Functionalized olefin cross-coupling to construct carbon—carbon bonds

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Carbon–carbon (C–C) bonds form the backbone of many important molecules, including polymers, dyes and pharmaceutical agents. The development of new methods to create these essential connections in a rapid and practical fashion has been the focus of numerous organic chemists. This endeavour relies heavily on the ability to form C–C bonds in the presence of sensitive functional groups and congested structural environments. Here we report a chemical transformation that allows the facile construction of highly substituted and uniquely functionalized C–C bonds. Using a simple iron catalyst, an inexpensive silane and a benign solvent under ambient atmosphere, heteroatom-substituted olefins are easily reacted with electron-deficient olefins to create molecular architectures that were previously difficult or impossible to access. More than 60 examples are presented with a wide array of substrates, demonstrating the chemoselectivity and mildness of this simple reaction.

New methods for the construction of C–C bonds have the potential to shift paradigms in retrosynthetic analysis (the strategy used to design syntheses of molecules)1. Historically, those that have been most successful feature simple experimental procedures, exhibit broad scope and allow access to chemical space previously deemed challenging or inaccessible. A recent exercise in total synthesis drew our attention to radical-based olefin hydrofunctionalizations of the sorts pioneered in refs 2–9. Those illuminating studies led to the invention of a reductive coupling10–12 of simple olefins with electron-deficient olefins such as that depicted in Fig. 1a13. In that work, an adduct bearing an all-carbon quaternary centre such as A could be easily accessed in minutes and in an open flask from olefin B, presumably via the intermediacy of radical A’. Although a useful and practical method, the compounds it produced could already be obtained from readily accessible functionalized hydrocarbons such as alkyl halides14, alcohols15,16 and carboxylic acids17 via conventional radical-generating processes.

In contrast, the functionalized hydrocarbons required to access adducts such as C, D and E (Fig. 1a) would either require extensive functional group (FG) manipulations or are unfeasible donors owing to FG incompatibilities and chemoselectivity difficulties arising from the heteroatoms present (B, S and I). By analogy to previous work, if olefins could be used as a surrogate for the intermediate radicals C’, D’ and E’, easily accessible compounds such as F could be employed directly, avoiding FG manipulations completely.

**Development of functionalized olefin cross-coupling**

Although this idea is conceptually simple, examining the hypothetical mechanistic pathway revealed numerous obstacles that would need to be addressed, as shown in Fig. 1b. The initiating step, radical formation from the donor olefin G by an in situ-generated Fe hydride, could be complicated by issues of both regioselectivity and chemoselectivity. Furthermore, depending on the nature of the X substituent, several competing pathways could arise involving the Fe complexes in the catalytic cycle (for example, transmetallation of a C–B bond, desulfonylation of a C–S bond, and oxidative addition of a C–I bond). If the first step did occur as intended, the intermediate radical H could be prone to premature reduction18–20, trapping with O2 (ref. 2), or homodimerization. Provided that H undergoes the desired conjugate addition to the electron-deficient olefin coupling partner, the newly generated radical I could undergo homodimerization, intramolecular hydrogen atom abstraction or consecutive conjugate additions leading to uncontrollable oligomerization. Formation of J from a single-electron reduction of I would result in a substantially basic and nucleophilic site that could prove to be incompatible with the X group and its substituents. In order for the reaction to prove successful, the conditions must be mild enough to tolerate both the various intermediate species in the catalytic cycle, as well as the final coupled product K.

With these potential difficulties in mind, we used the model system depicted in Fig. 2a, with silyl enol ether 1 serving as the donor and cyclohexenone (2) as the acceptor, to develop a functionalized olefin cross-coupling. Application of conditions similar to those previously developed, using Fe(acac)3 (4, acac, acetylacetone) as a catalyst and PhSiH3, as a stoichiometric reductant21, formed the reductively coupled product 3 in 53% yield based on GC/MS (gas chromatography/mass spectrometry) using an internal standard. Analysis of the side products from the model system and related reactions led to the identification of compounds 14–17 (Fig. 2b). As 16 and 17 presumably arise from pathways where Fe(acac)3 behaves as a Lewis acid21, we hoped to attenuate the Lewis acidity of the catalyst by increasing the amount of steric shielding of the Fe centre. Increasing the size of the substitution on the dione ligands (5–9) led to decreased amounts of 16, with Fe(dibm)3 (5, dibm, diisobutylmethane)22 providing the best balance between reactivity and steric shielding. Although attempts to alter the electronic structure of the ligand with electron-deficient (10 and 11) and electron-rich (12 and 13) substituents eliminated reactivity, the addition of Na2HPO4 increased the yield of the desired product 3 from 69% to 78% when using Fe(dibm)3 as the catalyst. The use of about 45 other inorganic and amine bases as additives did not result in increased yields, suggesting that Na2HPO4 does not simply serve as a buffering agent. Additionally, Fe(dibm)3 enabled product formation with donors that were unreactive with Fe(acac)3 (18, Fig. 2c), which instead provided significant quantities of by-products 16 and 17. Over the course of the project, it was found that Fe(dibm)3 provided the highest yields when the heteroatom substitution on the donor olefin contained Lewis-basic lone pairs.
A new C–C bond formation method via cross-coupling

**Figure 1**  Functionalized olefin cross-coupling as a strategy for convergent chemical synthesis.  
(a) Functionalized olefin cross-coupling would facilitate the exploration of chemical space that has previously been difficult to access (for example, C–E). Such a strategy would use readily available heteroatom-substituted olefins as donors (F) to access nucleophilic radical intermediates (for example, C′–E′), which would couple with electrophilic acceptor olefins. This approach would avoid difficulties that could arise from the use of other radical precursors (greyed box, bottom right).  
(b) The functionalized olefin cross-coupling would occur by the Fe hydride-mediated conversion of the donor olefin G to the nucleophilic radical H, which would undergo conjugate addition to the acceptor olefin to form intermediate I. Single-electron reduction to form the stabilized anion J followed by protonation would form the final product K.  
Examination of the postulated mechanism for the cross-coupling reveals several potential complications (bulleted) that could arise due to the intermediacy of radicals or the heteroatom (X) present on the donor olefin. EWG, electron-withdrawing group; FG, functional group; (pin), pinacolato; TBS, tert-butyldimethylsilyl; X, heteroatom; L, ligand.

whereas Fe(acac)₃ proved superior in the absence of such moieties (see below).

**Scope and functional group tolerance**

The optimized conditions were then applied to a wider variety of donor and acceptor olefins, initially focusing on enol ethers (Fig. 3a). Using Fe(dibm)₃ (5 mol%), silyl enol ethers could be coupled to cyclic and acyclic enones, an enol and an acrylamide to generate adducts 3 and 20–25 with yields that generally increased with decreasing substitution on the silicon atom (19 and 22–24). Remarkably, even a severely congested oestrone derivative could undergo addition to methyl vinyl ketone to generate steroidal adduct 25 with the stereochemistry of the newly formed neopentyl quaternary stereocentre corresponding to that obtained through a conventional organometallic addition of an alkyl group to oestrene. Alkyl and aryl vinyl ethers could also be used, although higher yields were generally obtained by using the donor olefin in excess (26–33).

**Figure 2**  Functionalized olefin cross-coupling optimization studies.  
(a) Top row, reaction studied (ligand I, shown bottom left). Altering the ligands on the Fe centre (by using compounds 4–13) had the greatest influence on the outcome of the reaction, with Fe(dibm)₃ (5) giving the highest yields. The addition of 1 equiv. Na₂HPO₄ further increased the yield. (Yields here and in c are based on GC/MS analysis using 1,3,5-trimethoxybenzene as an internal standard.) Greyed-out ligands gave 0% yield.  
(b) Side products that were observed when Fe(acac)₃ (4) was used as the catalyst. The formation of compounds 16 and 17 could be attributed to the Lewis acidity of 4. The use of 5 as the catalyst reduced the formation of compounds 16 and 17.  
(c) Two olefins unreactive with Fe(acac)₃, but able to be coupled using Fe(dibm)₃.

Endocyclic enol ethers were also tolerated, as shown by the formation of 30–33. Additionally, enecarbamates and enamides could undergo cross-coupling under the reaction conditions (Fig. 3b). Adducts 34 and 35 were formed by the coupling of a Cbz (benzoxycarbonyl)-protected dihydroxypyrrole with benzyl acrylate and cyclopent-2-enone, respectively, although these couplings necessitated larger amounts of PhSiH₃ than the enol ethers. The amount of PhSiH₃ needed could be decreased by using more electronically activated acceptors, as the formation of 36 and 37 demonstrated. Other cyclic and acyclic enecarbamates could also be employed and added to various acceptor olefins (38, 39 and 41–46), although higher loadings (15 mol%) of Fe(dibm)₃ were typically required for useful yields. The formation of 40 also demonstrated that the nitrogen atom present on the donor olefin could be protected as an amide instead of a carbamate. Mono- and 1,1-disubstituted acyclic donor olefins were competent donors (41–46), however attempts to control the stereochemistry of the cross-coupling by using α-phenylethylamine as a chiral auxiliary provided only modest amounts of diastereoselectivity (45 and 46).

Vinyl thioethers proved to be unique donor olefins, with the cross-couplings of those surveyed taking place at ambient temperature to generate adducts 47–56 (Fig. 3c). Although the cross-coupling to form 49
Heteroatoms (X) tolerated on donor: O, N, S, B, Si, F, Cl, Br I
60 examples
Air and moisture compatible
Typically complete in under 1 h

For certain recalcitrant substrates (50, 51, 53 and 54). Syringe pump addition of the acceptor and PhSiH₃ to the reaction mixture could also improve yields in certain cases (51 and 55).

Figure 3 | Adducts synthesized by functionalized olefin cross-coupling.
Top, the reaction studied. The donor component is shown in green and the acceptor component is shown in blue. Couplings using donor olefins with heteroatom substitution containing Lewis basic lone pairs (a, O; b, N; c, S) proceeded in higher yields with Fe(dibm), whereas couplings without such moieties (d, B; e, Si; f, halogens) proceeded in higher yields with Fe(acac). *3 equiv. donor and 1 equiv. acceptor used. †6 equiv. PhSiH₃ used. ‡3 equiv. donor and 1 equiv. acceptor used. $THF used as a cosolvent. || 15 mol% [Fe] used. *Second portion of [Fe], acceptor and PhSiH₃ added after 1 h. #Heated at 60 °C. ¥Run on gram-scale. **100 mol% [Fe] used. ¶Na₂HPO₄ omitted. TMS, trimethylsilyl; TES, triethylsilyl; TIPS, triisopropylsilyl; Bn, benzyl; Cbz, benzylxycarbonyl; Boc, tert-butyloxycarbonyl; (MIDA), N-methylimidodiacetate; (dan), 1,8-diaminonaphthyl.
An isopropenyl pinacolato (pin) boronic ester, N-methyliminodiacetate (MIDA) boronate\textsuperscript{23,26}, and a 1,8-diaminonaphthyl (dan) boronamide\textsuperscript{27} could all be coupled to N,N-dimethyl acrylamide (57–59, Fig. 3d), although the use of THF as a cosolvent was required to solubilize the MIDA boronate. Additionally, methyl allyl could be used as an acceptor (60 and 61), and oxygen- and nitrogen-containing functionalities could be tolerated at allylic positions (61 and 62).

Vinyl silanes could also be used as donor olefins, although highest yields were obtained using a stoichiometric amount (50 mol%) of Fe(acac)\textsubscript{3}. Additionally, switching the solvent from EtOH to n-PrOH and heating the reactions to 80 °C instead of 60 °C resulted in higher yields. With these slight modifications, an isopropenyl and vinyl silane could be coupled to a wide variety of acceptor olefins to form 63–70 (Fig. 3e), although the coupling to obtain the phenyl vinyl sulfone adduct 66 required a stoichiometric amount of Fe(acac)\textsubscript{3}. With the omission of Na\textsubscript{2}HPO\textsubscript{4}, unprotected acrylic acid could be used as an acceptor to provide the coupled product 67 in a transformation difficult to achieve using conventional conjugate addition techniques\textsuperscript{28,29}.

As a final testament to the mildness of this C–C bond forming reaction, alkenyl halides were found to take part in the cross-coupling in reasonable yields using stoichiometric amounts of Fe(acac)\textsubscript{3}. Alkenyl fluorides, chlorides, bromides and even iodides could all be used as donors, with the 2-haloallyl alcohol derivatives delivering products 71, 72, 76 and 77 (Fig. 3f), where the halogen atom remained intact. Interestingly, acrylic acid could once again be used as an acceptor (73, 75), and the reaction proceeded readily with a free alcohol (74), demonstrating the notable chemoselectivity of this method.

To highlight the efficiency of the newly developed coupling reaction, we chose to target glucal derivative 79 (Fig. 4a). This compound has previously been prepared in three steps from readily available 78 in 52% yield, although that route required the use of excess gaseous HCl, toxic and harsh organometallic reagents and cryogenic temperatures\textsuperscript{80}. By contrast, olefin cross-coupling allowed the desired product 79 to be synthesized directly from 78 in a single step over two hours in 68% isolated yield, although it did require the slow addition of a large excess (12 equiv.) of both methyl vinyl ketone and PhSiH\textsubscript{3}.

Finally, the resilience of the functionalized olefin cross-coupling to adverse conditions was evaluated by performing the reaction in a variety of unconventional solvents. As indicated by GC/MS, the coupling to form silyl ether 80 proved to be successful in a selection of beer, wine and various spirits (see Supplementary Table 2 and Supplementary Figs 23–30). In addition to showing the ability of the reaction to proceed under aconid conditions, these results demonstrate the reaction’s tolerance of a host of organic compounds\textsuperscript{11} and microorganisms, suggesting possible downstream applications to the area of biocorruption\textsuperscript{12}.

**Discussion and limitations**

From a strategic perspective, this methodology grants access to areas of chemical space that, in most cases, were previously inaccessible. Historically, heteroatom-substituted quaternary centres have been synthesized with multiple FG manipulations and rarely, if ever, through a direct C–C disconnection as enabled here. Thus, ~90% of the compounds listed in Fig. 3 are new chemical entities despite their simplicity. In the case of 30, 31 and 34–37, where a comparison to contemporary reactivity modes could be made, it was found that the olefin cross-coupling route offers a complementary approach to the recently reported decarboxylative method\textsuperscript{33}. Furthermore, the olefin cross-coupling reaction set-up was operationally simple, as no precautions were made with regards to moisture or air exclusion, and reactions were typically done within a few minutes to an hour. The reaction is also readily scalable, with the coupling to form 65 being conducted on the gram scale (51% yield).

However, no reaction is without limitations. Although nearly all of the substrate classes tested delivered the expected product, the 1,2-disubstituted vinyl boronic ester 80 and vinyl silane 82 exclusively provided adducts 81 and 83, respectively, where bond formation occurred distal to the heteroatom (Fig. 4b). Additionally, excessive allylic substitution on the acceptor olefin was not well tolerated, with trisubstituted acceptors (for example, 84 and 85) and disubstituted acceptors containing allylic β branching (for example, 86 and 87) generally giving little or no product. Cases where the isolated yield was ~50% and below could be attributed to incomplete conversion, premature reduction or substrate

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**Figure 4 | Additional functionalized olefin cross-coupling studies.**

a. Functionalized olefin cross-coupling (top route) offers a direct route to glucal derivative 79 that circumvents the harsh reagents, superstoichiometric organometallic reagents and cryogenic temperatures used in conventional approaches (bottom route). b. Top two rows: the use of certain 1,2-disubstituted donor olefins (80 and 82) gave adducts where the C–C bond formed distal instead of adjacent to the heteroatom (81 and 83). Bottom row: the use of acceptors with excessive aliphatic substitution (84–87) gave trace or no product. c. The use of vinyl cyclopropane 88 resulted in the isolation of 89, where the fragmentation of the cyclopropane “radical clock” supports the formation of a radical adjacent to the heteroatom in the donor. Isolation of compounds 90 and 91 from deuterium labelling studies further support the mechanism depicted in Fig. 1b.

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**Legend:**

- **a** Comparison of olefin cross-coupling and traditional routes to 79
  - Olefin cross-coupling
    - 1 step, 68% isolated
  - Conventional route\textsuperscript{27}
    - 3 steps, 52% overall

- **b** Limitations of olefin cross-coupling
  - Examples of currently unexpected regiochemistry

- **c** Mechanistic studies
  - Radical clock experiment
    - Using PhSiD\textsubscript{3} >99% D incorporation
  - Labelling studies
    - Using C\textsubscript{2}D\textsubscript{2}OD or C\textsubscript{3}D\textsubscript{2}OD >99% D incorporation

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dimerization. It is finally worth noting that as Fig. 3 demonstrates, the stereochemical outcomes of this reaction are all currently substrate-controlled.

Although a thorough mechanistic investigation has not been pursued, several observations are consistent with the mechanism depicted in Fig. 1b. Subjecting a donor olefin bearing a vinylcyclopropane (88, Fig. 4c) to the reaction conditions led to the isolation of adduct 89, arising from cleavage of the cyclopropane ring. Furthermore, the utilization of PhSiH₃ instead of PhSiH₄ resulted in the isolation of C₆ deuterated adduct 90. These two observations support the notion that a hydrogen atom originating from PhSiH₃ is incorporated into donor olefin electrophilic positions, resulting in a reversal in typical reactivity. Furthermore, the utilization of PhSiH₃ instead of PhSiH₄ resulted in the isolation of C₆ deuterated adduct 90. These two observations support the notion that a hydrogen atom originating from PhSiH₃ is incorporated into donor olefin electrophilic positions, resulting in a reversal in typical reactivity. Functionalized olefin cross-coupling ultimately represents a method of reversing the native reactivity⁴⁴ of heteroatom-substituted olefins (Fig. 5), thus permitting the facile exploration of underdeveloped chemical space and serving as an alternative to other powerful retrosynthetic C–C bond disconnections⁴⁵–⁴⁷. Although achieving ligand control of stereo- and regiochemical outcomes and a deeper understanding of the mechanism are prominent future goals, potential applications of this method, even in its current form, to numerous areas of chemical science can be envisioned.

Figure 5 | Functionalized olefin cross-coupling reverses conventional reactivity expectations. The substrates employed as donors in this study are typical of electrophilic (a) at the position adjacent to the heteroatom. Functionalized olefin cross-coupling reverses this native reactivity by generating radical intermediates through the use of an Fe catalyst and a silane. These radicals induce nucleophilic properties (“δ−”) at those formerly electrophilic positions, resulting in a reversal in typical reactivity.
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Supplementary Information is available in the online version of the paper.

Acknowledgements Financial support for this work was provided by NIH/NIGMS
(GM-097444). The National Science Foundation supported a predoctoral fellowship for J.C.L.; the Shanghai Institute of Organic Chemistry, Zhejiang Medicine Co. and Pharmaron supported a postdoctoral fellowship for J.G.; and the Japan Society for the Promotion of Science supported a postdoctoral fellowship for Y.Y. We are grateful to D.-H. Huang and L. Pasternack (TSRI) for assistance with NMR spectroscopy, and A. L. Rheingold and C. E. Moore (UCSD) for X-ray crystallographic analysis. We thank R. A. Shenvi (TSRI) and Y. J. (TSRI) for discussions.

Author Contributions J.C.L. and P.S.B. conceived the work; J.C.L. conducted initial feasibility studies; J.C.L., J.G., Y.Y. and C.-M.P. performed the experiments and analysed the data; J.C.L., J.G., Y.Y. and C.-M.P. performed the experiments; and J.C.L. and P.S.B. wrote the manuscript.

Author Information Crystallographic data for the structure of Fe(dibm)2 (5) is available free of charge from the Cambridge Crystallographic Data Centre under deposition number CCDC 1022625. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to P.S.B. (pbaran@scripps.edu).