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Guillaume Lefèvre

► To cite this version:

| Guillaume Lefèvre. Iron-catalyzed coupling of three reactants. Science, 2021. hal-03437179

HAL Id: hal-03437179

<https://hal.science/hal-03437179>

Submitted on 19 Nov 2021

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Iron-catalyzed coupling of three reactants

Vinyl boronates couple under mild conditions to two partners through carbon-carbon bonds

By Guillaume Lefèvre

New methods that efficiently form carbon-carbon bonds are welcomed by organic chemists if they run with high yield in few steps, introduce structural diversity, and if catalysts and co-reactants are required, are

as inexpensive and nontoxic as possible. Multicomponent reactions (MCR) that allow reaction of three or more species in a single, convergent process introduce structural diversity in one step. Efficient MCR-based processes can provide an easy access to the synthesis of molecule libraries, which is a valuable asset for the fabrication of families of drug-like compounds. On page 432 of this issue, Liu *et al.* (1) describe an efficient three-component reaction that difunctionalizes vinyl boronates by means of iron coordinated with a bulky phosphine ligand. Grignard reagents (ArMgX , where Ar is an aryl group and X is a halide) and alkyl halides (R'X) are partners in these transformations that occur under very mild conditions (see the figure, top).

Iron-catalyzed cross-couplings have been extensively exploited in carbon-carbon bond formation processes developed during

the past few decades [for a complete review, see (2)]. Those methods involve the creation of a covalent bond between two reagents through the reaction of an electrophile (typically an electron-poor derivative, such as an organic halide or pseudo-halide such as tosylate) with a nucleophile (typically an organometallic reagent bearing an electron-rich metalated carbon atom—for example, an organomagnesium, an organozinc, or less often, an organoboron compound). The low cost and the environmentally friendly and biocompatible nature of iron make this metal particularly suitable for synthetic applications in the development of products of pharmaceutical or biological interest (3). Many iron-catalyzed two-component cross-couplings have been reported, and some of them are now used on large preparative scales. However, the state of the art for iron-mediated multicomponent transformations that involve organoboron derivatives has been particularly limited so far.

Vinyl boronates are particularly useful platforms in radical processes because of ease of generation of α -boryl radicals that have been used as MCR partners in nickel-photoredox catalysis, given their intrinsic enhanced stability (4). The methodology discussed by

Liu *et al.* relies on the successful association of a simple iron salt with an electron-rich bulky diphosphino [or (P,P)] ligand—in this case, 1,2-bis-dicyclohexylphosphinoethane (dcype)—and encompasses a large scope of reagents. This method also enables the use of fluoroalkyl halides as radical precursors, which leads to the incorporation of fluoro-alkyl chains in the final product as well as the development of annulation-arylation sequences. These capabilities help address two outstanding challenges of iron-coupling catalysis. Such a versatility opens the way for a large number of synthetic combinations and makes a broad range of organic scaffolds accessible in a single step.

Liu *et al.* performed thorough mechanistic studies using iron-57 Mössbauer spectroscopy as well as isolation and characterization of key intermediates by use of x-ray diffraction. These studies demonstrate the crucial role of the number of hydro-carbonyl groups transferred by the Grignard reagent ArMgX onto the starting iron(II) complex [for a recent report on the benefits of physical-inorganic techniques in the elucidation of mechanistic facets of iron-mediated processes, see (5)]. Depending on their coordination number, organoiron(II) species can display very distinct reactivities, and their oxidation-reduction properties

Iron mediates a three-component reaction

Structural diversity can be achieved more rapidly if three reactants can form a single product in one step.

Liu *et al.* report the difunctionalization of a vinylboron mediated by an iron catalyst under mild conditions.

Double addition to vinyl boronates

The one-step reaction between a vinyl boronate (Bpin, vinylboronic acid pinacol ester), a Grignard reagent (where Ar is aryl), and an organic halide (where R' is an alkyl group and X is a halide) is catalyzed by a bulky diphosphine-ligated iron complex (the structure of the dcype ligand is shown on the right).

Mechanistic steps

Key steps of the transformation are shown. The bulky dcype ligand prevents binding of a second ligand that would form an inert complex. The activated alkyl radical reacts with the vinyl boronate to create a second radical, which undergoes a final redox step to complete the catalytic cycle.

also strongly vary (6–9). Thus, mastering and exploiting the reactivity panel offered by the diverse coordination possibilities of organoiron species is often the key of a successful iron-catalyzed coupling sequence.

The catalytic process was initiated by a single-electron transfer between in situ generated bis-arylated complex $(\text{P,P})\text{Fe}^{\text{II}}(\text{Ar})_2$ and the alkyl halide. As is often observed in iron-catalyzed two-component cross-coupling chemistry, this step ensures the formation of a free carbon-centered radical. The latter does not undergo a fast recombination with a transient organoiron, which is the usual final step in a classic two-component cross-coupling process. Instead, this radical is added to the carbon-carbon double bond of the vinyl boronate (see the figure, bottom). The newly formed radical then forms the expected difunctionalized product after recombination with a

mono-aryliro(II) intermediate, and a final redox comproportionation step completes the catalytic cycle.

Elucidation of the structure of the active species also showed that control of the chelation of the (P,P) ligand (dcype in this case) to iron(II) is critical. This ligand helps selectively form unsaturated intermediates bearing only one dcype, unlike other (P,P) ligands with similar electronic properties, which formed saturated octahedral (P,P)₂Fe^{II}(Ar)₂ species. Those species are unable to undergo a single-electron transfer with the organic halide, so no catalytic activity is observed.

The selective formation of species ligated by one dcype ligand originates in the high steric pressure brought by the cyclohexyl substituents of dcype, which hampers the inclusion of a second dcype in the iron coordination sphere. Thus, the judicious choice of this substituent limits the distribution of iron-containing intermediates to mono-dcype species and allows the crucial formation of the unsaturated bis-arylated (P,P)Fe^{II}(Ar)₂ after transmetalation with the Grignard reagent. Both steric and electronic effects of the dcype ligand contribute to the feasibility of this step.

The combination of a cutting-edge design of the interlocking of coordination properties with stereoelectronic ligand effects governing the reactivity of this bulky iron-di-phosphine platform allowed Liu *et al.* to develop a new and robust synthetic strategy. It can potentially benefit various fields—such as synthesis of pharmaceuticals, materials, and pesticides—in the near future. Beyond this breakthrough in synthetic applications, this work also illustrates the importance of accurate mechanistic investigations in the field of iron catalysis. The distinctive and complex reactivity displayed by iron, involving both one- and two-electron processes, as well as a broad range of oxidation and spin states should spur the development of new synthetic methods that will require a detailed understanding of the mechanistic aspect of these transformations (10).

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