A Bimolecular Homolytic Substitution-Enabled Platform for Multicomponent Cross-Coupling of Unactivated Alkenes

Fei Cong[†], Guo-Quan Sun[†], Si-Han Ye[†], Rui Hu[†£], Weidong Rao[£] and Ming Joo Koh[†*]

[†]Department of Chemistry, National University of Singapore, 4 Science Drive 2, Republic of Singapore, 117544

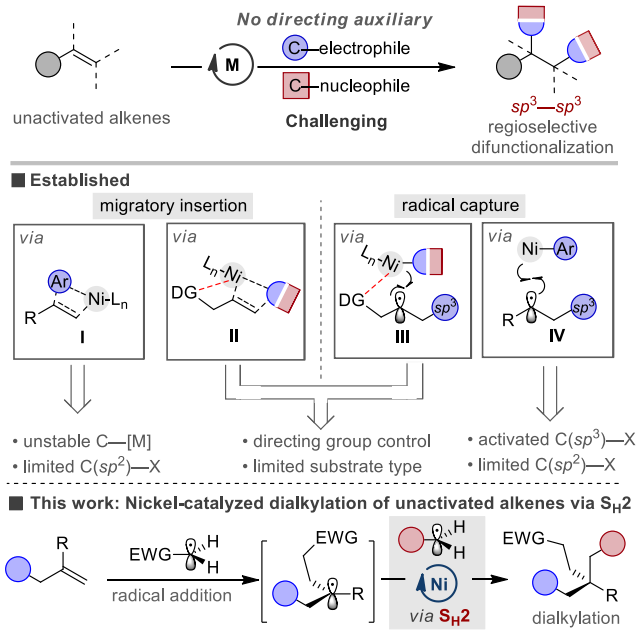
[£]Jiangsu Co-Innovation Center for Efficient Processing and Utilization of Forest Resources, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China

Supporting Information Placeholder

ABSTRACT: The construction of C(sp^3)–C(sp^3) bonds remains one of the most difficult challenges in cross-coupling chemistry. Here, we report a photoredox/nickel dual catalytic approach that enables the simultaneous formation of two C(sp^3)–C(sp^3) linkages via trimolecular cross-coupling of alkenes with alkyl halides and hypervalent iodine-based reagents. The reaction harnesses a bimolecular homolytic substitution (S_H2) mechanism and chemoselective halogen-atom transfer (XAT) to orchestrate the regioselective addition of electrophilic and nucleophilic alkyl radicals across unactivated alkenes without the need for a directing auxiliary. Utility is highlighted through late-stage (fluoro)alkylation and (trideutero)methylation of C=C bonds bearing different substitution patterns, offering straightforward access to drug-like molecules comprising sp^3-hybridized carbon scaffolds.

Unactivated (alkyl-substituted) alkenes belong to one of the most abundant categories of feedstock chemicals in organic chemistry; these building blocks are produced on large scale and are readily accessible by established synthetic methodologies.[1] As such, unactivated alkenes are ideal starting points to selectively introduce functionalities and build molecular complexity and diversity in organic synthesis.[2] In recent years, the site-selective incorporation of carbon-based motifs through transition metal-catalyzed 1,2-dicarbofunctionalization of alkenes has attracted significant interest by promoting double carbon-carbon (C–C) bond formation to deliver saturated hydrocarbon frameworks.[3] In contrast to activated alkenes, related transformations of unactivated alkenes are more challenging as a consequence of the innately weak electronic/steric bias of these substrates, thereby diminishing reactivity and regioselectivity.[4,5] Added to this problem is the susceptibility of organometallic intermediates to undesired β-H elimination and other side reactions.[6] These complications are further exacerbated in dialkylation processes that employ aliphatic nucleophiles and/or electrophiles to furnish C(sp^3)-rich molecules[7] (Scheme 1); such three-dimensional products are prized in pharmaceutical development based on studies that correlate increased C(sp^3) character with greater solubility, selectivity and potency in small-molecule drugs.[2,8]

Scheme 1. Leveraging S_H2 as a Tool to Achieve Regioselective 1,2-Dialkylation of Unactivated Alkenes.

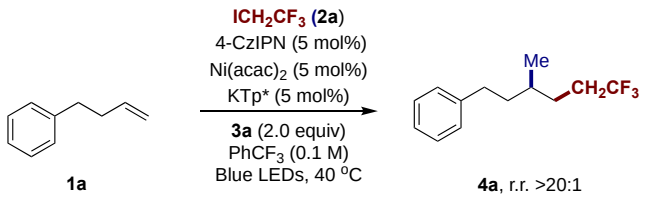


Established Ni-catalyzed paradigms for 1,2-dicarbofunctionalization of unactivated alkenes involve either two-electron pathways (**I** or **II** by migratory insertions)[3f,9] or single-electron pathways (**III** or **IV** by radical capture/relay sequences).[3f,3g,10] *N*-Heterocyclic carbene-Ni complexes were reported to mediate regioselective non-radical aryl-functionalizations of unactivated alkenes via steric control[11] (**I**), but the analogous dialkylation reactions with sp^3-hybridized substrates were ineffective. In other disclosures, pre-installation of strongly coordinating directing auxiliaries was necessary to enhance the efficiency and site selectivity of alkylation[12] (**II**). On the other hand, transformations that proceed through radical-based mechanisms often rely on activated C(sp^3)-electro-

philes (e.g. *tert*-alkyl) to generate stabilized radical intermediates, which then undergo regioselective addition to the C=C bond and recombination with the organonickel species en route to the final product (**III** or **IV**). Likewise, most dialkylations in this area are directed in nature.

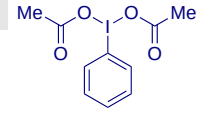
Generally speaking, a directing group-free manifold that enables site-selective 1,2-dialkylation of unactivated alkenes remains synthetically elusive. To overcome this challenge, we envisioned a catalytic platform that takes advantage of bimolecular homolytic substitution (S_H2) reactivity, which was successfully used to merge primary (1°) alkyl radicals and hindered secondary (2°)/tertiary (3°) alkyl radicals in two-component sp^3–sp^3 cross-coupling.[13,14] *In situ* formation of an electrophilic alkyl radical followed by regioselective addition to the C=C bond leads to a sterically more congested alkyl radical, which selectively undergoes outer-sphere bimolecular homolytic substitution with another *in situ*-generated nucleophilic alkyl radical to construct the second C(sp^3)–C(sp^3) linkage. Key to this reaction design is the identification of an appropriate nickel catalyst that effectively distinguishes the different radical intermediates in the system by selectively associating with the nucleophilic 1° alkyl radical (vs. electrophilic or hindered radicals). Herein, we describe the successful realization of this goal by developing a photoredox/nickel-catalyzed system to reliably access synthetically valuable dialkylated products.[15]

Table 1. Reaction Optimization[a]

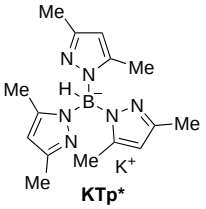


1a **4a**, r.r. >20:1

Entry	Deviation from standard conditions	**4a** (%)[b]
1	none	86 (85)[c]
2	dtbpy instead of KTp*	13
3	terbutylterpyridine instead of KTp*	2
4	using $NiCl_2$·glyme	79
5	using $Cu(TMHD)_2$	11
6	using Fe(TPP)Cl	0
7	*fac*-Ir(ppy)$_3$ instead of 4-CzIPN	21
8	TXO instead of 4-CzIPN, 370 nm	45
9	using DMF instead of $PhCF_3$	trace
10	using CH_3CN instead of $PhCF_3$	18
11	no KTp* or no $Ni(acac)_2$	trace
12	no 4-CzIPN or in the dark	0



3a



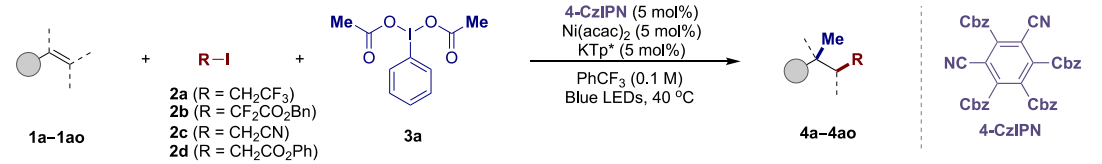
KTp*

[a]**1a** (0.1 mmol), **2a** (0.15 mmol), $Ni(acac)_2$ (5 mol%), KTp* (5 mol%), 4-CzIPN (5 mol%), **3a** (0.2 mmol) in $PhCF_3$ (0.1 M) at 40 °C under 456 nm irradiation. [b] GC yields using tetradecane as internal standard. [c] Isolated yield. KTp = Potassium trispyrazolylborate, TXO = 9*H*-thioxanthen-9-one.

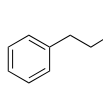
We started our studies by examining the trimolecular coupling of unactivated alkene **1a**, iodoalkane **2a** (source of electrophilic radical) and (diacetoxyiodo)benzene **3a** (source of nucleophilic radical) under various reaction parameters (Table 1). After extensive optimization[16], we found that the desired dialkylation product **4a** was secured in 85% isolated yield and essentially perfect regioselectivity (entry 1) using a combination of Ni catalyst derived from $Ni(acac)_2$ and potassium tri(3,5-dimethyl-1-pyrazolyl)borohydride (KTp*), 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4-CzIPN) as photocatalyst and $PhCF_3$ as solvent under blue light-emitting diode (LED) irradiation (456 nm) at 40 °C. Control experiments showed that all reaction components are essential for the best performance. Replacing KTp* with redox-active ligands that are commonly used in nickel-catalyzed reductive cross-coupling was detrimental to the reaction (entries 2 and 3), whereas switching $Ni(acac)_2$ to another Ni precursor slightly diminished the yield (entry 4). Poor reactivity was observed in the presence of Cu- or Fe-based complexes (entries 5 and 6). Likewise, changing the photocatalyst to *fac*-Ir(ppy)$_3$ or TXO led to lower yields (entries 7 and 8). The reaction medium had a profound impact on efficiency, as exemplified by the drastically decreased yields when $PhCF_3$ was replaced with more polar solvents such as DMF or CH_3CN (entries 9 and 10). As expected, no productive dialkylation was detected when the Ni precursor, ligand, photocatalyst or light were individually excluded (entries 11 and 12).

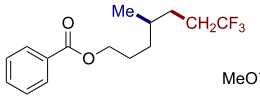
With the optimized conditions in hand, we began to evaluate the reaction scope using unactivated alkenes of different substitution patterns (Table 2). In the presence of **3a** and electrophilic alkyl iodides **2a**–**d**, dialkylation proceeded smoothly to furnish the desired products **4a**–**4ao** bearing tertiary or quaternary carbon centers in excellent chemoselectivity with up to 92% yield and >20:1 regioisomeric ratios (r.r.). Terminal alkenes containing a vast array of common acidic and basic functional groups such as ester (**4b**, **4m**, **4q**, **4s**, **4v**–**x**), alkyl bromide (**4e**), alkyl tosylate (**4f**), alkyl iodide (**4m**), (hetero)aryl halide (**4v, 4x**), amide (**4g**), silane (**4h**), phosphine oxide (**4i**), phthalimide (**4j**), epoxide (**4k**), carbonate (**4l**), acetal (**4o**), alkyne (**4r**), silyl ether (**4t**) and heterocycles (**4n**, **4p**, **4u**, **4w**–**y**) are well-tolerated in our system. Remarkably, sp^3- and sp^2-hybridized organohalides (**4e**, **4f**, **4m**, **4v, 4x**) which are typically prone to reaction with low-valent nickel species[17] did not interfere with dialkylation, providing complementarity to established catalytic regimes (see Scheme 1) and facilitating access to molecules with useful halogen handles for downstream functionalizations.[18]

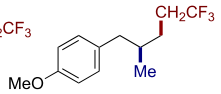
Table 2. Scope of Unactivated Alkenes in S_H2-Enabled Catalytic Dialkylation[a]

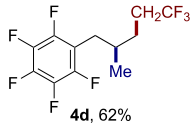


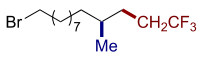
unactivated alkene scope

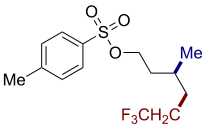

4a, 85%

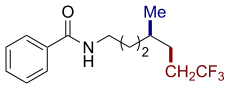

4b, 81%

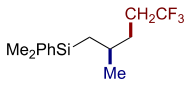

4c, 77%

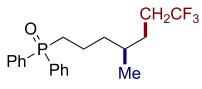

4d, 62%

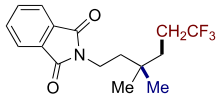

4e, 62%


4f, 57%

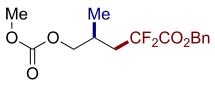

4g, 33%

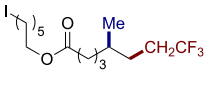

4h, 71%

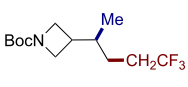

4i, 57%

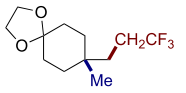

4j, 90%

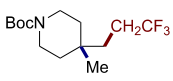

4k, 77%

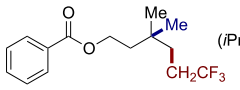

4l, 46%

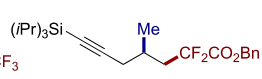

4m, 56%

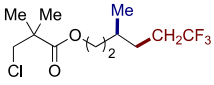

4n, 56%

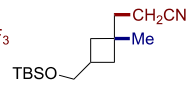

4o, 92%

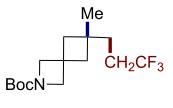

4p, 77%

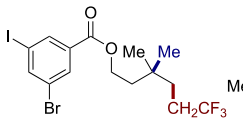

4q, 86%

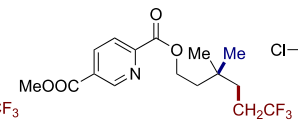

4r, 57%

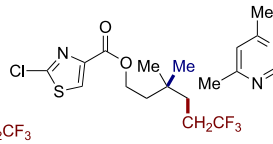

4s, 67%

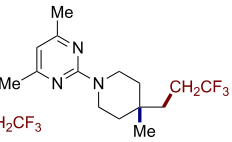

4t, 59%, d.r. = 3.7:1


4u, 63%

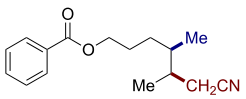

4v, 52%

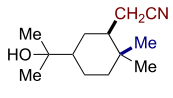

4w, 84%

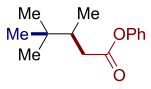

4x, 87%

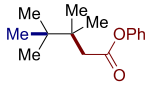

4y, 59%

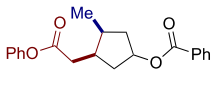
internal alkene


4z, 33%, r.r. = 1.2:1, d.r. = 1:1

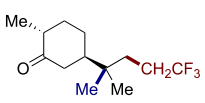

4aa, 70%, r.r. =3.5:1, d.r. = 1.2:1

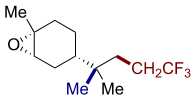

4ab, 70%, r.r. = 5:1

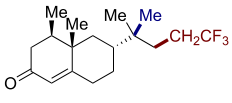

4ac, 42%

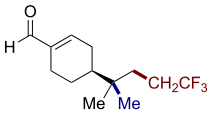

4ad, 44%, d.r. = 4:1

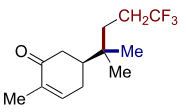
late-stage functionalization

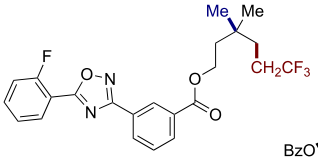

from (+)-Dihydrocarvone
4ae, 71%, d.r. >20:1

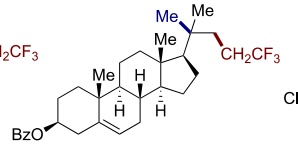

from (+)-Limonene oxide
4af, 68%, d.r. = 1.8:1

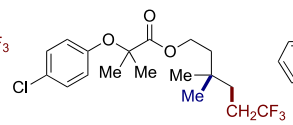

from Nootkatone
4ag, 68%, d.r. >20:1

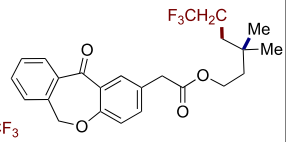

from (-)-Perillaldehyde
4ah, 60%


from (-)-Carvone
4ai, 54%


from Ataluren
4aj, 90%


from Pregnenolone
4ak, 70%


from Clofibric acid
4al, 61%


from Isoxepac
4am, 81%

radical probes

from α-Pinene
4an, 52%, d.r. = 1:1

from Caryophyllene oxide
4ao, 91%, d.r. = 4:1

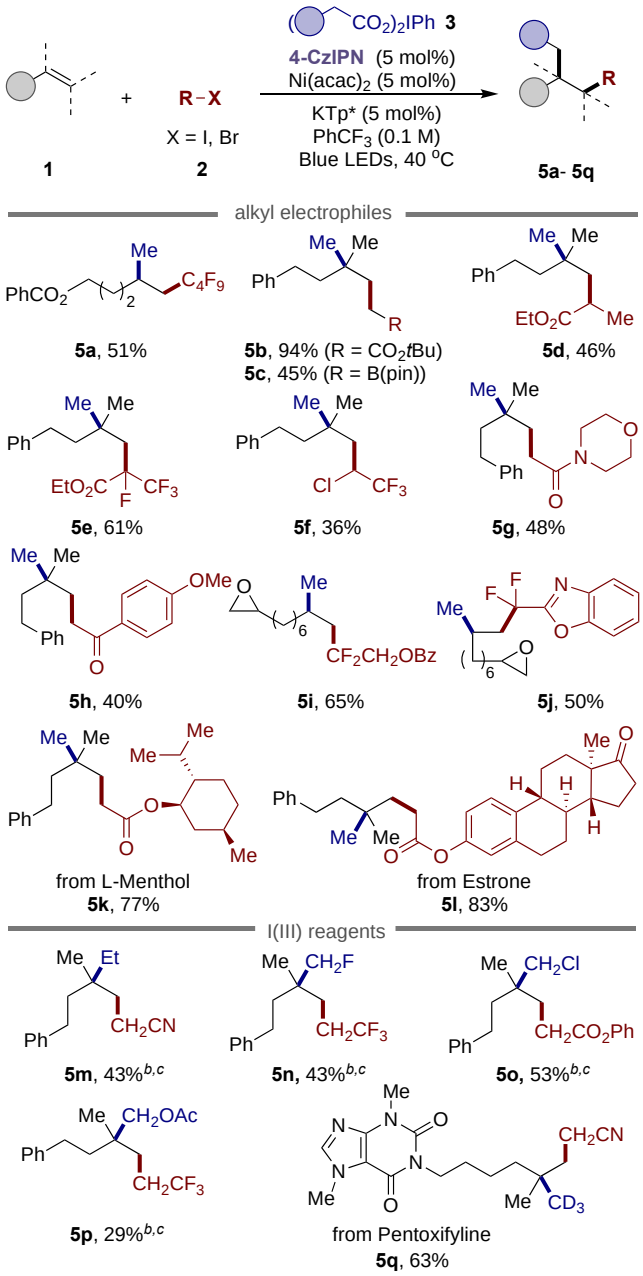
https://doi.org/10.26434/chemrxiv-2023-mpqdw **ORCID:** https://orcid.org/0000-0002-2534-4921

[a]As in Table 1 (entry 1), using alkene **1** (0.20 mmol); Isolated yields.

Sterically demanding internal alkenes which sometimes pose reactivity challenges in Ni catalysis[12f] also served as effective substrates for S_H2-enabled alkene cross-coupling. Cyclic and acyclic 1,2-disubstituted (**4z**, **4ad**), trisubstituted (**4aa**, **4ab**) and even tetrasubstituted (**4ac**) C=C bonds are amenable to dialkylation, although regio- and diastereochemical control prove difficult in some cases. To further showcase functional group compatibility, we extended the catalytic dialkylation manifold to the late-stage functionalization of alkenes embedded within or appended to multifunctional bioactive compounds. Gratifyingly, dialkylated products **4ae**–**4am** were secured in good yields and site selectivities, highlighting the robustness of our transformation towards the construction of complex C(sp^3)-rich architectures at advanced stages of synthetic processes. The reactions affording **4ag**–**ai** and **4ak** took place selectively at the sterically less hindered C=C bond. It merits mention that there was no competitive addition of the intermediate open-shell species to the electron-deficient π-bonds of *α,β*-unsaturated carbonyl units in **4ag**–**ai**, underscoring the remarkable chemoselectivity. Notably, when dialkylation was executed on alkenes with neighboring strained four-membered rings such as natural products α-pinene and caryophyllene oxide, ring-opening was observed to give **4an** and **4ao**, respectively. These results suggest the plausible intermediacy of cyclobutylcarbinyl radicals[19] generated by initial addition of the iodoalkane-derived electrophilic radical, which are susceptible to ring cleavage before the second C(sp^3)–C(sp^3) bond-forming event.

We next assessed the dialkylation scope by examining various haloalkane (bromide, iodide) and hypervalent iodine(III) reaction partners (Table 3). Besides trifluoroethyl group (derived from coupling with **2a**), different medicinally relevant fluoroalkyl[20] or *gem*-difluoroalkyl[21] moieties could be efficiently and site-selectively introduced to deliver **5a**, **5e**, **5f**, **5i** and **5j**, by reaction with the corresponding alkyl halides. Dialkylation products containing other classes of electron-deficient alkyl motifs bearing carboxylic ester (**5b**, **5d**, **5e**, **5k**, **5l**), amide (**5g**), ketone (**5h**) and boronate (**5c**) functionalities that can be subjected to further derivatization, were successfully secured in up to 94% yield as single regioisomers. Synthesis of bioactive molecule-derived **5k** and **5l** demonstrates the exceptional functional group compatibility of the transformation. For the nucleophilic 1° alkyl radical component, we investigated a range of iodine(III) compounds (readily accessible from cheap and abundant aliphatic carboxylic acids[14d]) possessing different substituents including ethyl (**5m**), fluoromethyl (**5n**), chloromethyl (**5o**), acetoxymethyl (**5p**) and trideuteromethyl (**5q**), all of which participated in site-selective dialkylation across the board. Access to **5q** highlights the method's capability as a practical and position-precise tool for late-stage deuterium incorporation into complex molecules, which has beneficial outcomes in drug discovery.[22]

Table 3. Scope of Alkyl Halides and Hypervalent Iodine Compounds in S_H2-Enabled Catalytic Dialkylation[a]



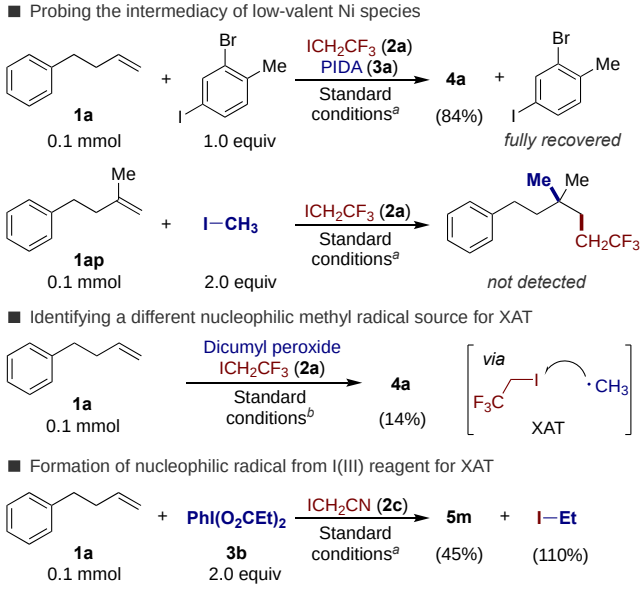
[a]As in Table 1 (entry 1), using alkene **1** (0.20 mmol); Isolated yields. [b]**1** (0.2 mmol), **2** (0.3 mmol), $Ni(acac)_2$ (5 mol%), KTp* (5 mol%), TXO (10 mol%), **3** (0.4 mmol) in $PhCF_3$ (0.1 M) at 25 °C under under 370 nm irradiation. [c] Using $PhI(O_2CPh)_2$ (0.2 mmol).

To unravel the mechanistic intricacies that underpin the high efficiency and site selectivity of the catalytic dialkylation, we carried out a series of experiments to probe the mechanism (Scheme 2). Repeating the standard reaction

in the presence of an exogenous equivalent of haloarene did not have any impact on the efficiency, and the halide additive was fully recovered. Consistent with a previous study[14d], this observation suggests that low-valent organonickel (Ni(0) or Ni(I)) species are probably not involved, since they tend to promote oxidative insertion into C(sp^2)–halide bonds.[17]

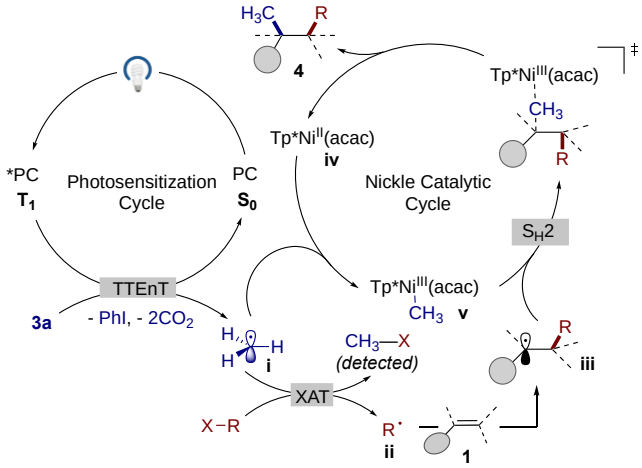
Simply replacing the hypervalent iodine reagent **3a** with methyl iodide failed to induce any dialkylation under standard conditions. This result supports the unlikely presence of low-valent Ni intermediates which are known to react with iodoalkanes[6,17], and further shows that the second C(sp^3)–C(sp^3) linkage did not arise from reaction with methyl iodide. During the course of our studies, we speculated that the nucleophilic 1° alkyl radical (derived from **3**) is responsible for triggering formation of the electrophilic alkyl radical from haloalkane **2** via a chemoselective halogen-atom transfer (XAT) process that is favored by matching enthalpic and polar effects[23] (c.f. bond-dissociation energy of H_3C–I bond is much higher than that of (EWG)C–I bond). In this vein, we reasoned that switching **3** to another nucleophilic radical source would also promote the desired alkylation. This hypothesis was supported through the reaction of dicumyl peroxide, which is known to afford methyl radicals after photolysis.[24] Indeed, the expected product **4a** was detected in 14% yield under our established conditions. A control experiment by coupling **1a**, **2c** and **3b** afforded the desired **5m** in 45% yield along with ethyl iodide by-product, lending further credence to the XAT proposal (ethyl radical selectively abstracts iodine from **2c**).

Scheme 2. Mechanistic Studies.



Based on our results and previous studies[14], we propose a tentative dual catalytic pathway for the S_H2-enabled alkene dialkylation. Blue LED irradiation of the photocatalyst (4-CzIPN) forms a high-energy triplet state which transfers the energy (via triplet−triplet energy transfer (TTenT)[25]) to the iodine(III) compound (**3a** as example), leading to I–O bond homolysis to give carboxyl radicals that rapidly fragment to release methyl radicals **i**, PhI and CO_2.[26] The nucleophilic and unhindered **i** is selectively trapped by the *in situ*-generated Ni(II) complex **iv** to form Ni(III) species **v**. Concurrently, another equivalent of methyl radical undergoes chemoselective XAT with the electron-poor alkyl halide **2**, giving rise to an electrophilic alkyl radical **ii** and Me–X by-product. **ii** regioselectively adds to the unactivated C=C bond of **1** (polarity matching) to afford a sterically more congested alkyl radical **iii**, which favors S_H2 coupling[14,27] with **v** to deliver the dialkylation product **4** and turn over the nickel catalytic cycle. The success of this exquisitely orchestrated dialkylation system relies on the ability of the organonickel catalytic species to differentiate among the various radical intermediates **i**, **ii** and **iii** (the nucleophilic and unhindered **i** preferentially associates with the Ni center in **iv**), as well as the pivotal role of nucleophilic **i** to induce selective XAT with **2** to form the requisite electrophilic **ii** for reaction. More detailed mechanistic investigations are ongoing and will be reported in due course.

Scheme 3. Proposed Mechanism.



By leveraging S_H2 as an enabling tool for forging C–C bonds, we have successfully achieved three-component 1,2-dialkylation of a wide assortment of unactivated alkenes. The catalytic method exhibits broad scope and provides an expedient route to assemble medicinally valuable C(sp^3)-rich building blocks. We expect this work to find utility in the synthesis of natural products and pharmaceuticals, and provide a new blueprint for the development of multicomponent alkene cross-coupling transformations to generate molecular complexity and diversity.

AUTHOR INFORMATION

Corresponding Author

***Ming Joo Koh** – Department of Chemistry, National University of Singapore, 4 Science Drive 2, Republic of Singapore, 117544; ORCID: 0000-0002-2534-4921; Email: chmkmj@nus.edu.sg.

Funding Sources

The authors declare no competing interests.

ACKNOWLEDGMENT

M.J.K. acknowledges funding support from the IMRE-NUS Chemistry joint collaboration project (A-8000301-00-00) and the Ministry of Education of Singapore Academic Research Fund Tier 2 (A-8000941-00-00).

REFERENCES

(1) (a) Patai, S., Ed.The chemistry of double bonded functional groups. Wiley: Chichester, U.K., **1997**. (b) Zhu, J.; Wang, Q.; Wang, M. Multicomponent reactions in organic synthesis. Wiley-VCH., **2015**.

(2) (a) Geist, E.; Kirschning, A.; Schmidt, T. sp^3-sp^3 Coupling reactions in the synthesis of natural products and biologically active molecules. Natural Prod. Rep. **2014**, *31*, 441-448. (b) Lovering, F.; Bikker, J.; Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem*. **2009**, *52*, 6752-6756. (c) Derosa, J.; Tran, V. T.; van der Puyl, V. A.; Engle, K. M. Carbon–carbon π bonds as conjunctive reagents in cross-coupling. *Aldrichimica Acta*. **2018**, *51*, 21–32.

(3) For selected references, see: (a) Jensen, K. H.; Sigman, M. S. Mechanistic approaches to palladium-catalyzed alkene difunctionalization reactions. *Org. Biomol. Chem*. **2008**, *6*, 4083–4088. (b) McDonald, R. I.; Liu, G. S.; Stahl, S. S. Palladium(II)-catalyzed alkene functionalization via nucleopalladation: stereochemical pathways and enantioselective catalytic applications. *Chem. Rev.* **2011**, *111*, 2981–3019. (c) Yin, G.; Mu, X.; Liu, G. Palladium(II)-catalyzed oxidative difunctionalization of alkenes: bond forming at a high-valent palladium center. *Acc. Chem. Res*. **2016**, *49*, 2413–2423. (d) Zhang, J. S.; Liu, L.; Chen, T.; Han, L. B. Transition-metal-catalyzed three- component difunctionalizations of alkenes. *Chem. Asian J.* **2018**, *13*, 2277–2291. (e) Dhungana, R. K.; Kc, S.; Basnet, P.; Giri, R. Transition metal-catalyzed dicarbofunctionalization of unactivated olefins. *Chem. Rec*. **2018**, *18*, 1314–1340. (f) Tu, H-Y.; Zhu, S.; Qing, F.-L.; Chu, L. Recent advances in nickel-catalyzed three-Component difunctionalization of unactivated alkenes. *Synthesis* **2020,** *52*, 1346–1356. (g) Badir, S. O.; Molander, G. A. Developments in photoredox/nickel dual-catalyzed 1,2-difunctionalizations.

(4) (a) Chapdelaine, M. J.; Hulce, M. Tandem vicinal difunctionalization: *β*-addition to *α,β*-unsaturated carbonyl substrates followed by α-functionalization. *Org. React*. **1990**, *38*, 225–653. (b) Giri, R.; Kc, S. Strategies toward dicarbofunctionalization of unactivated olefins by combined heck carbometalation and cross-coupling. *J. Org. Chem.* **2018**, *83*, 3013−3022. (c) Wang, H.; Koh, M. J. Directing group-free approaches for three-component catalytic dicarbofunctionalization of unactivated alkenes. *Cell Rep. Phys. Sci*. **2022**, *3*, 100901.

(5) For selected references on difunctionalization of activated alkenes: (a) Sun, S.-Z., Duan, Y., Mega, R. S., Somerville, R. J.; Martin, R. Site- selective 1,2-dicarbofunctionalization of vinyl boronates through dual catalysis. *Angew. Chem. Int. Ed.* **2020**, *59*, 4370–4374. (b) Mega, R. S., Duong, V. K., Noble, A.; Aggarwal, V. K. Decarbox- ylative conjunctive cross-coupling of vinyl boronic esters using metallaphotoredox catalysis. *Angew. Chem. Int. Ed.* **2020**, *59*, 4375–4379. (c) Campbell, M. W., Compton, J. S., Kelly, C. B.; Molander, G. A. Three-component olefin dicarbofunctionalization enabled by nickel/photoredox dual catalysis. *J. Am. Chem. Soc*. **2019**, *141*, 20069–20078. (d) García-Domínguez, A., Mondal, R.; Nevado, C. Dual photo- redox/nickel-catalyzed three-component carbofunctionaliza- tion of alkenes. *Angew. Chem. Int. Ed*. **2019**, *58*, 12286–12290. (e) Guo, L., Tu, H.-Y., Zhu, S.; Chu, L. Selective, intermolecular alky- larylation of alkenes via photoredox/nickel dual catalysis. *Org. Lett*. **2019**, *21*, 4771–4776.

(6) (a) Leatherman, M. D.; Svejda, S. A.; Johnson, L. K.; Brookhart, M. Mechanistic studies of nickel(II) alkyl agostic cations and alkyl ethylene complexes: investigations of chain propagation and isomerization in (α-diimine)Ni(II)-catalyzed ethylene polymerization. *J. Am. Chem. Soc*. **2003**, *125*, 3068−3081. (b) Xu, H.; White, P. B.; Hu, C.; Diao, T. Structure and isotope effects of the *β*-H agostic (α-diimine)nickel cation as a polymerization intermediate. *Angew. Chem., Int. Ed*. **2017**, *56*, 1535−1538. (c) Choi, J.; Fu, G. C. Transition metal-catalyzed alkyl-alkyl bond formation: Another dimension in cross-coupling chemistry. *Science* **2017**, *356*, 152–160. (d) Kaga, A.; Chiba, S. Engaging radicals in transition metal-catalyzed cross-coupling with alkyl electrophiles: recent advances. *ACS Catal*. **2017**, *7*, 4697–4706. (e) Gu, J.; Wang, X.; Xue, W.; Gong, H.; Nickel-catalyzed reductive coupling of alkyl halides with other electrophiles:concept and mechanistic considerations. *Org. Chem. Front*. **2015**, *2*, 1411–1421 (f) Weix, J.D. Methods and mechanisms for cross-electrophile coupling of Csp^2 halides with alkyl electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767–1775.

(7) (a) Shrestha, B.; Basnet, P.; Dhungana, R.; KC, S.; Thapa, S.; Sears, J. M.; Giri, R. Ni-catalyzed regioselective 1,2-dicarbofunctionalization of olefins by intercepting Heck intermediates as imine-stabilized transient metallacycles. *J. Am. Chem. Soc*. **2017**, *139*, 10653–10656. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in transition metal (Pd, Ni, Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners. *Chem. Rev.* **2011**, *111*, 1417–1492. (c) Hu, X. Nickel-catalyzed cross-coupling of non-activated alkyl halides: a mechanistic perspective. *Chem. Sci.* **2011**, *2*, 1867–1886. (d) Ma, X.; Murray, B.; Biscoe, Mark. R. Stereoselectivity in Pd-catalysed cross-coupling reactions of enantioenriched nucleophiles. *Nature Reviews Chemistry.* **2020**, *4*, 584–599.

(8) (a) Meyers, J.; Carter, M.; Mok, N. Y.; Brown, N. On the origin of three-dimensionality in drug-like molecules. *Future Med. Chem*. **2016**, *8*, 1756–8919. (b) Lovering, F. Escape from flatland 2: complexity and promiscuity. *Med. Chem. Commun*. **2013**, *4*, 515–519.

(9) (a) Li, Y.; Wu, D,; Cheng, H.-G.; Yin, G. Difunctionalization of alkenes involving metal migration. *Angew. Chem. Int. Ed*. **2020**, *59*, 7990–8003. (b) Qi, X.; Diao, T. Nickel-catalyzed dicarbofunctionalization of alkenes. *ACS Catal*. **2020**, *10*, 8542−8556.

(10) (a) Lin, Q.; Diao, T. Mechanism of Ni-catalyzed reductive 1,2-dicarbofunctionalization of alkenes. (b) Joseph Derosa, Omar Apolinar, Taeho Kang, Van T. Tran and Keary M. Engle. Recent developments in nickel-catalyzed intermolecular dicarbofunctionalization of alkenes. *Chem. Sci*. **2020**, *11*, 4287–4296. (c) García-Domínguez, A.; Li, Z.; Nevado, C. Nickel-catalyzed reductive dicarbofunctionalization of alkenes. *J. Am. Chem. Soc*. **2017**, *139*, 6835−6838. (d) Shu, W.;́García-Domínguez, A.; Quirós, M. T.; Mondal, R.;

Cańdenas, D. J.; Nevado, C. Ni-catalyzed reductive dicarbofunctionalization of nonactivated alkenes: scope and mechanistic insights. *J. Am. Chem. Soc*. **2019**, *141*, 13812−13821.

(11) (a) Wang, H.; Liu, C.-F.; Martin, R. T.; Zhao, H.; Gutierrez, O.; Koh, M. J. Directing-group-free catalytic dicarbofunctionalization of unactivated alkenes. *Nat. Chem.* **202**2, 4,188–195. (b) Lee, B. C.; Liu, C.-F.; Lin, L. Q. H.; Yap, K. Z.; Song, N.; Ko, C. H. M.; Chan, P. H.; Koh, M. J. N-Heterocyclic carbenes as privileged ligands for Nickel-catalysed alkene functionalisation. *Chem. Soc. Rev*. **2023**, *52*, 2946−2991.

(12) For Directed Ni-catalyzed difunctionalization, see: (a) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. Nickel-catalyzed *β,γ*-dicarbofunctionalization of alkenyl carbonyl compounds via conjunctive cross-coupling. *J. Am. Chem. Soc.* **2017**, *139*, 10657−10660. (b) Derosa, J.; van der Puyl, V. A.; Tran, V. T.; Liu, M.; Engle, K. M. Directed nickel-catalyzed 1,2- dialkylation of alkenyl carbonyl compounds. *Chem. Sc*i. **2018**, *9*, 5278−5283. (c) Thapa, S.; Dhungana, R. K.; Magar, R. T.; Shrestha, B.; Kc, S.; Giri, R. Ni-catalysed regioselective 1,2-diarylation of unactivated olefins by stabilizing Heck intermediates as Pyridylsilyl-coordinated transient metalla- cycles. *Chem. Sci*. **2018**, *9*, 904−909. (d) Yang, T. Jiang, Y. Luo, Y.; Lim, J. J. H.; Lan, Y.; Koh, M. J. Chemoselective union of olefins, organohalides, and redox-active esters enables regioselective alkene dialkylation. *J. Am. Chem. Soc*. **2020**, *142*, 21410–21419. (e) Yang, T.;, Chen, X.; Rao, W.;,Koh, M. J. Broadly applicable directed catalytic reductive difunctionalization of alkenyl carbonyl compounds. *Chem.* **2020**, *6*, 738-751. (f) Dhungana, R. K.; Sapkota, R. R.; Wickham, L. M.; Niroula, D.; Giri, R. Ni-catalyzed regioselective 1,2-dialkylation of alkenes enabled by the formation of two C(sp^3)–C(sp^3) bonds. *J. Am. Chem. Soc*. **2020**, *142*, 20930–20936.

(13) Ingold, K. U.; Roberts, B. P. Free-radical substitution reactions. bimolecular homolytic substitutions (S_H2 Reactions) at saturated multivalent atoms, 1st ed.; John Wiley & Sons Inc., 1971.

(14) For cross-coupling based on S_H2 homolytic substitution, see: (a) Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J. MacMillan, D. W. C. A biomimetic S_H2 cross-coupling mechanism for quaternary sp^3-carbon formation. *Science*. **2021**, *6572*, 1258–1263. (b) Tsymbal, A. V.; Bizzini, L. D.; MacMillan, D. W. C. Nickel catalysis vis S_H2 homolytic substitution: the double decarboxylative cross-coupling of aliphatic acids. *J. Am. Chem. Soc*. **2022**, *144*, 21278–21286. (c) Mao, E.; MacMillan D. W. C. Late-stage C(sp^3)-H methylation of drug molecules. *J. Am. Chem. Soc*. **2023**, *145*, 2787–2793. (d) Sakai, H. A.; MacMillan, D. W. C., Nontraditional fragment coupling of alcohol and carboxylic acids: C(sp^3)–C(sp^3) cross-coupling via radical sorting. *J. Am. Chem. Soc*. **2022**, *144*, 6185–6192. (e) Gould, C. A.; Pace, A. L.; MacMillan, D. W. C. Rapid and modular access to quaternary carbons from tertiary alcohols via bimolecular homolytic substitution. *J. Am. Chem. Soc*. **2023**, *145*, 16330–16336. (f) Gan, X.; Kotesova, S.; Castanedo, A.; Green, S. A.; Moller, S. L. B.; Shenvi, R. A. Iron-catalyzed hydrobenzylation: Stereoselective synthesis of (-)- Eugenial C. *J. Am. Chem. Soc*. **2023**, *145*, 15714–15720.

(15) During the course of preparing our manuscript, a paper on alkene dialkylation involving S_H2 mechanism appeared on *ChemRxiv*: Wang, J. Z.; Lyon,W. L.; MacMillan, D. W. C. Alkene dialkylation via triple radical sorting. *ChemRxiv*. November 21, 2023. DOI: 10.26434/chemrxiv-2023-q4whd.

(16) For details, see Supporting information.

(17) (a) Diccianni, J. B.; Diao, T. Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions. *Trends Chem*. **2019**, *1*, 830−844. (b) Diccianni, J.; Lin, Q.; Diao, T. Mechanisms of Nickel-Catalyzed Coupling Reactions and Applications in Alkene Functionalization. *Acc. Chem. Res*. **2020**, *53*, 906−919.

(18) (a) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. From Noble Metal to Nobel Prize: Palladium-Catalyzed Coupling Reactions as Key Methods in Organic Synthesis. *Angew. Chem., Int. Ed*. **2010**, *49*, 9047−9050. (b) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald−Hartwig Amination After 25 Years. *Angew. Chem., Int. Ed*. **2019**, *58*, 17118−17129. (c) Everson, D. A.; Shrestha, R.; Weix, D. J. Nickel-catalyzed reductive cross-coupling of aryl halides with alkyl halides. *J. Am. Chem. Soc*. **2010**, *132*, 920–921. (d) Frisch, A. C.; Beller, M. Catalysts for cross-coupling reactions with non-activated alkyl halides. *Angew. Chem., Int. Ed*. **2015**, *4*, 674−688.

(19) Zhou, Wei.; Dmitriev, I. A. Melchiorr, P. Reductive cross-coupling of olefins via a radical pathway. *J. Am. Chem. Soc*. **2023**, *145*, 25098−25102.

(20) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **2007**, *317*, 1881–1886. (b) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev*. **2008**, *37*, 308–319. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev*. **2008**, *37*, 320–330. (d) Börgel, J.; Ritter, T. Late-stage functionalization. *Chem* **2020**, *6*, 1877–1887.

(21) Wang, Y.; Callejo, R.; Slawin, A. M. Z.; O'Hagan, D. The difluoromethylene (CF_2) group in aliphatic chains: Synthesis and conformational preference of palmitic acids and nonadecane containing CF_2 groups. *Beilstein J. Org. Chem*. **2014**, *10*, 18–25.

(22) (a) Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev*. **2011**, *111*, 5215−5246. (b) Gant, T. G. Using Deuterium in Drug Discovery: Leaving the Label in the Drug. *J. Med. Chem*. **2014**, *57*, 3595−3611. (c) Steverlynck, J.; Sitdikov, R.; Rueping, M.The deuterated "Magic Methyl" group: a guide to site-selective trideuteromethyl incorporation and labeling by using CD_3 reagents. *Chem. Eur. J*. **2021**, *27*, 11751–11772.

(23) Juliá, F.; Constantin, T.; Leonori, D. Applications of halogen-atom transfer (XAT) for the generation of carbon radicals in synthetic photochemistry and photocatalysis. *Chem. Rev*. **2022**, *122*, 2292−2352.

(24) Wang, Z.; Dong, J.; Hao, Y.; Li, Y.; Liu, Y.; Song, H.; Wang, Q. Photoredox-mediated Minisci C-H alkylation reactions between N-heteroarenes and alkyl iodides with peroxyacetate as a radical relay initiator. *J. Org. Chem*. **2019**, *84*, 16245−16253.

(25) a) See Supporting Information for Stern−Volmer fluorescence quenching studies and CV results. (b) Sakakibara, Y.; Itami, K.; Murakami, K. Switchable Decarboxylation by Energy- or Electron-Transfer Photocatalysis. *J. Am. Chem. Soc*. **2023**, doi.org/10.1021/jacs.3c11588.

(26) Hilborn, J. W.; Pincock, J. A. Rates of Decarboxylation of acyloxy radicals formed in the photocleavage of substituted 1- naphthylmethyl alkanoates. *J. Am. Chem. Soc.* **1991**, *113*, 2683−2686.

(27) (a) Chip, L.; Chen, T. Q.; Liang, Y.; Zhang, P; MacMillan D. W. C. A radical approach to the copper oxidative addition problem: trifluoromethylation of bromoarenes. *Science* **2018**, *360*, 1010–1014. (b) Bour, J. R.; Ferguson, D. M.; McClain, E. J.; Kampf, J. W.; Sanford, M. S. Connecting organometallic Ni(III) and Ni(IV): reactions of carbon-centered radicals

with high-valent organo- nickel complexes. *J. Am. Chem. Soc*. **2019**, *141*, 8914−8920.