General and Practical Route to Diverse 1,3-(Difluoro)alkyl bicyclo[1.1.1]-Aryl Pentanes Enabled by an Fe-Catalyzed Multicomponent Radical Coupling

Angel Rentería-Gómez,[‡1] Wes Lee, [‡2] Shuai Yin,[1] Michael Davis,[2] Achyut Ranjan Gogoi,[1], Osvaldo Gutierrez*[1,2]

[1]*Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States*

[2]*Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States.*

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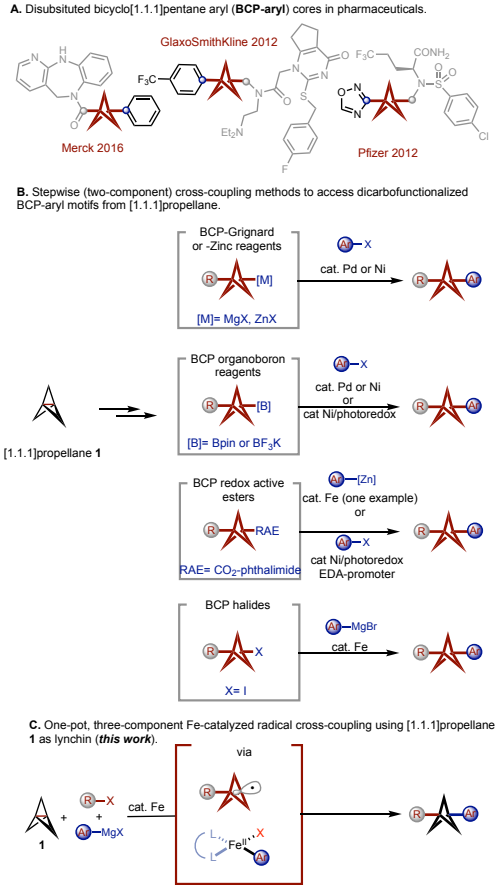
ABSTRACT: Bicyclo[1.1.1]pentanes (BCPs) are of great interest to the agrochemical, materials, and pharmaceutical industries. In particular, synthetic methods to access 1,3-dicarbosubsituted BCP-aryls have recently been developed but most protocols rely on stepwise C-C bond formation via initial manipulation of BCP core to make the BCP-electrophile or -nucleophile followed by a second step (e.g., transition-metal mediated cross-coupling step) to form the second key BCP-aryl bond. Moreover, despite prevalence of C-F bonds in bioactive compounds, one pot, multicomponent cross-coupling methods to directly functionalize BCP to the corresponding fluoroalkyl BCP-aryl scaffolds are lacking. In this work, we describe a conceptual different approach to access diverse (fluoro)alkyl BCP-aryls at low temperatures and fast reaction times enabled by an iron-catalyzed multicomponent radical cross-coupling reaction from readily available (fluoro)alkyl halides, bicyclo[1.1.1]pentane, and Grignard reagents. Further, experimental and computational mechanistic studies provide insights into mechanism and ligand effects on the nature of C-C bond formation. Finally, these studies are used to develop a new method to rapidly access synthetic versatile 1-(fluoro)alkyl,3-bromo and -iodo BCPs via bisphosphine iron catalysis.

INTRODUCTION

Bicyclo[1.1.1]pentanes (BCPs) are of great interest to the agrochemical, materials and pharmaceutical industries.[1] In particular, the BCP motif is important in drug design because of their well-known use as bioisosteres for *para*-substituted arenes, *tert*-butyl motifs, and alkynes to improve the pharmacokinetic profile of drug candidates by increasing metabolic stability, aqueous solubility, and membrane permeability.[2] In this vein, 1,3-dicarbosubstituted BCP-aryls are found in numerous pharmaceutical relevant molecules (Scheme 1A) and the development of new synthetic methods to access diverse BCP-aryls continues to be an active area of research. However, most methods rely on stepwise C-C bond formation via initial functionalization of BCP to the corresponding electrophile or nucleophile followed by a second transition-metal cross-coupling step (Scheme 1B). For example, Szeimies,[3] de Meijere,[4] Knochel[5] have taken advantage of the addition of organometallic reagents to promote ring-opening of [1.1.1]propellane to form BCP-Grignard or zinc nucleophiles which can then be cross-coupled with aryl halides under palladium or nickel catalysis. Uchiyama,[6] Walsh,[7] and VanHeyst[8] reported the use of organoboron BCPs as effective coupling partners in Pd- and dual Ni/photoredox-catalyzed BCP-aryl cross-couplings. The Baran[9] and Molander[10] groups have reported the use of substituted redox-active esters in Fe- and Ni-catalyzed BCP-aryl cross-couplings with aryl zinc reagents and aryl halides, respectively. Finally, Anderson[11] has the reported the use of BCP-iodides to cross-couple with (hetero)aryl Grignard reagents under iron catalysis.



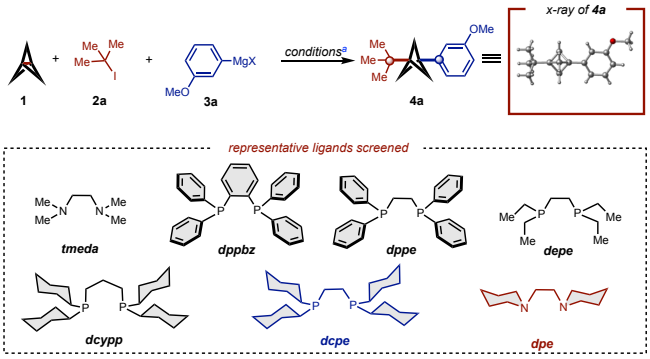
Scheme 1. Cross-coupling methods to construct 1,3-difunctionalized substituted BCP-aryls.

However, in contrast to the aforementioned two-component cross-coupling approaches to diversify BCP-aryls, the development of one-step, multicomponent catalytic cross-coupling (MC-CCR) methods could provide a more synthetically advantageous, versatile, and sustainable route to rapidly access diverse BCP-aryls.[12] In this context, despite the growing number of synthetic methods for accessing functionalized BCPs from **1** via multicomponent reactions,[13141516] reports of MC-CCR to form the difunctionalized BCP-aryls are rare[17] and the use of inexpensive and abundant iron complexes as catalysts in this type of process remains elusive. Finally, despite the omnipresence of C-F bonds in approved drugs,[18] general, multicomponent, and catalytic methods for the synthesis of (difluoro)alkyl dicarbosubstituted BCP-aryl motifs are lacking likely due to challenges associated with a) controlling formation of alkyl radicals and, at the same time, b) trapping the *in situ* generated BCP radicals selectively with a transition metal-*aryl* species prior to undergoing potential side reactions such as H-atom abstraction, elimination, polymerization, single electron transfer, etc. Based on our program in Fe-catalyzed MR-CCRs,[19] we hypothesized that we could take advantage of the rapid kinetics associated with bisphosphine-iron catalysis to form and trap BCP alkyl radicals under slow addition of Grignard reagents. If successful, in contrast to prior methods, this protocol will allow formation of disubstituted BCP-aryl directly from bicyclo[1.1.1]pentane. Here we present a general strategy for the synthesis of diverse 1,3-difluoro(alkyl)-BCP-aryls that uses inexpensive iron salts and proceeds with low temperatures and exceeding fast reaction times (Scheme 1C). Finally, experimental and computational mechanistic studies shed light into the role of ligand in BCP-aryl bond formation and provide a catalytic platform to access synthetically useful (difluro)alkyl BCP halides primed for further functionalization.

RESULTS AND DISCUSSION

To evaluate the feasibility of our designed multicomponent strategy, we selected [1.1.1]propellane (**1**, 1.1 equiv), *tert*-butyl iodide (**2a**, 1.0 equiv) and 3-methoxyphenylmagnesium bromide (**3a**, 1.2 equiv) as the model substrates (Table 1). Notably, using our previously reported conditions for multicomponent dcpe-iron-catalyzed cross-couplings, we were able to observe the formation of the desired product **5** albeit low (29%) yield (entry 1). Gratifyingly, additional optimization through variation of the alkyl halide, lynchpin **1**, and aryl Grignard reagent led to significant increase in overall yield (up to 70%) (entries 2-6). Not surprisingly, we observed that lowering the Grignard reagent (added via syringe pump over the course of 1 hour) had a drastic effect on overall efficiency (29 % yield) (entry 7) while increasing the alkyl halide had a slight detrimental effect on overall yield (entry 8). From these studies, it is clear that subtle changes to the relative concentrations among the three components is crucial for overall efficiency. Control experiments show the importance of the unique iron precatalyst and ligand combination to achieve good yields (entries 9-12). Finally, to

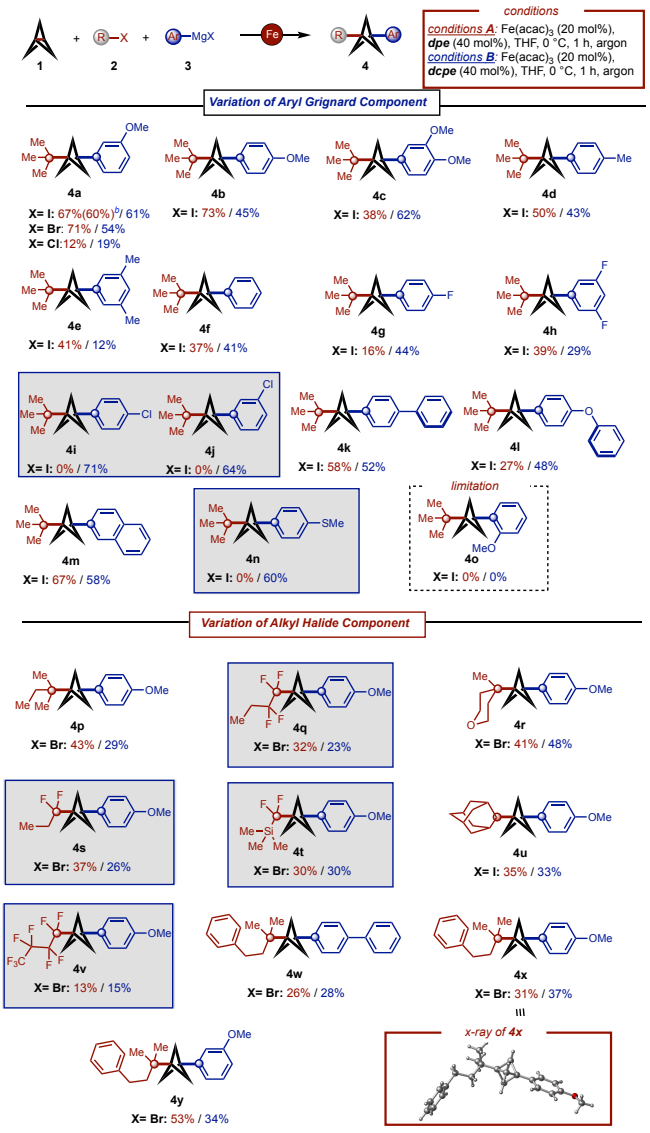
Table 1. Optimization of the one-step, multicomponent Fe-catalyzed cross-coupling method to form 1,3-difunctionalized substituted BCP-aryls.



Entry	**1**/**2a**/**3a** (equiv.)	Fe/Ligand	**4a** Yield (%)[b]
1	1.1/1.0/1.2	$Fe(acac)_3$/dcpe	29
2	2.0/1.0/3.0	$Fe(acac)_3$/dcpe	30
3	4.0/1.0/3.0	$Fe(acac)_3$/dcpe	7
4	1.0/2.0/4.2	$Fe(acac)_3$/dcpe	70
5	1.0[c]/2.0/4.2	$Fe(acac)_3$/dcpe	69 (61)[e]
6	1.0[d]/2.0/4.2	$Fe(acac)_3$/dcpe	70
7	1.0/2.0/2.2	$Fe(acac)_3$/dcpe	29
8	1.0/4.0/4.2	$Fe(acac)_3$/dcpe	41
9	1.0/2.0/4.2	none/dcpe	0
10	1.0/2.0/4.2	$Fe(acac)_3$/none	13
11	1.0/2.0/4.2	$FeBr_2$/dcpe	34
12	1.0/2.0/4.2	$FeCl_3$/dcpe	9
13	1.0/2.0/4.2	$Fe(acac)_3$/TMEDA	67
14	1.0/2.0/4.2	$Fe(acac)_3$/DPE	77 (67)[e]
15	1.0/2.0/4.2	$Fe(acac)_3$/dppbz	0
16	1.0/2.0/4.2	$Fe(acac)_3$/dppe	0
17	1.0/2.0/4.2	$Fe(acac)_3$/depe	0
18	1.0/2.0/4.2	$Fe(acac)_3$/dcypp	53
19[f]	1.0/2.0/4.2	$Fe(acac)_3$/dcpe	41

[a] Reaction conditions: Fe catalyst (20 mol %), ligand (40 mol %), THF (1.0 M), 0 °C, 1 h, argon atmosphere. [b]Determined by ^{1}H NMR using 1,2-dibromomethane as an internal standard. [c]Solution of [1.1.1]propellane 0.45 M in Et_2O. [d]Solution of [1.1.1]propellane 1.0 M in Et_2O. [e]Yield (%) of isolated product. [f]$Fe(acac)_3$ (10 mol %), dcpe (20 mol %).

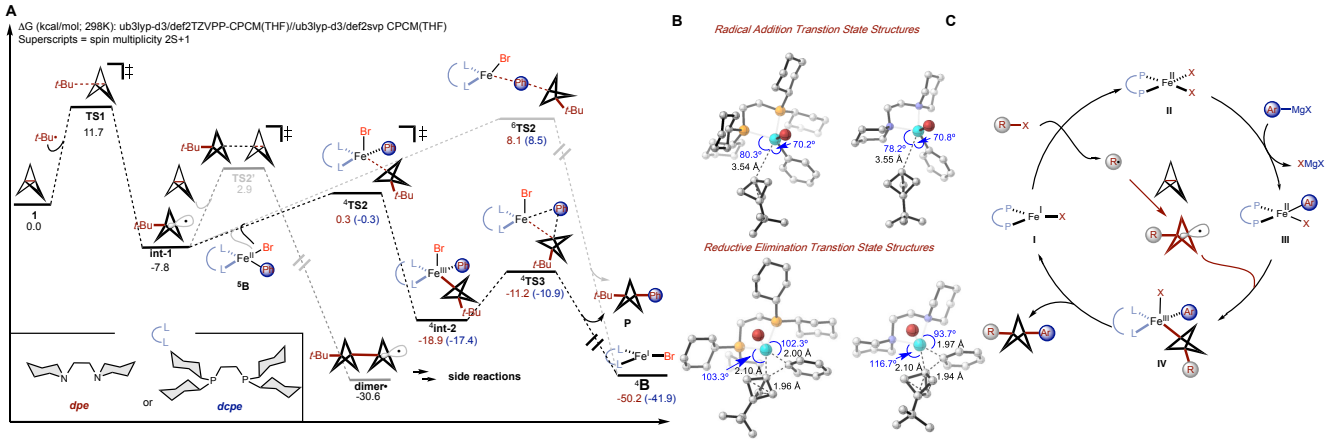
assess the ligand effect on this multicomponent transformation, we screened several commercially available diamines and bisphosphine ligands (entry 13-18). To our surprise, while all other bisphosphine ligands screened were found less efficient, *diamines* ligands i.e., tmeda and, more specifically, hindered 1,2-dipiperidinoethane (dpe), lead to similar overall yields (~77%) as with the dcpe ligand (entry 13-14). Presumably, under these conditions, the crucial *mono*-ligated halo Fe-aryl and Fe-bisaryl species required for tandem effective radical formation and cross-coupling are formed.[19a] Notably, at lower catalyst/ligand loadings the reaction proceeded smoothly albeit with slightly reduced overall yield (entry 19). Overall, the two sets of optimized conditions [i.e., *conditions A*: $Fe(acac)_3$ (20 mol %) and dcpe (40 mol %) or *conditions B*: $Fe(acac)_3$ (20 mol %) and dpe (40 mol %)] in THF at 0 ºC led to the formation of the sterically encumbered BCP-aryl **4a** in 61% (dcpe) and 67% (dpe) isolated yield. Lastly, the product of the one-step Fe-catalyzed dicarbofunctionalization of the [1.1.1]propellane was confirmed by X-ray diffraction analysis of compound **4a**.



Scheme 2. Scope of bisphosphine- and diamine-iron catalytic systems to construct 1,3-difunctionalized substituted BCP-aryls.

With catalytic diamine- and bisphosphine-iron optimized conditions in hand (i.e., *conditions A* and *B*, respectively) the scope of aryl Grignard reagent in this unique one-step, three-component reaction to form 1,3-dicarbofunctionilized BCP-aryls was first evaluated. A shown in Scheme 2, both *conditions A* and *B* allowed the Fe-catalyzed multicomponent cross-coupling of aryl Grignard **3a** with *tert*-butyl iodide, *tert*-butyl bromide, and even *tert*-butyl chloride, albeit at lower yields, to form the desired BCP-aryl **4a** with similar efficiency. Notably, at larger scale (2.0 mmol) the reaction proceeded smoothly forming the desired product **4a** in 60% isolated yield. Overall, a wide range of aryl Grignard reagents were compatible in this one-pot procedure to form two carbon-carbon bonds with sterically-hindered *tert*-butyl iodide and BCP **1** leading to the corresponding 1,3-dicarbofunctionalized BCP-aryls **4a-n** in modest to good yields (up to 73%). In some cases, such as **4a** (67% / 61%), **4d** (50% / 43%), **4f** (37% / 41%) and **4k** (58% / 52%), both dcpe and dpe-iron catalytic systems led to similar overall efficiency. However, in other cases, there were significant differences in the overall outcome between these two catalytic systems. For example, for the formation of **4b** and **4e**, the dpe-iron catalytic system (*condition A*) was far superior. On the other hand, with aryl Grignard reagents bearing weak carbon-chlorine and -sulfur bonds (e.g., **4i**, **4j** and **4n**), the dcpe-iron (*condition B*) was uniquely suited to form the desired three-component radical cross-coupling (60-71% overall yields) while the dpe-iron system failed to form any product. Finally, while *meta*- and *para*-substituted Grignard reagents afforded products, *ortho*-substituted Grignard reagents were not compatible (**4o**) presumably due to a higher energetic barrier to trap the BCP radical with sterically hindered Fe-aryl species thus opening opportunities for side reactions (e.g., oligomerization) prior to BCP-aryl cross-coupling (*vide infra*). Having investigated the aryl Grignard scope, we then turn our attention to explore the scope alkyl halides as radical precursors in this radical multicomponent cross-coupling reaction. As shown in Scheme 2 (bottom), this method tolerated a range of sterically hindered alkyl halides (**4p**, **4r**, **4u**, **4w**, **4x**, and **4y**) although slightly lower yields were observed with tertiary alkyl radicals bearing β-hydrogens, independent of *conditions A* or *B*, presumably due to competitive β-elimination prior to the desired radical addition to **1** thus lowering overall the efficiency of the three-component reaction. Notably, we found that this method is uniquely suited towards the rapid and modular synthesis of difluoro-BCP-aryls (**4q**, **4s**, **4t**, **4v**), which to date remain unprecedented in one-pot, multicomponent cross-coupling reactions, using readily available difluoroalkyl bromides as radical precursors. Although lower yields were observed in this transformation, we envision that in the initial stages of pharmaceutical drug discovery, where rapid access to diverse analogs are needed for screening, this method could be broadly applicable. Finally, the dicarbofunctionalization of the [1.1.1]propellane was unequivocally confirmed by X-ray diffraction analysis of compound **4x**.

To gain insight into the nature of the ligand in the C–C bond formation, we turned to dispersion-corrected density functional theory (DFT) calculations (see the SI for additional details). Based on prior mechanistic studies from our group and others,[19a,20,21,22,23] we envisioned alkyl radical undergoing halogen abstraction by an iron species (not shown) to form ***t*-Bu•** radical. In turn, as shown in Scheme 3A, radical addition to [1.1.1]propellane **1** (via **TS1**) proceeds via a low energy barrier (11.7 kcal/mol) a leading to *tert*-butyl BCP radical **int-1**. Notably, in contrast to prior work with *acyclic* tertiary alkyl radicals,[19a] in both diamine- and bisphosphine-iron model systems, this strained, cyclic alkyl radical can rapidly and *irreversibly* add to ligated mono-aryl Fe(II) species ^{5}**B** via spin-selective ^{4}**TS2** (barrier, ~8.0 kcal/mol) to form the corresponding distorted square pyramidal Fe(III)-alkyl intermediate ^{4}**int-2**. Finally, irreversible reductive elimination via ^{4}**TS3** (barrier only

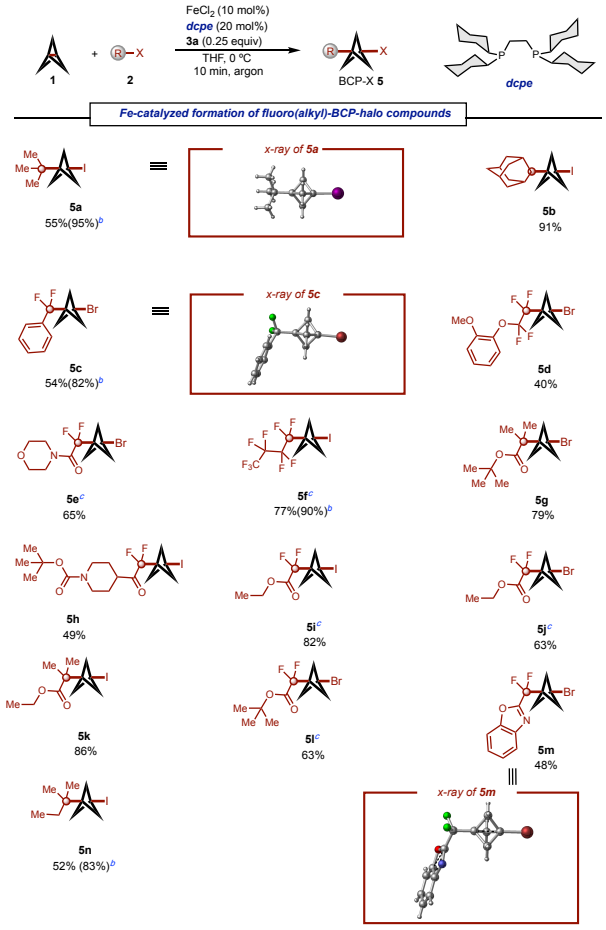


Scheme 3. (a) Computational studies on the ligand effects (red using dpe and blue using dcpe) on the mechanism of three-component alkyl-arylation of BCP (**A**); (b) comparison of the relevant lowest energy radical addition and reductive elimination transition state structures demonstrating similar energetic profiles and transition states for C-C bond formation with bisphosphine- and diamine-iron catalytic systems and (c) proposed catalytic cycle.

~6.5 kcal/mol) will lead to the desired product BCP-aryl product **P** and Fe(I) species ^{4}**B**, which can then restart the catalytic cycle (*vide infra*). In addition, we also considered an alternative pathway in which the C–C bond is formed through outer-sphere ^{6}**TS4** but, consistent with prior studies,[19,22,23] this pathway is ruled out this pathway based on a much higher energy barrier (~16.0 kcal/mol) compared with the inner-sphere stepwise C–C bond formation in *both* diamine- and bisphosphine systems. To highlight the crucial effect of relative concentrations in these transformations, we also computed radical addition of **int-1** to another BCP molecule (grey). These calculations show that the barrier for radical addition is only 2-3 kcal/mol higher in energy than addition to the mono-aryl Fe(II) species. Thus, for effective three-component radical cross-coupling, it is crucial to couple the addition of Grignard reagent to generate the corresponding mono-aryl Fe(II) *in situ* (so it can rapidly trap the BCP radical) without over transmetallating this species to the unproductive diaryl Fe(II). Otherwise, other side reactions (e.g., oligomerization)[21] can quickly take place. Finally, we note that both ligands (dcpe and dpe) gave extremely similar energy profiles for C-C bond formation which we attribute to comparable sterics imposed by both of these ligands in the key radical addition and reductive elimination transition states (Scheme 3B). As such, on the basis of the aforementioned controls and prior mechanistic studies,[19,20,21,22,23] a possible catalytic cycle is depicted in Scheme 3C. Upon the formation of putative Fe(I) **I**, this can, in turn, undergo halogen-atom abstraction to form the alkyl radical and Fe(II) **II** species. Alkyl radical **R•** can escape the solvent cage to undergo radical addition to [1.1.1]propellane and form BCP radical with concomitant formation of organoiron **III** from transmetallation of **II** with aryl Grignard reagent. Finally, under slow addition of Grignard reagent to prevent over transmetallation of **III**, stepwise C-C formation will occur thus restarting the catalytic cycle. However, at this stage, further mechanistic studies are needed to convincingly identify the iron species responsible for radical formation and C-C bond formation.

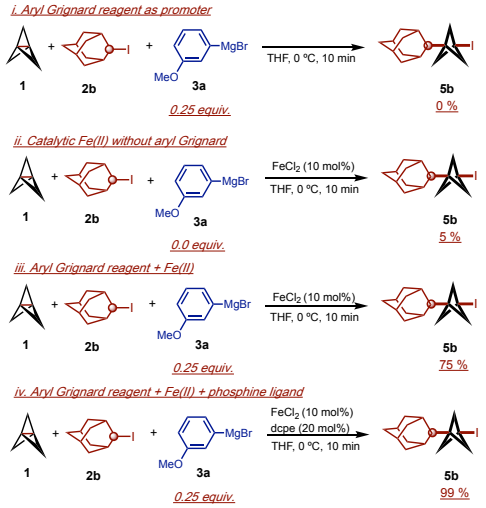
En route to optimizing the three-component dicarbofunctionalization of BCP **1**, we noticed formation of the 1,3-*tert*-butyl BCP-iodide **5a**, presumably from the competing Fe-catalyzed atom-transfer radical addition (ATRA) to BCP (*vide infra*). Although **5a** could be an intermediate in the multicomponent dicarbofunctionalization of BCP, we hypothesize that under *conditions A* or *B* the *alkyl halo BCP is an off-cycle species* in the current Fe-catalyzed three-component radical cross-coupling. Nonetheless, given the current interest in generating (fluoro)alkyl halo BCP species as key intermediates for subsequent modifications in pharmaceutical research and the limitations in the methodologies reported,[2k, 24] we proceeded to optimize reaction conditions for bisphosphine-Fe-catalyzed atom-transfer radical addition (ATRA) to BCP. Notably, although $Fe(acac)_3$ gives the best yield for the three-components reaction (Table 1, entry 14), we found that the use of $FeCl_3$ is more efficient to obtain the halogen transfer product **5**. (Table S1). Gratifyingly, after several rounds of optimization, we found suitable reaction conditions that afforded the corresponding alkyl BCP iodide **5a** in excellent yields (up to 95% yield). With the optimized conditions in hand, the scope varying the nature of alkyl halides was thoroughly examined. As shown in Scheme 4, acyclic and cyclic tertiary alkyl iodides and α-tertiary alkyl bromides provided the desired 1,3-alkylhalo BCPs (**5a**, **5b**, **5g**, and **5n**) including those bearing versatile ester functionalities for further modifications (e.g., via radical cross-couplings).[25] In addition, given that ~20% of drugs in the market contain at least one fluorine atom,[18] we found that a wide range of difluoroalkyl *bromides and iodides* were also compatible in this transformation yielding the desired 1,3-fluoroalkyl-halo BCPs (**5c-f**, and **5h-m**). Notably, additional control experiments revealed that when $FeCl_2$, dcpe, and aryl Grignard **3a** are omitted, in some cases significant background reaction is

operative leading to the corresponding (**5e**, **5f**, **5i**, and **5l**) in similar yields, presumably from radical-induced atom transfer radical addition (See Supporting Information). Finally, the structure for the BCP-halides **5a**, **5c** and **5m** were confirmed by X-ray diffraction analysis. We anticipate that this catalytic method will provide an attractive complementary approach to current use of photoredox catalysts, triethylborane initiators, heating with organometallic reagents, or high-pressure mercury lamp irradiation to provide access to carbon-substituted halo BCP intermediates.



Scheme 4. Substrate scope of bisphosphine-Fe-catalyzed atom-transfer radical addition (ATRA) to BCP. [a]Reactions were carried out using **1** (0.2 mmol), **2** (0.4 mmol), **3a** (0.1 mmol), $FeCl_2$ (10 mol %), dcpe (20 mol %), THF (0.2 mL) at 0 °C under an argon atmosphere, and isolated yields were reported. [b] ^{1}H NMR yield (in parenthesis) determined by using 1,2-dibromomethane as an internal standard. [c] Similar yields were obtained in the absence of $FeCl_2$, dcpe and **3a**.

To gain insight into the mechanism of this transformation to form alkyl halo BCPs, control experiments were carried out (**Scheme 5**). Stirring a solution of compounds **1** and **2b** in THF with only 0.25 equiv. of Grignard (**3a**) did not afforded the desired product. Further, traces of compound were observed when the reaction is carried out using catalytic amounts of $FeCl_2$ in absence of Grignard reagent. However, the combination of catalytic $FeCl_2$ with 0.25 equiv. of aryl Grignard reagent afforded the desired product in good yield. Nonetheless, the use of catalytic bisphosphine ligand significantly increases the yield. Overall, we attribute the reactivity to form the alkyl-BCP-halides to a unique bisphosphine-iron catalytic system that, under aryl Grignard as promoter, is able to generate the active bisphosphine-iron species that enables halogen-atom abstraction from the alkyl halide to form alkyl radical which, in turn, adds to the BCP and, finally, undergoes halogen rebound to restart the catalytic cycle. On the other hand, under three-component catalytic conditions and with $Fe(acac)_3$ (using either bisphosphine or diamine ligand), the aryl-iron catalytic species traps BCP radical (prior halogen transfer to BCP from alkyl halide or Fe-halo species) to form the final BCP-aryl (Scheme 3C). In this case, the ATRA is a background reaction leading to unproductive formation of off-cycle 1,3-alkylhalo BCP. Detailed mechanistic studies are underway to determine the origin of Fe-catalyzes ATRA vs. multicomponent cross-coupling and will be reported in due course.



Scheme 5. Control reactions to shed light into the role of iron and ligand in the atom-transfer radical addition reaction using BCP as radical acceptor. ^{1}H NMR yield determined by using 1,2-dibromomethane as an internal standard.

CONCLUSION

In summary, we have developed a multicomponent, one-pot three-component reaction that utilize [1.1.1]propellane as lynchpin to form a range of synthetically valuable 1,3-difunctionalized BCP-aryls under diamine- and bisphosphine-iron catalysis. In addition, using a mechanistic-driven approach, we have developed an efficient iron promoted method to

synthesize (fluoro)alkyl halo substituted bicyclo[1.1.1]pentanes from readily available (fluoro)alkyl -iodide and -bromide starting materials. Further mechanistic studies are underway to elucidate the factors controlling halogen rebound vs. C-C bond formation in these transformations.

ASSOCIATED CONTENT

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

Accession Codes

CCDC 2118415, 2113560, 2189723, 2189728 and 2189730 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/ cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

*Corresponding Authors

Osvaldo Gutierrez − Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States; orcid.org/0000-0001-8151-7519
Email: og.labs@tamu.edu

Authors

Angel Rentería-Gómez- Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States; https://orcid.org/0000-0002-9411-8805

Wes Lee-Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States; https://orcid.org/0000-0002-8754-6481

Shuai Yin- Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States. https://orcid.org/0000-0001-6911-7416

Michel Davis-Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States.

Achyut Ranjan Gogoi- Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States; https://orcid.org/0000-0002-7609-3720

Author Contributions

‖These authors contributed equally

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