Article

Copper-Catalyzed Direct C–H Alkylation of Polyfluoroarenes by Using Hydrocarbons as an Alkylating Source

Weilong Xie, Joon Heo, Dongwook Kim, and Sukbok Chang

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c00169 • Publication Date (Web): 31 Mar 2020

Copper-Catalyzed Direct C–H Alkylation of Polyfluoroarenes by Using Hydrocarbons as an Alkylating Source

Weilong Xie,[†,‡] Joon Heo,[†,‡] Dongwook Kim,[‡,†] and Sukbok Chang*[,‡,†]

[†]Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 34141, Republic of Korea

[‡]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea

Supporting Information Placeholder

ABSTRACT: Construction of carbon–carbon bonds is one of the most important tools in chemical synthesis. In the previously established cross-coupling reactions, pre-functionalized starting materials are employed usually in the form of aryl- or alkyl (pseudo)halides or their metallated derivatives. However, direct use of arenes and alkanes via a twofold oxidative C–H bond activation strategy to access chemoselective C(sp^2)–C(sp^3) cross-couplings is highly challenging due to the low reactivity of carbon–hydrogen (C–H) bonds and the difficulty in suppressing side reactions such as homocouplings. Herein, we present the new development of a copper-catalyzed cross-dehydrogenative coupling of polyfluoroarenes with alkanes under mild conditions. Not only relatively weak sp^3 C–H bonds being at the benzylic or allylic positions but also non-activated hydrocarbons could be alkylated by the newly developed catalyst system. A moderate to high site-selectivity was observed among various C–H bonds present in hydrocarbon reactants even including gaseous feedstocks and complex molecules. Mechanistic information was obtained by performing combined experimental and computational studies to reveal that copper catalyst plays a dual role in activating both sp^3 C–H bonds of alkanes and sp^2 polyfluoroarene C–H bonds. It was also suggested that non-covalent π–π interaction and weak hydrogen bonds formed *in situ* between the optimal ligand and arene substrates are key to facilitate the current coupling reactions.

■ INTRODUCTION

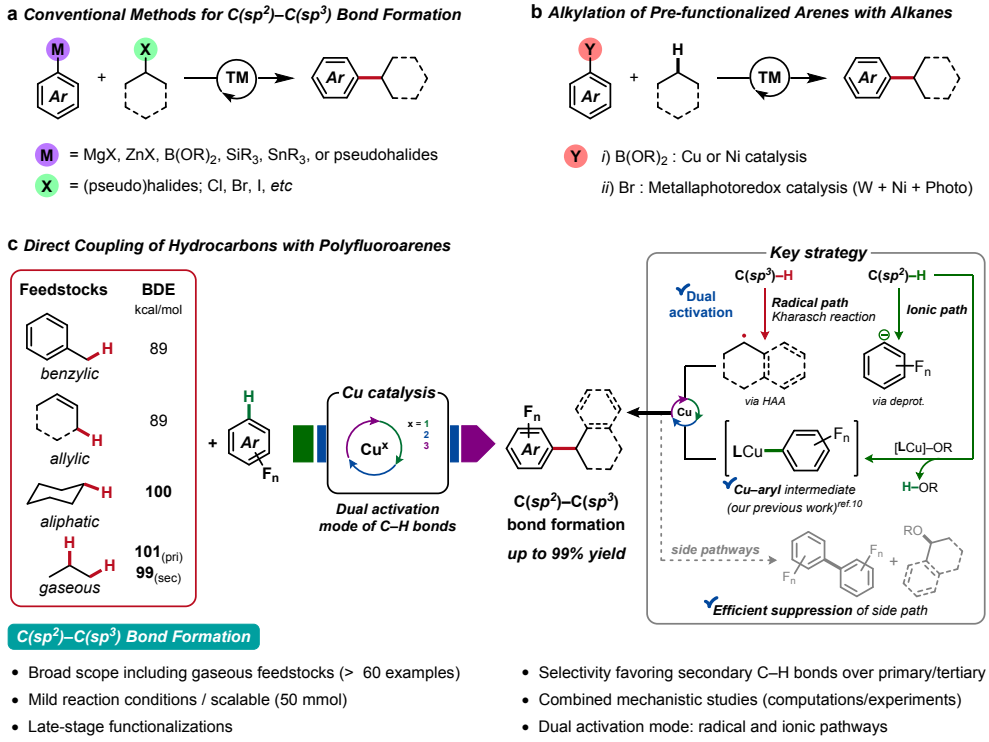
Formation of carbon–carbon bonds is crucial to increase molecular diversity in synthesis.[1] In particular, arylation reactions serve as an important toolbox in preparation of numerous chemical building units as well as commercial products containing phenyl chains. Transition metal-catalyzed cross-couplings between organo-nucleophiles and aryl (pseudo)halides are most widely employed in this context.[2] This approach has been further expanded its scope to include alkyl electrophiles as a coupling partner (Scheme 1a). However, there is room to improve in this case mainly because a key metal alkyl intermediate is prone to undesired β-hydride elimination.[3] While direct arylation of inert hydrocarbons via C–H bond activation is highly attractive,[4] on the other hand, catalytic C–H arylation of alkanes with aryl nucleophiles/electrophiles has only recently been reported,[5] where a single-electron transfer pathway was found to be more effective (Scheme 1b).

Despite the recent promise, a direct coupling between alkanes and arenes via a twofold oxidative C–H bond activation to yield C(sp^2)–C(sp^3) bonds is largely underdeveloped as a synthetic tool.[6,7] Indeed, only a few examples have been revealed with limited scope and/or under harsh conditions. For instance, a ruthenium-catalyzed cross-dehydrogenative coupling (CDC) of arenes with cycloalkanes (135 °C) was reported while it requires directing groups to facilitate an *ortho*-metallacyclic intermediate.[7a] A copper/pyridine-mediated stoichiometric reaction of methyl C–H bonds of aliphatic quinoline amides with polyfluoroarenes (140 °C) was recently developed.[7d] Additionally, direct alkylation of *N*-heteroarenes with alkanes via a Minisci-type pathway was well investigated.[8] The biggest challenge in the coupling of arenes with alkanes via a twofold C–H activation approach without relying on the chelation-assistance is to secure its high chemoselectivity to maximize the desired cross-coupled products by effectively suppressing the side-pathways such as homocoupling or over-alkylation (arylation).[6,9]

Based on our previous (NHC)Cu-catalyzed amidation of (hetero)arenes,[10] we envisioned that *in stiu* generated copper-aryl intermediates might be able to couple with sp^3-hybridized carbon radicals to form the desired alkylation products (Scheme 1c). In the Kharasch–Sosnovsky reaction,[11] allylic C–H bonds are activated by a copper/peroxide system to afford carbon radicals that eventually give rise to ether[12] or amine products[13]. More recently, Cu-catalyzed oxidative arylation at the benzylic C–H bonds was achieved by using arylboronic esters to afford diarylalkanes.[5c]

Polyfluoroarenes are widely utilized in medicinal chemistry[14] and materials science[15] owing to their unique properties derived from the fluorine moiety. Direct functionalization of polyfluoroarenes such as arylation[16], olefination[17], alkynylation[18], allylation[19] and amination[10] has been achieved by several research groups including us. In contrast, only a few examples of C–H alkylation of polyfluoroarenes are known; Pd or Cu-catalyzed benzylation with benzyl chlorides[20a,16b] and Cu-catalyzed alkylation with diazo compounds[20b]. In the palladium catalysis system, the coupling reagents were limited to primary benzyl halides, probably due to the competing β-hydride elimination pathway of alkyl-metal species. In addition, Rh-catalyzed conjugate addition of polyfluoroarenes to activated olefins was reported to form alkylated polyfluoroarenes.[20c] The paucity of the alkylation procedure can be ascribed to the low reactivity of the polyfluoroaryl–metal intermediates (due to the strong σ-bonds of M–C_6F_5) towards alkyl electrophiles.[21] Meanwhile, a competing path for the homocoupling of polyfluoroarenes would also give rise to a challenging chemoselectivity issue.[18,22]

Scheme 1. Ligand-Enabled Cu-Catalyzed Alkylation of Polyfluoroarenes with Hydrocarbons



The importance of alkylated fluoroarene moieties (i.e., sitagliptin, omarigliptin and isavuconazole) in the pharmaceutical industry further drew our interest to develop a general and practical strategy for the alkylation reactions. Herein, we report the development of a copper-catalyzed direct alkylation of polyfluoroarenes with various types of hydrocarbons (Scheme 1c). Not only benzylic and allylic C–H bonds (bond dissociation energy; BDE = ~90 kcal/mol) but also more challenging hydrocarbon C–H bonds (BDE = ~100 kcal/mol) are readily coupled under the currently developed catalytic conditions.[23] It was found that the electronic and steric properties of the optimized *β*-diketimine ligand are crucial in achieving the desired chemoselectivity by harnessing the high reactivity of key intermediates. Mechanistically, the present copper catalyst system was found to induce selective dual activation of both fluoroarenes and alkanes, eventually merging them into a combined product-generating process. Non-covalent π–π interaction and weak hydrogen bonds formed *in situ* between ligands and arene substrates were rationalized to facilitate the current cross-couplings.[24] The developed alkylation of polyfluoroarenes is convenient to operate even in a decagram scale and is broad in scope of hydrocarbons including gaseous hydrocarbons and complex molecules.

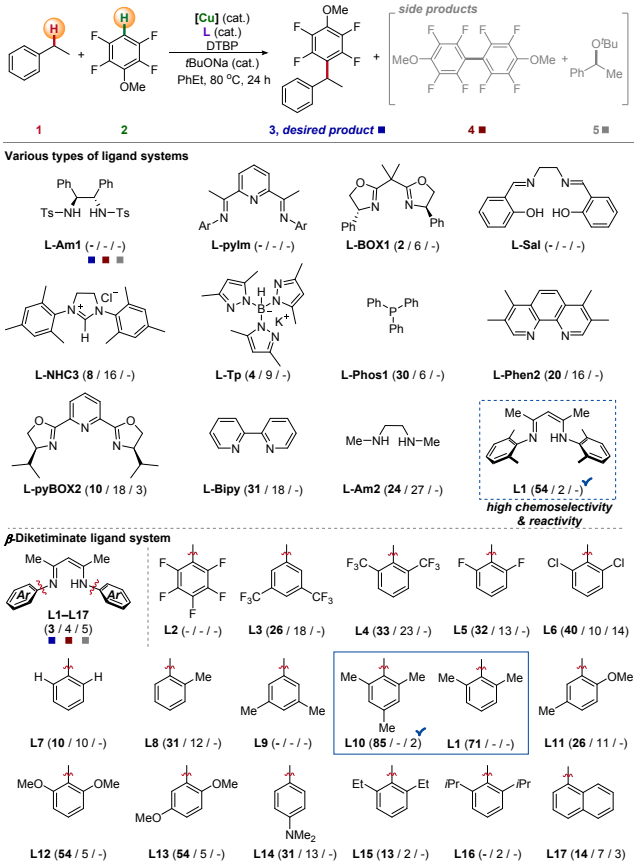
■ RESULTS AND DISCUSSIONS

Reaction Optimization. We embarked on our studies by examining a model reaction of ethylbenzene (**1**) with 2,3,5,6-tetrafluoroanisole (**2**) under various conditions (see Tables S1–S7 in the Supporting Information for details). Various types of ligands were extensively screened in combination with catalytic amounts of copper salts in the presence of oxidants and bases. The desired C(sp^2)–C(sp^3) cross-coupled product (**3**) was observed to form along with a homo-coupled bisarene (**4**)[22] and an ether byproduct (**5**)[12]. While moderate to low product yields were obtained with such conventional ligands as bisoxazolines, NHCs, phosphines, bipyridines or trispyrazolylborate, the use of *β*-diketimine ligand (**L1**) showed a promise by effectively surprising side products (Table 1).

From the additional screening of synthetically readily accessible *β*-diketimine scaffolds, the most optimal ligand turned out to be **L10** giving rise to the desired product **3** in 85% yield with <5% of side products (**4** + **5**) at 80 °C. Notably, electronic and/or steric variations on *β*-diketimines greatly affected the reaction efficiency and chemoselectivity. For instance, while ligands with highly electron-deficient or electron-rich aryl moieties (i.e. **L2**–**L6**, **L12**–**L14**) gave lower product yields and the presence of *ortho*-methyl group on the phenyl imine displayed high reactivity. When ligand **L4** having 2,6-bistrifluoromethyl substituents was applied, the alkylation took place with lower efficiency and decreased selectivity compared to **L1**, thus demonstrating that the ligand structure displays a high impact on the reaction performance. In the same line, ligands containing sterically hindered substituents such as 2,6-isopropyl group on the phenyl ring could not form the desired product (**L16**). It is worth mentioning that *β*-diketimine copper complexes were elegantly utilized in the etherification and amidation reactions by Warren *et al.*[12,13b] While a base additive were essential, catalytic amounts of *t*BuONa were found to be viable albeit with longer reaction time (Figure 1a, 71% of **3** with 0.8 equiv of *t*BuONa in 24 h and 72% with 0.2 equiv of *t*BuONa in 40 h). The result that weak bases such as K_2CO_3 and Cs_2CO_3 were ineffective was rationalized to be closely related to the efficiency in generating the catalytically active copper species (*vide infra* and see also the Mechanistic Studies in the Supporting Information). Further investigations on the reaction temperature disclosed that the catalytic system showed the highest coupling efficiency at 80 °C (Figure 1b). Among various oxidants evaluated in combination with

L10, di-*tert*-butyl peroxide (DTBP) was especially effective in obtaining the desired coupling. Other oxidants such as $(PhMe_2CO)_2$, $(BzO)_2$, *t*BuOOBz and NFSI gave lower product yields, and various first row metal catalysts including iron, cobalt and nickel were observed to be ineffective for the cross-coupling reaction. The alkylation efficiency was slightly decreased by employing reduced equivalents of the alkane reactant (e.g, 64% product yield with 5 equiv of ethylbenzene and 78% with 10 equiv of ethylbenzene). It is worth mentioning that most of unreacted ethylbenzene could be recovered (89%) and a trace amount (<5%) of dimerization byproduct of ethylbenzene was observed under the optimal conditions.

Table 1. Ligand Screening for the C–H Alkylation of Tetrafluoroanisole with Ethylbenzene[a]



[a]See the Supporting Information for the experimental details.

Scope of Hydrocarbons and Polyfluoroarenes. With the optimized conditions in hands, the scope of alkanes was next explored in reaction with naphthalen-2-oxy-2,3,5,6-tetrafluorobenzene (**6**) as a representative arene counterpart in benzene solvent (Table 2). The choice of this model substrate **6** was based on the ease of isolation of alkylated products although the scope of fluoroarenes was found to be broad (*vide infra*). Secondary benzylic C–H bonds were readily arylated to provide the desired alkylation products in high yields (**7** and **8**). Primary benzylic C–H bonds were also viable irrespective of the presence of positional substituents with 63%–94% yields of the corresponding products (**9**–**12**). Halide substituents were all compatible with the current conditions (**13**–**16**). Monoarylated products were obtained efficiently from the reaction of mesitylene or 1,3,5-triethylbenzene (**17** and **18**). Substrates bearing longer alkyl chains displayed a selective arylation at the secondary benzylic C–H bonds (**19**–**21**), and the structure of the product **19** was confirmed by an X-ray crystallographic analysis. Of special note is that a readily obtained product **21** can serve as a precursor to pharmaceutically relevant derivatives of 3,3-diarylpropylamines such as tolpropamine and segontin. 1-Ethylnaphthalene was arylated in good yield (**22**) and cyclic benzyl C–H bonds were also highly facile (**23** and **24**). Heterocyclic moieties were competent as demonstrated in an arylation of 2-ethylthiophene (**25**).

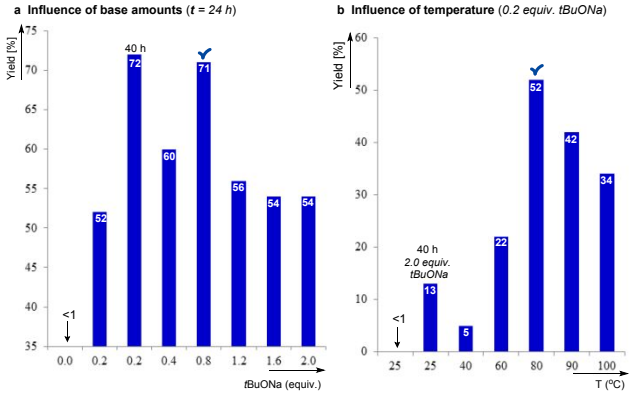
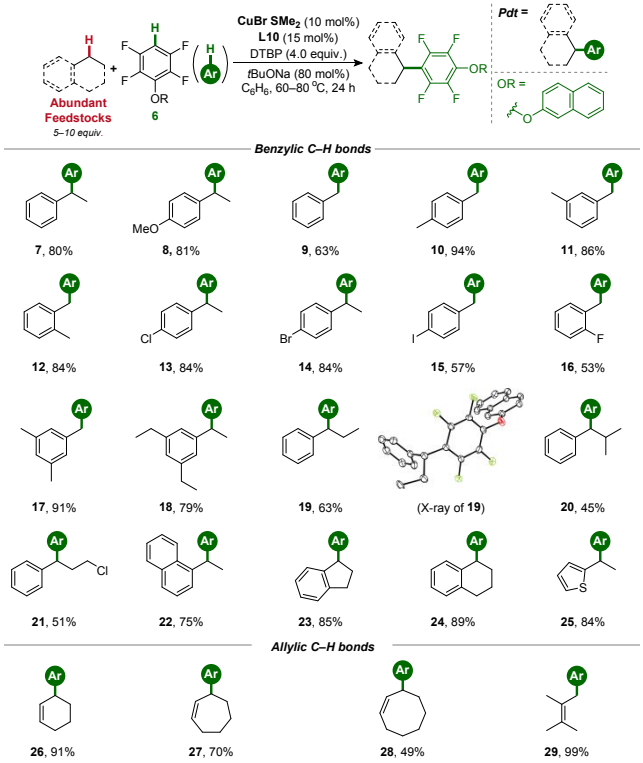


Figure 1. (**a**) Influence of the base amounts for the current alkylation reactions with ligand **L1**. (**b**) Influence of the reaction temperature for the alkylation system with ligand **L1**.

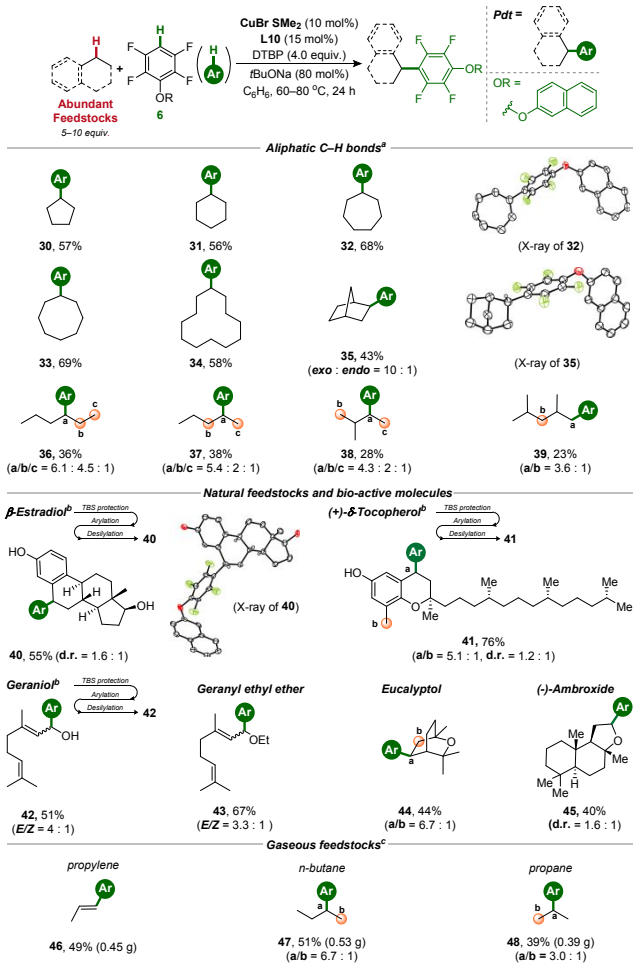
Table 2. Scope of Hydrocarbons Reacting at the Benzylic[a] **and Allylic**[b] **C–H Bonds**



[a]For the arylation of benzylic C–H bonds: alkylarenes (2 mmol, 10 equiv.), fluoroarene (0.2 mmol), $CuBr{\bullet}SMe_2$ (0.02 mmol), ligand **L10** (0.03 mmol), *t*BuONa (0.16 mmol) and oxidant DTBP (0.8 mmol) in benzene solvent at 80 °C for 24 h. Isolated product yields. [b]For the arylation of allylic C–H bonds: reactions were carried out with alkenes (1 mmol, 5 equiv.) and fluoroarene (0.2 mmol) at 60 °C.

Given the versatile utility of an allyl phenyl scaffold as synthetic and medicinal/materials building units,[19,25] the feasibility of direct allylic C–H arylation was subsequently examined in reaction with fluorobenzene (**6**) as a representative arene counterpart (Table 2). Pleasingly, we observed that cyclohexene (5 equiv) was smoothly reacted at 60 °C to afford **26** exclusively in 91% yield (see the Supporting Information for the optimization conditions). Seven- and eight-membered cycloalkenes were also readily arylated at the allylic position (**27** and **28**). A reaction of tetramethylethylene smoothly took place to provide the corresponding product **29** in quantitative yield.

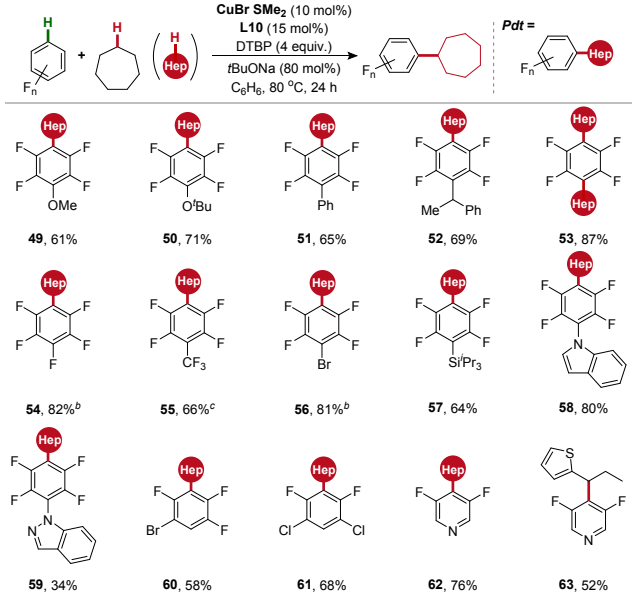
Table 3. Scope of Aliphatic, Gaseous Hydrocarbons and Complex Molecules[a]



[a]For the arylation of alphatic C–H bonds: alkanes (2 mmol, 10 equiv.), fluoroarene (0.2 mmol), CuBr•SMe_2 (0.02 mmol), ligand **L10** (0.03 mmol), *t*BuONa (0.16 mmol), and oxidant DTBP (0.8 mmol) in benzene solvent at 80 °C for 24 h. Isolated product yields. Orange circles denote sites where regiomeric products are formed. [b]Three-step sequence constitutes: (i) silyl protection of free hydroxyl group, (ii) arene-alkane coupling, and (iii) silyl deprotection. [c]For gaseous feedstocks: 3 mmol scale reactions.

As shown in Scheme 1, while the bond dissociation energy (BDE) of benzylic and allylic C–H bonds is in the range of ~90 kcal/mol, that of cycloalkanes is higher by ~10 kcal/mol, thus achieving a direct coupling of those hydrocarbons to be more challenging.[23] In turn, low molecular weight acyclic hydrocarbons (mainly gaseous alkane feedstocks) having similar BDE of C–H bonds (~100 kcal/mol) are extremely difficult to functionalize.[26] This consideration led us to investigate their feasibility in the current cross-coupling system (Table 3). We were pleased to observe that cycloalkanes (10 equiv) were readily reacted with naphthalen-2-oxy-2,3,5,6-tetrafluorobenzene (**6**) in satisfactory yields (56%–69%) irrespective of the ring size (**30**–**34**). Norbornane was reacted exclusively at the ethylene C–H bonds in 43% yield with high *exo*/*endo* selectivity (10:1, **35**), and the structure of a major isomeric product was confirmed by an X-ray diffraction analysis. Significantly, acyclic hydroalkanes were also viable under the present reaction conditions leading to arylated products albeit in moderate yields. For instance, *n*-hexane was reacted mainly at the secondary C–H bonds along with minor arylation at the primary C–H bonds (**36**) in 36% yield. *n*-Pentane showed the similar reactivity and selectivity (**37**). 2-Methylbutane was reacted preferentially at the secondary C–H bonds (**38**), and interestingly, no arylation was observed at the tertiary C–H bond. In contrast, primary C–H bonds were reacted more favorably when the secondary position is sterically congested (**39**). However, reaction of substrates having tertiary benzylic C–H bond (e.g. cumene) did not afford the desired product under the present conditions.

Table 4. Scope of Polyfluoroarene Substrates[a]



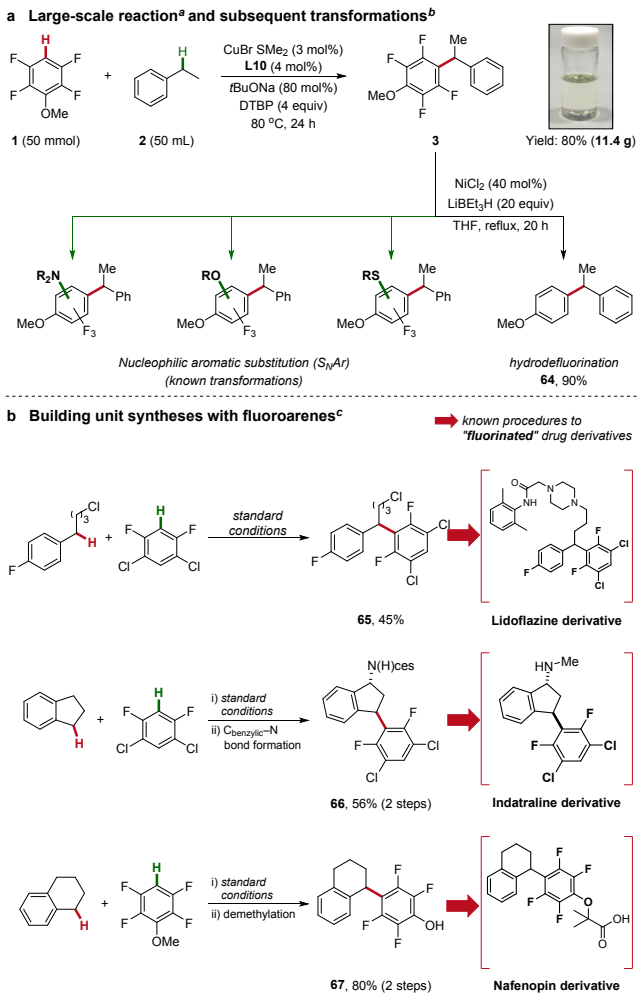
[a]Reaction conditions: polyfluoroarene (0.2 mmol), cycloheptene (2 mmol, 10 equiv), CuBr•SMe_2 (0.02 mmol), ligand **L10** (0.03 mmol), *t*BuONa (0.16 mmol), and oxidant DTBP (0.8 mmol) in benzene solvent at 80 °C for 24 h. [b]*t*BuONa (0.6 equiv.). [c]*t*BuOLi was employed as the base.

The present cross-coupling procedure was successfully applied to the C–H arylation of naturally occurring hydrocarbons or bio-active synthetic compounds (Table 3). For instance, *β*-estradiol was reacted selectively at the secondary benzylic C–H bonds in 55% (**40**, d.r. = 1.6) and its structure was confirmed by an X-ray crystallographic analysis. (+)-*δ*-Tocopherol (a type of vitamin E) was converted to its arylated derivative by reacting mainly at the secondary C–H bond of the benzylic positions in high yield (**41**). Geraniol was also viable for this transformation leading to α-aryl

alcohol product (**42**) in 51%. Significantly, this arylation was found to be selective at the α-allyl silylether site even in the presence of 5 additional types of allylic C–H bonds. Likewise, geranyl ethyl ether was reacted at the allylic C–H bonds adjacent to the heteroatom in good yield (**43**, 67%). Alcoholic hydrocarbons were subjected to a three-step arylation sequence: (i) hydroxyl group protection as silyl ethers, (ii) C–H arylation, and (iii) silyl deprotection. A biomass-drived chemical of eucalyptol was reacted at the secondary C–H bonds with good regioselectivity (**44**, **a**/**b** = 6.7:1) in 44%, and (-)-ambroxide was arylated at the secondary C–H bonds adjacent to the oxygen atom in moderate yield (**45**). It needs to be mentioned that excessive amounts of the complex hydrocarbon reactants could be recovered in the current system. For instance, the recovered yields of unreacted *β*-estradiol and (+)-*δ*-tocopherol were 89% and 88%, respectively (see S30–S37 in the Supporting Information for details).

Taking one step forward, we attempted to employ gaseous hydrocarbon feedstocks as an alkylating source[27] under the current copper catalyst system. A reaction of propylene (3.0 mmol scale, 8 bar, 70 °C) furnished an isomerized (*E*)-vinylarene product in 49% (**46**).[19c] *n*-Butane (2 bar) and propane (5 bar) were reacted preferentially at the secondary C–H bonds albeit in moderate yields (**47** and **48**) at 80 °C.

Scheme 2. Synthetic Applications

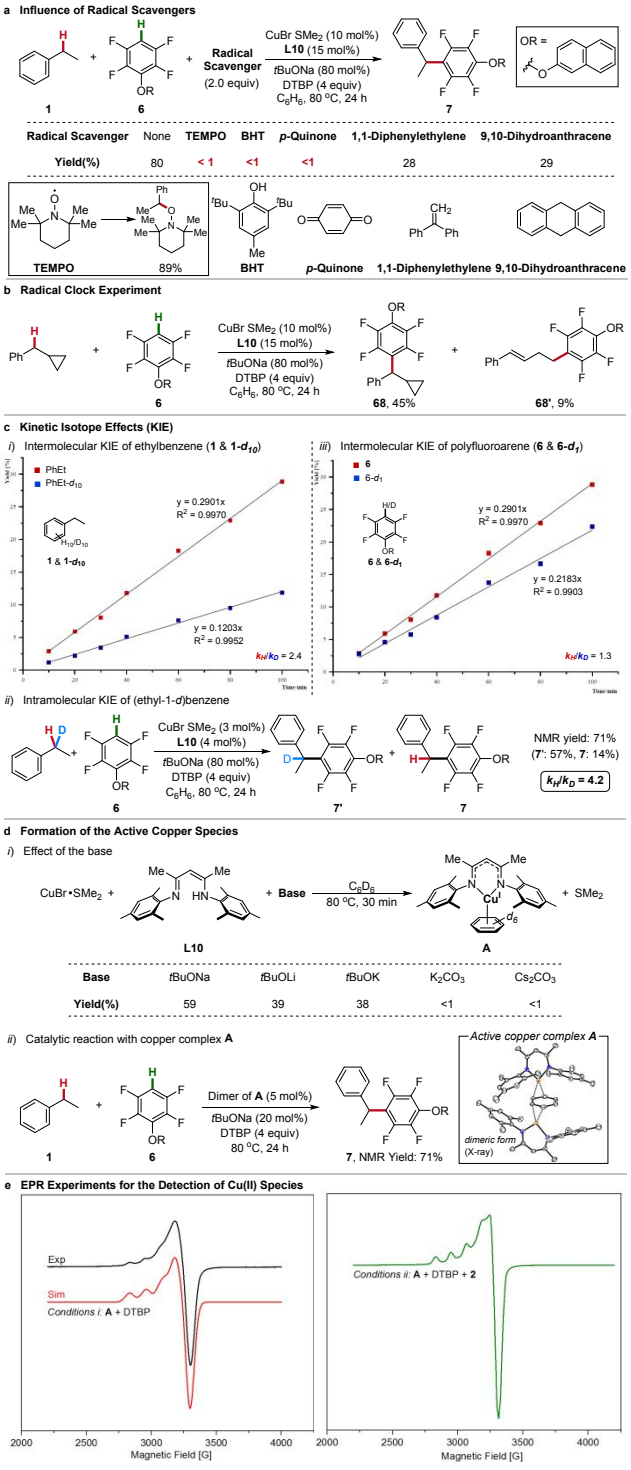


After surveying the scope of hydrocarbon reactants, the availability of fluoroarene substrates was further investigated in reaction with cycloheptane as a representive coupling partner (Table 4). Tetrafluorobenzenes bearing a methoxy or *t*-butoxy substituent were smoothly reacted to afford good yields of the desired products (**49** and **50**, 61% and 71%, respectively). Derivatives substituted with phenyl or alkyl groups were also viable for the alkylation with cycloheptane with similar efficiency (**51** and **52**). Of note was that a weaker benzylic tertiary C–H bond[23] in the latter substrate was compatible with the current reaction conditions. When two chemically equivalent sp^2 C–H bonds are present as in case of 1,2,4,5-tetrafluorobenzene, bis-alkylation could be achieved in high efficiency by increasing the stoichiometry of cycloheptane and oxidant (**53**). Pentafluorobenzene and its analogue were facile for this alkylation (**54** and **55**). Functional group tolerance was examined to reveal that bromo, silyl, indole, and indazole groups were all tolerant to the present conditions (**56**–**59**). When two non-equivalent C–H bonds are present, the alkylation was found to occur selectively at the more acidic position in good yields (**60** and **61**). 3,5-Ddifluoropyridine was alkylated exclusively at the C4-position (**62**) in high yield, and no reaction occurred at the C2-position. Finally, a reaction of 3,5-difluoropyridine with 2-propylthiophene was also fruitful to afford 1,1-diheteroarylalkane in 52% yield (**63**). However, the current alkylation protocol was not applied to such arenes as 1,2,3-trifluorobenzene, fluorobenzene, 1,2,4,5-tetrachlorobenzene, or 1,2,4,5-tetrabromobenzene, wherein no alkylation product was observed.

Synthetic Application. The synthetic utility of the current cross-dehydrogenative coupling of alkanes with polyfluoroarenes was briefly examined, as summarized in Scheme 2 (see also Synthetic Application in Supporting Information for details). Practicability of the present alkylation protocol was tested in a decagram-scale reaction of 2,3,5,6-tetrafluoroanisole (**2**, 50.0 mmol) with ethylbenzene (**1**) by using 3 mol % of CuBr•SMe_2 and 4 mol % of ligand **L10** at 80 °C to afford the desired product **3** in 80% yield (11.4 g). The obtained products could be further utilized in subsequent transformations. For instance, a catalytic hydrodefluorination of **3** ($NiCl_2$) was readily performed to obtain 1,1-diarylethane **64** in high yield (90%).[28] Moreover, a nucleophilic aromatic substitution of fluorine atom in fluoroarenes is an established procedure in the literatures.[14d] Given that 1,1-diarylalkanes constitute a pharmacophore in numerous drugs,[29] our protocol was briefly examined as a viable route to fluorinated analogues (Scheme 2b). Indeed, fluorinated drug precursors such as lidoflazine, indatraline, and nafenopin were readily obtained in good to high yields (**65**–**67**). 1-(4-Chlorobutyl)-4-fluorobenzene reacted with 1,5-dichloro-2,4-difluorobenzene under the current cross-dehydrogenative coupling system to afford a benzylic C–H arylation product **65** in 45% yield. Interestingly, a *trans*-configured product **66** was formed in 56% over two steps from an abundant chemical of indane via two steps: benzylic C–H arylation with the current system and then direct amination at the other secondary benzylic C–H bonds by a reported manganese system.[30] Finally, 1,2,3,4-tetrahydronaphthalene was also facile to couple with 2,3,5,6-tetrafluoroanisole to furnish an arylation product, which subsequently underwent demethylation with boron tribromide (BBr_3) leading to **67** (80%).

■ MECHANISTIC STUDIES

Scheme 3. Mechanistic Experiments



To obtain mechanistic insights into the present cross-coupling reactions, a number of experimental studies were carried out (Scheme 3 and also see the Supporting Information for details). The effect of radical scavengers on the current alkylation system was examined (Scheme 3a). No desired product (**7**) was observed in the presence of several radical inhibitors such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), and *p*-quinone, suggesting that the current alkane-polyfluoroarene coupling reaction proceeds likely via a radical pathway. The proposed sp^3-carbon centered radical was trapped by TEMPO in 89% NMR yield.[31] In addition, 1,1-diphenylethylene and 9,10-dihydroanthracene also displayed apparent inhibition effects on the reaction efficiency. Next, a radical clock experiment was carried out to show that a ring-opened compound (**68'**) was formed albeit in low yield along with **68** (Scheme 3b), thus supporting the intermediacy of alkyl radicals.[32] As shown in Scheme 3c, a series of kinetic isotope effect (KIE) experiments was subsequently performed at 80 °C by using a pregenerated species **A** (Scheme 3d), and significant KIE value was observed in parallel comparison reactions between ethylbenzene (**1**) and its deuterated derivative (**1-*d*$_{10}$**) (k_H/k_D = 2.4). Moreover, an intramolecular KIE value of (ethyl-1-*d*)benzene was measured to be 4.2. These results imply that the sp^3 C–H cleavage of alkanes is probably involved in the rate-limiting step.[33] On the other hand, a lower KIE effect was observed (k_H/k_D = 1.3) in a competition reaction between tetrafluoroarene (**6**) and its deuterated derivative (**6-*d*$_1$**). The base effect on the formation of active copper species was further investigated (Scheme 3d). Treatment of ligand **L10** and CuBr•SMe_2 with a range of bases revealed that *t*BuONa worked best in forming an active copper species **A** while weak bases such as K_2CO_3 or Cs_2CO_3 were ineffective (see the Supporting Information for details). The yellow copper complex **A** was isolated in a dimer form and its solid structure was fully characterized by an X-ray diffraction analysis. Importantly, this isolated species **A** was found to run a catalytic coupling reaction. Electron paramagnetic resonance (EPR) study was performed to see whether plausible copper intermediates could be observed (Scheme 3e, and also see the Supporting Information for details). While the isolated Cu(I) complex **A** was treated with DTBP oxidant in benzene, a four-hyperfine-line signal was observed at 100 K (*Conditions i*; black curve), which were assigned to be [LCu]–O*t*Bu. When 2,3,5,6-tetrafluoroanisole **2** was added to a solution of complex **A** and DTBP in benzene for 1 h at 80 °C, a new set of EPR signals appeaerd (*Conditions ii*; green curve), which was assumed to be the propsoed (aryl)Cu(II) intermediate. Based on the above experiments and literature precedents,[11,12,22b,34] Cu(II) intermediates are proposed to be involved in the present reaction system.

■ COMPUTATIONAL STUDIES

To provide further mechanistic aspects, computational studies with density functional theory were also carried out. Based on the previous studies that copper(I) species mediate a homolytic cleavage of peroxides,[12a] it was postulated that the copper complex **A** will react with DTBP to furnish 1 equiv of [LCu]–O*t*Bu (**C**) along with *t*BuO· radical (ΔG = –10.3 kcal/mol, Figure 2a, see also SI for detailed mechanism with full energy profiles). Upon the formation of **C**, two pathways were then envisaged to operate in the activation of sp^3 C–H bonds of alkanes as illustrated in Figure 2b. While a direct hydrogen atom abstraction (HAA) by a *free* *t*BuO· radical could be conceived (Path a), a copper-mediated activation was also considered (Path b). The observation of the primary kinetic isotope effects of ethylbenzene implies that the irreversible cleavage of sp^3 C–H bonds would be relevant to be rate-limiting, which was consistent with the computational investigations ($\Delta G^{\ddagger}$ = 26.0 kcal/mol). In SOMO of the alkoxy copper species **C**, the radical character was found to be delocalized both in the copper center

(0.46 e⁻) and in the oxygen atom (0.24 e⁻), as shown in Figure 2a. Considering the fact that *free* alkoxy radicals are generally known to activate tertiary C–H bonds preferentially in the presence of secondary and primary counterparts,[35] our observation that tertiary C–H bonds are intact under the current conditions (e.g. products **35**, **38**–**41**, **44**, **45**) led us to propose that the alkane activation mainly operates via a copper-mediated process (Path b). In fact, certain Cu(II) species were reported to mediate sp^3 C–H bond activation.[36] This process is postulated to proceed via a transition state **C-TS-1** leading to Cu(I) species **D-1** which then interacts with *t*BuO· radical to afford eventually an alkyl radical. This type of copper-mediated alkyl radical-releasing process was proposed independently by Kochi and Dong.[37] As we previously proved the facile activation of polyfluoroarenes by (NHC)Cu-alkoxide,[10] the present [LCu]–O*t*Bu (**C**) is proposed to readily deprotonate fluoroarene leading to an (aryl)Cu^{II} intermediate **D-2** (*Ionic pathway*, $\Delta G^{\ddagger}$ = 25.9 kcal/mol). In the final stage, the *in situ* generated alkyl radical is interacted with the aryl copper intermediate **D-2** to furnish the desired alkyl-aryl coupled product via an (alkyl)(aryl)Cu^{III} species **F** with negligible energy barriers (Figure 2c, see the Supporting Information for details). However, we were not able to observe distinct experimental signals which can be assignable to Cu(III) species. In fact, reductive elimination of the proposed (alkyl)(aryl)Cu^{III} intermediate **F** was calculated to proceed with very low activation barrier ($\Delta G^{\ddagger}$ = 0.3 kcal/mol) as shown in Figure 2c.[38]

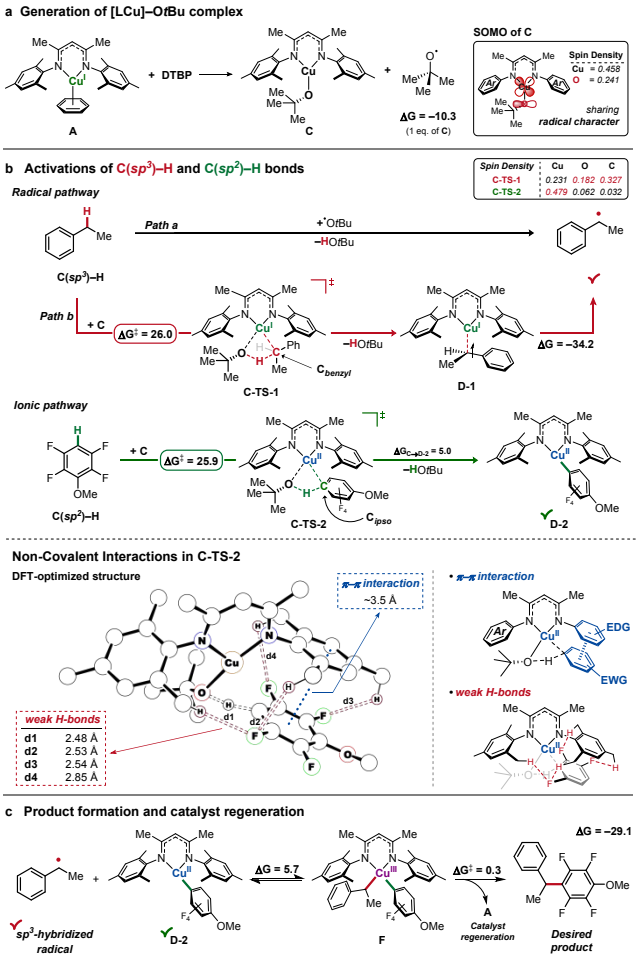
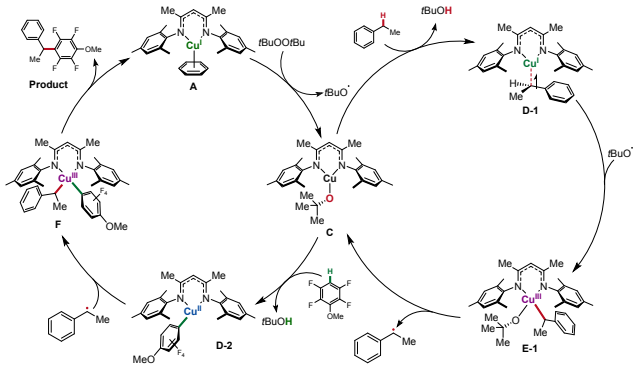


Figure 2. DFT calculations for the activations of C(sp^3)–H and C(sp^2)–H bonds.

Analysis on the transition states of the proposed Cu-mediated dual activation of sp^3 and sp^2 C–H bonds (**C-TS-1** and **C-TS-2**, respectively) revealed a notable difference in the spin density. In the former process, a significant radical character is located on the oxygen (0.18 e⁻) of *t*-butoxy ligand along with benzylic carbon atom (0.33 e⁻) of approaching ethylbenzene, implicating a radical pathway (HAA).[39] In stark contrast, spin density in **C-TS-2** is localized mainly at the copper center (0.48 e⁻), thus leading us to propose that the C–H bond activation of polyfluoroarene will take place most likely via an ionic pathway (see the Supporting Information for frontier molecular orbital analysis). Of special note is that strong π–π interaction was shown to be present between the employed ligand **L10** and fluoroarene substrates (~3.5 Å), wherein fluorine atom serves as a temporary directing group to form weak hydrogen bonds with the benzylic hydrogens of the mesityl ligand. These non-covalent interactions were assumed to facilitate the sp^2 C–H bond activation as well as the stabilization of the corresponding copper aryl intermediates.[40,41]

Scheme 4. Proposed Mechanism



In accordance with the above mechanistic investigations, a proposed pathway of the current alkane-fluoroarene coupling reaction is depicted in Scheme 4. First, the active copper complex **A**, formed from the copper precursor by reacting with *t*BuONa and ligand **L10**, promotes the homolytic cleavage of DTBP to afford the key intermediate [LCu]–O*t*Bu (**C**) along with *t*BuO· radical. An alkoxy copper complex **C** activates sp^3 C–H bonds of ethylbenzene via a radical pathway to give an alkyl radical-coordinated intermediate **D-1** that will interact with *t*BuO• radical resulting in an (alkyl)(alkoxy)Cu(III) intermediate **E-1**. Then, an alkyl radical will be released with the regeneration of the intermediate **C**. It is proposed that alkane activation takes place mainly via a copper-mediated process leading to an alkyl radical although an alkoxy radical-mediated direct cleavage of sp^3 C–H bonds cannot be completely ruled out. On the other hand, the copper alkoxide complex **C** is believed to activate fluoroarnes via an ionic pathway to give an (aryl)Cu^{II} intermediate **D-2** that interacts with an alkyl radical to generate a (alkyl)(aryl)Cu(III) intermediate **F**. Product will be released upon the reductive elimination of **F** along with the regeneration of the active copper complex **A**.

■ CONCLUSION

The present study demonstrates for the first time that a copper-catalyzed selective alkylation of polyfluoroarenes is enabled by using

hydrocarbons. A broad range of alkanes could be successfully utilized to include non-activated hydrocarbons with moderate to high site-selectivity. Dual activation mode was postulated to operate in activating sp^3 C–H and sp^2 C–H bonds via a radical and ionic pathway, respectively. Non-covalent interactions formed *in situ* between the copper ligand and fluoroarenes such as π–π interaction and hydrogen bonds are proposed to facilitate the arene activation process. Upon further improvement of reaction conditions and arene scope, our approach offers a future research direction to utilize hydrocarbon feedstocks directly in synthesis.

■ ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, experimental details, computational details, characterization data, and crystallographic data for **19**, **32**, **35**, **40**, **Copper Complex A** (PDF)
Crystallographic data of **19** (CIF)
Crystallographic data of **32** (CIF)
Crystallographic data of **35** (CIF)
Crystallographic data of **40** (CIF)
Crystallographic data of **Copper Complex A** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail for S. C.: sbchang@kaist.ac.kr

ORCID

Joon Heo: 0000-0001-5275-9279

Sukbok Chang: 0000-0001-9069-0946

Notes

The authors declare no competing financial interest.

■ ACKNODGEMENTS

This research was supported by the Institute for Basic Science (IBS-R010-D1) in Korea. The authors acknowledge Prof. Mi Hee Lim, Mr. Jong-Min Suh, Ms. Yelim Yi (KAIST) for helpful discussion in EPR spectroscopy, and thank Prof. Mu-Hyun Baik for grateful advice in computational study.

■ REFERENCES

(1) Diederich. F.; Stang, P. J. Metal-catalyzed cross-coupling reactions (Wiley-VCH, 2004).

(2) For selected references on alkylation reactions with pre-functionalized reagents, see: (a) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. Palladium-catalyzed coupling of alkyl chlorides and Grignard reagents. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059. (b) González-Bobes, F.; Fu, G. C. Amino alcohols as ligands for nickel-catalyzed Suzuki reactions of unactivated alkyl halides, including secondary alkyl chlorides, with arylboronic acids. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361. (c) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. Efficient cross-coupling of secondary alkyltrifluoroborates with aryl chlorides–reaction discovery using parallel microscale experimentation. *J. Am. Chem. Soc.* **2008**, *130*, 9257–5259. (d) Han, C; Buchwald, S. L. Negishi coupling of secondary alkylzinc halides with aryl bromides and chlorides. *J. Am. Chem. Soc.* **2009**, *131*, 7532–7533. (e) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing conventional carbon nucleophiles with electrophiles: nickel-catalyzed reductive alkylation of aryl bromides and chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159.

(3) Hartwig, J. F. Organotransition metal chemistry: from bonding to catalysis (University Science, Sausalito, CA, 2010).

(4) (a) Labinger, A.; Bercaw, J. E. Understanding and exploiting C–H bond activation. *Nature* **2002**, *417*, 507–514. (b) Tang, X.; Jia, X.; Huang, Z. Challenges and opportunities for alkane functionalisation using molecular catalysts. *Chem. Sci.* **2018**, *9*, 288–299. (c) Shao, B.; Bagdasarian, A. L.; Popov, S.; Nelson, H. M. Arylation of hydrocarbons enabled by organosilicon reagents and weakly coordinating anions. *Science*, **2017**, *355*, 1403–1407.

(5) For selected references on C–H arylation of alkanes, see: (a) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. Functionalization of C(sp^3)–H bonds using a transient directing group. *Science* **2016**, *351*, 252–256. (b) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. Direct arylation of strong aliphatic C–H bonds. *Nature* **2018**, *560*, 70–75. (c) Vasilopoulos, A.; Zultanski, S. L.; Stahl, S. S. Feedstocks to pharmacophores: Cu-catalyzed oxidative arylation of inexpensive alkylarenes enabling direct access to diarylalkanes. *J. Am. Chem. Soc.* **2017**, *139*, 7705–7708. (d) Zhang, W.; Chen, P.; Liu, G. Copper-catalyzed arylation of benzylic C–H bonds with alkylarenes as the limiting reagents. *J. Am. Chem. Soc.* **2017**, *139*, 7709–7712.

(6) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C–H bond activation strategy for C–C and C–N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083.

(7) For selected references on the cross-dehydrogenative coupling (CDC) of arenes with alkanes, see: (a) Deng, G.; Zhao, L.; Li, C.-J. Ruthenium-catalyzed oxidative cross-coupling of chelating arenes and cycloalkanes. *Angew. Chem. Int. Ed.* **2008**, *47*, 6278–6282. (b) Li, C.-J. Cross-dehydrogenative coupling (CDC): exploring C–C bond formations beyond functional group transformations. *Acc. Chem. Res.* **2009**, *42*, 335–344. (c) Aihara, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. Ni(II)-catalyzed oxidative coupling between C(sp^2)–H in benzamides and C(sp^3)–H in toluene derivatives. *J. Am. Chem. Soc.* **2014**, *136*, 15509–15512. (d) Wu, X.; Zhao, Y.; Ge, H. Pyridine-enabled copper-promoted cross dehydrogenative coupling of C(sp^2)–H and unactivated C(sp^3)–H bonds. *Chem. Sci.* **2015**, *6*, 5978–5983. (e) Shi, J.-L.; Wang, D.; Zhang, X.-S.; Li, X.-L.; Chen, Y.-Q.; Li, Y.-X.; Shi, Z.-J. Oxidative coupling of sp^2 and sp^3 carbon–hydrogen bonds to construct dihydrobenzofurans. *Nat. Commun.* **2017**, *8*, 238. (f) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent advances in radical C–H activation/radical cross-coupling. *Chem. Rev.* **2017**, *117*, 9016–9085. (g) Wang, H.; Gao, X.; Lv, Z.; Abdelilah, T.; Lei, A. Recent advances in oxidative R^1–H/R^2–H cross-coupling with hydrogen evolution via photo-/electrochemistry. *Chem. Rev.* **2019**, *119*, 6769–6787. (h) Yazaki, R.; Ohshima, T. Recent strategic advances for the activation of benzylic C–H bonds for the formation of C–C bonds. *Tetrahedron Lett.* **2019**, *60*, 151225–151236.

(8) Antonchick, A. P.; Burgmann, L. Direct selective oxidative cross-coupling of simple alkanes with heteroarenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3267–3271.

(9) (a) Stuart, D. R.; Fagnou, K. The catalytic cross-coupling of unactivated arenes. *Science* **2007**, *316*, 1172–1175. (b) Bugaut, X.; Glorius, F. Palladium-catalyzed selective dehydrogenative cross-couplings of heteroarenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 7479–7481. (c) Yang, Y.; Lan, J.; You, J. Oxidative C–H/C–H coupling reactions between two (hetero)arenes. *Chem. Rev.* **2017**, *117*, 8787–8863. (d) Doba, T.; Matsubara, T.; Ilies, L.; Shang, R.; Nakamura, E. Homocoupling-free iron-catalysed twofold C–H activation/cross-couplings of aromatics via transient connection of reactants. *Nat. Catal.* **2019**, *2*, 400–406.

(10) Xie, W.; Yoon, J. H.; Chang, S. (NHC)Cu–Catalyzed mild C–H amidation of (hetero)arenes with deprotectable carbamates: scope and mechanistic studies. *J. Am. Chem. Soc.* **2016**, *138*, 12605–12614.

(11) Kharasch, M. S.; Sosnovsky, G. The reactions of *t*-butyl perbenzoate and olefins–A stereospecific reaction. *J. Am. Chem. Soc.* **1958**, *80*, 756.

(12) (a) Gephart, R. T. III.; McMullin, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. Reaction of Cu^{I} with dialkyl peroxides: Cu^{II}–alkoxides, alkoxy radicals, and catalytic C–H etherification. *J. Am. Chem. Soc.* **2012**, *134*, 17350–17353. (b) Salvador, T. K.; Arnett, C. H.; Kundu, S.; Sapiezynski, N. G.; Bertke, J. A.; Boroujeni, M. R.; Warren, T. H. Copper catalyzed sp^3 C–H etherification with acyl protected phenols. *J. Am. Chem. Soc.*, **2016**, *138*, 16580–16583.

(13) (a) Pelletier, G.; Powell, D. A. Copper-catalyzed amidation of allylic and benzylic C–H bonds. *Org. Lett.* **2006**, *8*, 6031–6034. (b) Gephart, R. T. III.; Huang, D. L.; Aguila, M. J. B.; Schmidt, G.; Shahu, A.; Warren, T. H. Catalytic C–H amination with aromatic amines. *Angew. Chem., Int. Ed.* **2012**, *51*, 6488–6492. (c) Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. H. Copper-catalyzed intermolecular amidation and imidation of unactivated alkanes. *J. Am. Chem. Soc.* **2014**, *136*, 2555–2563.

(14) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **2007**, *317*, 1881–1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (c) Iverson, S.; Larson, G.; Lai, C.; Yeh, L.-T.; Dadson, C.; Weingarten, P.; Appleby, T.; Vo, T.; Maderna, A.; Vernier, J.-M.; Hamatake, R.; Miner, J. N.; Quart, B. RDEA119/BAY 869766: a potent, selective, allosteric inhibitor of MEK1/2 for the treatment of cancer. *Cancer Res.* **2009**, *69*, 6839–6847. (d) Amii, H.; Uneyama, K. C–F Bond activation in organic synthesis. *Chem. Rev.* **2009**, *109*, 2119–2183. (e) Biftu, T.; Qian, X.; Chen, P.; Feng, D.; Scapin, G.; Gao, Y.-D.; Cox, J.; Roy, R. S.; Eiermann, G.; He, H.; Lyons, K.; Salituro, G.; Patel, S.; Petrov, A.; Xu, F.; Xu, S. S.; Zhang, B.; Caldwell, C.; Wu, J. K.; Weber, A. E. Novel tetrahydropyran analogs as dipeptidyl peptidase IV inhibitors: profile of clinical candidate (*2R*,*3S*,*5R*)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4*H*)-yl]-tetrahydro-2*H*-pyran-3-amine (23). *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5361–5366. (f) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.: Izawa, K.; Liu, H. Next generation of fluorine-containing pharmaceuticals, compounds currently in phase II–III clinical trials of major pharmaceutical companies: new structural trends and therapeutic areas. *Chem. Rev.* **2016**, *116*, 422–518.

(15) (a) Weck, M.; Dunn, A. R.; Matsumoto, K.; Coates, G. W.; Lobkovsky, E. B.; Grubbs, R. H. Influence of perfluoroarene–arene interactions on the phase behavior of liquid crystalline and polymeric materials. *Angew. Chem., Int. Ed.* **1999**, *38*, 2741–2745. (b) Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Tokito, S.; Taga, Y. Synthesis, characterization, and electron-transport property of perfluorinated phenylene dendrimers. *J. Am. Chem. Soc.* **2000**, *122*, 1832–1833. (c) Nitschke, J. R.; Tilley, T. D. Efficient, high-yield route to long, functionalized *p*-phenylene oligomers containing perfluorinated segments, and their cyclodimerizations by zirconocene coupling. *J. Am. Chem. Soc.* **2001**, *123*, 10183–10190. (d) Tsuzuki, T.; Shirasawa, N.; Suzuki, T.; Tokito, S. Color tunable organic light-emitting diodes using pentafluorophenyl-substituted iridium complexes. *Adv. Mater.* **2003**, *15*, 1455–1458. (e) Meyer, E. A.; Castellano, R. K.; Diederich, F. Interactions with aromatic rings in chemical and biological recognition. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250. (f) Murphy, A. R.; Fréchet, J. M. J. Organic semiconducting oligomers for use in thin film transistors. *Chem. Rev.* **2007**, *107*, 1066–1096. (g) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. Fluorinated organic materials for electronic and optoelectronic applications: the role of the fluorine atom. *Chem. Commun.* **2007**, 1003–1022.

(16) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. Catalytic intermolecular direct arylation of perfluorobenzenes. *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756. (b) Do, H.-Q.; Daugulis, O. Copper-catalyzed arylation and alkenylation of polyfluoroarene C–H bonds. *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129. (c) Simonetti, M.; Perry, G. J. P.; Cambeiro, X. C.; Juliá-Hernández, F.; Arokianathar, J. N.; Larrosa, I. Ru-Catalyzed C–H arylation of fluoroarenes with aryl halides. *J. Am. Chem. Soc.* **2016**, *138*, 3596–3606. (d) Li, W.; Yuan, D.; Wang, G.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. Cooperative Au/Ag dual-catalyzed cross-dehydrogenative biaryl coupling: reaction development and mechanistic insight. *J. Am. Chem. Soc.* **2019**, *141*, 3187–3197.

(17) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. $Pd(OAc)_2$ Catalyzed olefination of highly electron-deficient perfluoroarenes. *J. Am. Chem. Soc.* **2010**, *132*, 4506–4507.

(18) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. Copper-catalyzed direct alkynylation of electron-deficient polyfluoroarenes with terminal alkynes using O_2 as an oxidant. *J. Am. Chem. Soc.* **2010**, *132*, 2522–2523.

(19) (a) Fan, S.; Chen, F.; Zhang, X. Direct palladium-catalyzed Intermolecular allylation of highly electron-deficient polyfluoroarenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 5918–5923. (b) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. Stereospecific copper-catalyzed C–H allylation of electron-deficient arenes with allyl phosphates. *Angew. Chem., Int. Ed.* **2011**, *50*, 2990–2994. (c) Xie, W.; Chang, S. [Cu(NHC)]-Catalyzed C–H allylation and alkenylation of both electron-deficient and electron-rich (hetero)arenes with allyl halides. *Angew. Chem., Int. Ed.* **2016**, *55*, 1876–1880.

(20) (a) Fan, S.; He, C.-Y.; Zhang, X. Direct Pd-catalyzed benzylation of highly electron-deficient perfluoroarenes. *Chem. Commun.*, **2010**, *46*, 4926–4928. (b) Xu, S.; Wu, G.; Ye, F.; Wang, X.; Li, H.; Zhao, X.; Zhang, Y.; Wang, J. Copper(I)-catalyzed alkylation of polyfluoroarenes through direct C–H bond functionalization. *Angew. Chem., Int. Ed.* **2015**, *54*, 4669–4672. (c) Sun, Z.-M.; Zhang, J.; Manan, R. S.; Zhao, P. Rh(I)-Catalyzed olefin hydroarylation with electron-deficient perfluoroarenes. *J. Am. Chem. Soc.* **2010**, *132*, 6935–6937.

(21) (a) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B.; Milstein, D. Catalytic system for heck reactions involving insertion into Pd-(perfluoro-organyl) bonds. *J. Am. Chem. Soc.* **2001**, *123*, 11504–11505. (b) Albéniz, A. C.; Espinet, P.; Martn-Ruiz, B.; Milstein, D. Catalytic system for the Heck reaction of fluorinated haloaryls. *Organometallics* **2005**, *24*, 3679–3684. (c) Clot, E.; Mégret, C.; Eisenstein, O.; Perutz, R. N. Exceptional sensitivity of metal–aryl bond energies to *ortho*-fluorine substituents: influence of the metal, the coordination sphere, and the spectator ligands on M–C/H–C bond energy correlations. *J. Am. Chem. Soc.* **2009**, *131*, 7817–7827. (d) Evans, M. E.; Burke, C. L.; Yaibuathes, S.; Clot, E.; Eisenstein, O.; Jones, W. D. Energetics of C–H bond activation of fluorinated aromatic hydrocarbons using a [Tp′Rh(CNneopentyl)] complex. *J. Am. Chem. Soc.* **2009**, *131*, 13464–13473.

(22) (a) Do, H.-Q.; Daugulis, O. An aromatic Glaser-Hay reaction. *J. Am. Chem. Soc.* **2009**, *131*, 17052–17053. (b) Kundo, S.; Greene, C.; Williams, K. D.; Salvador, T. K.; Bertke, J. A.; Cundari, T. R.; Warren, T. H. Three-coordinate copper(II) aryls: key intermediates in C–O bond formation. *J. Am. Chem. Soc.* **2017**, *139*, 9112–9115.

(23) Luo, Y.-R. Handbook of bond dissociation energies in organic compounds; CRC Press, 2002.

(24) Neel, A. J.; Hilton, M. J.; Sigman, M. S.; Toste, F. D. Exploiting non-covalent π interactions for catalyst design. *Nature* **2017**, *543*, 637–646.

(25) (a) Cuthbertson, J. D.; MacMillan, D. W. C. The direct arylation of allylic sp^3 C–H bonds via organic and photoredox catalysis. *Nature* **2015**, *519*, 74–77. (b) Mishra, N. K.; Sharma, S.; Park, J.; Han, S.; Kim, I. S. Recent advances in catalytic C(sp^2)–H allylation reactions. *ACS Catal.* **2017**, *7*, 2821–2847. (c) Lerchen, A.; Knecht, T.; Koy, M.; Ernst, J. B.; Bergander, K.; Daniliuc, C. G.; Glorius, F. Non-directed cross-dehydrogenative (hetero)arylation of allylic C(sp^3)–H bonds enabled by C–H Activation. *Angew. Chem., Int. Ed.* **2018**, *57*, 15248–15252.

(26) (a) Cook, A. K.; Schimler, S. D.; Matzger, A. J.; Sanford, M. S. Catalyst-controlled selectivity in the C–H borylation of methane and ethane. *Science* **2016**, *351*, 1421–1424. (b) Smith, K. T.; Berritt, S.; González-Moreiras, M.; Ahn, S.; Smith III, M. R.; Baik, M.-H.; Mindiola, D. J. Catalytic borylation of methane. *Science* **2016**, *351*, 1424–1427. (c) Hu, A.; Guo, J.-J.; Pan, H.; Zuo, Z. Selective functionalization of methane, ethane, and higher alkanes by cerium photocatalysis. *Science* **2018**, *361*, 668–672.

(27) Mo, F.; Dong, G. Regioselective ketone α-alkylation with simple olefins via dual activation, *Science* **2014**, *345*, 68–72.

(28) Wu, J.; Cao, S. Nickel-catalyzed hydrodefluorination of fluoroarenes and trifluorotoluenes with superhydride (lithium triethylborohydride). *ChemCatChem* **2011**, *3*, 1582–1586.

(29) Drugbank, http://drugback.ca/.

(30) Clark, J. R.; Feng, K.; Sookezian, A.; White, M. C. Manganese-catalysed benzylic C(sp^3)–H amination for late-stage functionalization. *Nat. Chem.* **2018**, *10*, 583–591.

(31) Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. Cu-Facilitated C–O bond formation using *N*-hydroxyphthalimide: efficient and selective functionalization of benzyl and allylic C–H bonds. *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825.

(32) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. Calibration of new horology of fast radical clocks. ring-opening rates for ringand α-alkyl-substituted cyclopropylcarbinyl radicals and for the bicyclo[2.1.0]pent-2-yl radical. *J. Am. Chem. Soc.* **1991**, *113*, 5687–5698.

(33) Simmons, E. M.; Hartwig, J. F. On the interpretation of deuterium kinetic isotope effects in C–H bond functionalizations by transition-metal complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072.

(34) Wang, F.; Chen, P.; Liu, G. Copper-catalyzed radical relay for asymmetric radical transformations. *Acc. Chem. Res.* **2018**, *51*, 2036–2046.

(35) (a) Walling, C.; Jacknow, B. B. Positive halogen compounds. I. The radical chain halogenation of hydrocarbons by t-butyl hypochlorite. *J. Am. Chem. Soc.* **1960**, *82*, 6108–6112. (b) Li, Y.; Lei, M.; Gong, L. Photocatalytic regio- and stereoselective C(sp^3)–H functionalization of benzylic and allylic hydrocarbons as well as unactivated alkanes. *Nat. Catal.* **2019**, *2*, 1016–1026.

(36) Wiese, S.; Badiei, Y. M.; Gephart, R. T.; Mossin, S.; Varonka, M. S.; Melzer, M. M.; Meyer, K.; Cundari, T. R.; Warren, T. H. Catalytic C–H amination with unactivated amines through copper(II) amides. *Angew. Chem. Int. Ed.* **2010**, *49*, 8850–8855.

(37) (a) Kochi, J. K.; Bemis, A.; Jenkins, C. L. Mechanism of electron transfer oxidation of alkyl radicals by copper(II) complexes. *J. Am. Chem. Soc.* **1968**, *90*, 4616–4625. (b) Chen, M.; Dong, G. Copper-catalyzed desaturation of lactones, lactams, and ketones under pH-neutral conditions. *J. Am. Chem. Soc.* **2019**, *141*, 14889–14897.

(38) (a) Huffman, L. M.; Stahl, S. S. Carbon–nitrogen bond formation involving well-defined aryl–copper(III) complexes. *J. Am. Chem. Soc.* **2008**, *130*, 9196–9197. (b) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. Direct observation of Cu^{I}/Cu^{III} redox steps relevant to Ullmann–type coupling reactions. *Chem. Sci.* **2010**, *1*, 326–330. (c) Zhang, H.; Yao, B.; Zhang, L.; Wang, D.-X.; Xu, B.-Q.; Wang, M.-X. Direct synthesis of high-valent aryl–Cu(II) and aryl-Cu(III) compounds: mechanistic insight into arene C–H bond metalation. *J. Am. Chem. Soc.* **2014**, *136*, 6326–6332.

(39) Fan, H.; Adhikari, D.; Saleh, A. A.; Clark, R. L.; Zuno-Cruz, F. J.; Cabrera, G. S.; Huffman, J. C.; Pink, M.; Mindiola, D. J.; Baik, M.-H.. Understanding and predicting distorted T- vs. Y-geometries for neutral chromous complexes supported by a sterically encumbering β-dikitiminate ligand. *J. Am. Chem. Soc.* **2008**, *130*, 16812–16822.

(40) A red shift of an absorption peak of the coordinated **L10** ligand was observed in UV-Vis spectroscopy when hexafluorobenzene was added to a solution of *in-situ* generated [LCu]–O*t*Bu species (see the supporting information for details).

(41) Reichenbächer, K.; Süss, H. I.; Hulliger, J. Fluorine in crystal engineering–"the little atom that could". *Chem. Soc. Rev.* **2005**, *34*, 22–30.

Table of Contents