Iron-Catalyzed Enantioselective Multicomponent Cross-Couplings of α-Boryl Radicals

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ABSTRACT: Despite recent interest in the development of iron-catalyzed transformations, methods that use iron-based catalysts capable of controlling enantioselectivity in carbon-carbon cross-couplings are underdeveloped. Herein, we report a practical and simple protocol that uses commercially available and expensive iron salts in combination with chiral bisphosphine ligands to enable the regio- and enantioselective (up to 91:9) multicomponent cross-coupling of vinyl boronates, (fluoro)alkyl halides, and Grignard reagents. Preliminary mechanistic studies are consistent with rapid formation of α-boryl radical followed by *reversible* radical addition to mono-aryl bisphosphine-Fe(II) and subsequent enantioselective inner-sphere reductive elimination. From a broader perspective, this work provides a blueprint to develop asymmetric Fe-catalyzed multicomponent cross-couplings via the use of alkenes as lynchpins to translocate alkyl radicals, modify their steric and electronic properties, and induce stereocontrol.

Transition metal-catalyzed cross-coupling reactions (CCRs) are recognized as powerful methods for the synthesis of pharmaceuticals, polymers, and commercial products.[1] Despite pioneering works by Kochi in the 1970's revealing the potential of simple iron salts as catalysts for carbon-carbon CCRs,[2] this field has been dominated by palladium and nickel catalysis. Considering the inherent attractive features of iron (e.g., low toxicity, earth abundance, environmentally benign, and low cost), in the last two decades, there has been a surge in the development and, equally important, mechanistic understanding of iron-catalyzed cross-couplings.[3-7] However, in contrast to other transition metal-catalyzed CCRs, general and practical examples of asymmetric Fe-catalyzed cross-couplings involving sp^3-hybridized coupling partners are extremely rare. [8-10,11d] To highlight the state-of-the-art, seminal reports by the Nakamura and Byers groups disclosed *two-component* asymmetric Fe-catalyzed cross-couplings between alkyl halides and organometallic nucleophiles (Figure 1A). However, these methods are severely limited to the use of activated radical precursors (i.e., α-halo esters and benzyl alkyl chlorides) and formation of one carbon-carbon bond (i.e., two-component cross-couplings). In part, the lack of general asymmetric Fe-catalyzed CCR methods can be attributed to the high reactivity and instability of alkyl radicals that are prone to undergo a plethora of side reaction (e.g., SET, β-hydride elimination, dimerization, H-atom abstractions, etc.) prior to undergoing enantioselective C-C bond formation with a chiral organoiron species. Another major and long-standing challenge in this area is the lack of detailed understanding of the factors (i.e., speciation, spin state, oxidation state, and coordination, etc.) controlling selectivity and reactivity of iron species under catalytic conditions.

We have initiated a program aimed at using experimental and computational tools to elucidate the mechanisms of iron-catalyzed cross-coupling reactions and, in turn, use this information to develop Fe-catalyzed multicomponent CCRs.[11] Inspired by these results and elegant work by the Morken[12] and Nevado[13] groups on nickel-catalyzed asymmetric CCRs (Figure 1B), we hypothesized that vinyl boronates could serve as effective lynchpins to promote radical capture, relay, and *enantioselective* cross-coupling of α-boryl radicals with well-defined *chiral bisphosphine-iron* species (Figure 1C). If successful, this work can not only completement existing nickel-based catalytic systems for the synthesis of diverse and chiral alkyl boron reagents (Figure 1B) but also open the doors for the development of multicomponent iron-catalyzed asymmetric cross-couplings. Herein we report the first general and broadly applicable use of commercially available iron salts and chiral bisphosphine ligands to promote asymmetric multicomponent radical cross-coupling between a range of (difluoro)alkyl halides, Grignard reagents, and vinyl boronates.

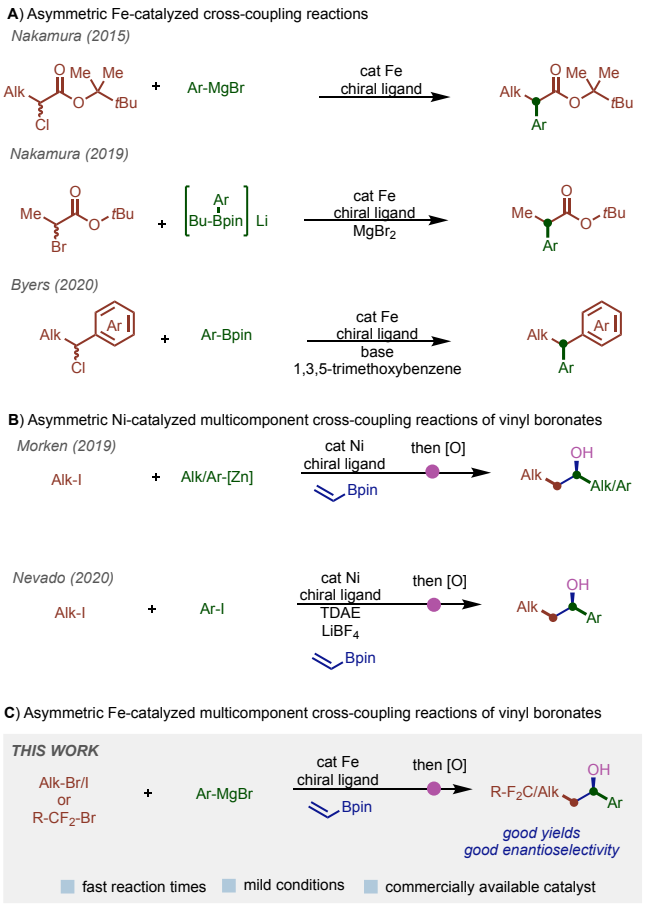

Figure 1. A) Current state-of-art in asymmetric Fe-catalyzed cross-coupling reactions. B) Asymmetric dicarbofunctionalization of vinyl

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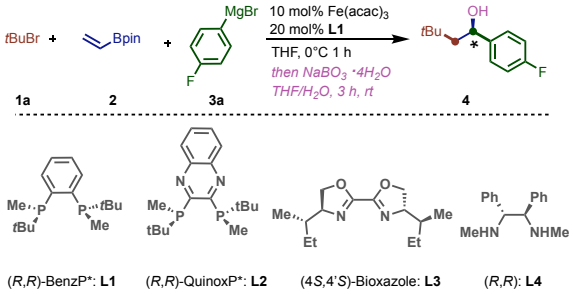
boronates using nickel catalysis. C) Asymmetric Fe-catalyzed three-component CCR of vinyl boronates, (fluoro)alkyl halides, and aryl Grignard reagents.

Based on prior work by us[11f] and others,[14-17] we initiated our studies using *tert*-butyl bromide, vinylB(pin), and 4-fluorophenylmagnesium bromide as model substrates to investigate the asymmetric three-component iron-catalyzed CCR. We hypothesized that under slow addition of Grignard reagent, we could generate the active *chiral* monoaryl- and

Table 1. Optimization of Asymmetric Dicarbofunctionalization of Vinyl Boronates using Iron Catalysis.[a]



Entry	Deviations	Yield	er
1	none	56	80:20
2	*t*BuI instead of *t*BuBr	43	68:32
3	**L2**	41	87:13
4	**L3**	21	84:16
5	**L4**	7	74:26
6	using $FeBr_3$ (10 mol%)	28	racemic
7	using $FeBr_2$ (10 mol%)	50	75:25
8	using $FeCl_3$ (10 mol%)	20	racemic
9	using 2-MeTHF	51	racemic
10	using $(iPr)_2O$	43	54.5:45.5
11	using DMA	19	91:9
12	at -15°C	39	87:13
13	addition of **3a** over 2 hours	59	66:34
14	using $Pd(PPh_3)_2Cl_2$ (10 mol%)	0	N/A
15	no $Fe(acac)_3$	0	N/A
16	no **L1**	0	N/A
17	no $Fe(acac)_3$ and no **L1**	0	N/A

[a] Reaction conditions: All reactions were performed using *t*-butyl bromide **1** (0.2 mmol, 2 equiv.), vinylboronic acid pinacol ester **2** (0.1 mmol, 1 equiv.), 4-fluorophenyl Grignard **3** (0.2mmol, 2 equiv.), and 1 mL of 1.0 M solution of THF. Aryl Grignard was added dropwise over an hour via syringe pump. Crude product was directly oxidized with 3.0 equiv. $NaBO_3{\cdot}4H_2O$ in 1:1 H_2O:THF and purified. Er was determined by HPLC using a chiral stationary phase on Daicel's CHIRALPAK® AD-H column.

bisaryl BenzP*Fe(II) species (i.e., without promoting chiral ligand dissociation) that are responsible for radical generation and C-C bond formation, respectively.[11f, 18] At the same time, this iron mechanistic manifold would permit electron-rich *tert*-butyl radical to add regioselectively to the electron-deficient vinyl boronate to form a stabilized α-boryl radical.[11f] In turn, effective capture of α-boryl radical with chiral mono-aryl BenzP*Fe(II)[18] species could lead to enantioselective C-C bond formation. Gratifyingly, after extensive experimentation (see Supporting Information), we identified the use of $Fe(acac)_3$ and (*R*,*R*)-BenzP* **L1** as suitable combination to form the desired multicomponent cross-coupling product **4** in good yield (56%) and enantioselectivity (80:20 er) (entry 1). Notably, despite the complexity of three-components and potential side products arising from the formation of alkyl radicals in the presence of organometallic reagents and potentially redox active iron species (i.e., H-atom transfer, β-hydride elimination, polymerization, two-component cross-coupling, etc.) the observed enantioselectivities are up to par with current state-of-the-art *two-component* iron-catalyzed cross-coupling reactions.[8-10] Moreover, as shown in entry 2, changing the alkyl radical precursor to *tert*-butyl iodide decreased both the yield and enantioselectivity while using chiral bisphosphine ligand **L2** slightly improved enantioselectivity but decreased product yield (entries 2-3). Ligands that proved effective in related nickel-catalyzed transformations by Morken[12] and Nevado[13] were also less effective in this iron-catalyzed transformation (entries 4 and 5). In addition to the choice of ligand, we also found a drastic effect imposed by the precatalysts on both the yield and enantioselectivity. Specifically, while iron(III0 halide salts ($FeBr_3$ and $FeCl_3$) provided no enantiocontrol, $FeBr_2$ was significantly less effective than $Fe(acac)_3$ (entries 6-8). The use of other ethereal solvents, including non-coordinating solvent 2-Me-THF, which is known to accelerate transmetallation of mono-aryl BenzP*Fe(II) to the corresponding, and non-selective, bisaryl BenzP*Fe(II),[18] led to significantly lower enantioselectivity (entries 9-10). These results are consistent with the role of solvent in controlling *iron speciation* and, as a consequence, enantioselectivity in BenzP*-iron catalyzed cross-couplings.[18] Presumably, as non-coordinating solvents decrease the concentration of the mono-aryl BenP*Fe(II) species that is required for trapping alkyl radicals and promote enantioselectve C-C bond formation (*vide infra*). Consistent with this hypothesis, dimethylacetamide (DMA), a strongly coordinating solvent, significantly improved the enantioselectivity (up to 91:9) but decrease the product yields (only 19% of the desired cross-coupled product). A palladium precatalyst was also used to examine potential catalytic activity this reaction but did not

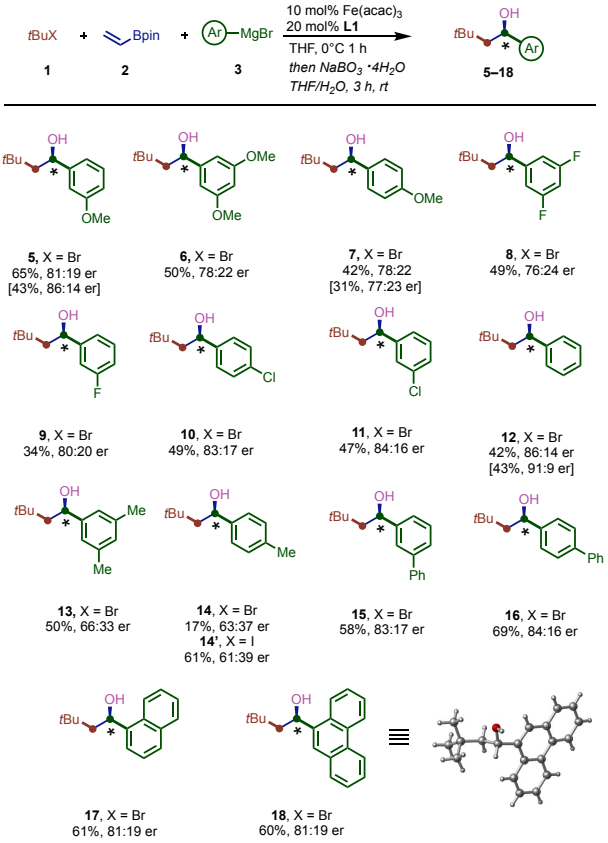


Figure 2. Scope of Grignard nucleophile in the three-component dicarbofunctionalization with vinylboronic acid pinacol ester. Reactions carried out under the optimized conditions (table 1, entry 1) with 0.2 mmol of **2**. Er determined by HPLC using a chiral stationary phase. Yields

and enantiomeric ratios using ligand (*R,R*)-QuinoxP* are shown in brackets.

yield the desired product (entry 14). Finally, control experiments confirmed the necessity of both the iron precatalyst and the ligand to drive the enantioselective multicomponent transformation (entries 15-17). Thus, after extensive screening, we move forward with BenzP* in this transformation given the balance initial three-component product yield and enantioselectivity for further substrate exploration.

With the optimized conditions in hand, we turned our attention to exploring the reaction scope by first varying the Grignard nucleophile (Figure 2). A wide range of electron-rich and electron-poor aryl Grignard reagents work well in the reaction with good yields (up to 69% *over two steps*) and enantioselectivities (up to 91:9 er) that are comparable to the state-of-the-art Fe-catalyzed two component cross-coupling methods. In addition, this method tolerates a range of electron-rich and -poor *meta*- and *para*-substituents including C-Cl bonds that can be further handles in cross-coupling reactions (**10**-**11**).[19-20] Finally, extended π-systems work well in this transformation albeit modest enantiomeric ratios were observed for some systems (**15**-**18**). Notably, x-ray analysis of **18** unambiguously determined the absolute stereochemistry of the major enantiomer as (*S*).

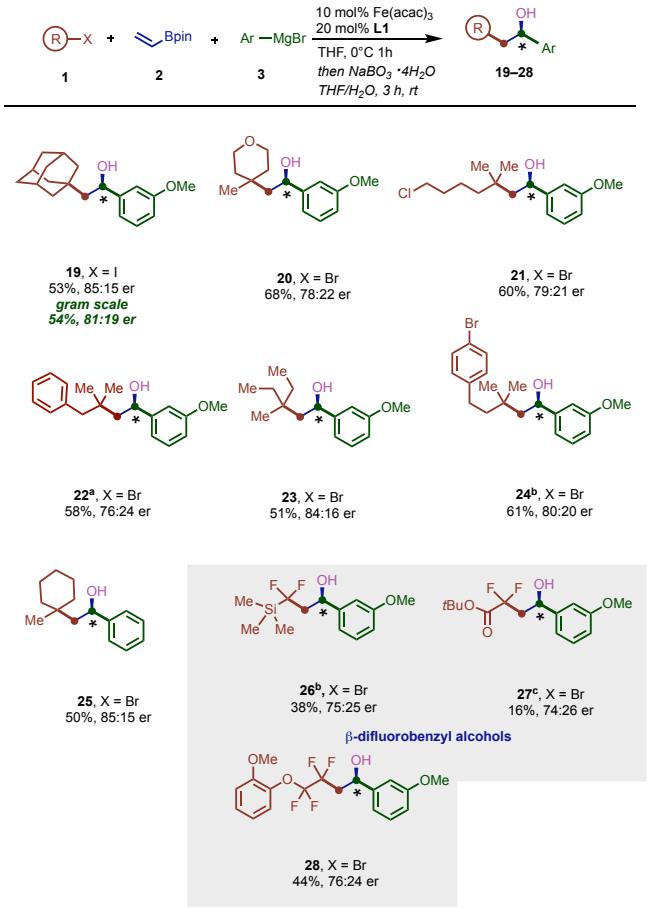


Figure 3. Scope of the alkyl halides in the three-component dicarbofunctionalization with vinylboronic acid pinacol ester and 3-methoxyphenyl magnesium bromide. Reactions were carried out under the optimized conditions (table 1, entry 1). Er determined by HPLC using a chiral stationary phase. [a]Using 2.5 equiv. of **1**. [b]Using 20 mol% $Fe(acac)_3$ and 40 mol% (*R,R*)-BenzP*, [c]Using 4 equiv. of **1** and 4.5 equiv. of **3**.

Next, we turned our sights to the radical precursor scope (Figure 3). The sterically encumbered cyclic tertiary 1-iodoadamantyl radical precursor provided an improved enantioselectivity (**19**; 85:15 er) over the acyclic tertiary system using the same Grignard reagent (68:32 er; table 1, entry 2). Further, the tertiary radical precursor bearing an oxygen-containing cyclohexyl ring gave the desired product **20** in good yield and modest enantioselectivity, revealing the potential applicability towards the practical synthesis of heteroatom-containing compounds with relevance to pharmaceutical research.[21] Notably, the reaction was selective towards tertiary alkyl bromides in the presence of other carbon-halogen bonds including $C(sp^2)$-Br and primary $C(sp^3)$-Cl bonds (**21** and **24**). In addition, other representative acyclic tertiary alkyl radical precursors, including benzylic systems, yield the desired products in good yields and modest enantioselectivities **(22**, **23**, **25)**.

Given that ~20% of drugs on the market contain at least one fluorine atom,[22-24] combined with the lack of enantioselective three-component methods using vinyl borates and difluoroalkyl radical precursors, we were also interested in investigating the possibility of rapidly producing diverse fluorine-containing enantioeneriched alkylboron reagents (inset; Figure 3). Indeed, in contrast to prior methods, fluorinated radical precursors were tolerated in the enantioselective iron-catalyzed multicomponent radical cross-coupling reaction, producing the enantioenriched fluorinated organoboron products (**26**, **27**, and **28**) albeit slightly lower yields and modest enantioselectivity were observed. Presumably, the lower yields are attributed to polarity mismatch between electron-deficient vinylB(pin) and electron-poor (poly)fluoroalkyl radicals that open opportunities for side reactions prior to undergoing the desired Giese addition to vinylB(pin).[25-26]

On the basis on prior experimental and mechanistic studies on Fe-catalyzed asymmetric cross-coupling reactions[18] and multicomponent cross-coupling involving α-boryl radicals,[11f] we turned to dispersion-corrected density functional theory (DFT) calculations to gain insight into the nature of C-C bond formation and the origin of enantioselectivity.

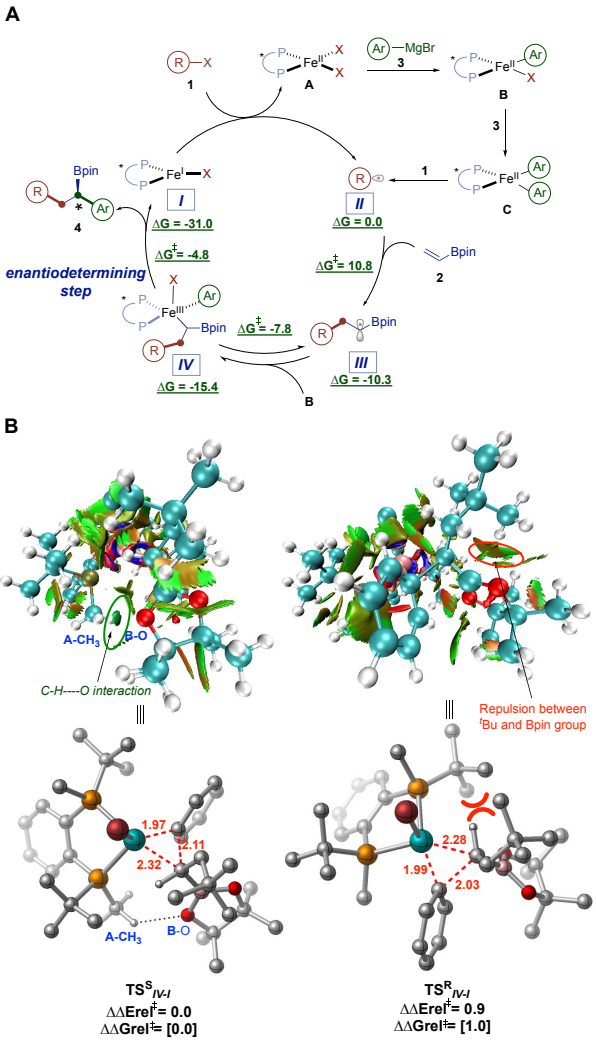


Figure 4. Working mechanistic manifold based on experiments and computational studies.

Specifically, Neidig has shown that bisaryl BenzP*-Fe(II) **C** could generate the alkyl radicals via halogen atom abstraction. In turn, this alkyl radical **I**, as supported by computations and radical trap experiments, could undergo irreversible Giese addition to the vinyl boronate **2** via a low energy barrier (10.8 kcal/mol) to form the α-boryl radical **III**. Finally, akin to 1,2-bis(cyclohexylohosphino)ethane-Fe-catalyzed cross-couplings,[11f] this α-boryl radical **III** can then undergo spin-selective radical addition/dissociation with the monophenylated BenzP*-Fe(II) species **B** to establish an equilibrium with the corresponding Fe(III) intermediate **IV** prior to undergoing C-C bond formation. Thus, consistent with prior work, the equilibrium with the chiral BenzP* ligand also favors the pentacoordinate Fe(III) intermediate (**IV**) as opposed to the dissociated α-boryl radical and iron(II) **B**. We hypothesize that this shift in equilibrium can have pronounced effects in preventing deleterious and unwanted radical pathways stemming from non-coordinated α-boryl radicals (i.e., polymerization, H-atom abstraction, SET oxidation, etc.). Finally, Fe(III) **IV** intermediate is poised to undergo a rapid and enantioselective C-C bond to form the desired enantioenriched multicomponent product **4** and Fe(I) species that can then restart the catalytic cycle.[11a, 27] Further, consistent with the observed enantioselectivity, the energy difference between the lowest energy diastereomeric transition states for the reductive elimination step is ~1.0 kcal/mol (Figure 4B) in favor of the (*S*)-product. As shown in Figure 4B, closer inspection of the lowest energy diastereomeric transition states revealed a favorable C-H---O interaction in **TS^S-IV-I**, which is absent in the competing transition state leading to minor (*R*) product. In addition, the repulsion between the ^{t}Bu group and the Bpin group is more prominent in the transition state leading to the (*R*) product as evident from the NCI (Non-Covalent Interaction) plots.

In conclusion, we have developed an enantioselective iron-catalyzed multicomponent radical cross-coupling reaction that enables to 1,2-dicarbofunctionalization of vinyl boronates with diverse (fluoro)alkyl halides and aryl Grignard reagents. Mechanisitic studies are consistent with radical translocation to form a α-boryl radial that is rapidly intercepted by a chiral mono-aryl bisphosphine-iron leading to enantioselective carbon-carbon bond formation. Further studies are underway to expand the scope of asymmetric multicomponent radical cross-coupling reactions with well-defined and readily available iron catalysts.

Associated Content

Experimental procedures, characterization data, and computational details (PDF)

This material is available free of charge via the Internet at http://pubs.acs.org

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Author Contributions
All authors have given approval to the final version of the manuscript. ‡C.R.Y. and M.H.Y. contributed equally. #A.R.G. and A.R.-G. contributed equally to the calculations.

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