

General and Practical Route to Diverse 1-(Difluoro)alkyl-3-aryl Bicyclo[1.1.1]pentanes Enabled by an Fe-Catalyzed Multicomponent Radical Cross-Coupling Reaction

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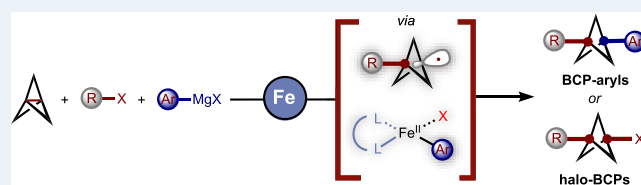
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ABSTRACT: Bicyclo[1.1.1]pentanes (BCPs) are of great interest to the agrochemical, materials, and pharmaceutical industries. In particular, synthetic methods to access 1,3-dicarbosubstituted BCP-aryls have recently been developed, but most protocols rely on the stepwise C–C bond formation via the 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 the prevalence of C–F bonds in bioactive compounds, one-pot, multicomponent cross-coupling methods to directly functionalize [1.1.1]propellane to the corresponding fluoroalkyl BCP-aryl scaffolds are lacking. In this work, we describe a conceptually 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, [1.1.1]propellane, and Grignard reagents. Further, experimental and computational mechanistic studies provide insights into the mechanism and ligand effects on the nature of C–C bond formation. Finally, these studies are used to develop a method to rapidly access synthetic versatile (difluoro)alkyl BCP halides via bisphosphine-iron catalysis.

KEYWORDS: multicomponent, cross-couplings, dicarbofunctionalization, sustainable catalysis, iron



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 the stepwise C–C bond formation via the initial functionalization of [1.1.1]propellane to the corresponding electrophile or nucleophile followed by a second transition-metal cross-coupling step (Scheme 1B). For example, Szeimies,³ de Meijere,⁴ and Knochel⁵ 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 VanHeyst⁸ reported the use of organoboron BCPs as effective coupling partners in Pd- and dual Ni/photoredox-catalyzed BCP-aryl cross-couplings. The Baran⁹ and Molander¹⁰ groups have reported the use of

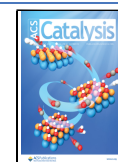
substituted redox-active esters in Fe- and Ni-catalyzed BCP-aryl cross-couplings with aryl zinc reagents and aryl halides, respectively. Finally, Anderson¹¹ has reported the use of BCP-iodides to cross-couple with (hetero)aryl Grignard reagents under iron catalysis.

However, in contrast to the aforementioned two-component cross-coupling approaches to diversify BCP-aryls, the development of one-step, multicomponent catalytic cross-coupling reactions (MC-CCR) 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,^{13–16} reports of MC-CCR to form the difunctionalized BCP-aryls are rare¹⁷ 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

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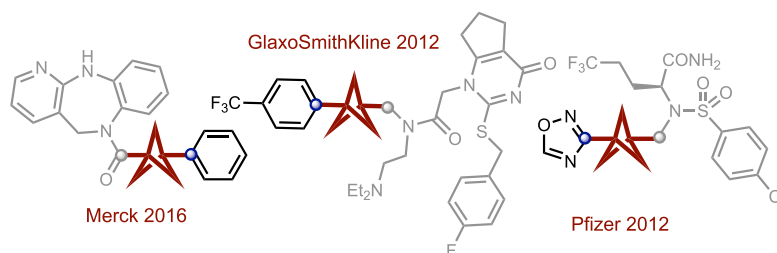
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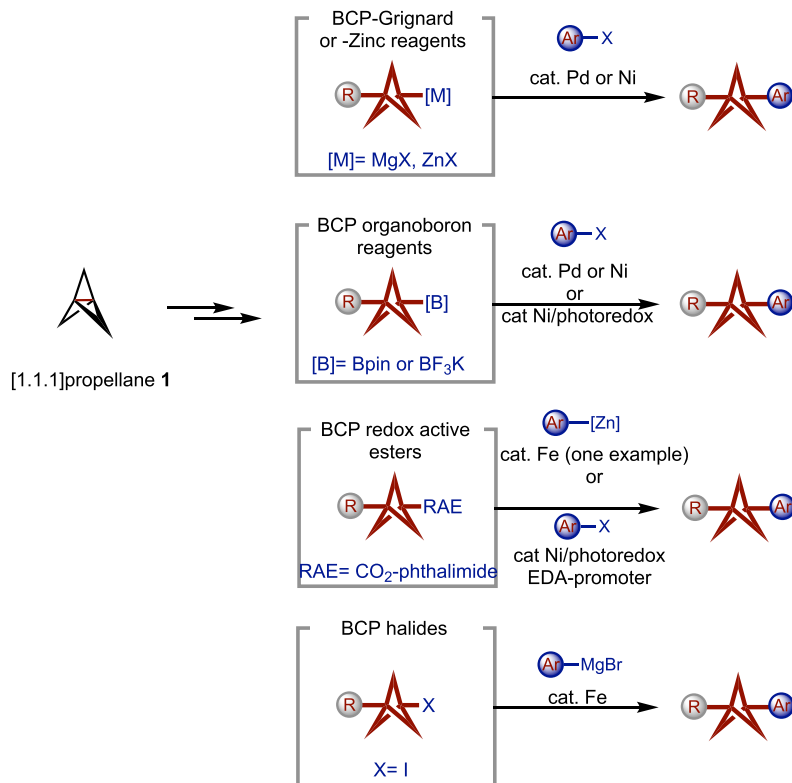
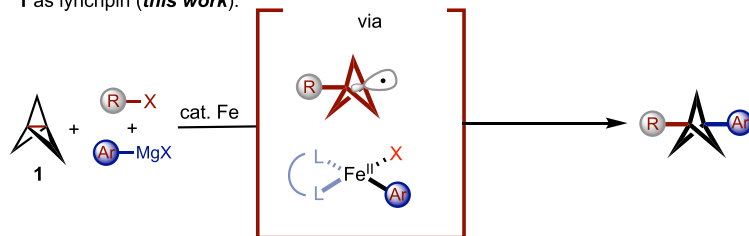


Scheme 1. Cross-Coupling Methods to Construct 1,3-Difunctionalized-Substituted BCP-Aryls

A. Disubstituted bicyclo[1.1.1]pentane aryl (BCP-aryl) cores in pharmaceuticals.

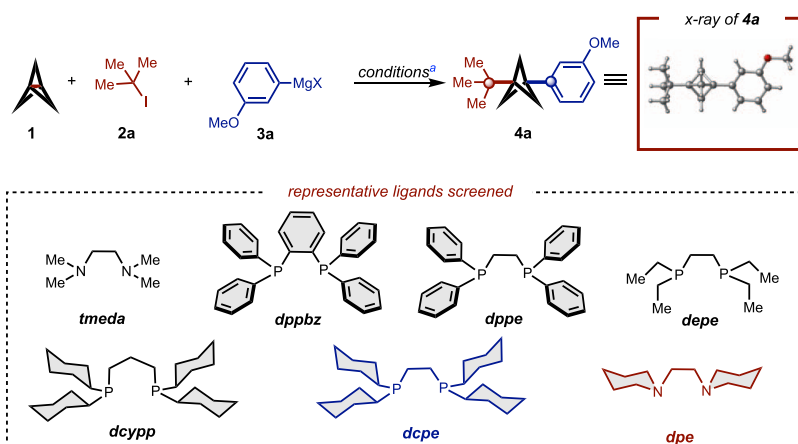


B. Stepwise (two-component) cross-coupling methods to access dicarbofunctionalized BCP-aryl motifs from [1.1.1]propellane.

C. One-pot, three-component Fe-catalyzed radical cross-coupling using [1.1.1]propellane 1 as lynchpin (*this work*).

(difluoro)alkyl dicarbosubstituted BCP-aryl motifs are lacking, likely due to challenges associated with (a) controlling the 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 MC-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 the slow addition of Grignard reagents. If successful, in contrast to prior methods,

this protocol will allow the formation of disubstituted BCP-aryl directly from [1.1.1]propellane. Here, we present a general strategy for the synthesis of diverse 1,3-disubstituted 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 (difluoro)alkyl BCP halides primed for further functionalization.

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 /dcyp	53
19 ^f	1.0/2.0/4.2	Fe(acac) ₃ /dcpe	41

^aReaction conditions: Fe catalyst (20 mol %), ligand (40 mol %), THF (1.0 M), 0 °C, slow addition of 3a in 1 h, argon atmosphere. ^bDetermined by ¹H NMR using 1,2-dibromomethane as an internal standard. ^cSolution of 0.45 M [1.1.1]propellane in Et₂O. ^dSolution of 1.0 M [1.1.1]propellane in Et₂O. ^eYield (%) of isolated product. ^fFe(acac)₃ (10 mol %), dcpe (20 mol %).

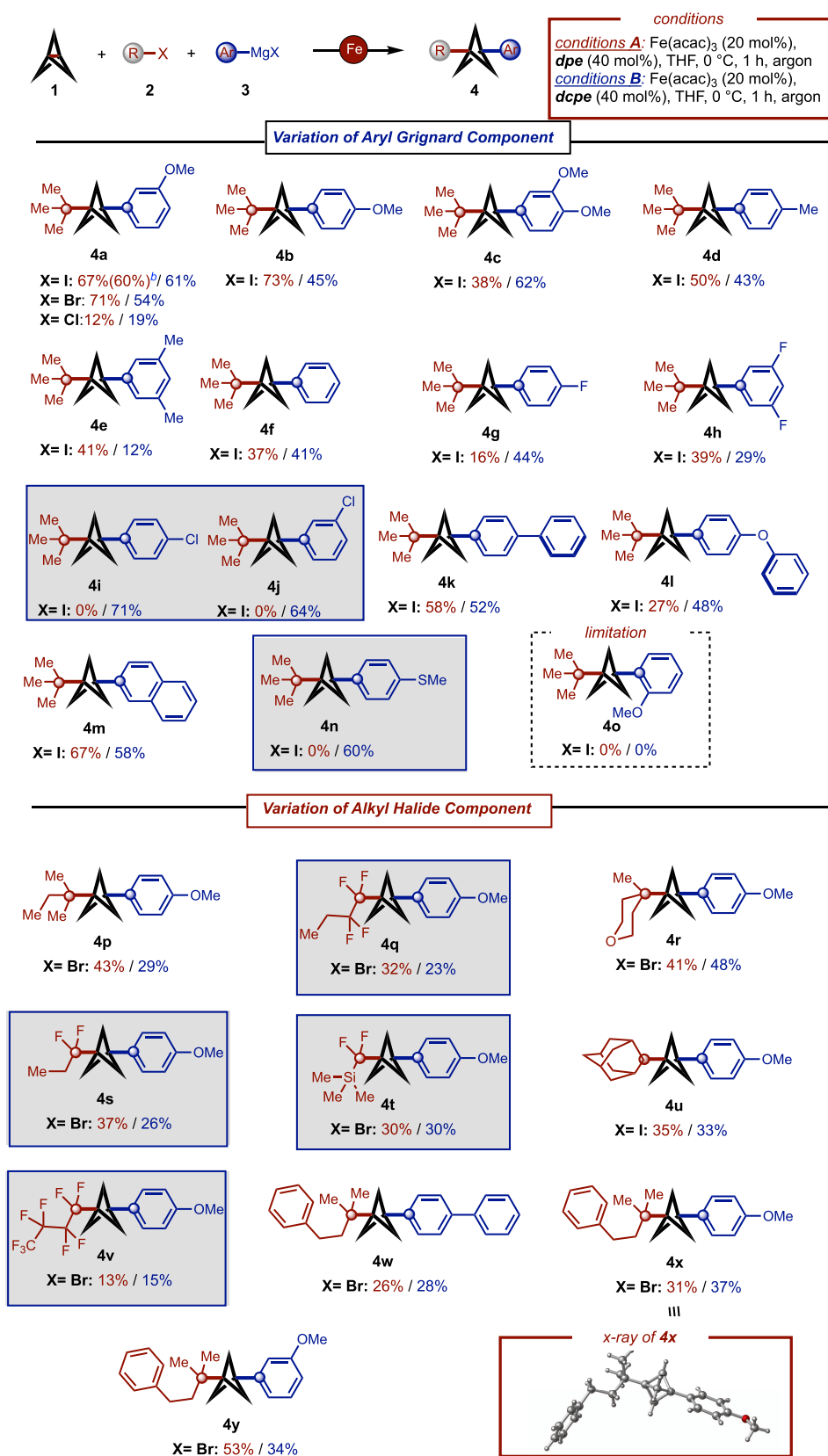
RESULTS AND DISCUSSION

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; X=Br) 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 **4a** albeit low (29%) yield (entry 1). Gratifyingly, additional optimization through variation of the alkyl halide, lynchpin **1**, and aryl Grignard reagent led to a significant increase in the overall yield (up to 70%) (entries 2–6). Not surprisingly, we observed that lowering the Grignard reagent (added via a syringe pump over the course of 1 h) had a drastic effect on the overall efficiency (29% yield) (entry 7), while increasing the alkyl halide had a slightly detrimental effect on the overall yield (entry 8). From these studies, it is clear that subtle changes to the relative concentrations among the three components can affect the overall efficiency. Control experiments show the

importance of the unique iron precatalyst and ligand combination to achieve good yields (entries 9–12).

Finally, to assess the ligand effect on this multicomponent transformation, we screened several commercially available diamines and bisphosphine ligands (entries 13–18). To our surprise, while all other bisphosphine ligands screened were found less efficient, diamine ligands, i.e., tmeda and, more specifically, hindered 1,2-dipiperidinoethane (dpe), lead to similar overall yields (~77%) as with the dcpe ligand (entries 13 and 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 a slightly reduced overall yield (entry 19). Overall, the two sets of optimized conditions [i.e., conditions A: Fe(acac)₃ (20 mol %) and dpe (40 mol %) or conditions B: Fe(acac)₃ (20 mol %) and dcpe (40 mol %)] in THF at 0 °C led to the formation of the sterically encumbered BCP-aryl **4a** in 61% (dcpe) and 67% (dpe) isolated yields. Lastly, the product of the one-step Fe-

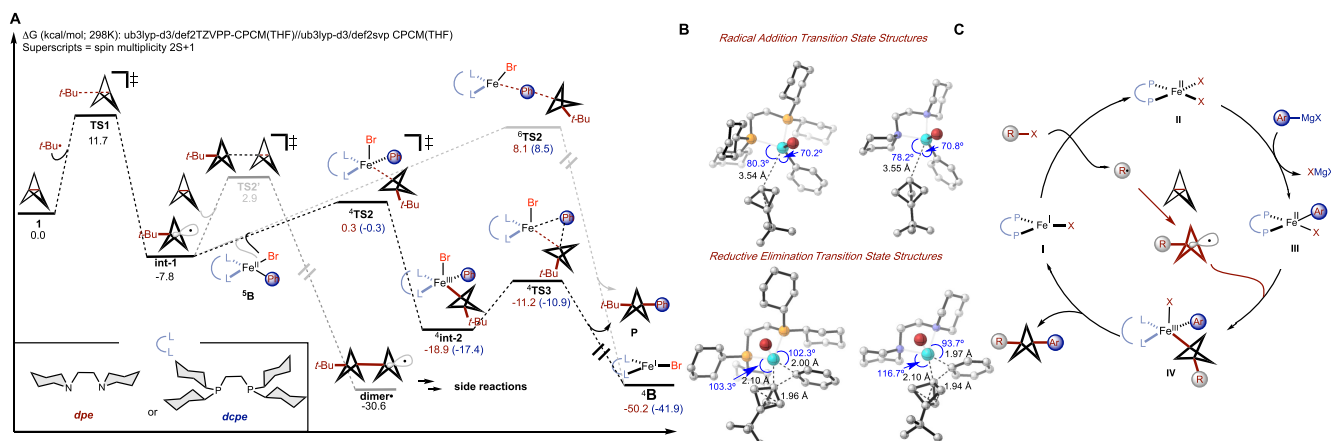
Scheme 2. Scope of Bisphosphine- and Diamine-Iron Catalytic Systems to Construct 1,3-Difunctionalized Substituted BCP-Aryls



catalyzed dicarbofunctionalization of the [1.1.1]propellane was confirmed by X-ray diffraction analysis of compound **4a**.

With catalytic diamine- and bisphosphine-iron optimized conditions in hand (i.e., conditions A and B, respectively), the

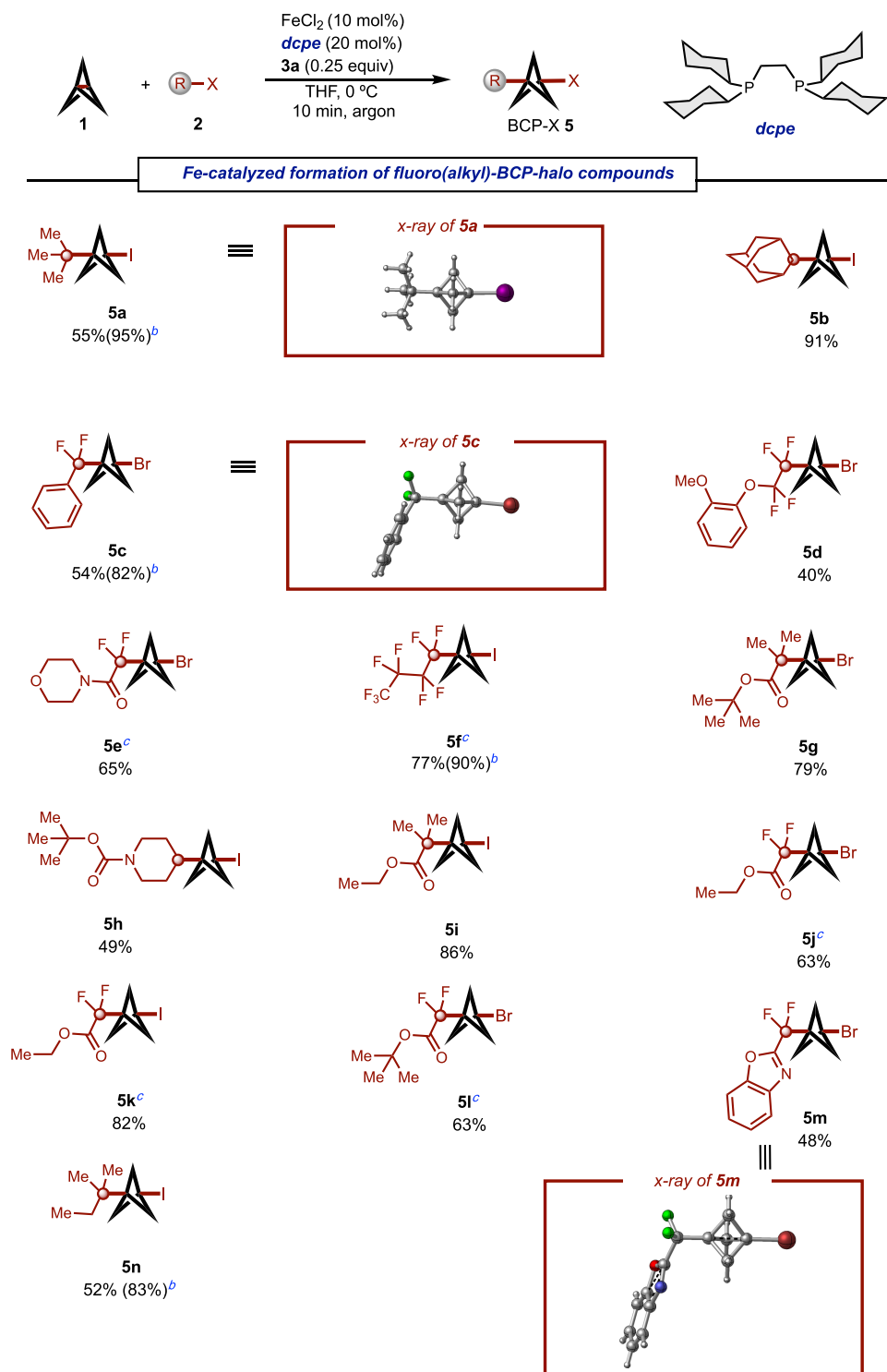
Scheme 3. (A) Computational Studies on the Ligand Effects (Red Using dpe and Blue Using dcpe) on the Mechanism of Three-Component Alkyl-Arylation of BCP (A); (B) Comparison of the Relevant Lowest Energy Radical Addition and Reductive Elimination Transition-State Structures Demonstrating Similar Energetic Profiles and Transition States for the C–C Bond Formation with Bisphosphine- and Diamine-Iron Catalytic Systems; and (C) Proposed Catalytic Cycle



scope of aryl Grignard reagent in this unique one-step, three-component reaction to form 1,3-dicarbofunctionalized BCP-aryls was first evaluated. As 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 a 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 [1.1.1]propellane **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 exploring the scope of 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 toward 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 is 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 Supporting Information for additional details). Based on prior mechanistic studies from our group and others,^{19a,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) 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 **5B** via spin-selective ⁴TS2 (barrier, ~8.0 kcal/mol) to form the corresponding distorted square pyramidal Fe(III)-alkyl intermediate ⁴int-2. Finally, irreversible reductive elimination via ⁴TS3 (barrier only ~6.5 kcal/mol) will lead to the desired product BCP-aryl product **P** and Fe(I) species **4B**, 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 ⁶TS4 but, consistent with prior studies,^{19,22,23} this pathway is ruled out 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 the radical addition of int-1 to another [1.1.1]-propellane molecule (gray). 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

Scheme 4. Substrate Scope of Bisphosphine-Fe-Catalyzed Atom-Transfer Radical Addition (ATRA) to [1.1.1]Propellane^a

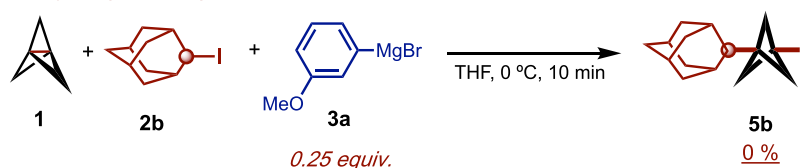
^aReactions were carried out using **1** (0.2 mmol), **2** (0.4 mmol), **3a** (0.1 mmol), FeCl₂ (10 mol %), dcpe (20 mol %), THF (0.2 mL) at 0 °C under an argon atmosphere, and isolated yields were reported. ^b¹H NMR yield (in parentheses) determined using 1,2-dibromomethane as an internal standard. ^cSimilar yields were obtained in the absence of FeCl₂, dcpe, and **3a**.

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

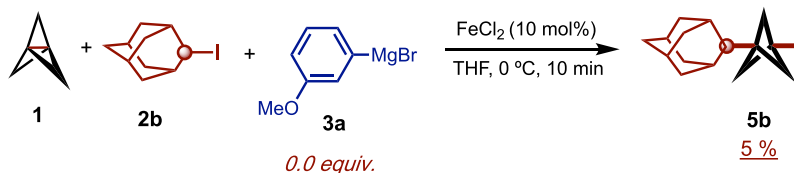
energy profiles for the C–C bond formation, which we attribute to comparable sterics imposed by both of these ligands in the key radical addition and reductive elimination transition states (Scheme 3B). As such, on the basis of the aforementioned controls and prior mechanistic studies,^{19–23} a possible catalytic cycle is depicted in Scheme 3C. Upon the

Scheme 5. Control Reactions to Shed Light into the Role of Iron and Ligand in the Atom-Transfer Radical Addition Reaction Using [1.1.1]-Propellane as a Radical Acceptor^a

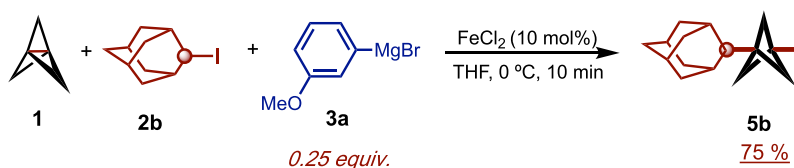
i. Aryl Grignard reagent as promoter



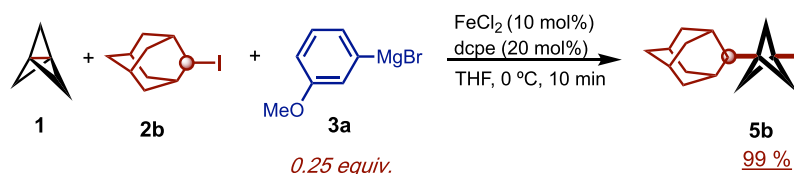
ii. Catalytic Fe(II) without aryl Grignard



iii. Aryl Grignard reagent + Fe(II)



iv. Aryl Grignard reagent + Fe(II) + phosphine ligand



^a¹H NMR yield determined using 1,2-dibromomethane as an internal standard.

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 the concomitant formation of organoiron III from transmetalation of II with aryl Grignard reagent. Finally, under the slow addition of Grignard reagent to prevent over transmetalation of III, the 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 [1.1.1]propellane 1, we noticed the formation of the 1,3-*tert*-butyl BCP iodide 5a, presumably from the competing Fe-catalyzed atom-transfer radical addition (ATRA) to [1.1.1]propellane. Although 5a could be an intermediate in the multicomponent dicarbofunctionalization of [1.1.1]propellane, 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 (vide infra). 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 ATRA to [1.1.1]propellane. Notably, although Fe(acac)₃ gives the best yield for the three-component reaction (Table 1, entry 14), we found that the use of FeCl₃ 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-halo-3-alkyl BCPs (5a, 5b, 5g, and 5n) including those bearing versatile ester functionalities for further modifications (e.g., via radical cross-couplings).²⁴ 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 5j–m). Notably, additional control experiments revealed that when FeCl₃, dcpe, and aryl Grignard 3a are omitted, in some cases significant background reaction is operative leading to the corresponding (5e, 5f, 5j, 5k, and 5l) in similar yields, presumably from radical-induced atom-transfer radical addition (see the Supporting Information). Finally, the structure for the BCP halides 5a, 5c, and 5m was confirmed by X-ray diffraction analysis. We anticipate that this catalytic method will provide an attractive complementary approach to the 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.

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 afford the desired product. Further, traces of compound were observed when the reaction is carried out using catalytic amounts of FeCl_2 in the 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 a 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 [1.1.1]propellane and, finally, undergoes halogen rebound to restart the catalytic cycle. On the other hand, under three-component catalytic conditions and with $\text{Fe}(\text{acac})_3$ (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 the unproductive formation of off-cycle 1-halo-3-alkyl 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.

CONCLUSIONS

In summary, we have developed a multicomponent, one-pot three-component reaction that utilizes [1.1.1]propellane as a 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

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.2c03498>.

General considerations, reaction optimization details, synthetic procedures, computational studies, and full characterization of all compounds synthesized (PDF)

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.

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Notes

The authors declare no competing financial interest.

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