Design and Development of Fe-Catalyzed Intra- and Intermolecular Carbofunctionalization of Vinyl Cyclopropanes

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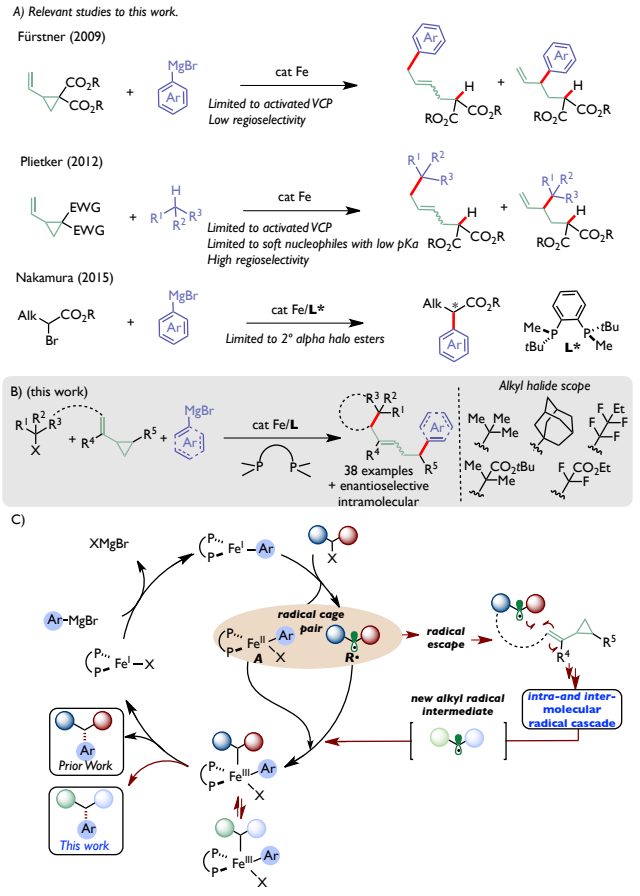
ABSTRACT: Design and implementation of the first (asymmetric) Fe-catalyzed intra- and intermolecular difunctionalization of vinyl cyclopropanes (VCPs) with alkyl halides and aryl Grignard reagents has been realized via a mechanistically driven approach. Mechanistic studies support the diffusion of the radicals intermediates out of the solvent cage to participate in an intra- or intermolecular radical cyclization/ring-opening followed by re-entering the Fe radical cross-coupling cycle to undergo C(sp^2)-C(sp^3) bond formation. Overall, we provide new design principles for Fe-mediated radical processes and underscore the potential of using combined computations and experiments to accelerate the development of challenging transformations.

INTRODUCTION

Iron-catalyzed C-C cross-coupling reactions have attracted much attention due to higher abundance, cost-effective, and lower toxicity of iron in comparison to precious transition metals.[1] Methods for ligand-supported (e.g., N-heterocyclic, bisphosphine, and diamines) and ligand-free systems for iron-catalyzed C-C cross-coupling reactions using C(sp), C(sp^2), and C(sp^3) partners have been developed.[2] In particular, bisphosphine-iron systems have emerged as highly versatile and promising manifolds for the formation of new C-C bonds with a range of organometallic nucleophiles including Mg-(Kumada),[3] Zn- (Negishi),[4] B- (Suzuki-Miyaura),[5] and Al[6] with alkyl halides and redox active esters.[4a] Electron-poor vinyl cyclopropanes have also been used as π-coupling partners in Fe-catalyzed C(sp^2)-C(sp^3) bond formations (**Scheme 1A**). In particular, Fürstner used low valent iron ferrates to promote C-C bond formation using aryl Grignard reagents and vinyl cyclopropanes (VCP).[7] Plietker used a low valent electronic rich ferrate complex ($Bu_4N[Fe(CO)_3(NO)]$) to promote coupling between a range of acidic pronucleophiles and electron-deficient VCPs.[8] Despite these advancements, to the best of our knowledge, there are only two reports of asymmetric iron-catalyzed cross-couplings: between aryl Grignards or lithium aryl borates as nucleophiles and □-halo esters as electrophile (**Scheme 1A**).[9,10] Thus, development of new (asymmetric) iron-catalyzed radical cascade/C(sp^2)-C(sp^3) cross-coupling reactions will expand the synthetic toolbox and lead to an increase in diversification of carbocycles.[11] Herein, we used a mechanistically-guided approach to design and develop new Fe-catalyzed *intra-* and *inter*-molecular dicarbofunctionalization of synthetically versatile vinyl cyclopropanes. (**Scheme 1B**).[12, 13]

Contributing to the scarcity of iron-catalyzed asymmetric methods is likely due to the fact that mechanistic details of iron-catalyzed cross-coupling are not well-understood, in comparison to palladium systems.[14] Pioneering mechanistic studies by Kochi[15] in the 1970s and more recent reports by Bedford,[16] Nakamura,[17] Norrby,[18] Fürstner,[19] Tonzetich,[20]

Scheme 1. Design and development of Fe-catalyzed intra- and inter-molecular functionalization of vinyl cyclopropanes via new radical cascade reaction.

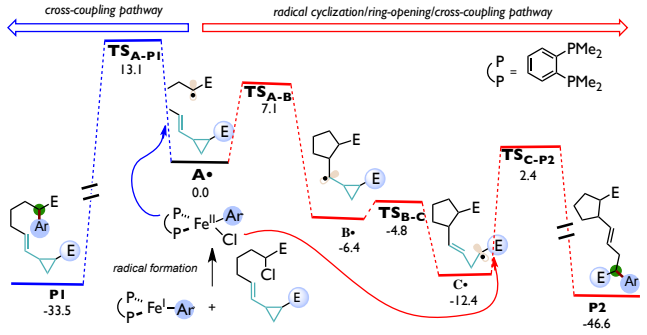


Koszinowski,[21] and Neidig[22] have led to greater understanding of these transformations. In 2017, parallel quantum mechanical studies in our lab[23] and by Morokuma[24] were reported on the mechanism of chiral bisphosphine cross- coupling reactions between □-chloro esters and aryl Grignard reagents. These studies revealed a mechanism involving halogen abstraction by aryl Fe(I) leading for an alkyl radical and halo aryl Fe(II) species (**Scheme 1C**; circled). In turn, these two species could combine leading to Fe(III) intermediate which will then undergo reductive elimination leading to the desired product. More experimental studies (i.e., spectroscopic and kinetic) are needed to assess the validity of the computational models and the mechanism likely depends on subtle changes to the alkyl halide, Grignard, and ligand structures. Nonetheless, based on these mechanistic studies, we envisage diverting the reactivity from the Fe radical cross-coupling catalytic cycle (black) to a programmed *intra-* and *inter*molecular radical cascade (red) with vinyl cyclopropanes leading to a new alkyl radical that could then re-enter the catalytic cycle and undergo C(sp^2)-C(sp^3) bond formation. Given that most of the transition-metal catalyzed cascade reactions terminate with C-H bond formation[25] and fail to control the stereoselectivity at the termination step, if successful, this approach could lead to rapid molecular complexity.

RESULTS AND DISCUSSION

Stereoselective *Intra*-molecular dicarbofunctionalization of VCP. Li's group demonstrated the use of cyclopropyl olefins to promote a radical alkylation, ring-opening, intramolecular arylation cascade reaction under photoredox conditions.[26] Fu and co-workers reported that chiral nickel catalysts could achieve enantioselective cross-couplings of a wide range of racemic alkyl halides (as radical precursors) with organometallic nucleophiles[27] including stereoconvergent radical cyclization/arylation.[28] We hypothesize that, upon radical formation and in the presence of a pendant vinyl cyclopropane, (**Scheme 1C**; right), we could diverge reactivity from the cross-coupling cycle to promote an *intra*-molecular radical cascade reaction. Specifically, we envisage a 5-*exo*-trig cyclization outcompeting radical rebound to aryl Fe species and *diverge* reactivity towards *Fe-catalyzed dicarbofunctionalization of vinyl*

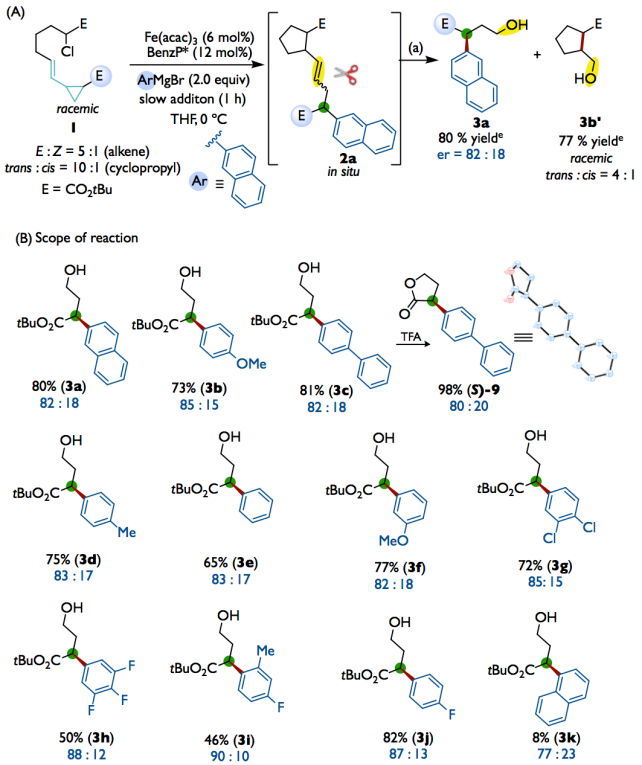
Scheme 2. Energetics for the in-cage (blue) and out-of-cage (red) arylation computed at the UPBEPBE/6-311+G(d,p)-SDD(Fe)-THF(SMD)//UB3LYP/6-31G(d) levels of theory.



cyclopropanes. As shown in **Scheme 2**, quantum mechanical calculations support our hypothesis. Specifically, the barrier for radical 5-*exo*-cyclization (via $\mathbf{TS_{A\text{-}B}}$) to form **B•** is 6.0 kcal/mol *lower* in energy than the barrier for radical rebound transition state $\mathbf{TS_{A\text{-}P1}}$ that will lead to cross-coupling product **P1** (7.1 kcal/mol vs. 13.1 kcal/mol, respectively). In turn, the kinetically-favored cyclic alkyl radical **B•** will then undergo radical ring-opening (barrier is only 1.6 kcal/mol) to form the thermodynamically favored alkyl radical **C•**. Finally, **C•** could then re-enter the iron cross-coupling cycle and undergo C(sp^2)-C(sp^3) bond formation (via $\mathbf{TS_{C\text{-}P2}}$; barrier is 14.8 kcal/mol from **C•**) leading, after reductive elimination (not shown), to the radical cascade product **P2**. Overall, these calculations suggest that the radical cyclization/ring-opening/cross-coupling pathway (leading to **P2**) is kinetically favored over cross-coupling pathway (leading to **P1**). Moreover, we anticipate that the chiral aryl iron species could control the final radical coupling step (with **C•**) and permit high-levels of stereocontrol.[29]

Gratifyingly, we found that we can diverge reactivity towards the *asymmetric intra*-molecular difunctionalization of vinyl cyclopropanes using **1** as substrate (**Scheme 3**). Specifically, using the standard conditions for Fe-catalyzed □-arylation,[30] the reaction of **1** with aryl Grignard gave a mixture of diastereomeric radical cascade products **2a** (see Supporting Information). To determine if the chiral iron species controlled the stereochemistry of terminating C(sp^2)–C(sp^3) arylation (green), we subjected **2a** to a one-pot procedure of ozonolysis followed by reduction by $NaBH_4$ that led to the corresponding product **3a** in good yields and enantioselectivities. Notably, as expected from radical cyclization event in the absence of chiral iron species (**Scheme 2**), the corresponding *racemic* cyclopentane fragment **3b'** was isolated in 77% yield in 4:1 dr. Moreover, as shown in **Scheme 3B**, the aryl Grignard scope is broad. Both electron-poor and electron-rich aryl Grignards participate in the diverted Fe-catalyzed intra-molecular difunctionalization of vinyl cyclopropanes to give the desired

Scheme 3. Design and application of asymmetric Fe-catalyzed intra-molecular dicarbofunctionalization of vinyl cyclopropanes.



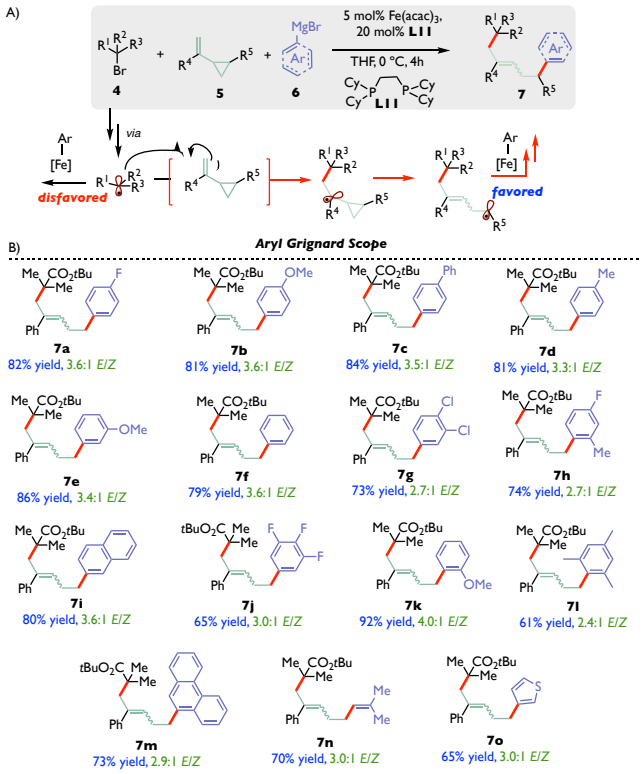
[a] O_3, CH_2Cl_2/MeOH -78 °C, 5 min then $NaBH_4$ (10 equiv) -78 °C to rt, 1 h.

products in good yields (up to 82% over three steps) and enantioselectivities (up to 90:10 er). Highly electron-deficient (i.e., 3,4,5-trifluorophenyl **3h**) and even sterically congested (e.g., *ortho*-methyl aryl **3i** and 1-naphthyl **3k**) aryl Grignard reagents

formed the desired products in good enantioselectivities (77:23 to 90:10 er) albeit lower yields (8-50%). However, at this moment, this method is limited to 5-*exo*-trig radical cyclization. Lengthening the tether by an extra methylene group lead to formation of the Fe radical cross-coupled product and no products from diverged 6-*exo*-trig radical cyclization are observed (See Supporting Information). Presumably the much higher energy barrier to undergo radical 6-*exo*-trig cyclization in comparison to 5-*exo*-trig radical cyclization prevents formation of radical cascade/arylation (see Figure S9 in the Supporting Information for energetics).

Design and application of *Inter*-molecular dicarbofunctionalization of vinyl cyclopropanes. Given the scarcity of stereoconvergent transition metal-catalyzed radical cyclization-arylation cascades, our proof-of-principle results with *intra*molecular functionalization of VCPs (**Scheme 2** and **3**) represent an attractive strategy towards this unmet need.[31] We envisage that by tuning the properties of alkyl halide, we could divert reactivity towards *inter*-molecular difunctionalization of VCPs. Specifically, we hypothesize that sterically hindered *tertiary* alkyl halides will lead to *higher* barriers for *Fe radical coupling* and, instead, favor *inter*-molecular radical addition to the vinyl cyclopropane (**Scheme 4A**). In turn, the incipient radical could then undergo cyclopropyl ring-opening and re-enter the Fe radical cross-coupling cycle to undergo C(sp^2)–C(sp^3) arylation at the least sterically hindered site (*vide infra*).

Scheme 4. Reaction Scope on Aryl Grignard of Fe-catalyzed intermolecular dicarbofunctionalization of vinyl cyclopropanes.

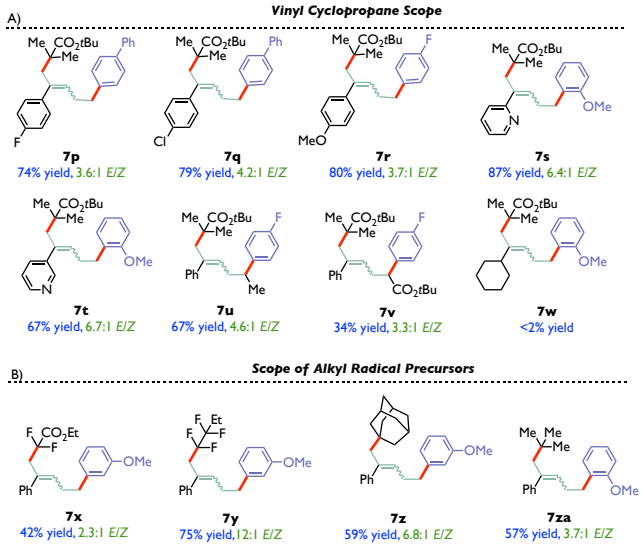


[a] Reactions were performed on a 0.20 mmol scale. [b] ArMgBr was added dropwise via syringe pump over 4 h. [c] Isolated yield.

Previous work by Fürstner and Plietker found that Fe-catalyzed carbofunctionalization of vinyl cyclopropanes (VCPs) terminates with C-H bond formation (**Scheme 1A**).[7, 8] Thus, if successful, this approach will expand the range of Fe-catalyzed transformations using vinyl cyclopropanes as valuable synthons in chemical synthesis.

We initiated our optimization studies using sterically hindered *tert*-butyl 2-bromo-2-methylpropanoate **4**, (1-cyclopropylvinyl)benzene **5** and aryl 4-flurophenylmagnium bromide **6** were selected as model substrates (**Scheme 4**). Gratifyingly, after extensive ligand screening using both bisphosphine, monophosphine, and diamine ligands (See Table S2 in the Supporting Information) and optimization studies, we identified acyclic 1,2-bis(dimethylphosphino)ethane ligand **L11** suitable to promote the desired transformation forming compound **7a** in 82% isolated yield and 3.6:1 *E*/*Z* ratio (**Scheme 4B**). We also performed quantum mechanical calculations on the intermolecular dicarbofunctionalization of this system, and the calculated result is consistent with our hypothesis and the experiment result (see Figure S10 in the Supporting Information for energetics). Specifically, *tertiary* alkyl radical is favored to undergo *inter*-molecular radical addition (with barrier of 14.0 kcal/mol) to the vinyl cyclopropane over radical coupling with Fe (with barrier of 18.2 kcal/mol).

Scheme 5. Vinyl and Alkyl Halide Reaction Scope.

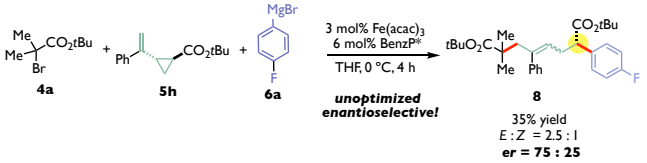


[a] Reactions were performed on a 0.20 mmol scale. [b] ArMgBr was added dropwise via syringe pump over 4 h. [c] Isolated yield.

With optimized conditions in hand, we next investigated the reaction scope of this transformation. As shown in **Scheme 4B**, the scope of this Fe-catalyzed 3-component dicarbofunctionalization is fairly broad with respect to the Grignard nucleophile. Specifically, the reaction tolerated both electron-withdrawing and electron-donating aryl nucleophiles forming the desired 1,5-dicarbofunctionalization products in 61-92% yield. Notably, the reaction tolerated sterically hindered *ortho*-substituted aryl Grignards (**7h**, **7k**, **7l**, **7m**) that proved problematic in previous Fe-catalyzed cross-coupling reactions.[32] To highlight the versatility of this method, we used both *vinyl* and *hetero*aryl nucleophiles and, gratifying, provided the desired products **7n** and **7o**, in good yield, 70% and 65% yield, respectively. We further explored the scope of the vinyl cyclopropane and alkyl radical precursors (**Scheme 5**). Installing electron-rich or electron-poor aryl groups in the vinyl cyclopropane moiety (R^4) formed the desired products with good yields (**Scheme 5A**). Further, the reaction tolerates medicinally relevant heterocyclic aryl groups (**7s**, **7t**) and the substituted cyclopropanes (R^5) were suitable for this catalytic system, affording **7u** and **7v** in 67% and 34% yield, respectively. It is

worth noting that alkyl VCPs is beyond the reach of the present Fe-based system such as **7w**. We next examined the substrate scope in regard to the alkyl radical precursor (**Scheme 5B**). Notably, we found that both alkyl fluorinated radical precursors are effective partners in the Fe-catalyzed intermolecular dicarbofunctionalization of VCPs yielding the desired products **7x** and **7y** in 42% and 75% yield, respectively. Further, we observed a much higher *E*/*Z* ratio for **7y** although the origin of this high selectivity is currently unknown. Finally, *unactivated 3° alkyl radical precursors also formed to the desired 3-component **7z** and **7za** products*. Pleasingly, as predicted by computations, preliminary results (**Scheme 6**) demonstrate that the chiral iron species could control enantioselectivity at the terminal site of C-C formation in the presence of an ester moiety although, at the current stage, this reaction suffers from low yields.

Scheme 6. Preliminary results of asymmetric Fe-catalyzed intermolecular dicarbofunctionalization of vinyl cyclopropanes.



[a] Reactions were performed on a 0.20 mmol scale. [b] ArMgBr was added dropwise via syringe pump over 4 h. [c] Isolated yield.[d] The enantiomeric ratio (er) value of (*E*)-**8** was determined using chiral HPLC analysis.

CONCLUSIONS

In summary, Fe-catalyzed *intra*- and *inter*-molecular dicarbofunctionalization of vinyl cyclopropanes have now been realized. In particular, we have used a mechanistically driven (computational and experimental) approach to diverge reactivity of the alkyl radical from the Fe radical cross-coupling cycle to undergo *intra*- and *inter*-molecular radical cascade reaction with vinyl cyclopropanes. In turn, the incipient alkyl radical could then re-enter the Fe cross-coupling cycle and undergo (stereoselective) C(sp^2)-C(sp^3) bond formation. We anticipate the intermolecular 3-component Fe-catalyzed dicarbofuncationalization reaction to impact the synthesis medicinally relevant molecules. Ongoing work is focused on expanding this strategy to a wide range of alkyl radicals and π-coupling partners participating in diverged Fe-catalyzed radical cascade/cross-coupling reactions and using quantum mechanical calculations to optimize asymmetric variations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental and computational details, coordinates, and spectral data (PDF)
Crystallographic data (CIF)

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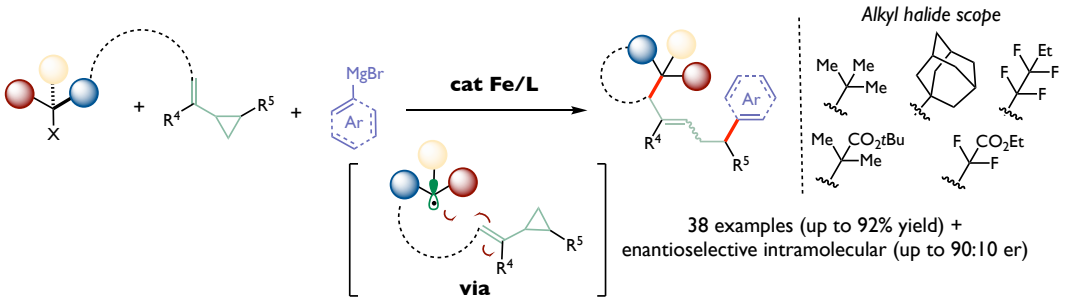
Table of Contents (TOC).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38 examples (up to 92% yield) +
enantioselective intramolecular (up to 90:10 er)