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Fe-Catalyzed dicarbofunctionalization of electron-rich alkenes with Grignard reagents and (fluoro)alkyl halides†

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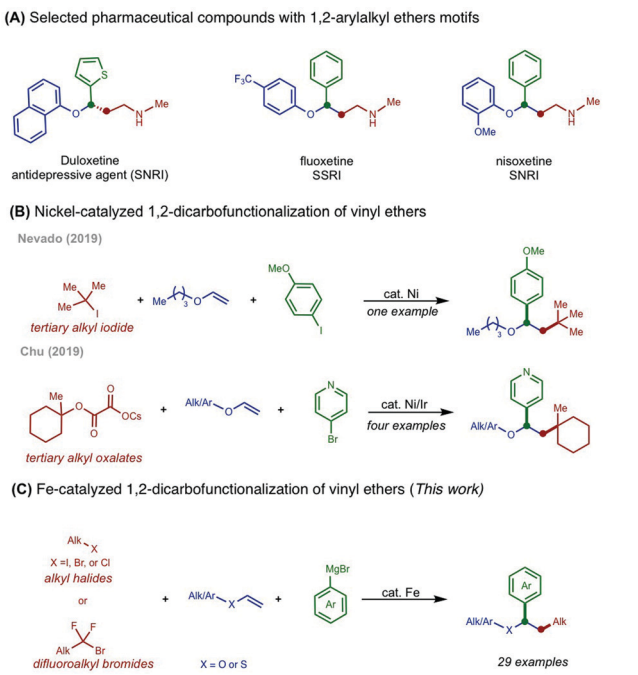
An iron-catalyzed regioselective dicarbofunctionalization of electron-rich alkenes is described. In particular, aryl- and alkyl vinyl ethers are used as effective linchpins to couple alkyl or (fluoro)alkyl halides and sp^2-hybridized Grignard nucleophiles. Preliminary results demonstrate the ability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

Alkenes are prevalent motifs in natural products and pharmaceuticals, and are valuable building blocks in organic synthesis.[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.[3–11] 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 the reactivity and selectivity.[12] As such, catalytic methods for the selective 1,2-dicarbofunctionalization of electron-rich alkenes, which could deliver straightforward access to complex compounds (Scheme 1A), are scarce[13] and most of them are limited to the use of nickel or dual nickel/photoredox as catalysts (Scheme 1B).[14–17]

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-hybridized 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]

Recently we developed an iron-catalyzed three-component radical cross-coupling reaction using strain-release vinyl cyclopropanes as the conjunctive reagent under exceptionally rapid reaction times (<1 h).[18a,b] Furthermore, the reaction scope was



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

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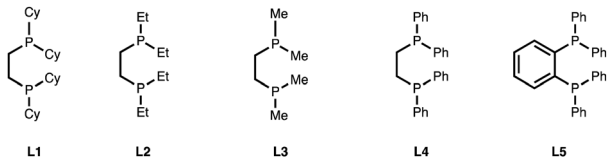
Table 1 Evaluation of reaction conditions

1a 2a 3a 4

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



L1 L2 L3 L4 L5

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* a syringe pump for 1 h. The yield was determined by ^{1}H NMR using dibromomethane as an internal standard.

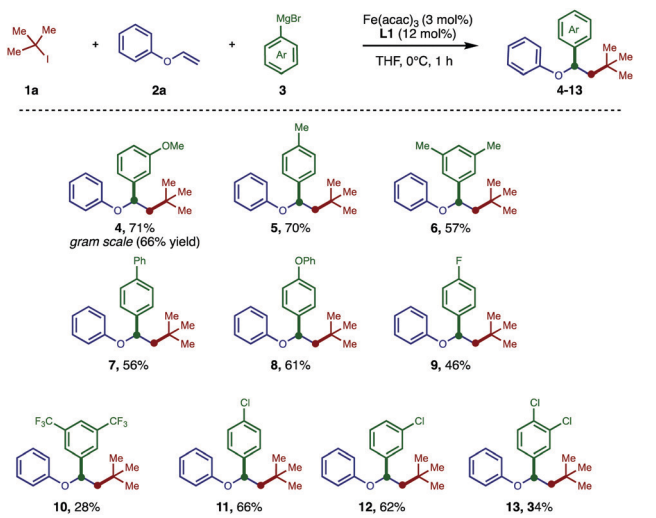
extended to the use of unactivated alkenes without the use of directing groups.[18c] However, the main drawback of this method is the need for a high concentration of alkene (*i.e.*, as solvent) to drive the equilibrium towards the Giese addition adduct (*i.e.*, alkyl radicals) for effective and subsequent cross-coupling with the presumed iron-aryl species. We hypothesized that the 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.

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, with excess alkene (14 equiv.), the desired three-component cross-coupling product **4** was formed with the 1,2-addition of the aryl Grignard and the alkyl group in high yields (89%; Table S1, entry 1, ESI†). 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 a 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. Furthermore, screening of various iron salts and ligands did not improve the yields (Table 1). Finally, control experiments verified that the solvent, ligand, and iron catalyst were essential to the reactivity (see Tables S1–S3 in the ESI† for full details of the reaction optimization).

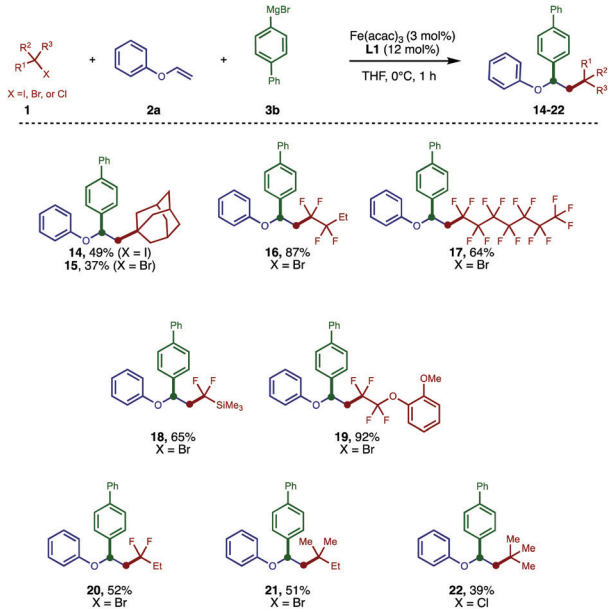
With the optimized conditions identified (Table 1, entry 1), we proceeded to study the generality of this iron-catalyzed dicarbofunctionalization reaction. Initially, we focused on examining the diversity of Grignard nucleophiles for this reaction (Scheme 2). Electron-rich Grignard reagents afforded products (**4–8**) in good yields 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, the *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).

With the scope of the Grignard reagent explored, the alkyl halide scope was then investigated (Scheme 3). In addition to the *tert*-butyl iodide used during reaction screening, we found that 1-iodo- and 1-bromoadamantane (**14**, **15**) and fluoroalkyl halides (**16–20**) were compatible in this transformation. Given that ~20% of drugs in 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 products in moderate yields (**21**, 51%). Finally, to highlight the 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).

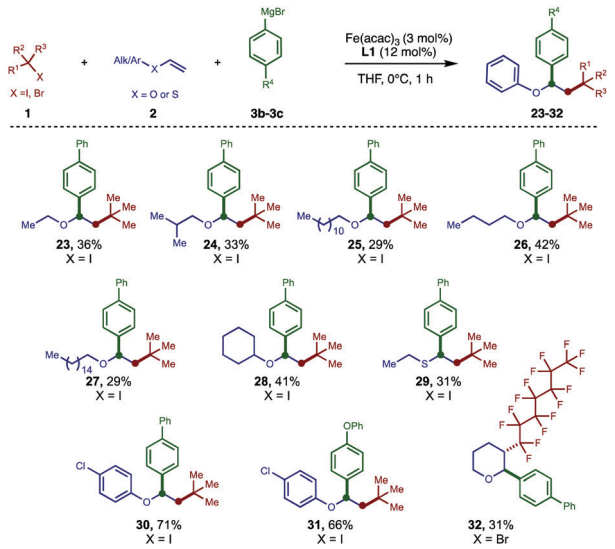
Finally, the alkene substrate scope was investigated (Scheme 4). Overall, attempts to extend the reaction to linear and branched alkyl vinyl ethers were modestly successful, giving products (**23–28**) in 29–42% yields. These results show that alkyl vinyl ethers, in addition to aryl vinyl ethers (**30**, **31**), can function as effective linchpins in this three-component reaction. To highlight the potential expansion to thioethers, we



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

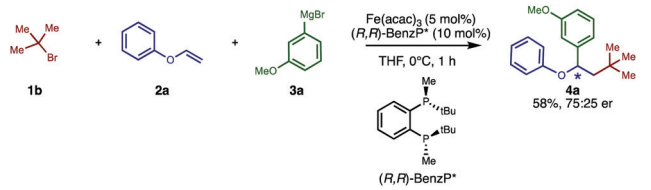


Scheme 3 Scope of alkyl halides in the 3-component cross-coupling reaction with phenyl vinyl ether and 4-biphenylmagnesium bromide **3b**. All the reactions were carried out under optimized conditions (Table 1, entry 1) using 0.2 mmol alkyl halide. Isolated yields are reported.



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

used vinyl ethyl thioether as an alternative π-acceptor and were pleased to observe the desired product in a 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 Fig. S4, ESI†). The ability of this reaction to functionalize internal vinyl ethers



Scheme 5 Preliminary results on the asymmetric version of the 3-component conjunctive cross-coupling reaction. 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.

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 an aim to improve the 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 Fig. S1–S3 in the ESI† for full details).

Finally, under optimized reaction conditions, preliminary results show the potential for an enantioselective variant of this transformation (Scheme 5 and Table S4 in the ESI†). 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]

In summary, we have developed an iron-catalyzed regioselective 1,2-dicarbofunctionalization of electron-rich alkenes with (fluoro) alkyl halides and aryl Grignard reagents. This reaction successfully gives products with both electron-donating aryl Grignard reagents and mildly electron-withdrawing aryl Grignard reagents. Furthermore, 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.

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Conflicts of interest

There are no conflicts to declare.

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