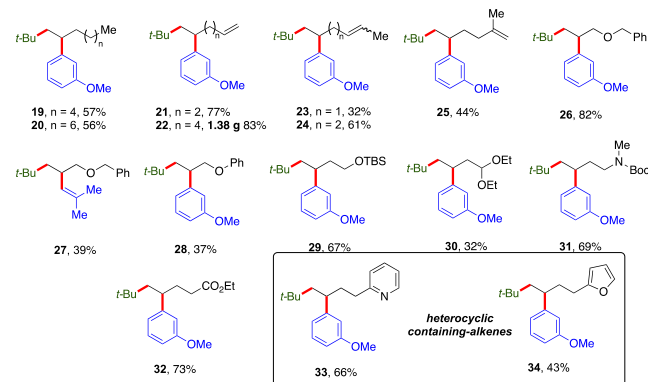[a]Unless otherwise stated, all reactions were under the optimized conditions (Table1, entry 10). Isolated yields.

Next, we explored the olefin scope using *tert*-butyl iodide **1** and *meta*-methoxy phenyl Grignard **3** as conjunctive cross-coupling partners (**Scheme 4**). In general, a wide range of unactivated olefinic partners were tolerated. Compatible conjunctive partners include olefins with tethered aliphatic chains (**19** and **20**), alkenes (**21–25**), alkoxy (**26–28**), protected alcohols (**29**) and aldehyde (**30**) and amine (**31**), esters (**32**),

and even pyridine (**33**) and furan (**34**) moieties giving the desired products in up to 83% yield. Importantly, this Fe-catalyzed three-component method provides unique reactivity with dienes. In particular, we found that the method is highly chemo- and regioselective for dienes (**21–22**) and less substituted alkene (**23–25**) without over difunctionalization (**23–25**) even in cases with identical alkene moieties (**21–22**). To showcase practical application of this method, we also scaled up the reaction that form the conjunctive cross-coupling **22** in 83% yield (1.38 g).

Scheme 4. Scope of Alkene on the Reaction

[Scheme 4: chemical structures of products 19–34]

19, n = 4, 57%
20, n = 6, 56%

21, n = 2, 77%
22, n = 4, **1.38 g** 83%

23, n = 1, 32%
24, n = 2, 61%

25, 44%

26, 82%

27, 39%

28, 37%

29, 67%

30, 32%

31, 69%

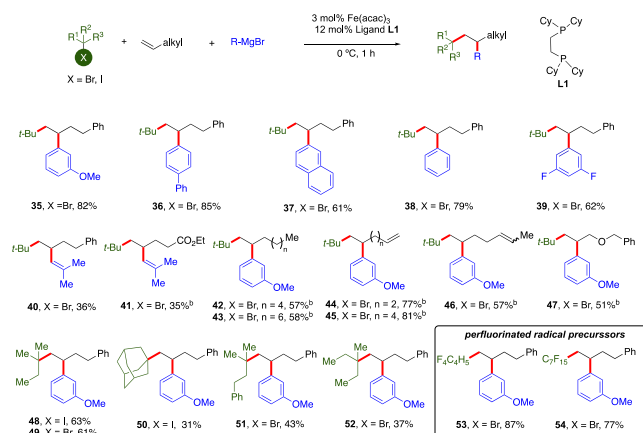32, 73%

heterocyclic containing-alkenes

33, 66%

34, 43%

aUnless otherwise stated, all reactions were under the optimized conditions (Table1, entry 10) in THF (0.2 mL). Isolated yields.

As shown in Scheme 5, contrary to current state-of-the-art TM-catalyzed three-component cross-couplings, this method tolerates a range of diverse radical precursors and operates under fast reaction times and low temperatures. Specifically, tertiary alkyl bromides also form the desired 1,2-alkylaryl cross-coupled products **35–47** with similar efficiency as alkyl iodides. These results represent the first examples of using alkyl bromides in a TM-catalyzed 3-component intermolecular 1,2-dicarbofunctionalization of unactivated olefins and can complement existing methods using reductive cross-couplings as reported by Nevado.[5] Furthermore, other tertiary alkyl iodides/bromides are compatible in this transformation yielding the desired products **48–52** in 31-63% yield. Finally, we also found that the much more reactive perfluororated *n*-alkyl radicals (from the corresponding alkyl bromides) were competent in this Fe-catalyzed three-component conjunctive cross-coupling reaction yielding the desired products **53–54** in 77-87% yield.

To expand the synthetic utility of this Fe-catalyzed 3-component conjunctive cross-coupling, we next explored the possibility to undergo a radical cascade cyclization/arylation with a series of 1,6-dienes leading to the formation of three carbon-carbon bonds in one synthetic step (**Scheme 6a**). We hypothesize that regioselective Giese addition to olefin will form the secondary alkyl radical intermediate **G•**. If the rates of Fe-arylation are slower than rate of ring-closing, then we should only observe ring-closed arylated product (e.g., **55**). However, if rate for Fe-arylation of **G•** is faster than rate of radical 5-*exo*-trig, then we should observe only the uncyclized product (i.e., **56**). As shown in Scheme 6a, we found that this method delivered the desired cyclic **55** in good yield (71%).
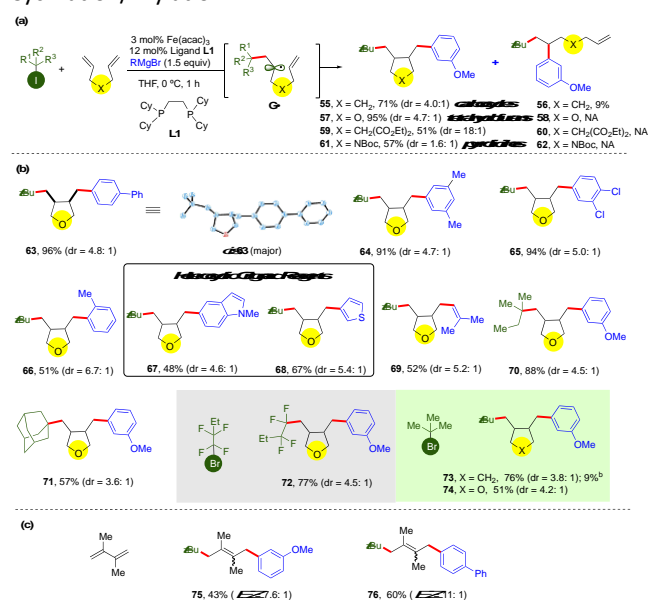
Scheme 5. Scope of Alkyl Halide on the Reaction

[Scheme 5: reaction conditions and product structures 35–54]

3 mol% Fe(acac)₃
12 mol% Ligand **L1**
0 °C, 1 h

X = Br, I

L1

35, X = Br, 82%

36, X = Br, 85%

37, X = Br, 61%

38, X = Br, 79%

39, X = Br, 62%

40, X = Br, 36%

41, X = Br, 35%[b]

42, X = Br, n = 4, 57%[b]
43, X = Br, n = 6, 58%[b]

44, X = Br, n = 2, 77%[b]
45, X = Br, n = 4, 81%[b]

46, X = Br, 57%[b]

47, X = Br, 51%[b]

48, X = I, 63%
49, X = Br, 61%

50, X = I, 31%

51, X = Br, 43%

52, X = Br, 37%

perfluorinated radical precurssors

53, X = Br, 87%

54, X = Br, 77%

aUnless otherwise stated, all reactions were under the optimized conditions (Table1, entry 10). bIn THF (0.2 mL). Isolated yields.

We also observed the uncyclized product **56**, presumably from direct arylation of **G•**, albeit in low yield (9%). Notably, incorporation of heteroatoms (O or N) or addition of diester linkage yield exclusive formation of the cyclic product. DFT calculations [UPBEPBE-D3/6-311+G(d,p)-CPCM(THF)//UB3LYP/6-31G(d)] using *t*Bu radical and 1,6-heptadiene predict a barrier of 13.2 kcal/mol for irreversible Giese addition leading to **G•**, 5.2 kcal/mol downhill in energy. In agreement with experiment, **G•** preferentially favors radical cyclization leading to *cis* isomer while (irreversible) radical cyclization leading to *trans* isomer is only 1.2 kcal/mol higher in energy. However, consistent with experiment, the rates for radical cyclization for X=O substituted diene are faster and the energy difference

Scheme 6. Scope and Energetics for Radical Cascade Cyclization/Arylation.

[Scheme 6: (a), (b), (c) reaction schemes and product structures 55–76]

(a)

3 mol% Fe(acac)₃
12 mol% Ligand **L1**
RMgBr (1.5 equiv)
THF, 0 °C, 1 h

L1

55, X = CH₂, 71% (dr = 4.0:1)
57, X = O, 95% (dr = 4.7: 1)
59, X = CH₂(CO₂Et)₂, 51% (dr = 18:1)
61, X = NBoc, 57% (dr = 1.6: 1)

56, X = CH₂, 9%
58, X = O, NA
60, X = CH₂(CO₂Et)₂, NA
62, X = NBoc, NA

(b)

63, 96% (dr = 4.8: 1)

cis-**63** (major)

64, 91% (dr = 4.7: 1)

65, 94% (dr = 5.0: 1)

66, 51% (dr = 6.7: 1)

67, 48% (dr = 4.6: 1)

68, 67% (dr = 5.4: 1)

69, 52% (dr = 5.2: 1)

70, 88% (dr = 4.5: 1)

71, 57% (dr = 3.6: 1)

72, 77% (dr = 4.5: 1)

73, X = CH₂, 76% (dr = 3.8: 1); 9%[b]
74, X = O, 51% (dr = 4.2: 1)

(c)

75, 43% (E/Z 7.6:1)

76, 60% (E/Z 11: 1)

aUnless otherwise stated, all reactions were under the optimized conditions (Table1, entry 10) in THF (0.2 mL). Isolated yields. bYield of acyclic/arylation product.

between *cis* and *trans* radical cyclization is much higher (1.7 kcal/mol; See Supporting Information). Given the prevalence of saturated heterocyclic compounds (tetrahydrofurans and pyrrolidines) in pharmaceuticals, we used oxygen-substituted diene as model compound to explore the reaction scope of this

Fe-catalyzed three-component radical cascade cyclization/arylation (**Scheme 6b**). As shown in Scheme 6b, this reaction is very robust with aryl Grignard nucleophiles forming the desired products **63**–**65** in excellent yields, and *cis*-isomer is the major product (crystal structure determination of **63**). The use of sterically hindered, heteroaryl or vinyl nucleophiles were also tolerated (**66**–**69**). Moreover, other tertiary alkyl iodides, perfluorinated alkyl and tertiary bromides also work in this transformation forming the radical cascade cyclization/arylation products **70**–**74** in 51-88% yield. Finally, the method is regioselective for addition to conjugated 1,3-diene to form 1,4-alkylaryl products **75**–**76** in good yield (up to 11: 1 *E:Z*, **Scheme 6c**).

In summary, we have developed a 3-component 1,2-alkylarylation of unactivated olefins using a bisphosphine iron as catalyst. Further, we demonstrated that this manifold can forge three carbon-carbon bonds in one synthetic step leading a diverse set of carbo- and hereterocyclic compounds. We expect that this method be adapted by the pharmaceutical community for the synthesis of bioactive products, fine chemicals, and late-stage diversification of promising leads. Although this method is currently limited to large excess of olefin, preliminary experiments show that the use of activated alkenes could circumvent the need to excess alkene and will be reported in due course.[19] Future work is ongoing to elucidate the mechanism of this transformation using computational, experimental, and spectroscopic tools. We are actively perusing other 3-component Fe-catalyzed reactions with other π-acceptors, nucleophiles, and electrophiles including asymmetric variants and will report in due course.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org. Experimental details, characterization data, spectral data, and computational results.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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