ChemComm

Fe-Catalyzed Dicarbofunctionalization of Electron-Rich Alkenes with Grignard Reagents and (Fluoro)Alkyl Halides

Journal:	*ChemComm*
Manuscript ID	CC-COM-08-2021-004619.R1
Article Type:	Communication

COMMUNICATION

Fe-Catalyzed Dicarbofunctionalization of Electron-Rich Alkenes with Grignard Reagents and (Fluoro)Alkyl Halides

Received 00th January 20xx,
Accepted 00th January 20xx

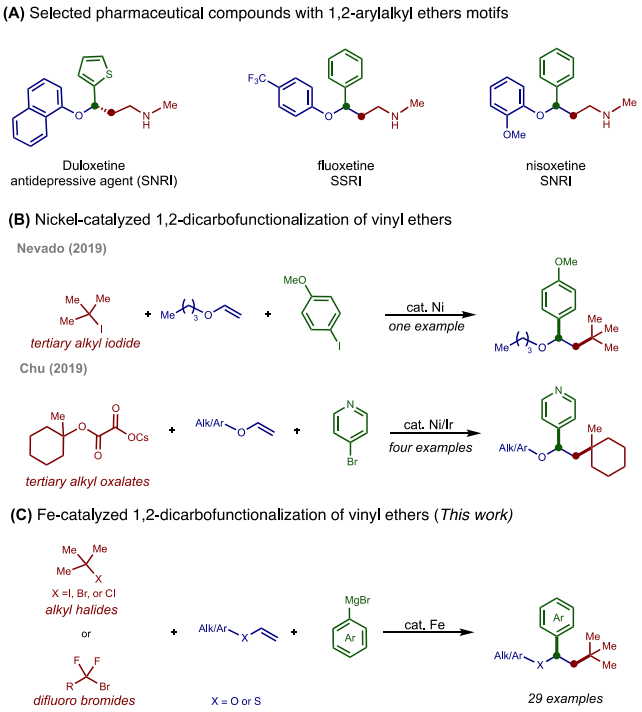
DOI: 10.1039/x0xx00000x

Madeline E. Rotella,[#a] Dinabandhu Sar,[#ab] Lei Liu,[ab] and Osvaldo Gutierrez*[ab]

An iron-catalyzed regioselective dicarbofunctionalization of electron-rich alkenes is described. In particular, aryl- and alkyl vinyl ethers are used as effective linchpins to couple alkyl or (fluoro)alkyl halides and sp^2-hybrized Grignard nucleophiles. Preliminary results demonstrate ability to engage thioethers as lynchpins and control enantioselectivity in these transformations, an area which is largely unexplored for iron-catalyzed three-component cross-coupling reactions.

Alkenes are prevalent motifs in natural products, pharmaceuticals, and represent valuable building blocks in organic synthesis (Scheme 1A).[1] Recently, the difunctionalization of alkenes has attracted interest from the pharmaceutical community due to the potential for cost-effective, rapid, and modular synthesis of complex scaffolds.[2] In this vein, transition metal-catalyzed three-component cross-coupling reactions have been used to selectively install functional groups across the alkene moiety, thereby building molecular complexity in one step.[3,4,5,6,7,8,9,10,11] However, much of the efforts in the development of these reactions has been spent on electron-deficient alkenes and alkenes bearing directing groups to control reactivity and selectivity.[12] As such, catalytic methods for the selective 1,2-dicarbofunctionalization of electron-rich alkenes are scarce[13] and most are limited to the use of nickel or dual nickel/photoredox as catalysts (Scheme 1B) .[14,15,16,17]

Seeking to continue to expand the utility of Fe-catalyzed multicomponent cross-couplings,[18] we hypothesized that bisphosphine-iron complexes could serve as cost-effective, practical, and sustainable catalysts to promote regioselective 1,2-dicarbofunctionalization of electron-rich vinyl ethers and, if successful, could complement existing nickel and dual nickel/photoredox methods. Herein we report a three-component iron-catalyzed regioselective dicarbofunctionalization of aryl- and alkyl vinyl ethers that engage both alkyl halides and (fluoro)alkyl bromides with sp^2-hybrized Grignard reagents (Scheme 1C). We expect that this method will find applications in the cost-effective synthesis of analogues of antidepressive drugs and, in particular, in the introduction of fluorine atoms into larger scaffolds with applications in pharmaceutical chemistry (Scheme 1A).[19]



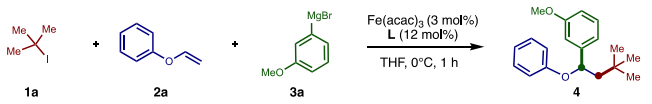
Scheme 1 Transition-metal catalyzed 1,2-dicarbofunctionalization of electron-rich alkenes and its pharmaceutical relevance.

Recently we developed an iron-catalyzed three-component radical cross-coupling using strain-release vinyl cyclopropanes as the conjunctive reagent under exceptionally rapid reaction times (< 1 hr).[18a,18b] Further, the reaction scope was extended to the use of unactivated alkenes without the use of directing groups.[18c] However, the main drawback of this method is the need for high concentration of alkene (i.e., as solvent) to drive the equilibrium towards the Giese addition adduct (i.e., alkyl radicals) for effective and subsequent

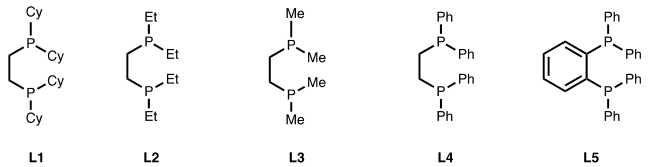
[a] *Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States.*
[b] *Department of* Chemistry, Texas A&M University, *College* Station, Texas 77843, *United States. Email: og.labs@tamu.edu*
[#] M. E. R. and D. S. contributed equally.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

cross-coupling with the presumed iron-aryl species. We hypothesized that Giese addition of alkyl radicals to vinyl ethers will lead to more stable α-oxy radicals and provide the driving force to ensure subsequent cross-coupling.

Table 1 Evaluation of Reaction Conditions



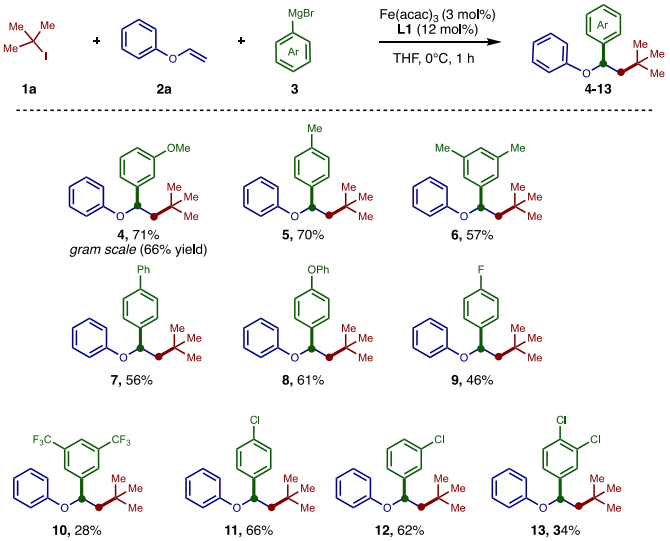
Entry	Deviations from standard conditions	NMR Yield [%]
1	**L1** (12 mol%)	75
2	**L2** (12 mol%)	0
3	**L3** (12 mol%)	0
4	**L4** (12 mol%)	45
5	**L5** (12 mol%)	0
6	using $FeBr_2$ (3 mol%)	63
7	using $FeCl_3$ (3 mol%)	60
8	using $Fe(OTf)_2$ (3 mol%)	63
9	neat	67
10	no **L1**	0
11	No $Fe(acac)_3$ and no **L1**	0



The reaction was performed with *tert*-butyl iodide **1a** (0.1 mmol, 1.0 equiv), phenyl vinyl ether **2a** (0.4 mmol, 4 equiv.) and 3-methoxyphenyl Grignard **3a** (0.15 mmol, 1.5 equiv.). Aryl Grignard **3a** was added dropwise via syringe pump over 1 h. The yield was determined by ^{1}H NMR using dibromomethane as internal standard.

To test this hypothesis, we began our study of iron-catalyzed dicarbofunctionalization of vinyl ethers with the commercially available phenyl vinyl ether as the alkene linchpin (Table 1). To our delight, under excess alkene (14 equiv.), the desired three-component cross-coupling product **4** was formed with a 1,2-addition of the aryl Grignard and the alkyl group in high yield (89%; Table S1, entry 1). However, we sought to lower our alkene loading from 14 equivalents to increase the practical application of this method. Notably, we found that 4 equiv. of phenyl vinyl ether also gave reasonably high yield (75%; Table 1, entry 1) and we were able to recover 2.4 equiv. of the alkene after workup. Overall, under these conditions, effectively only 1.6 equiv. of phenyl vinyl ether is consumed in the reaction. Further, screening of various iron salts and ligands did not improve the yields (Table 1). Finally, control experiments verified that solvent, ligand, and iron catalyst were essential to the reactivity (see Tables S1 – S3 in the Supporting Information for full details of the reaction optimization.)

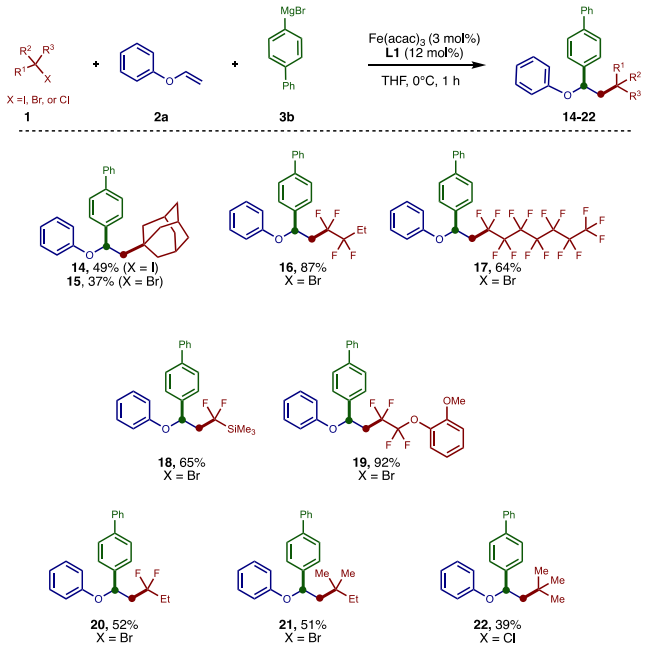
With the optimized conditions identified (Table 1, entry 1), we proceeded to study the generality of this iron-catalyzed dicarbofunctionalization reaction. Initially, we focused on examining the diversity of Grignard nucleophiles for this reaction (Scheme 2). Electron-rich Grignard reagents afforded products (**4**-**8**) in good yield while mildly electron-deficient Grignard reagents were tolerated as well, giving products (**11**, **12**) in moderate yields. Notably, electron-poor Grignard reagents gave products (**9,10,13**) albeit in lower yields. Although *meta*- and *para*-substituted Grignard reagents alike afforded products, *ortho*-methoxy Grignard reagent was not compatible, presumably due to the increased steric hindrance between the *ortho*-substituent and the incipient alkyl component. Finally, to demonstrate the scalability of the method, we prepared 1.02 g of compound **4** (66% yield; 3.59 mmol).



Scheme 2 Scope of Grignard nucleophile in the 3-component cross-coupling with *tert*-butyl iodide and phenyl vinyl ether. All reactions were performed under the optimized conditions (Table 1, entry 1) using 0.2 mmol *tert*-butyl iodide. Isolated yields are reported.

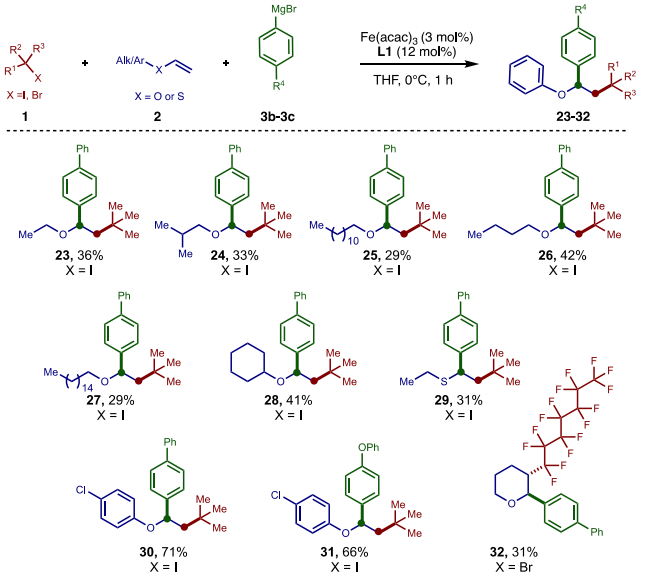
With the scope of Grignard reagent explored, the alkyl halide scope was then investigated (Scheme 3). In addition to the *tert*-butyl iodide used during the reaction screening, we found that 1-bromo- and 1-iodoadamantane (**14, 15**) and fluoroalkyl halides (**16**-**20**) were compatible in this transformation. Given that ~20% of drugs on the market contain at least one fluorine atom, this method shows

promise for applications in pharmaceutical settings.[20] In addition, 2-bromo-2-methylbutane successfully gave product in moderate yield (**21**, 51%). Finally, to highlight potential applications of an alkyl chloride as a viable radical precursor in multicomponent cross-coupling reactions, we used *tert*-butyl chloride as the alkyl halide and, gratifyingly, obtained product **22** in moderate yield (39%), albeit lower than when *tert*-butyl iodide was used as the alkyl halide (**7**, 56%, Scheme 2).



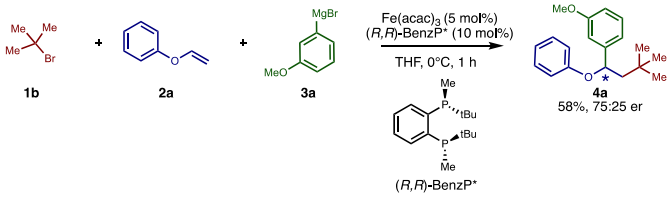
Scheme 3 Scope of alkyl halides in the 3-component cross-coupling with phenyl vinyl ether and 4-biphenylmagnesium bromide **3b**. All reactions were performed under the optimized conditions (Table 1, entry 1) using 0.2 mmol alkyl halide. Isolated yields are reported.

Finally, the alkene substrate scope was investigated (Scheme 4). Overall, attempts to extend the reaction to linear and branched alkyl vinyl ethers were modestly successful, giving products (**23-28**) in 29-42% yield. These results show that alkyl vinyl ethers, in addition to aryl vinyl ethers (**30, 31**) can function as effective linchpins in this three-component reaction. To highlight the potential expansion to thioethers, we used vinyl ethyl thioether as alternative π-acceptor and were pleased to observe the desired product in modest yield (**29**). Interestingly, even the internal alkene 3,4-dihydro-2*H*-pyran reacted in this method to give a moderate yield of product **32** as the *trans* isomer, as determined by NOESY (see Figure S4). The ability of this reaction to functionalize internal vinyl ethers opens the possibility for this method to be used in the formation of *C*-aryl glycosides from carbohydrate derivatives, thereby expanding the utility of this reaction. In aim to improve practicality of this method, we tested other vinyl ethers with more easily removed protecting groups but unfortunately these were not compatible in the reaction (see Figures S1 – S3 in the Supporting Information for full details).



Scheme 4 Scope of vinyl ethers in the 3-component conjunctive cross-coupling with alkyl halides and 4-biphenylmagnesum bromide **3b** or 4-phenoxyphenylmagnesum bromide **3c**. All reactions were performed under the optimized conditions (Table 1, entry 1) using 0.2 mmol of alkyl halide. Isolated yields are reported.

Finally, using optimized reaction conditions, preliminary results show the potential for an enantioselective variant of this transformation (Scheme 5 and Table S4 in the Supporting Information). The development of enantioselective three-component radical cross-coupling reactions remains a considerable challenge in the field and currently is being pursued in our laboratories.[21]



Scheme 5 Preliminary results on the asymmetric version of the 3-component conjunctive cross-coupling. The given yield is an isolated yield and the enantiomeric ratio was determined by chiral HPLC, both determined as an average of the results from four trials.

In summary, we have developed an iron-catalyzed regioselective 1,2-dicarofunctionalization of electron-rich alkenes with (fluoro)alkyl halides and aryl Grignard reagents. This reaction successfully gives product with both electron-donating aryl Grignard reagents and mildly electron-withdrawing aryl Grignard reagents. Further, we have shown that this method functionalizes both aryl and alkyl vinyl ethers. Notably, this method can introduce fluoroalkyl groups to a vinyl ether in a one-step synthesis, whereby molecular complexity for pharmaceutical applications can be rapidly increased. Ongoing work on the asymmetric variant of this reaction is currently underway in our laboratory and will be reported in due course.

This research was supported by the NSF (CAREER 1751568) and by the NIGMS of the NIH (R35GM137797).

There are no conflicts to declare.

References

X. Qi and T. Diao. *ACS Catal.* **2020**, *10*, 8542–8556.

[2] H. Cao, H. Liu, and A. Domling. *Chem. Eur. J.* **2010**, *16*, 12296–12298.

[3] (a) J. Derosa, V. T. Tran, V. A. van der Puyl, and K. M. Engle. *Aldrichimica Acta*, **2018**, ***51*, 21–32**. (*b*) R. Giri and S. KC. *J. Org. Chem.* **2018**, ***83***, 3013–3022. (c) L. Liao, R. Jana, K. B. Urkalan, and M. S. Sigman. *J. Am. Chem. Soc.*, **2011**, ***133***, 5784–5787. (*d*) A. García-Domínguez, Z. Li, and C. Nevado. *J. Am. Chem. Soc.*, **2017**, *139*, 6835–6838.

[4] H. Tu, F. Wang, L. Huo, Y. Li, S. Zhu, X. Zhao, H. Li, F. Qing, and L. Chu. *J. Am. Chem. Soc.* **2020**, *142*, 9604–9611.

[5] M. Yan, J. C. Lo, J. T. Edwards, and P. S. Baran. *J. Am. Chem. Soc.* **2016**, *138*,12692–12714.

[6] M. W. Campbell, J. S. Compton, C. B. Kelly, and G. A. Molander. *J. Am. Chem. Soc.* **2019,** *141*, 20069–20078.

[7] T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, and P. S. Baran. *Science* **2016**, *352*, 801–805.

[8] P. Basnetm, S. KC, R. K. Dhungana, B. Shrestha, T. J. Boyle, and R. Giri. *J. Am. Chem. Soc.* **2018**, *140*, 15586–15590.

[9] For representative examples of Pd and Ni catalyzed conjunctive cross-couplings, refer to the following. (a) G. J. Lovinger and J. P. Morken. *J. Am. Chem. Soc*. **2017**, *139*, 17293–17296. (b) J. Derosa, R. Kleinmans, V. T. Tran, M. K. Karunananda, S. R. Wisniewski, M. D. Eastgate, and K. M. Engle. *J. Am. Chem. Soc*. **2018**, *140*, 17878–17883. (c) G. J. Lovinger, M. D. Aparece, and J. P. Morken. *J. Am. Chem. Soc*. **2017**, *139*, 3153–3160**.** (d) E. K. Edelstein, S. Namirembe, and J. P. Morken. *J. Am. Chem. Soc.* **2017**, *139*, 5027–5030. (g) L. Wu, F. Wang, X. Wan, D. Wang, P. Chen, and G. Liu. *J. Am. Chem. Soc.* **2017**, *139*, 2904–2907. (h) J. Lin, T. Li, J. Liu, G. Jiao, Q. Gu, J. Cheng, Y. Guo, X. Hong, and X. Liu. *J. Am. Chem. Soc.* **2019**, *141,* 1074–1083. (i) A. A. Kadam, T. L. Metz, Y. Qian, and L. M. Stanley. *ACS Catal.* **2019,** *9,* 5651–5656. (j) X. Wang, X. Lu, S. He, and Y. Fu. *Chem. Sci.* **2020,** *11,* 7950–7956. (k) Y. Zhang, G. Chen, and D. Zhao. *Chem. Sci.* **2019,** *10,* 7952–7957.

[10] D. Ni and M. K. Brown. *ACS Catal.* **2021**, *11*, 1858–1862.

[11] S. Xu, H. Chen, Z. Zhou, and W. Kong. *Angew. Chem. Int. Ed.* **2021**, *60*, 7405–7411.

[12] W. Shu, A. García-Domínguez, M. T. Quiros, R. Mondal, D. J. Cardenas, and C. Nevado. *J. Am. Chem. Soc*. **2019**, *141*, 13812–13821.

[13] X. Qi and T. Diao. *ACS Catal.* **2020,** *10,* 8542–8556.

[14] (a) B. A. Granger, Z. Wang, K. Kaneda, Z. Fang, and S. F. Martin. *ACS Comb. Sci.* **2013**, *15*, 379–386. (b) T. Li, K. Liang, Y. Zhang, D. Hu, Z. Ma, and C. Xia. *Org. Lett.* **2020**, *22*, 2386−2390. (c) Q. Wang, Y. Qu, H. Tian, Y. Liu, H. Song, and Q. Wang. *Chem. Euro. J.* **2019**, *25*, 8686–8690.

[15] L. Guo, H. Tu, S. Zhu, L. Chu. *Org. Lett.,* **2019**, *21*, 4771–4776.

[16] (a) A. García-Domínguez, R. Mondal, and C. Nevado. *Angew. Chem. Int. Ed.*, **2019**, *58*, 12286 – 12290. (b) W. Shu, A. García-Domínguez, M. T. Quiros, R. Mondal, D. J. Cardenas, and C. Nevado. *J. Am. Chem. Soc*. **2019**, *141*, 13812–13821.

[17] J. Derosa, O. Apolinar, T. Kang. V. T. Tran, and K. M. Engle. *Chem. Sci.,* **2020**, *11*, 4287–4296.

[18] (a) L. Liu, W. Lee, M. Yuan, C. Acha, M. B. Geherty, B. Williams, and O. Gutierrez. *Chem. Sci.,* **2020**, *11*, 3146–3151. (b) L. Liu, W. Lee, J. Zhou, S. Bandyopadhyay, and O. Gutierrez. *Tetrahedron*, **2019**, *75*, 129–136. (c) L. Liu, W. Lee, C. R. Youshaw, M. Yuan, M. B. Geherty, P. Y. Zavalij, and O. Gutierrez, O. *Chem. Sci.* **2020**, *11*, 8301–8305.

[19] I. Bauer and H. Knölker. *Chem. Rev.* **2015**, *115*, 3170–3387.

[20] (a) J. Wang, M. Sańchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, and H. Liu. *Chem. Rev.* **2014**, *114*, 2432−2506. (b) C. M. Hong, A. M. Whittaker, and D. M. Schultz. *J. Org. Chem.* 2021, **86**, 3999–4006.

[21] H. Tu, F. Wang, L. Huo, Y. Li, S. Zhu, X. Zhao, H. Li, F. Qing, and L. Chu. *J. Am. Chem. Soc*. **2020**, *142*, 9604–9611.