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Construction of carbon–carbon bonds is one of the most essential 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(sp²)–C(sp³) 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 a copper-catalyzed cross-dehydrogenative coupling of perfluoroarenes with alkanes. Mechanistic information was obtained by combining experimental and computational studies to suggest that the optimal diketimine copper catalyst system plays a dual role to activate both sp³ and sp² C–H bonds.

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Copper-catalyzed direct alkylation of perfluoroarenes with hydrocarbons

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Abstract

Construction of carbon–carbon bonds is one of the most essential 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 a copper-catalyzed cross-dehydrogenative coupling of perfluoroarenes with alkanes. Mechanistic information was obtained by combining experimental and computational studies to suggest that the optimal diketimine copper catalyst system plays a dual role to activate both *sp*³ and *sp*² C–H bonds.

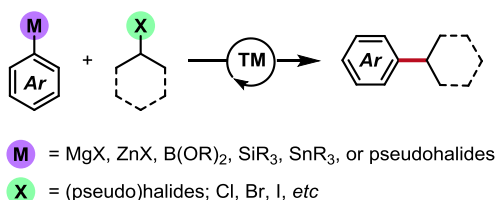
Introduction

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,^{2–5} wherein a series of two-electron processes are operative by involving oxidative addition, transmetalation, and reductive elimination.¹ This approach has been further investigated to expand its scope to include alkyl electrophiles as a coupling partner (Fig. 1a). However, this reaction remains rather unsatisfactory mainly because a key metal alkyl intermediate is prone to undesired β -hydride elimination.⁶ While direct arylation of intrinsically inert hydrocarbons via C–H bond activation is highly attractive,^{7–9} on the other hand, C–H arylation of alkanes with aryl nucleophiles/electrophiles has been reported only recently under catalytic conditions,^{10–13} where a single-electron transfer pathway was found to be more effective (Fig. 1b).

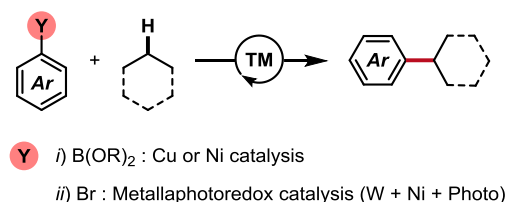
Despite the recent promise, a direct coupling between alkanes and arenes via a twofold oxidative C–H bond activation to yield C(*sp*²)–C(*sp*³) bonds is largely underdeveloped as a synthetic tool.^{14–20} Indeed, only a few examples have been revealed with limited scope and/or under harsh conditions. 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.¹⁵ A copper/pyridine-mediated stoichiometric reaction of methyl C–H bonds of aliphatic quinoline amides with polyfluoroarenes (140 °C) was recently developed.¹⁷ Additionally, direct alkylation of *N*-heteroarenes with alkanes via a Minisci-type pathway was well investigated.²¹

The biggest challenge in 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).^{14,22}

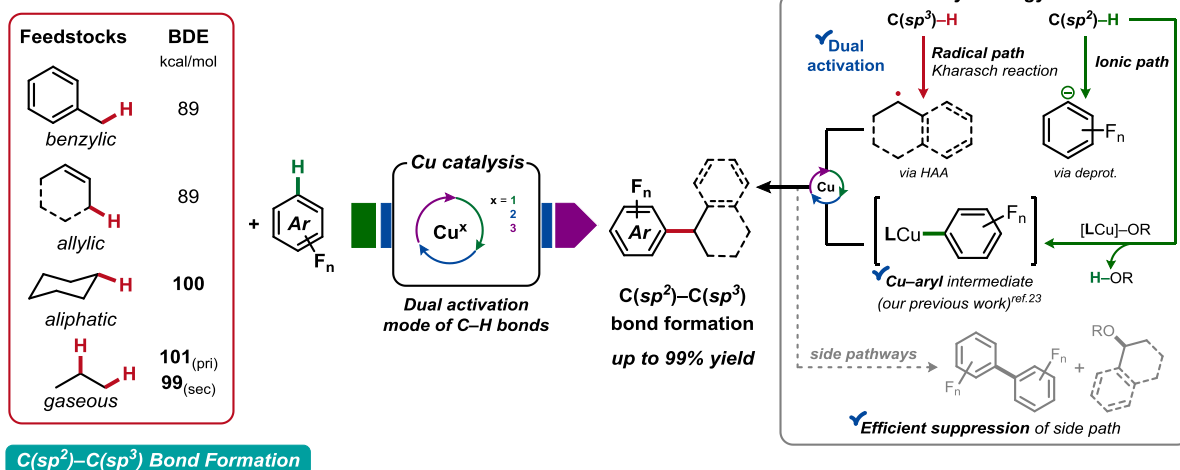
a Conventional Methods for C(sp²)–C(sp³) Bond Formation



b Alkylation of Pre-functionalized Arenes with Alkanes



c Direct Coupling of Hydrocarbons with Perfluoroarenes



- Broad scope including gaseous feedstocks (> 60 examples)
- Mild reaction conditions / scalable (50 mmol)
- Late-stage functionalizations
- Selectivity favoring secondary C–H bonds over primary/tertiary
- Combined mechanistic studies (computations/experiments)
- Dual activation mode: radical and ionic pathways

Figure 1. (a) Conventional methods to form C(sp²)–C(sp³) bonds. (b) Alkylation of pre-functionalized arenes with alkanes: i) Cu or Ni-catalyzed alkylation of aryl boronic acids, ii) Metallaphotoredox catalyst system. (c) Ligand-enabled Cu-catalyzed alkylation of polyfluoroarenes with hydrocarbon feedstocks under mild conditions and key working hypothesis. TM, transition-metal catalysts; R, alkyl group; Ar, aryl; BDE, bond dissociation energy; HAA, hydrogen atom abstraction.

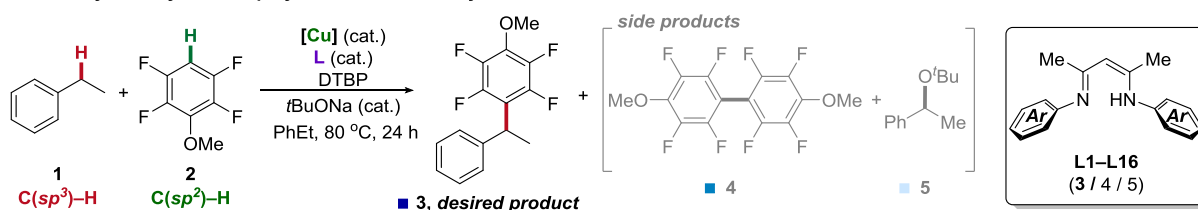
Based on our previous (NHC)Cu-catalyzed amidation of (hetero)arenes,²³ we envisioned that the *in situ* generated copper-aryl intermediates might be able to couple with sp³-hybridized carbon radicals to form the desired alkylation products (Fig. 1c). In the Kharasch–Sosnovsky reaction,²⁴ allylic C–H bonds are activated by a copper/peroxide system to afford carbon radicals that eventually give rise to ether^{25,26} or amine products.^{27–29} More recently, Cu-catalyzed oxidative arylation at the benzylic C–H bonds was achieved by using arylboronic esters to afford diarylalkanes.¹² Polyfluoroarenes are widely utilized in materials science and medicinal chemistry owing to their unique properties derived from the fluorine moiety.³⁰ Direct functionalization of polyfluoroarenes including arylation,^{31,32} olefination,³³ alkynylation,³⁴ allylation³⁵ and amination²³ has been achieved by several research groups including us. In contrast, only a few examples of C–H alkylation of perfluoroarenes are known, such as Pd-catalyzed benzylation with primary benzyl chlorides³⁶ or Cu-catalyzed alkylation with diazo compounds.³⁷ The paucity of the

alkylation procedure is rooted in the low reactivity of the perfluoroaryl–metal intermediates (due to the strong σ -bonds of M–C₆F₅) towards alkyl electrophiles.^{33,38} In addition, a competing path for the homocoupling of perfluoroarenes would also give rise to a challenging chemoselectivity issue.^{34,39} We report herein a copper catalyst system that enables the direct alkylation of polyfluoroarenes with various types of hydrocarbons (Fig. 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.⁴⁰ It was found that the electronic and steric properties of the optimized diketimine ligand are crucial in achieving the desired chemoselectivity by harnessing highly reactive 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 are also rationalized to facilitate the current cross-couplings (*vide infra*).⁴¹ The developed copper catalyst system is convenient to operate a decagram-scale reaction and is broad in scope of hydrocarbons even including gaseous hydrocarbons and complex molecules.

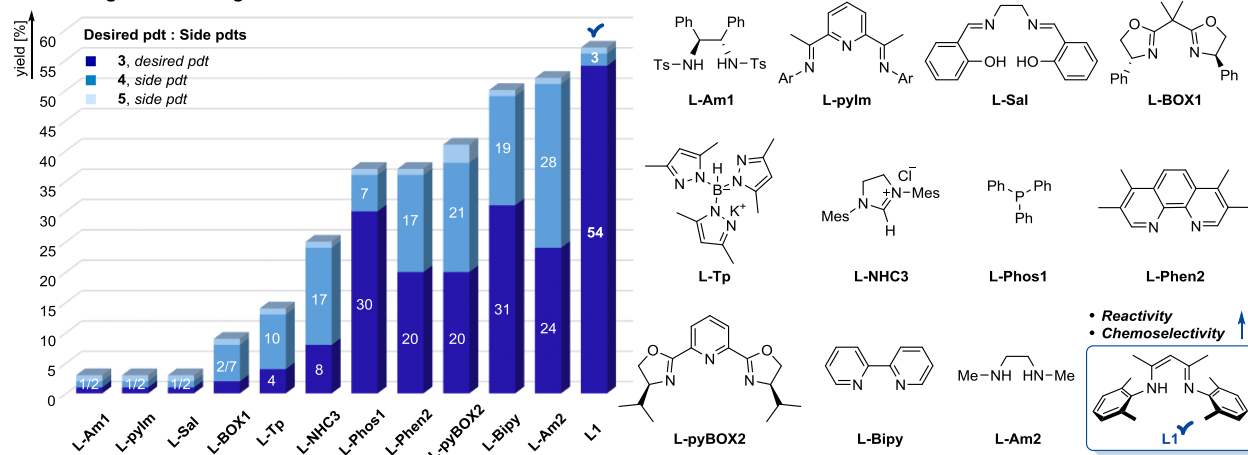
Result and Discussion

We embarked on experiments by examining a model reaction of ethylbenzene (**1**) with 2,3,5,6-tetrafluoroanisole (**2**) under various conditions (see the Fig. 2 and Supplementary 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 cross-coupled product (**3**) was observed to form along with a homo-coupled bisarene (**4**)^{39,42} and an ether byproduct (**5**).²⁵ While moderate to low product yields were obtained with such conventional ligands as NHCs, phosphines, or bipyridines, the use of β -diketimine ligand (**L1**) showed a promise with effective suppression of side products (Fig. 2b). While the amounts of bases turned out to be crucial, catalytic amounts of *t*BuONa were also viable with longer reaction time (Fig. 2c, 71% of **3** with 0.8 equiv. of *t*BuONa in 24 h and 72% with 0.2 equiv. in 40 h). The result that weak bases such as K₂CO₃ and Cs₂CO₃ were ineffective was rationalized to be closely related to the efficiency in generating the active copper species (see the Mechanistic Studies in the Supplementary Information). From the additional screening of β -diketimine ligands, the most optimal ligand turned out to be **L9** 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 influenced the reaction efficiency and chemoselectivity. For instance, the presence of *ortho*-methyl groups in the phenyl imine moiety was required for the high reactivity. It is worth mentioning that β -diketimine copper complexes were elegantly utilized in the etherification and amidation by Warren group.^{25,26,28} Among various oxidants evaluated in combination with **L9**, di-*tert*-butyl peroxide (DTBP) was especially effective in obtaining the desired coupling. The alkylation efficiency was slightly decreased by employing reduced amounts of reactant (e.g., 64% product yield with 5 equiv. of ethylbenzene and 10 equiv. afforded 78% yield).

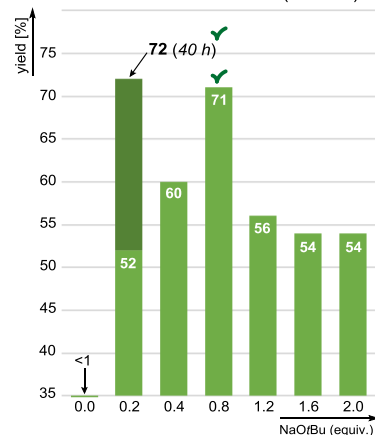
a Cu-Catalyzed alkylation of polyfluoroarenes with hydrocarbons



b Initial ligand screening



c Influence of base amounts ($t = 24\text{ h}$)



d Electronic & Steric variations on β -diketiminato ligands

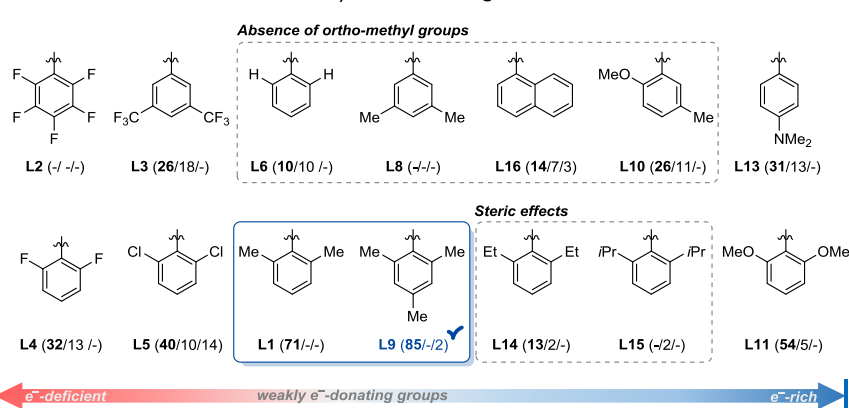


Figure 2. Ligand-enabled copper catalyst system for the alkane-arene couplings. (a) Cu-Catalyzed model reaction of 2,3,4,5-tetrafluoroanisole (2) with ethylbenzene (1). DTBP, di-*tert*-butylperoxide. (b) Initial ligand screening based on the reactivity and chemoselectivity. (c) Influence of base amounts in combination with ligand L1. (d) Electronic and steric variations on the β -diketiminato ligands. See the Supplementary Information for detailed reaction conditions.

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 (Fig. 3). 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 (**9–12**). Halide groups were 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**). 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-Ethynaphthalene 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**).

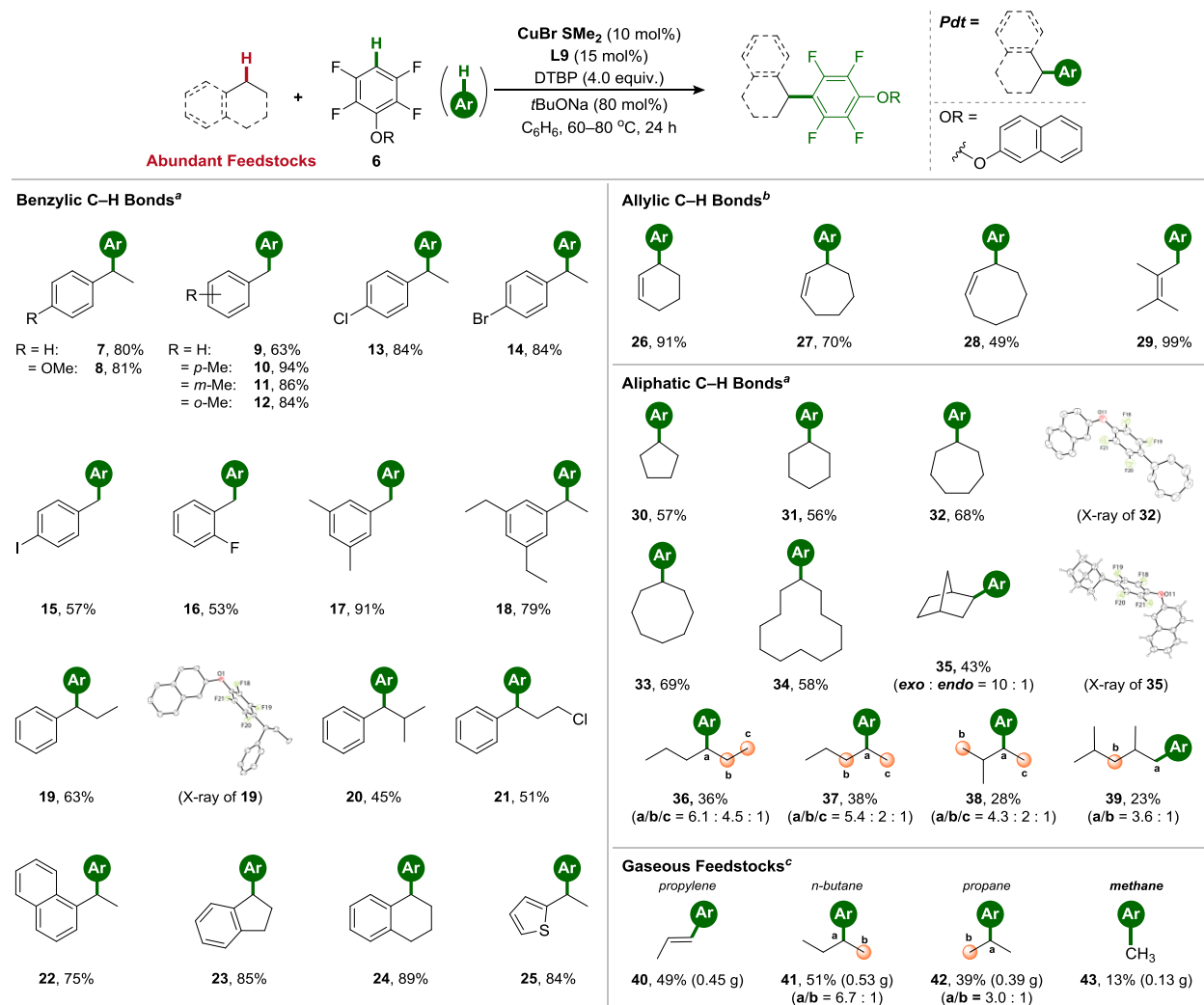


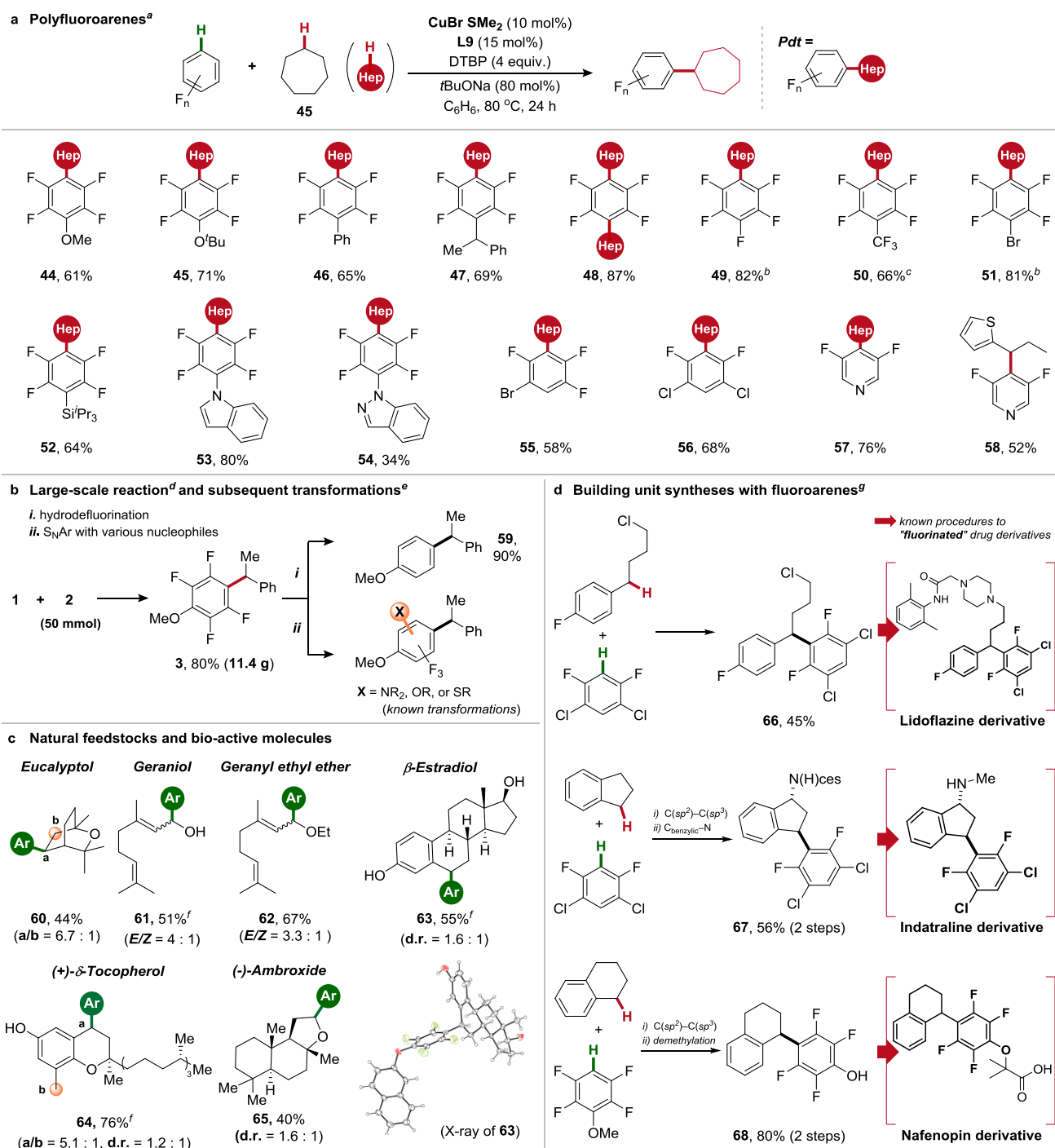
Figure 3. Scope of hydrocarbons reacting at the benzylic, allylic, aliphatic, and gaseous C–H bonds. A broad range of C–H bonds of readily available hydrocarbon feedstock chemicals are arylated: isolated product yields are shown. Orange circles denote sites where regiomer products are formed. See Supplementary Information for experimental details. ^aFeedstock chemical (2 mmol, 10 equiv.), fluoroarene **6** (0.2 mmol), CuBr·SMe₂ (0.02 mmol), ligand **L9** (0.03 mmol), tBuONa (0.16 mmol, 0.8 equiv.), and oxidant DTBP (0.8 mmol, 4 equiv.) in benzene solvent at 80 °C for 24 h. ^bReactions were carried out with hydrocarbons (1 mmol, 5 equiv.) and fluoroarene **6** (0.2 mmol) at 60 °C. ^c3 mmol scale reactions.

Given the versatile utility of an allyl phenyl scaffold as synthetic and medicinal/materials building units,^{35,43–45} the feasibility of direct allylic C–H arylation was subsequently examined in reaction with **6** as a representative arene counterpart. Pleasingly, we observed that cyclohexene (5 equiv.) was smoothly reacted even at 60 °C to afford **26** exclusively in 91% yield. Seven- and eight-membered cycloalkene substrates were also arylated at the allylic position (**27** and **28**). A reaction of tetramethylethylene readily took place to provide the corresponding product **29** in quantitative yield.

As shown in Fig. 1, while the bond dissociation energy (BDE) of benzylic and allylic C–H bonds is in the range of ~90 kcal/mol and that of cycloalkanes is higher by ~10 kcal/mol, thus achieving a direct coupling of those hydrocarbons to be more challenging.⁴⁰ In turn, low molecular weight acyclic hydrocarbons (mainly gaseous alkane feedstocks) having similar BDE of C–H bonds (~100 kcal/mol) are also highly difficult to functionalize.^{46–49} This consideration led us to investigate their feasibility in the current cross-coupling system. We were pleased to observe that cycloalkanes (10 equiv.) were readily reacted with **6** in satisfactory yields in benzene irrespective of the ring size (**30–34**). Norbornane was reacted exclusively at the ethylene C–H bonds 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, non-cyclic hydroalkanes were also viable, thus 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**). *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 only when the secondary position is sterically congested (**39**). Taking one step forward, we attempted to employ gaseous hydrocarbon feedstocks as the alkylating sources 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% yield (**40**).³⁵ *n*-Butane and propane were reacted preferentially at the secondary C–H bonds albeit in moderate yields (**41** and **42**). However, a methylated perfluorobenzene (**43**) was obtained in low yield from a reaction with methane gas.

After surveying the scope of hydrocarbon reactants, the availability of fluoroarene substrates was further investigated in reaction with cycloheptane as a representative coupling partner (Fig. 4a). Tetrafluorobenzenes bearing a methoxy or *t*-butoxy substituent were smoothly reacted (**44** and **45**). Derivatives substituted with phenyl or alkyl groups were also viable for the alkylation with cycloheptane (**46** and **47**). Of note was that a benzylic tertiary C–H bond 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 (**48**). Pentafluorobenzene and its analogue were facile for this alkylation (**49** and **50**). Functional group tolerance was examined to reveal that bromo, silyl, indole, and indazole groups were all tolerant to the present conditions (**51–54**). When two non-equivalent C–H bonds are present, the alkylation was found to occur selectively at the more acidic position (**55** and **56**). 3,5-Difluoropyridine was alkylated in high yield at the 4-position (**57**), and a reaction with 2-propylthiophene was also fruitful to afford 1,1-diheteroarylalkane (**58**). Practicability of the present alkylation protocol was briefly tested in a large scale reaction of 2,3,5,6-tetrafluoroanisole (**2**, 50.0 mmol) with ethylbenzene (**1**) by using 3 mol% of copper catalyst (Fig. 4b). The desired product **3** was isolated in 80% yield (11.4 g). We also envisioned that the obtained products could be further utilized in subsequent transformations. For instance, a catalytic hydrodefluorination of **3**

was readily performed to obtain 1,1-diarylethane compound **59** (90%). Moreover, a nucleophilic aromatic substitution of fluorine atom is known in the literature⁵⁰.



The present cross-coupling procedure was also successfully applied to the C–H arylation of naturally occurring hydrocarbons or bio-active synthetic compounds (Fig. 4c). Eucalyptol was reacted at the secondary C–H bonds with good regioselectivity (**60**, **a/b** = 6.7:1). Alcoholic hydrocarbons were subjected to a three-step sequence: (i) hydroxyl group protection as silyl ethers, (ii) C–H arylation, and (iii) silyl deprotection. For instance, geraniol was viable for this transformation leading to α -aryl alcohol product (**61**) in 51% yield. Significantly, this arylation was found to be selective at the α -allyl silylether site 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 (**62**). β -Estradiol was reacted selectively at the secondary benzylic C–H bonds in 55% yield (**63**, d.r. = 1.6). (+)- δ -Tocopherol (a type of vitamin E) was converted to its arylated derivative mainly at the secondary C–H bond in high yield (**64**). In addition, (-)-ambroxide was arylated at the secondary C–H bonds α to the oxygen atom in moderate yield (**65**). Finally, given that 1,1-diarylalkanes constitute a frequent pharmacophore in numerous drugs,⁵¹ our protocol was briefly examined as a straightforward route to fluorinated analogues (Fig. 4d). Indeed, perfluorinated drug precursors such as lidoflazine, indatraline, and nafenopin were readily obtained in good to high yields (**66–68**). It is worth mentioning that the excess amount of the complex reagents could be recovered in the current system. For instance, the recovered yields of β -estradiol and (+)- δ -tocopherol were 89% and 88%, respectively (see the Supplementary Information).

To obtain mechanistic insights into the present cross-coupling reactions, combined theoretical and experimental studies were carried out. The reaction progress can be divided into three stages as depicted in Fig. 5. A copper(I) complex **A** bearing the optimal β -diketimine ligand (**L9**) was isolated as a dimer, and its structure was confirmed by NMR and X-ray analysis. An alkylation reaction using the isolated complex **A** (dimeric form) afforded a similar product yield when compared to that obtained under the standard conditions (see the Supplementary Information). Based on the previous studies that copper(I) mediates a homolytic cleavage of peroxides,²⁵ it was postulated that **A** reacts with DTBP to furnish 1 equiv. of [LCu]–OtBu (**C**) along with *t*BuO• radical (Stage I, $\Delta G = -10.3$ kcal/mol). After the formation of **C**, two pathways were then envisaged to operate in the activation of sp^3 C–H bonds of alkanes. While a direct hydrogen atom abstraction (HAA) by a free *t*BuO• radical could be conceived (Stage II, Path a), a copper-mediated activation was also considered (Path b). The primary kinetic isotope effects of ethylbenzene was measured to be k_H/k_D (intra) = 4.2 and k_H/k_D (inter) = 2.2 (see the Supplementary Information). In addition, the activation barrier of Path b was calculated to be 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^-). Moreover, considering that free alkoxy radicals are known to activate tertiary C–H bonds preferentially in the presence of secondary and primary counterparts,^{53,54} we propose that the copper-mediated activation of alkane C–H bond operates more favorably (Path b).⁵² Indeed, the observation that tertiary C–H bonds in hydrocarbon reactants are intact under the current conditions (e.g. products **35**, **38**, **39** and **63**) and that tertiary benzylic C–H bonds in products are also inert is in agreement with this assumption. 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 Kochi⁵⁵ and Dong.⁵⁶ As we previously proved the facile activation of polyfluoroarenes by (NHC)Cu-alkoxide²³, the present [LCu]–OtBu (**C**) is postulated to readily deprotonate fluoroarene leading to an (aryl)Cu^{II} intermediate **D-2** ($\Delta G^\ddagger = 25.9$ kcal/mol).

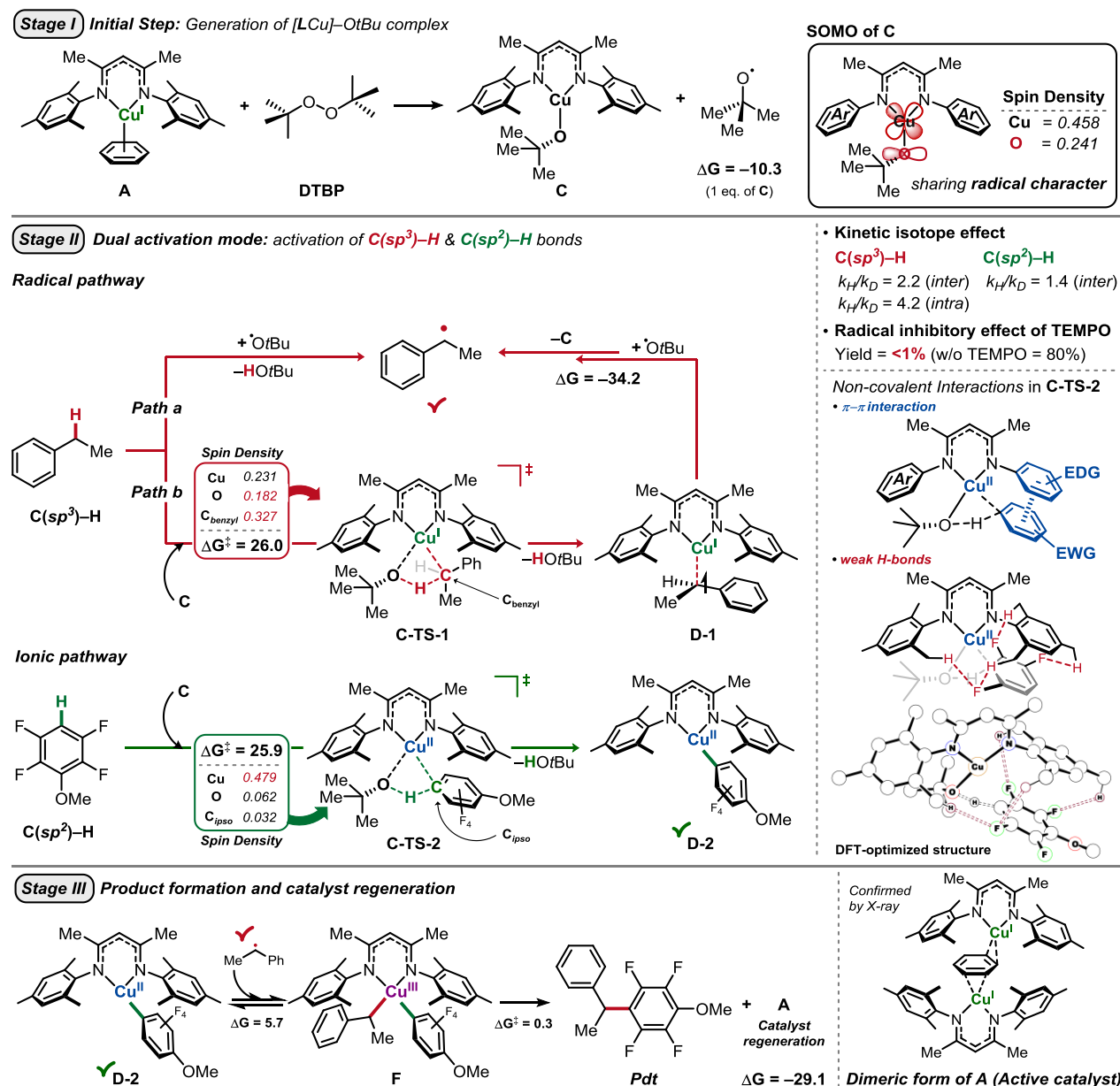


Figure 5. Mechanistic Investigations. The reaction progress can be divided into three stages. (Stage I) Initial step to form [LCu]–OtBu complex **C** and *t*BuO• radical. (Stage II) Dual activation mode consisted of the activation of $C(sp^3)\text{--}H$ bonds via two possible radical pathways and the activation of $C(sp^2)\text{--}H$ bonds via an ionic pathway. Kinetic isotopic effects in substrate and reactant were observed and the significant radical inhibition effect was obtained by TEMPO. Non-covalent interactions between ligand and polyfluoroarene substrate ($\pi\text{--}\pi$ interaction and weak hydrogen bondings) were observed in the DFT-optimized structure of **C-TS-2**. (Stage III) Final stage of product formation via reductive elimination of (alkyl)(aryl)Cu(III) intermediate **F**. The unit for the Gibbs free energies is kcal/mol. The computational details are in the Supplementary Information.

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 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).⁵⁷ 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 Supplementary Information for frontier molecular orbital analysis). Of special note is that strong π – π interaction was shown to be present between the employed ligand **L9** and fluoroarene substrates (~ 3.2 – $3.5\ \text{\AA}$), 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 C–H bond activation as well as the stabilization of the corresponding copper aryl intermediates. 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. We observed that the current reaction was largely inhibited by the presence of radical trapping reagents such as TEMPO (see the Supplementary Information).

Conclusion

The present study demonstrates that a selective alkylation of polyfluoroarenes is enabled by using hydrocarbons with the (β -diketimine)copper catalyst system. Dual activation mode is postulated to operate in activating sp^3 C–H and sp^2 C–H bonds via a radical and ionic pathway, respectively. Although there is room to improve in scope of arenes, our approach offers a future research direction to utilize hydrocarbon feedstocks directly in synthesis.

Data availability

Detailed information of experimental and computational procedures as well as analytical data including X-ray crystallographic data are provided in the Supplementary Information. CCDC 1961322–1961326 contain the crystallographic data for the products and the dimer form of complex **A**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Competing interests

The authors declare no competing financial interests.

Additional information

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