Article

Alkene dialkylation by triple radical sorting

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The development of bimolecular homolytic substitution (S_H2) catalysis has expanded cross-coupling chemistries by enabling the selective combination of any primary radical with any secondary or tertiary radical through a radical sorting mechanism[1–8]. Biomimetic[9,10] S_H2 catalysis can be used to merge common feedstock chemicals—such as alcohols, acids and halides—in various permutations for the construction of a single C(sp^3)–C(sp^3) bond. The ability to sort these two distinct radicals across commercially available alkenes in a three-component manner would enable the simultaneous construction of two C(sp^3)–C(sp^3) bonds, greatly accelerating access to complex molecules and drug-like chemical space[11]. However, the simultaneous in situ formation of electrophilic and primary nucleophilic radicals in the presence of unactivated alkenes is problematic, typically leading to statistical radical recombination, hydrogen atom transfer, disproportionation and other deleterious pathways[12,13]. Here we report the use of bimolecular homolytic substitution catalysis to sort an electrophilic radical and a nucleophilic radical across an unactivated alkene. This reaction involves the in situ formation of three distinct radical species, which are then differentiated by size and electronics, allowing for regioselective formation of the desired dialkylated products. This work accelerates access to pharmaceutically relevant C(sp^3)-rich molecules and defines a distinct mechanistic approach for alkene dialkylation.

A key goal of organic chemistry is the development of new methods for the rapid synthesis of C(sp^3)–C(sp^3) bonds en route to three-dimensional drug-like molecules[14–16]. Traditional cross-coupling paradigms rely on oxidative addition, transmetallation and reductive elimination mechanistic steps that limit the pool of potential coupling partners. By contrast, bimolecular homolytic substitution (S_H2) catalysis couples primary radicals with secondary or tertiary radicals through a radical sorting mechanism on the basis of carbon–metal bond strength[1–8,17]. As this unique radical sorting mechanism is functional group agnostic, abundant radical precursors, such as alcohols, acids and halides, can be coupled in any desired combination to generate complex products from simple feedstock chemicals[1–8] (Fig. 1a). This approach greatly expands access to C(sp^3)-rich chemical space and enables formation of otherwise elusive all-C(sp^3) quaternary centres[18]. Although radical-sorting S_H2 catalysis has been shown to construct a single C(sp^3) bond from a variety of radical precursors, the more challenging three-component radical sorting mechanism has yet to be demonstrated.

A one-step protocol for the regioselective dialkylation of unactivated alkenes is highly desirable[11]. Alkenes are widely available, and the simultaneous construction of two C(sp^3)–C(sp^3) bonds across an alkene would greatly accelerate access to therapeutically advantageous C(sp^3)-rich small molecules[14]. Because of the propensity of alkyl–metal complexes to undergo β–H elimination[19–21], existing methods for alkene dialkylation remain greatly limited, relying either on auxiliary functional groups to direct dialkylation[22–24] or the presence of specific ground-state radical traps[25]. A general method in which two distinct radicals are formed and regioselectively added across any unactivated alkene represents an ideal approach.

We envisioned a catalytic alkene dialkylation platform commencing with the addition of an electrophilic alkyl radical—such as trifluoromethyl or difluoroacyl radical—into an alkene. Subsequent radical–radical recombination of the resultant radical species with a nucleophilic alkyl radical would yield the dialkyl adduct in a single transformation (Fig. 1b). The proposed dialkylation would be expected to proceed with good regioselectivity and enable installation of electron-poor alkyl groups that are typically not compatible with nickel catalysis[26]. Through the course of the reaction, three distinct radicals would be formed and must be efficiently sorted. Unsurprisingly, the envisioned transformation does not proceed in the absence of any sorting catalysts; instead, deleterious pathways, including disproportionation, alkyl–alkyl dimerization and hydrogen atom transfer, predominate[12,13]. We postulated that an appropriate S_H2 catalyst, which has been shown to facilitate outer-sphere C(sp^3)–C(sp^3) bond formation, might be used to sort these three simultaneously generated radicals toward productive alkene dialkylation. For the hypothesized radical sorting to be operative, the catalyst used must be capable of preferentially binding primary alkyl radicals over high-energy electrophilic alkyl radicals and secondary or tertiary radicals while still being capable of performing outer-sphere bimolecular homolytic substitution for C(sp^3)–C(sp^3) bond formation. Herein, we disclose a general strategy for the dialkylation of alkenes through the simultaneous generation of electrophilic alkyl radicals and primary nucleophilic radicals in the presence of unactivated alkenes (Fig. 1c). The functional group-agnostic nature of S_H2 catalysis permits the use of commercially available primary alcohols and electron-poor alkyl chlorides as radical precursors, giving potential access to 2×10^{15} C(sp^3)-rich dialkylated products.

Mechanism

We envisioned that the alkene dialkylation would proceed by the mechanism outlined in Fig. 2. Condensation of primary

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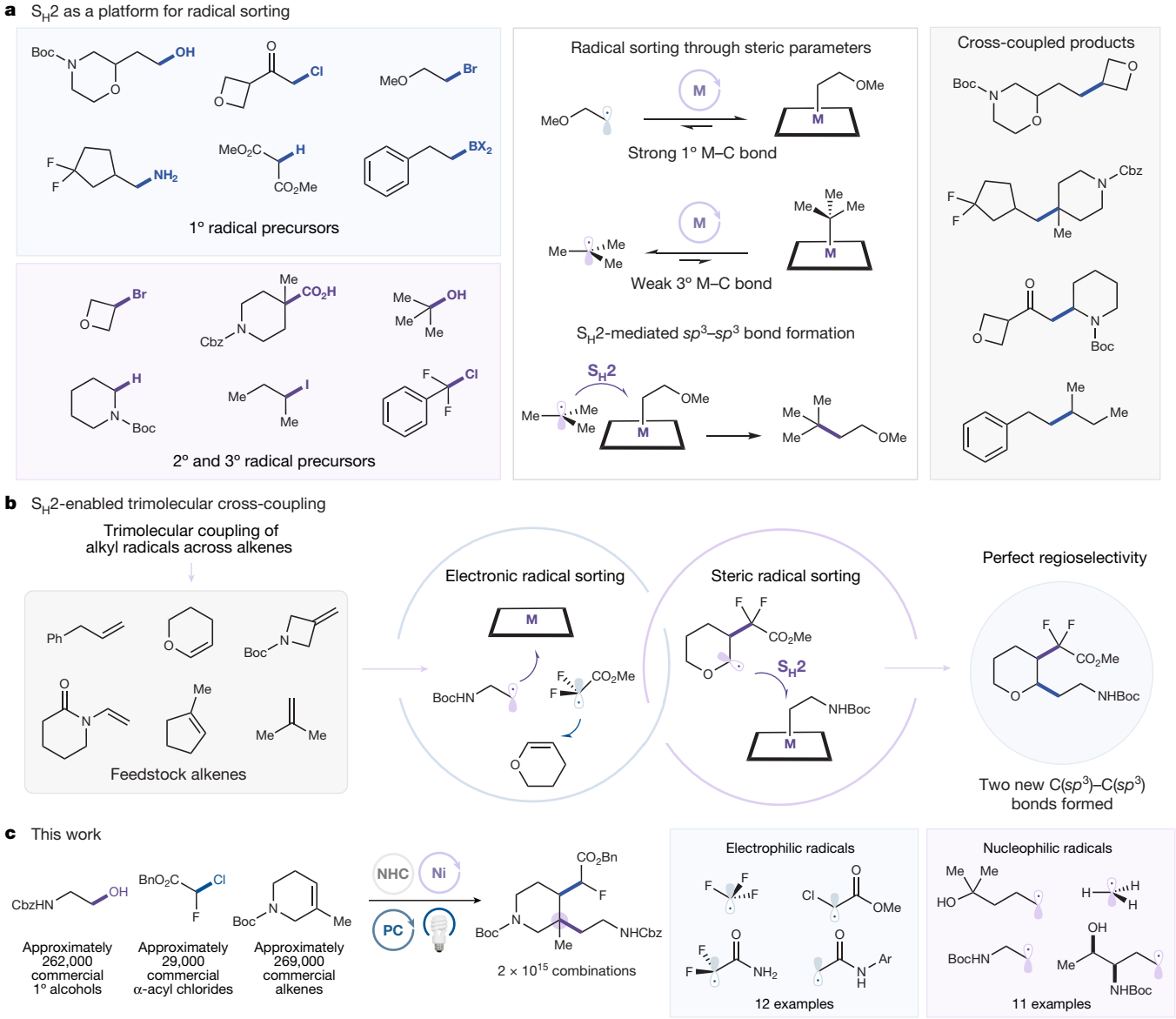


Fig. 1 | Radical-sorting-enabled alkene dialkylation. a, Bimolecular homolytic substitution (S$_H$2) radical sorting enables the use of any functional group in any combination for C(sp^3)–C(sp^3) bond formation. **b**, Three-component radical sorting enables alkene dialkylation. **c**, This work shows alkene dialkylation of unactivated alkenes using primary alcohols and α-acyl chlorides as radical precursors. Commercial availability was determined through a Reaxys search from October 2023 of commercially available fragments: 1° alcohols (261,696), α-acyl chlorides (29,000), alkenes (268,553). Ar, aryl; Bn, benzyl; Boc, *tert*-butylcarbonyl; Cbz, carbobenzyloxy; Me, methyl; Ni, nickel; PC, photocatalyst; Ph, phenyl.

alcohol **1** onto a benzoxazolium salt (N-heterocyclic carbene (**NHC**)) forms adduct **2** in situ[27]. Meanwhile, blue light excitation of (Ir[dF(CF$_3$)ppy]$_2$(dtbbpy))PF$_6$ (**3**) accesses a long-lived, triplet excited state **4** ($E_{1/2}^{red}$[*Ir^{III}/Ir^{II}]) = +1.21 V versus saturated calomel electrode in MeCN)[28]. Stern–Volmer analysis (Supplementary Information) suggests that **4** undergoes reductive quenching with **2**. Subsequent deprotonation and facile β-scission provide the desired primary alkyl radical (**6**) and a benign aromatized by-product. The primary alkyl radical can then be captured by high valent nickel S$_H$2 catalyst **7**, producing nickel–alkyl complex **8** (ref. 2). To close the photocatalytic cycle, reduced-state Ir^{II} (**9**) is capable of reducing an α-acyl alkyl chloride **10** (or dimesityl(trifluoromethyl)sulfonium trifluoromethanesulfonate (dMesSCF$_3$(OTf))) to produce an electrophilic carbon-centred radical (**11**) that can add into an unactivated alkene (**12**). Radical probes (Supplementary Information) support the formation of a tertiary radical (**13**), which is capable of being further functionalized[29–31]. This nucleophilic tertiary radical can undergo an S$_H$2 reaction with **8**, thereby regenerating **7** and forming the desired dialkylated product (**14**) (Supplementary Information has select mechanistic experiments). Key to the success of this reaction is the radical sorting of the many transient radicals, both electronically through the addition to the alkene and sterically through binding to a high valent nickel complex. We envisioned that this mechanistic paradigm might provide a general, modular strategy for the dialkylation of unactivated olefins.

Alkene scope

We first sought to interrogate the scope of the alkene coupling partner (Fig. 3). We selected trifluoromethyl and difluoroacetamide radicals as the electrophilic alkyl radical partners as both groups are important in drug discovery[32,33]. For the primary radical partner, we opted to use the methyl radical both for its ability to favourably influence the properties of drugs (termed the magic methyl effect) and because of the challenge often posed by its incorporation into complex molecules[34].

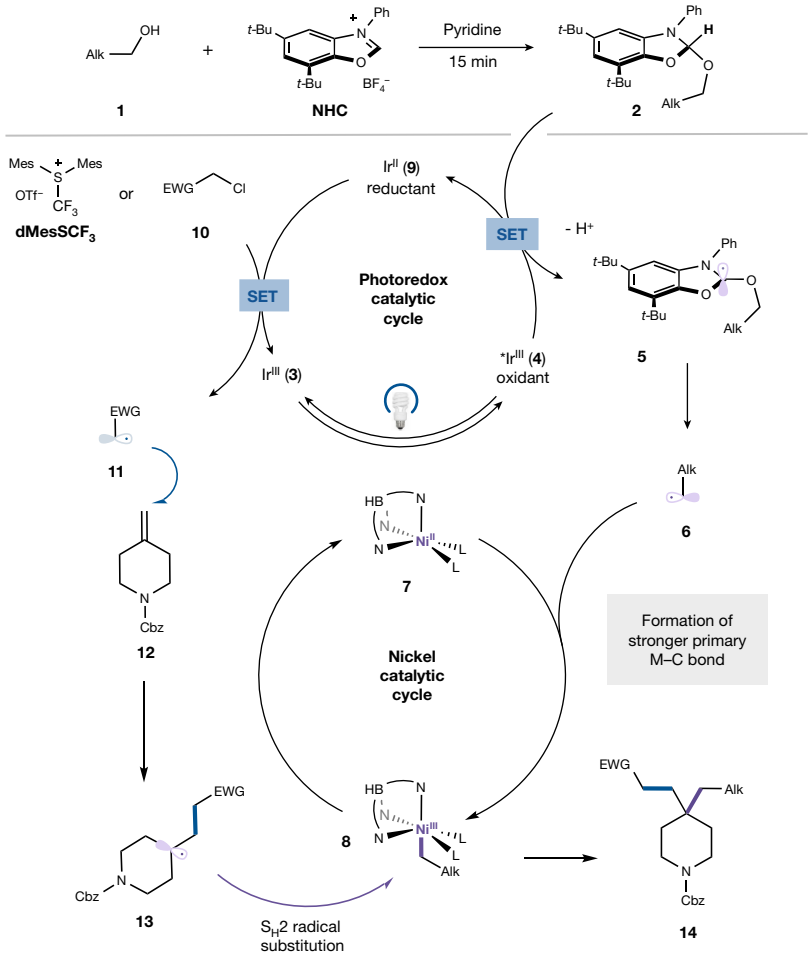


Fig. 2 | Proposed mechanism of alkene dialkylation. Alk, alkyl; *t*-Bu, *tert*-butyl; EWG, electron withdrawing group; L, ligand.

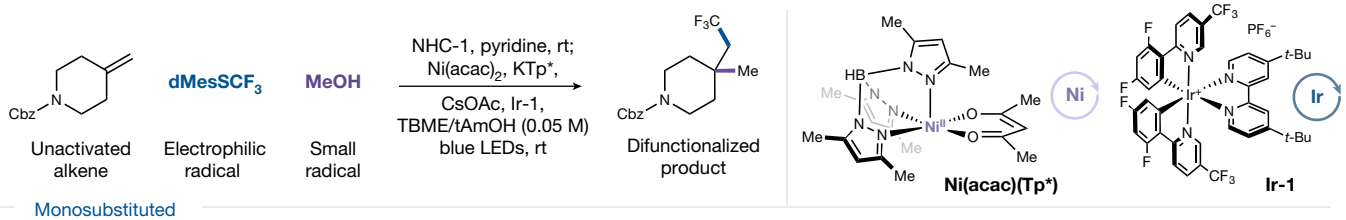
Gratifyingly, the coupling reaction proceeded efficiently across a wide range of alkenes. Unactivated terminal alkenes with relatively low π-nucleophilicity[35] were dialkylated in good yields, tolerating protic functionality (**15**, **16**) as well as homolytically labile allyl–benzylic C–H bonds (**17**, **18**). The coordinatively saturated S_H2 catalyst is incapable of oxidative addition; as such, aryl and alkyl halide-containing vinyl ethers and enamides were dialkylated in good yield (**19**–**21**). The generation of quaternary centres, a long-standing challenge in organic synthesis, can be achieved from four-, five-, six- and seven-membered rings as well as from acyclic 1,1-disubstituted alkenes (**22**–**27**). Notably, tertiary boronic esters (**28**), ethers (**29**) and ureas (**30**) were effectively formed under our reaction conditions. Moreover, a range of 1,2-disubstituted and trisubstituted alkenes were competent substrates (**31**–**34**). As a demonstration of the mild and robust nature of the reaction conditions, we successfully dialkylated several complex bioactive molecules. Specifically, efinconazole (**35**), paroxetine derivative (**36**), vinclozolin (**37**), retapamulin (**38**), quinine (**39**) and ataluren derivative (**40**) were dialkylated in good yields, showcasing the ability of the reaction to tolerate tertiary amines, alcohols, sulfides, quinuclidines and oxidative addition-prone oxadiazole functionality. These results suggest that the protocol should be applicable to the late-stage dialkylation of alkenes.

Alkyl chloride scope

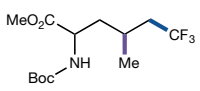
We next turned our attention to exploring the scope of the electrophilic radical partner (Fig. 4). Alkyl chlorides were selected as radical precursors for their ease of synthesis, commercial availability and enhanced stability over their bromide counterparts. We found that α-acyl radicals spanning a range of electrophilicity profiles, from α-ester to α-difluoroester radicals (**41**–**43**), reacted in good yields. Both acetamide (**44**), a ubiquitous moiety in drugs, and substituted difluoroacetamides (**45**), which are particularly important in fragment-based drug discovery, could be incorporated through the dialkylation protocol. Synthetically useful Horner–Wadsworth–Emmons reagents (**46**) and α-acyl chlorides (**47**) were prepared in good yields and offer the potential for further elaboration. In addition to α-acyl radicals, we found numerous other electrophilic carbon-centred radicals to be viable electrophilic radical partners, including α-difluorosulfonyl (**48**), difluorobenzyl (**49**) and α-nitrile (**50**) radicals.

Primary alcohol scope

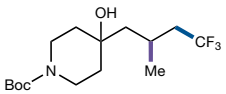
Finally, we explored the scope of the primary alcohol coupling partner. As shown in Fig. 4, a broad scope of pharmaceutically relevant alkyl fragments was incorporated through our protocol. Coupling with commercially available ^{13}C methanol served to install an isotopically labelled methyl group at the quaternary centre (**51**). Moreover, a range of alcohols were found to be effective alkyl coupling partners, including ether alcohol (**52**), threonine (**53**), serine (**54**), guaifenesin (**55**) and other diols (**56**, **57**). Reaction of diol substrates proceeds with full regioselectivity for the primary alcohol. These complex, coupled products (**53**–**57**) bear a free hydroxyl group that can be subjected to further elaboration through NHC activation. Moreover, 1,1-disubstituted alkenes in four-membered rings (**58**) or acyclic substrates (**59**) were observed to undergo efficient alkylation with carbobenzyloxy-glycinol. Notably, 1,2-disubstituted alkenes (**60**) were also readily dialkylated, providing an orthogonally protected morpholine scaffold. The complexity-building potential of this protocol



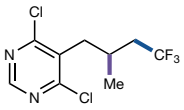
Monosubstituted



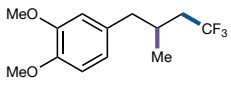
(±)-**15**, 71% yield[a]



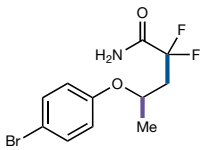
(±)-**16**, 63% yield[a]



(±)-**17**, 70% yield[a]

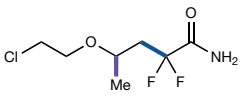


(±)-**18**, 72% yield[a]

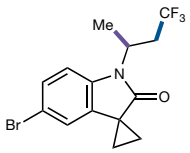


(±)-**19**, 75% yield[b]

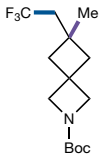
1,1-disubstituted



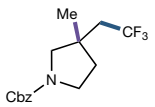
(±)-**20**, 57% yield[b]



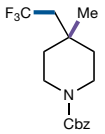
(±)-**21**, 85% yield[a]



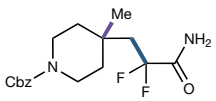
22, 57% yield[a]



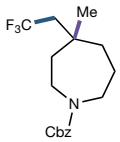
(±)-**23**, 62% yield[a]



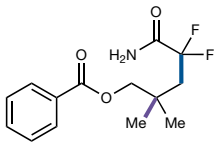
24, 79% yield[a]



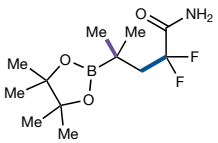
25, 66% yield[b]



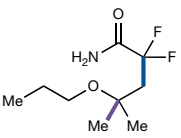
(±)-**26**, 64% yield[a]



27, 72% yield[b]

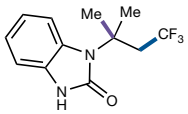


28, 49% yield[b]

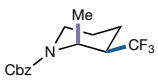


29, 69% yield[b]

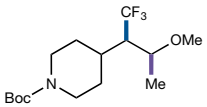
1,2-disubstituted



30, 63% yield[a]

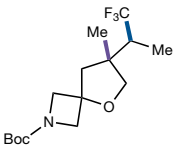


(±)-**31**, 64% yield[a]

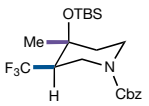


(±)-**32**, 61% yield[a]

Trisubstituted

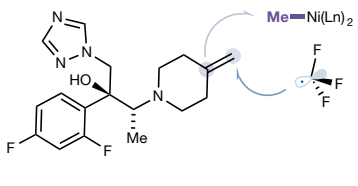


(±)-**33**, 57% yield[a]

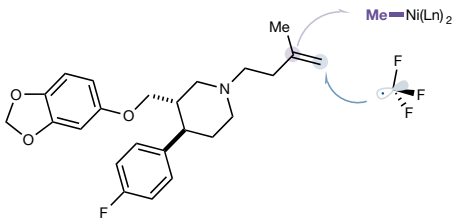


(±)-**34**, 58% yield[a]

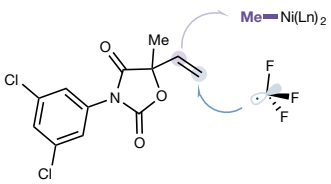
Complex examples



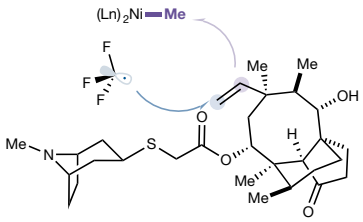
35, efinconazole, 77% yield[a]



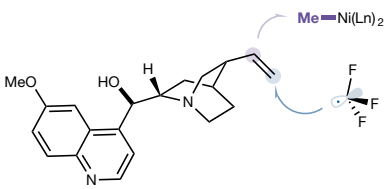
36, from paroxetine, 43% yield[a]



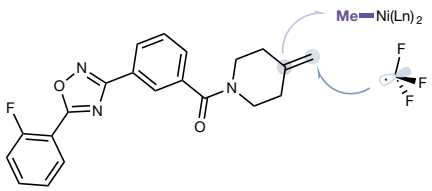
(±)-**37**, vinclozolin, 62% yield[a]



38, retapamulin, 76% yield[a]



39, quinine, 59% yield[a]



40, from ataluren, 79% yield[a]

Fig. 3 | Alkene scope. [a]MeOH (2 equiv.), NHC-1 (2.1 equiv.), pyridine (2.1 equiv.), $Ni(acac)_2$ (15 mol%), KTp* (15 mol%), (Ir[dF(CF_3)ppy]$_2$(dtbbpy))PF_6 (1 mol%), dMesSCF_3(OTf) (2 equiv.), alkene (0.50 mmol), CsOAc (2.5 equiv.), TBME/*t*AmOH (1:1, 0.05 M) and IPR (2% light intensity, 12 h). [b]MeOH (2 equiv.), NHC-1 (2.1 equiv.), pyridine (2.1 equiv.), $Ni(acac)_2$ (25 mol%), 4CzPN (1 mol%), difluorochloroacetamide (2 equiv.), alkene (0.50 mmol), CsOAc (2.5 equiv.), TBME/MeCN (1:1, 0.05 M) and IPR (50% light intensity, 12 h). Isolated yields. equiv., equivalents; TBME, *tert*-butyl methyl ether; 4CzPN, 3,4,5,6-tetra(9*H*-carbazol-9-yl)phthalonitrile; IPR, integrated photoreactor; Ir, iridium; Ir-1, Ir($dFCF_3ppy$)$_2$(dtbbpy)PF_6; KTp*, potassium tris(3,5-dimethyl-1-pyrazolyl)borate; LED, light-emitting diode; rt, room temperature; Ln, ligand; $Ni(acac)_2$, nickel(II) bis(acetylacetonate); Ni(acac)(Tp*), nickel(acetylacetonate) tris(3,5-dimethyl-1-pyrazolyl)borate; TBS, *tert*-butyldimethylsilyl.

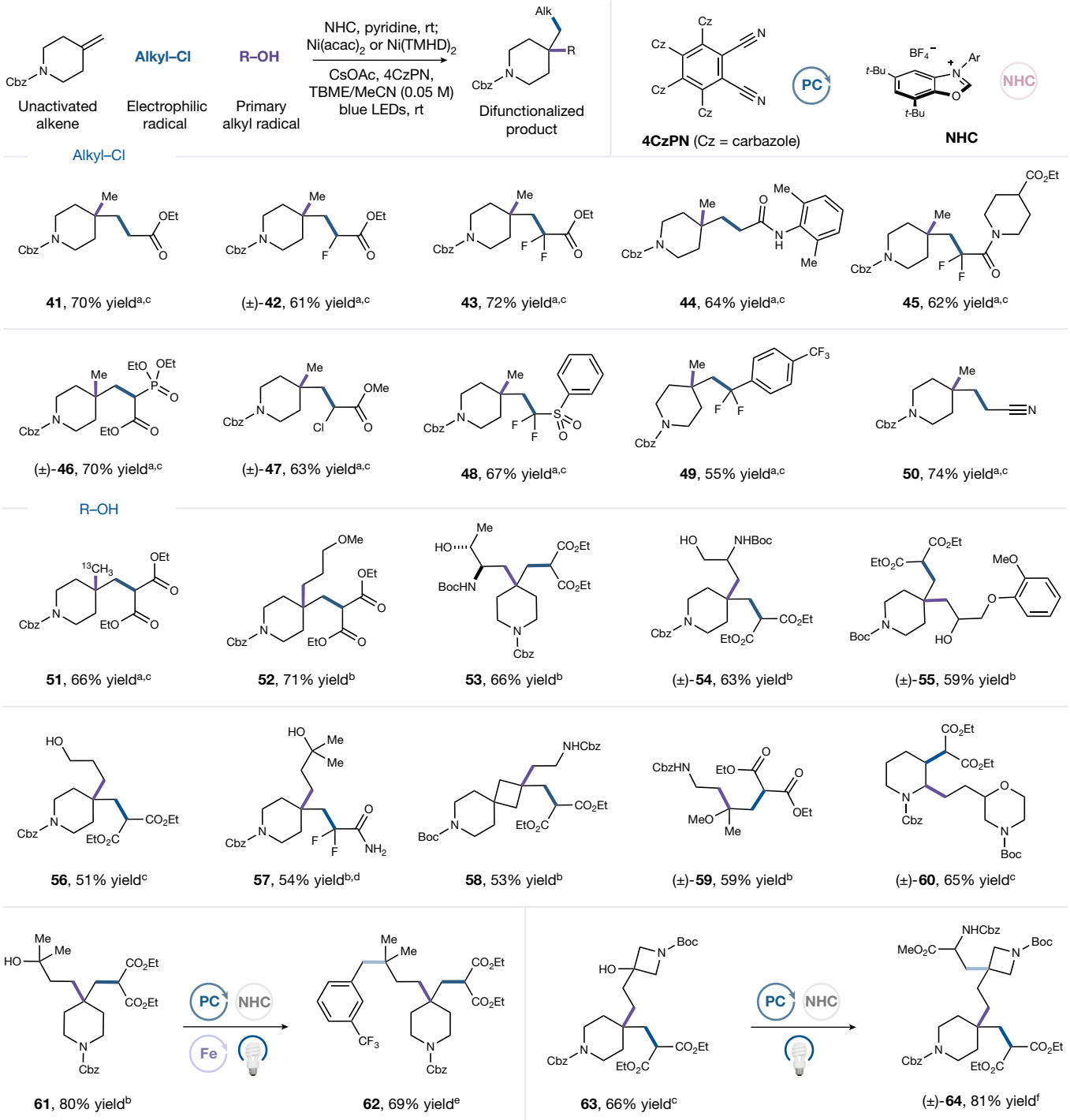


Fig. 4 | Scope of electrophilic and nucleophilic radicals. [a]MeOH (2.0 equiv.), NHC-1 (2.1 equiv.), pyridine (2.1 equiv.), $Ni(acac)_2$ (25 mol%), 4CzPN (1 mol%), alkyl chloride (2 equiv.), alkene (0.50 mmol), CsOAc (2.5 equiv.) and TBME/MeCN (1:1, 0.05 M). [b]Primary alcohol (2.5 equiv.), NHC-pCF_3 (2.6 equiv.), pyridine (2.6 equiv.), $Ni(TMHD)_2$ (25 mol%), 4CzPN (1 mol%), alkyl chloride (2.5 equiv.), alkene (0.50 mmol), CsOAc (3.0 equiv.), TBACl (0.6 equiv.), TBME/*t*AmOH (1:1, 0.05 M) and IPR (5% intensity, 16 h). [c]Supplementary Information has experimental details. [d]Yield determined by ^{19}F nuclear magnetic resonance analysis with 1,4-difluorobenzene as an internal standard. [e]Utilizing 3-(trifluoromethyl)benzyl bromide as a cross-coupling partner; Supplementary Information has experimental details. [f]Utilizing methyl 2-(((benzyloxy)carbonyl) amino)acrylate as a cross-coupling partner; Supplementary Information has experimental details. All yields are isolated unless otherwise noted. Et, ethyl; $Ni(TMHD)_2$, nickel(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate).

was demonstrated through elaboration of dialkylated products into complex C(sp^3)-rich frameworks (**61**, **63**). The tertiary alcohol of **61** was activated by NHC, and subsequent benzylation[5] proceeded efficiently to generate a second quaternary centre (**62**). In the case of **63**, the tertiary alcohol served as a radical precursor en route to alkylation with dehydroalanine[36] to yield complex scaffold, **64**.

Conclusion

Key to the strategy described herein is an outer-sphere C(sp^3)–C(sp^3) bond formation capable of forming quaternary centres. A wide range of unactivated alkenes were dialkylated, including tertiary amines, alcohols, aryl halides and other reactive functionalities. Several examples

of both the electrophilic radical and primary radical partners containing sites for further elaboration were demonstrated in good yield. Modulation of all three reaction components should allow for the rapid synthesis of C(sp^3)-rich small molecule libraries. Furthermore, the described approach provides a framework for future developments in C(sp^3)–C(sp^3) bond-forming alkene difunctionalization.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-024-07165-x.

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Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information.

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Author contributions J.Z.W., W.L.L. and D.W.C.M. designed the experiments. J.Z.W. and W.L.L. performed and analysed the experiments. J.Z.W., W.L.L. and D.W.C.M. prepared this manuscript.

Competing interests D.W.C.M. declares a competing financial interest with respect to the Penn PhD Integrated Photoreactor, which is used to irradiate reactions in this work. The other authors declare no competing interests.

Additional information

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