Reaction Cascades Hot Paper

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An Iron-Catalyzed Bond-Making/Bond-Breaking Cascade Merges Cycloisomerization and Cross-Coupling Chemistry

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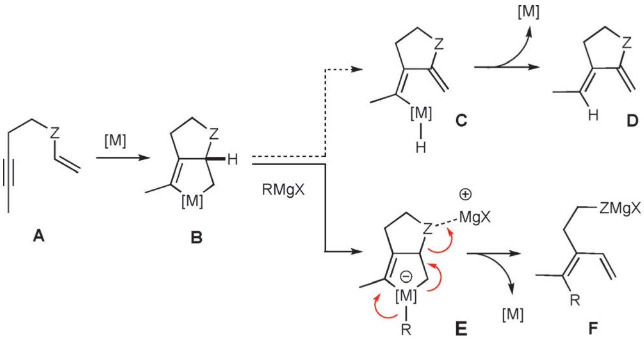
***Abstract:** Treatment of readily available enynes with alkyl-Grignard reagents in the presence of catalytic amounts of Fe(acac)$_3$ engenders a remarkably facile and efficient reaction cascade that results in the net formation of two new C–C bonds while a C–Z bond in the substrate backbone is broken. Not only does this new manifold lend itself to the extrusion of heteroelements (Z = O, NR), but it can even be used for the cleavage of activated C–C bonds. The reaction likely proceeds via metallacyclic intermediates, the iron center of which gains ate character before reductive elimination occurs. The overall transformation represents a previously unknown merger of cycloisomerization and cross-coupling chemistry. It provides ready access to highly functionalized 1,3-dienes comprising a stereodefined tetrasubstituted alkene unit, which are difficult to make by conventional means.*

The growing awareness of the many favorable attributes of homogeneous iron catalysis fertilizes, amongst other things, the development of new methodology for the selective formation of C–C bonds.[1–6] In this context, early work by our group has helped to demonstrate that this cheap, benign, readily available, and—for a surprisingly long time—underutilized element can serve as a substitute for palladium in various cross-coupling reactions.[7] In addition to this "noble task", its use allows the scope to be extended, since catalysts generated in situ from simple iron salts and Grignard reagents are capable of engaging certain electrophilic partners into cross-coupling that fail to react under conventional conditions.[8]

Along similar lines, the ability of low-valent iron to induce a host of cycloisomerization or cycloaddition reactions becomes increasingly apparent, which are otherwise also dominated by the use of noble-metal catalysts.[9–12] Once again, it is reasonable to assume that this metal cannot only emulate well-established reactivity patterns, but might provide opportunities for innovation.



Scheme 1. A possible new way of harnessing the reactivity of metallacycles; the proposed scenario merges the ability of low-valent iron to catalyze cycloisomerization and cross-coupling reactions.

Under the proviso that many such reactions proceed via metallacyclic intermediates,[9–13] we envisaged an unorthodox reaction mode (Scheme 1). Thus, it seems unlikely that a reactive intermediate of type **B** comprising a potential leaving group Z within the bicyclic core will evolve by canonical β-hydride elimination, since the fairly rigid framework prevents efficient orbital overlap with the hydrogen atom at the bridgehead position from occurring.[14,15] Rather, the alignment of the electron-rich [M]–C bond and the σ*-orbital of the adjacent C–Z entity should lead to ring opening. This manifold might allow one to extrude heteroelements and could even lend itself to the cleavage of (activated) C–C bonds.[16] The challenge in reducing this plan to practice, however, lies in the downstream chemistry: whereas any conventional decomposition of a metallacycle by β-hydride elimination forms a reactive metal hydride species that ultimately safeguards catalyst turnover (compare **C**→**D**), a separate reaction has to juxtapose with the envisaged ring opening to ensure regeneration of the active principle [M]. We conjectured that iron catalysis is adequate for this purpose, in that the envisaged cycloisomerization could be merged with cross-coupling; in so doing, functionalized 1,3-diene products of type **F** come into reach. It is tempting to assume that the ability of iron to form ate complexes[17,18] provides further assistance, since alkylation of the ferracycle **B** (M = Fe) primarily formed will facilitate the ring opening through the increased electron density of the reacting site in **E**; at the same time, the escorting cation might engage with the leaving group, relieve possible geometric constraints in the transition state, and hence lower the barriers along the reaction coordinate.

The readily available enyne **1a**[19] was deemed an adequate model compound to test this hypothesis (Scheme 2). The electron-deficient alkene unit of **1a** will favor oxidative cyclization with formation of a metallacycle **2a**, which in turn should benefit from the partial enolate character that the ester imposes. At the same time, this functional group will report whether the projected iron-catalyzed manifold is fast enough to outperform competing attack of the Grignard reagent at the electrophilic sites of the substrate. Finally, the good leaving group properties of

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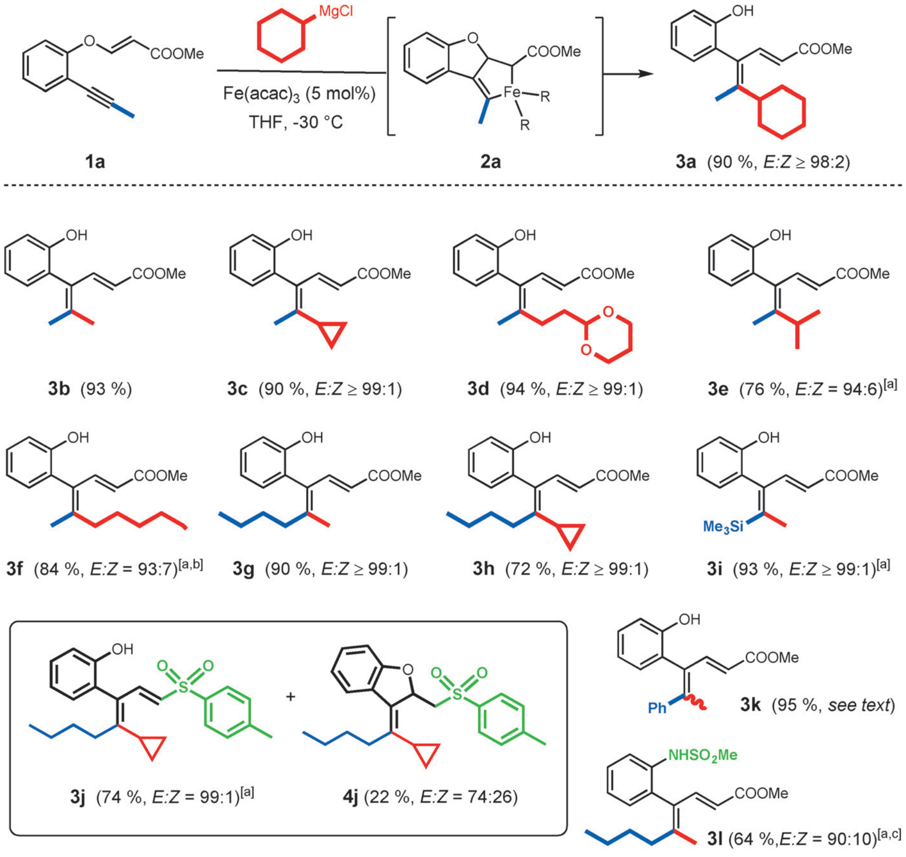


Scheme 2. Iron-catalyzed cycloisomerization/cross-coupling cascade; [a] using 20 mol% of Fe(acac)$_3$; [b] slow addition of the Grignard reagent; [c] yield based on recovered starting material; R = neutral or anionic ligand; Z = O, NR; X = halide.

a phenolate are thought to expedite the envisaged bond cleavage.

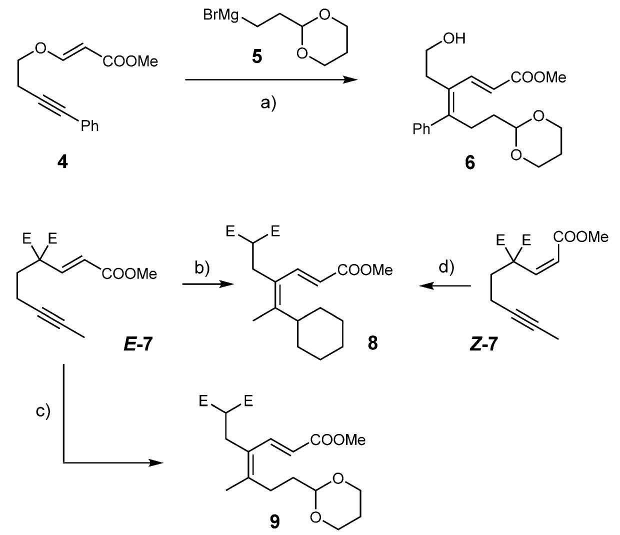
Gratifyingly, addition of cyclohexylmagnesium chloride (2 M in Et$_2$O) to a solution of **1a** and Fe(acac)$_3$ (5 mol%) in THF at −30 °C led to the clean and rapid formation of the tetrasubstituted alkene **3a**, which was isolated in 90% yield as a single regio- and stereoisomer ($E/Z \geq 98{:}2$, NMR).[20] This outcome is consistent with intervention of a metallacyclic intermediate **2a**, the alkenyliron unit of which eventually succumbs to cross-coupling while the alkyliron side leads to reductive ring opening; although other mechanisms are conceivable, they are less likely (see below). In any case, the underlying cascade engenders the regio- and stereoselective formation of two vicinal C−C bonds at the expense of the C−O bond of the former enol ether.

These ligand-free conditions are practical and broadly applicable.[21] As evident from the additional examples compiled in Scheme 2, various (functionalized) primary and secondary alkyl-Grignard reagents can be used, but higher catalyst loadings were necessary in some cases. Only Me_3SiCH_2MgCl proved nontransferrable, most likely because of the well-known β-silicon effect on the transient organoiron intermediate.[22,23] Variations of the substrate were also well accommodated. This relates to the substituent on the alkyne as well as to the use of acceptor groups other than esters, as exemplified by the sulfone derivative **3j**; interestingly, partial cyclization with formation of the Michael adduct **4j** was observed in this case. Although this transformation awaits further optimization, it holds promise for the development of even more involved reaction cascades.[24] Moreover, a sulfonamide proved suitable as a leaving group, although formation of **3l** did not go to completion and some starting material was recovered.

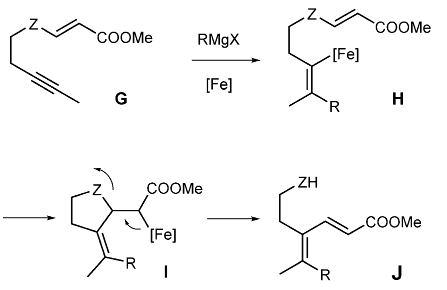
In general, the products were formed with good to excellent isomeric purity. A series of X-ray structures proved that the substituent delivered by the Grignard reagent and the transferred alkenyl entity reside on the same side of the central tetrasubstituted alkene unit.[19] Any erosion of the diastereomeric ratio is likely due to a secondary isomerization process that was particularly prominent for the aryl-substituted alkyne derivative **3k**: in this case, the Z/E ratio decreased from an appreciable 96:4 after 10 min to 41:59 after 90 min reaction time. A high degree of charge delocalization together with the steric congestion caused by the two aryl rings on the same side of the double bond are thought to drive this process.

The examples shown in Scheme 3 prove that the aromatic backbone is not necessary for the reaction to proceed: although aliphatic substrates such as **4** are conformationally much less biased for cyclization than **1a** and an alkoxide is certainly a less favorable leaving group than a phenolate, the overall transformation proceeded nicely at a slightly higher temperature to afford the stereochemically well-defined 1,3-diene **6**; note that the lateral oxygen substituents in **6** are at the alcohol, aldehyde, and acid oxidation state and, therefore, provide ample opportunity for the selective functionalization of this kind of building block.

While one might contend that an oxygen atom as the tether favors the breakdown of the key metallacyclic intermediate of type **B** (Z = O), this argument does not necessarily pertain to substrates with an all-carbon backbone ($Z = CR_2$). However, the readily available malonate derivative (E)-**7**[19] was transformed under the standard conditions within minutes into product **8**, in which two C−C bonds were formed while another C−C bond must have been broken.[25] The isomeric substrate (Z)-**7** afforded the very same compound in virtually identical yield and isomeric purity, thus showing that the reaction is stereoconvergent rather than stereospecific. As expected, the choice of the Grignard reagent has little bearing on the outcome, as evident from the formation of the highly functionalized diene **9**.

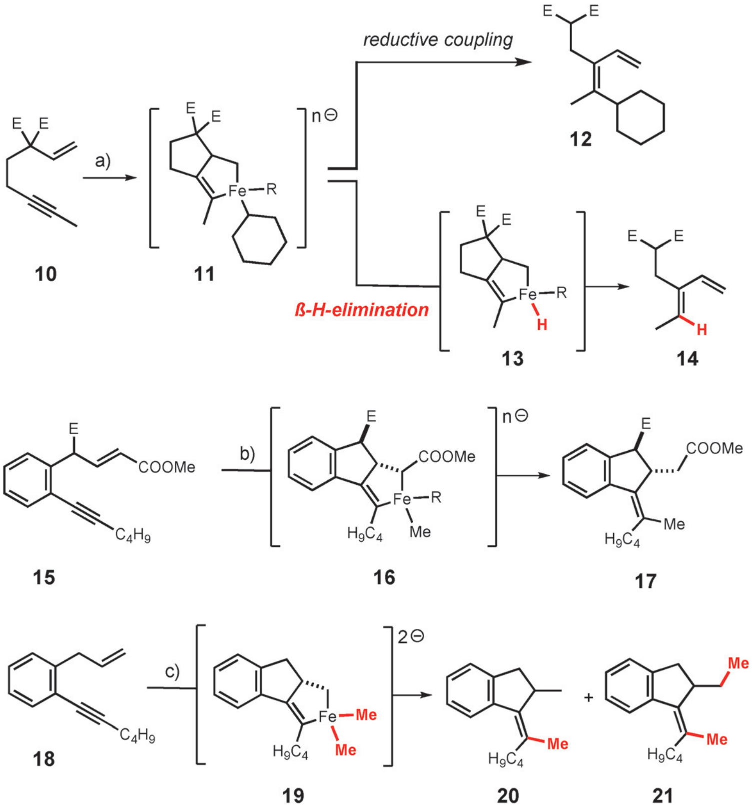


Scheme 3. Reaction cascades of flexible substrates: a) **5**, Fe(acac)$_3$ (20 mol %), THF, 0 °C, 81 % (*E*/*Z* = 95:5); b) $C_6H_{11}MgCl$, Fe(acac)$_3$ (20 mol %), THF, −30 °C, 70 % (*E*/*Z* = 99:1); c) **5**, Fe(acac)$_3$ (20 mol %), THF, −15 °C, 63 % (*E*/*Z* = 98:2); d) $C_6H_{11}MgCl$, Fe(acac)$_3$ (20 mol %), THF, −30 °C, 70 % (*E*/*Z* = 99:1). E = COOMe.



Scheme 4. Conceivable but unlikely alternative mechanism comprising an iron-catalyzed carbometalation followed by 1,4-addition and reductive elimination.

As mentioned above, most iron-catalyzed cycloisomerization and cycloaddition reactions known to date are believed to proceed via metallacyclic intermediates formed in the first place by oxidative cyclization.[9–13] A priori, however, the present reaction manifold could also be explained by an alternative mechanism (Scheme 4). Since iron catalysts are able to effect carbometalation reactions of alkynes,[26–28] one could envisage formation of an alkenyliron species **H** which then undergoes an entropically favored intramolecular 1,4-addition to the electron-deficient alkene partner followed by reductive elimination of **I** with formation of products of type **J**. Although a final decision on this issue must await further study, the currently available information argues against this scenario (Scheme 5). Importantly, the presence of a Michael acceptor in the substrate is not necessary, even though an electron-deficient alkene renders the process more facile. This is evident from the reaction of compound **10** with a terminal alkene unit, which underlies the full cascade to give product **12** by formation of two new C−C bonds and one C−C bond cleavage. As the overall transformation is slower, however, notable amounts of compound **14** accumulate in the mixture, in which hydride rather than the cyclohexyl group has been transferred. This outcome is best explained by assuming formation of an intermediate of type **11**, which is poised for reductive coupling to give **12** as the major product, but which can also succumb to competing β-hydride elimination with formation of **14** via **13** as the most likely immediate precursor.



Scheme 5. a) $C_6H_{11}MgCl$, Fe(acac)$_3$ (20 mol %), THF, −30 °C, 53 % (**12**/**14** = 3.8:1); b) MeMgBr, Fe(acac)$_3$ (20 mol %), THF, −30 °C, 67 %; c) MeMgBr, Fe(acac)$_3$ (1 equiv), THF, −30 °C → RT, quant. (NMR, **20**/**21** = 69:31). E = COOMe.

Such β-hydride elimination is impossible when MeMgBr is used. To check for the response, we conceived compounds **15** and **18**, which were expected to be less reactive than the malonate derivative **10** since the C−C bonds destined to cleave are less activated. In fact, the cascade stopped after the two new C−C bonds had formed in both cases; however, the conversion of **15** into **17** remained fast and clean, delivering this densely decorated dihydroindene derivative in diastereomerically pure form. Compound **18**, comprising a terminal alkene rather than an enoate, proved more reluctant: although **20** was the major product, it allowed for a competing incorporation of a second methyl group—one on either end of the original π-system. Under the standard reaction conditions, only traces of compound **21** were detected, but when the iron loading was increased to 1 equivalent, **21** accounted for no less than 31 %

of the crude material. This outcome is likely indicative of a metallacyclic ate complex of type **19** as the reactive intermediate, in which the iron center is already loaded with two (or more) methyl substituents.[17,18] Since C(sp^2)−Me coupling is arguably easier than C(sp^3)−Me coupling, **20** is expected to be the major product after work-up, whereas **21** eventually accumulates on prolonged reaction time and/or under more forcing conditions.

Together with additional but indirect evidence,[19] we take these results as a strong indication that the new cascade process indeed manifests a nontraditional way of harnessing the reactivity of metallacyclic compounds. The immediate preparative merit lies in the formation of tetrasubstituted alkenes as part of highly functionalized 1,3-dienes, which have hardly any precedent. Attempts at generalizing the underlying principle and at studying the reactivity of these now readily available products are underway and will be reported in due course.

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Keywords: 1,3-dienes · cross-coupling · cycloisomerization · enynes · Grignard reagents · iron catalysis

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