ORGANIC CHEMISTRY

Alcohol-alcohol cross-coupling enabled by S_H2 radical sorting

Ruizhe Chen[1]†, Nicholas E. Intermaggio[1]†, Jiaxin Xie[1]†, James A. Rossi-Ashton[1]†, Colin A. Gould[1], Robert T. Martin[1], Jesús Alcázar[2], David W. C. MacMillan[1]*

Alcohols represent a functional group class with unparalleled abundance and structural diversity. In an era of chemical synthesis that prioritizes reducing time to target and maximizing exploration of chemical space, harnessing these building blocks for carbon-carbon bond-forming reactions is a key goal in organic chemistry. In particular, leveraging a single activation mode to form a new C(sp^3)–C(sp^3) bond from two alcohol subunits would enable access to an extraordinary level of structural diversity. In this work, we report a nickel radical sorting–mediated cross-alcohol coupling wherein two alcohol fragments are deoxygenated and coupled in one reaction vessel, open to air.

Practitioners of the chemical sciences have long sought methods to reduce the time and resources required to access valuable synthetic targets (*1*, *2*). To this end, a key goal of organic chemistry has been the discovery of synthetic methods capable of forming new C–C bonds from abundant and bench-stable starting materials (*3*). Decades of progress have culminated in the development of transition metal–mediated cross-coupling reactions that construct new C–C bonds from a variety of precursors (*4*, *5*). In nearly all cases, two functional groups must be activated in an orthogonal manner, allowing each coupling partner to engage a metal catalyst through a distinct mechanistic step (e.g., oxidative addition, transmetallation, or reductive elimination) (*4*, *6*–*9*). Although highly enabling, this fundamental feature limits the scope of each method to mutually compatible activation modes.

Alternatively, single–functional group cross-coupling between two separate fragments through a common functional group would circumvent this requirement. Such a platform would apply a single activation mode for both partners and obviate the need to integrate bespoke mechanistic paradigms. Olefin cross metathesis is a key example of a highly impactful single–functional group coupling, which forms a new C(sp^2)=C(sp^2) bond from two olefin building blocks through a single catalytic platform (*10*). Key to the widespread adoption of this platform has been the ubiquity of the olefin starting materials and the operational simplicity of the reaction setup. We anticipated that an analogous single–functional group cross-coupling to form C(sp^3)–C(sp^3) bonds from highly abundant building blocks would have immediate implications for the applied chemical sciences.

To this end, single–functional group cross-coupling has been demonstrated for two functional group classes—alkyl bromides (*11*) and carboxylic acids (*12*–*15*). However, the span of chemical space that these cross-couplings can access is limited by the structural diversity of their starting materials. By contrast, alcohol is a C(sp^3)-rich native functional group ubiquitous among both natural and commercial sources (*16*–*18*). A single–functional group cross-coupling between two alcohol fragments would draw from reservoirs such as natural products, biomolecules, small-molecule therapeutics, biomass feedstocks, and commercial vendors, which would enable access to an unprecedented degree of chemical space (Fig. 1A).

Reaction design

Our laboratory recently disclosed the photoredox-enabled in situ deoxygenation of alcohols using N-heterocyclic carbene (NHC) salts (*19*). To date, this platform has been used to activate one alcohol building block, converting it to a transient alkyl radical, which is then capable of forming new bonds with a variety of partners (*20*–*23*). We anticipated that these NHC reagents could be used to simultaneously activate two alcohol building blocks within the same flask, providing the basis for a highly modular cross-alcohol coupling. Furthermore, NHC-alcohol adducts rapidly quench the excited state of a photocatalyst regardless of alcohol substitution pattern, which prevents preferential consumption of one coupling partner over another (fig. S2). As such, this platform would offer a distinct advantage over previous single–functional group cross-couplings mediated by silyl radical abstraction or open-shell decarboxylation that are subject to this kinetic bias (*24*, *25*). Despite this, the reaction pathway would proceed through the intermediacy of two distinct free radicals, a scenario that typically leads to complex mixtures of rec
bination and disproportionation products (

To address this challenge, we sought to leverage the ability of transition metals to stabilize and differentiate alkyl radicals on steric grounds (*27*, *28*). The strength of metal-alkyl bonds decreases as the degree of alkyl substitution increases (*12*, *29*, *30*). This property leads to a "radical sorting" effect, wherein the less substituted of two radicals is selectively captured, leading to a more stable metal-alkyl complex. Furthermore, we recognized that a suitable metal catalyst had the potential to not only sort radicals but also mediate C(sp^3)–C(sp^3) bond formation through bimolecular homolytic substitution (S_H2). Previous studies from our laboratory have shown that the combination of radical sorting and S_H2 can successfully mediate cross-selective C(sp^3)–C(sp^3) coupling between two transient alkyl radicals (Fig. 1B) (*12*, *21*, *31*). We sought to combine these mechanistic principles with NHC alcohol activation to achieve cross-alcohol coupling.

Our mechanistic design is detailed in fig. S4. In the event, two alcohol partners would be premixed with benzoxazolium **1** (NHC–**1**), simultaneously forming two NHC-alcohol adducts in a single reaction vessel. Subsequent engagement of either adduct with the excited state of a suitable photocatalyst would lead to the formation of the corresponding alkyl radical through oxidation-deprotonation followed by β scission (*19*). A mild oxidant could rapidly turn over the reduced photocatalyst, returning it to the Ir(III) ground state and priming it for a second photooxidation event, generating the alternate alkyl radical. Once formed, the alkyl radicals would be sorted by a suitable metal catalyst and would subsequently undergo C(sp^3)–C(sp^3) cross-coupling.

Reaction development

Initially, we focused our optimization campaign on the cross-coupling of secondary (2°) alcohols with methanol. The resulting C(sp^3)–methyl motif is highly sought after in medicinal chemistry programs for its ability to improve the potency and metabolic stability of drug candidates (*32*). Historically, aliphatic methylation has required multiple synthetic steps (*33*) or harsh organometallic reagents (*34*). Despite progress in recent years, the simplest functional methyl source—methanol—has remained underused for aliphatic methylation (*35*).

We discovered that simply mixing both alcohol substrates with NHC salt **1** under mildly basic conditions followed by the direct addition of in situ–generated S_H2 catalyst Tp*Ni(acac) (*36*), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, quinuclidine, benzoyl peroxide, and dimethyl sulfoxide (DMSO) delivered high yields of methylated products after irradiation with blue

[1]Merck Center for Catalysis at Princeton University, Princeton, NJ 08544, USA. [2]Discovery Chemistry, Janssen Research and Development, Janssen-Cilag, S.A., C/Jarama 75A, 45007 Toledo, Spain.
*Corresponding author. Email: dmacmill@princeton.edu
†These authors contributed equally to this work.

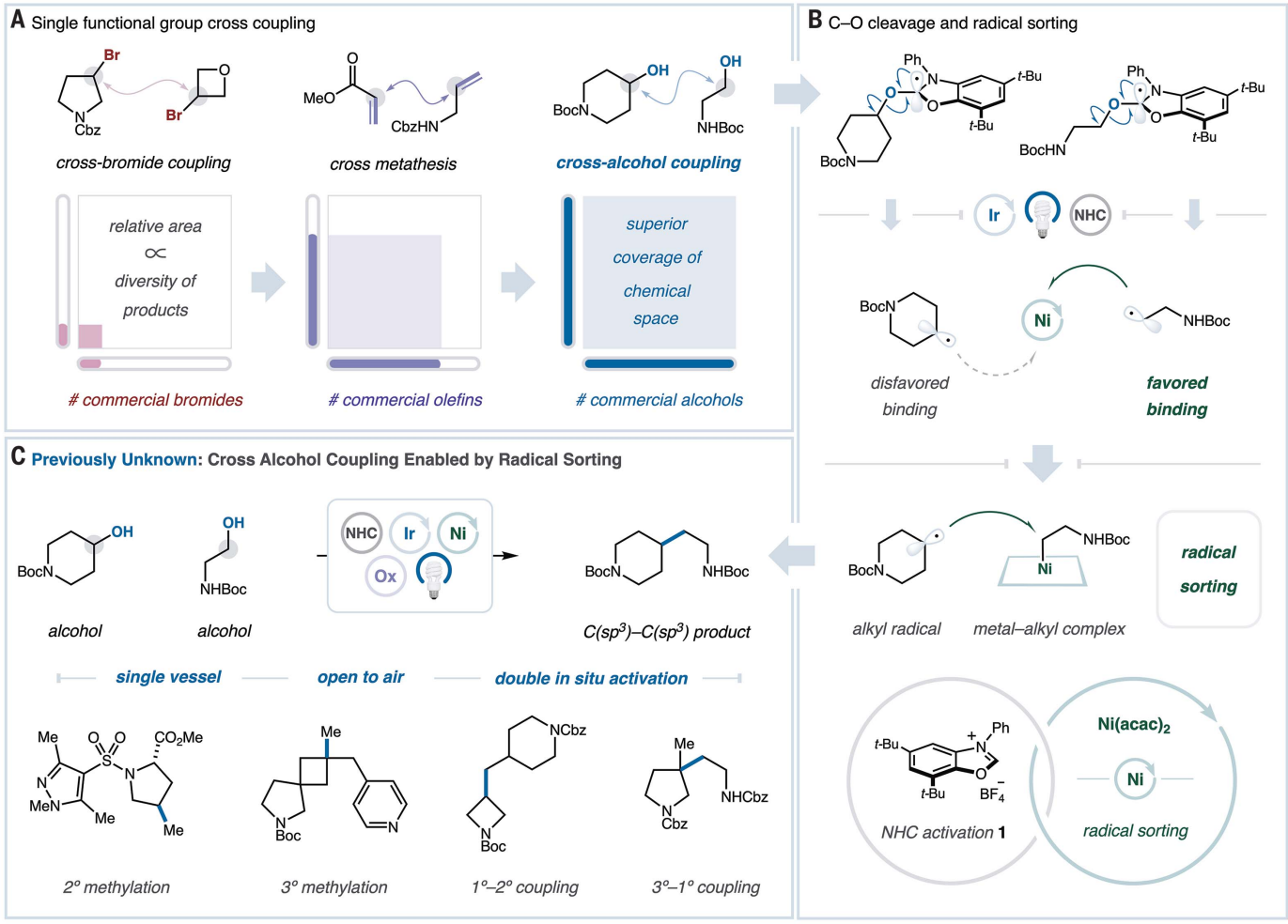

Fig. 1. Reaction design. (**A**) Influence of functional group abundance on accessibility of theoretical chemical space. (**B**) Alcohol deoxygenation and radical sorting principles. (**C**) Cross-alcohol coupling enabled by NHC alcohol activation and radical sorting–mediated bond formation (this work). $Ni(acac)_2$, nickel(II) acetylacetonate.

light-emitting diodes (LEDs) for 1 hour. Notably, control experiments revealed that 2° alcohol methylation proceeds with slightly higher efficiency in the absence of the [Tp*] ligand (table S9), which demonstrates that $Ni(acac)_2$ itself is a competent radical sorting catalyst (*21*, *28*, *37*, *38*). The magnitude of this ligand effect proved to be substrate dependent, with S_H2 catalyst Tp*Ni(acac) providing substantially higher yields for tertiary alcohol partners (vide infra).

Control experiments confirmed that the $Ni(acac)_2$ plays a critical role in promoting cross-selectivity and suppressing by-products arising from background radical-radical reactions. In the presence of $Ni(acac)_2$, the yield of the cross-coupled product increases by more than fourfold (16 to 70%). Furthermore, the ratio of cross-coupled product to 2°–2° homodimer increases from 2:1 in the absence of metal to 17.5:1 in the presence of metal. These results strongly support the hypothesis that a radical sorting mechanism is operative, enabling two transient alkyl radicals to combine with substantially higher efficiency compared with stochastic radical-radical recombination. For a full discussion of product distribution with and without a metal catalyst, see table S15.

Notably, in other NHC-based reactions developed in our laboratory, we have observed that the pyridinium salt generated upon alcohol activation must be removed using a syringe filter to ensure high yields of the deoxyfunctionalized product (*19*). In the present transformation, however, no pyridinium salt filtration is required, which allows for a streamlined reaction setup in which alcohols are activated, deoxygenated, and cross-coupled in a single reaction flask. Critically, no precautions to exclude air or moisture are necessary to maintain reaction efficiency, a feature that highlights the robust and user-friendly nature of this protocol.

Furthermore, previously reported examples of single–functional group cross-coupling have often required large excesses of one coupling partner to achieve cross-selectivity (*11*, *15*). By contrast, the present cross-alcohol coupling typically requires only 1.0 to 1.5 equiv of methanol to achieve high yield.

Evaluation of methanol coupling scope

With optimized conditions in hand, we sought to explore the scope of this cross-alcohol coupling with methanol (Fig. 2). We found that, despite only small differences in radical substitution pattern, primary alcohols could be efficiently cross-coupled with methanol to deliver methylated products **2** (51% yield) and **3** (55% yield). The substantial influence of radical sorting is underscored by suppression of 1° homodimerization in these cases. During formation of **2**, cross product and 1°–1° homodimer are formed in an ~10:1 molar ratio (*39*). In formation of **3**, 1°–1° dimerization was only observed in trace quantities. We propose that the neopentyl radical generated en route to **3** exerts a stronger steric influence compared with other 1° radicals, which leads to higher sorting efficiencies.

With respect to secondary alcohols, a wide variety of ring systems, including seven-, six-,

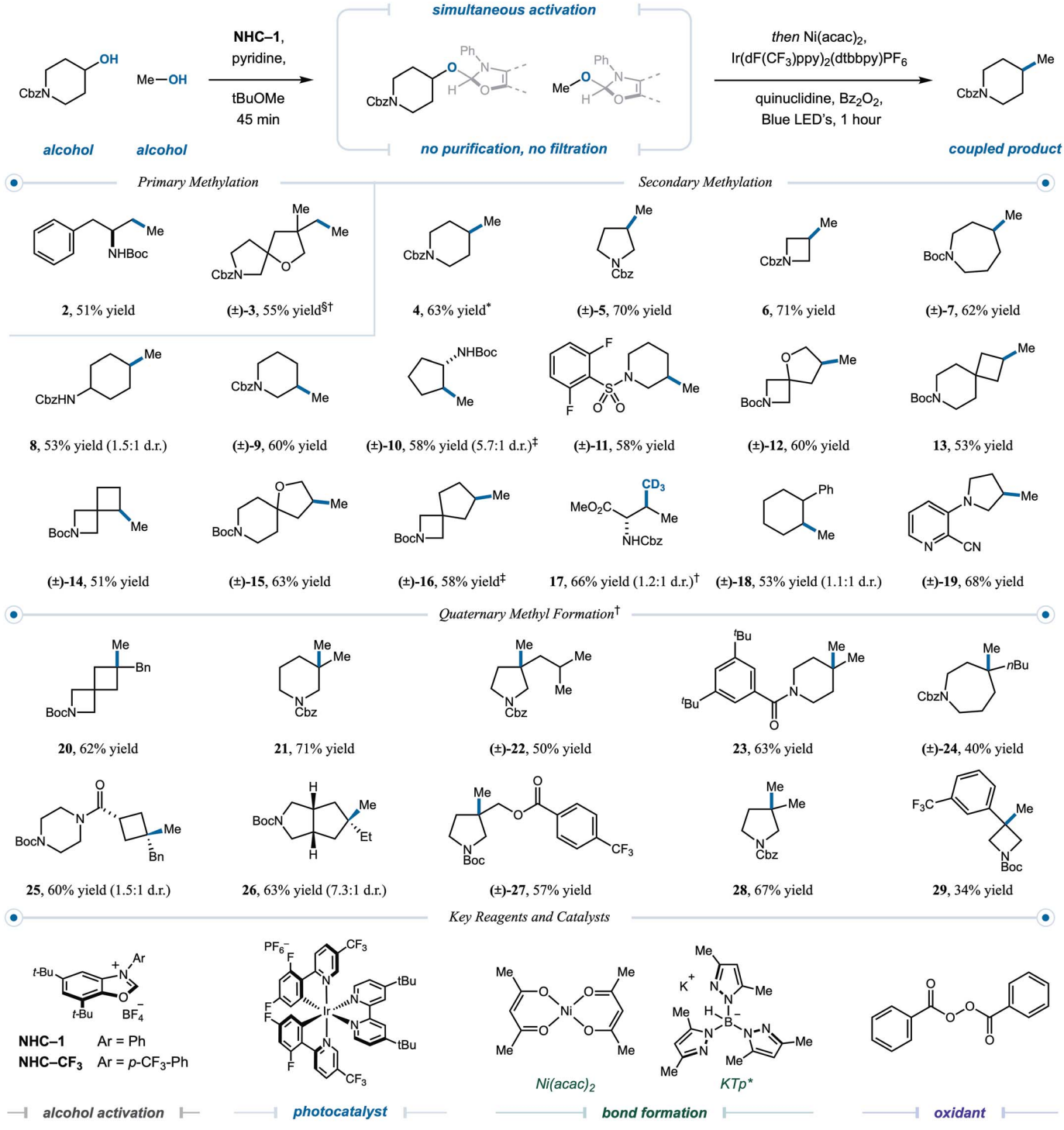

Fig. 2. Scope of cross-alcohol coupling with methanol. All yields are isolated unless otherwise noted. Performed on a 0.5-mmol scale with 2° alcohol (1.0 equiv), methanol (1.5 equiv), NHC–**1** (2.7 equiv), pyridine (2.7 equiv), *t*BuOMe (0.1 M), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 to 2 mol %), $Ni(acac)_2$ (25 mol %), quinuclidine (5 equiv), Bz_2O_2 (1.5 equiv), and DMSO (0.05 M) using an integrated photoreactor (450 nm, 100% light intensity) for 1 hour at room temperature. †With NHC–CF_3 (3.3 equiv), KTp* (20 mol %), 2 equiv methanol; see supplementary materials for full detailed experimental conditions. *1.0 equiv methanol; see supplementary materials for detailed experimental conditions. ‡Yield determined by proton NMR (^{1}H NMR) versus mesitylene. §Alcohol starting material was a 1.1:1 mixture of diastereomers. KTp*, potassium tris(3,5-dimethyl-1-pyrazolyl)borate; d.r., diastereomeric ratio.

five-, and four-membered saturated heterocycles, could be methylated in good to excellent yields (**4** to **11**, 55 to 70% yields). A series of spirocyclic ring systems also underwent efficient cross-coupling in good yields (**12** to **15**, 51 to 63% yields). Furthermore, the acyclic secondary alcohol, *L*-threonine methyl ester, was directly converted to noncanonical *L*-valine-d_3 (**17**) in 66% yield by simply exchanging methanol

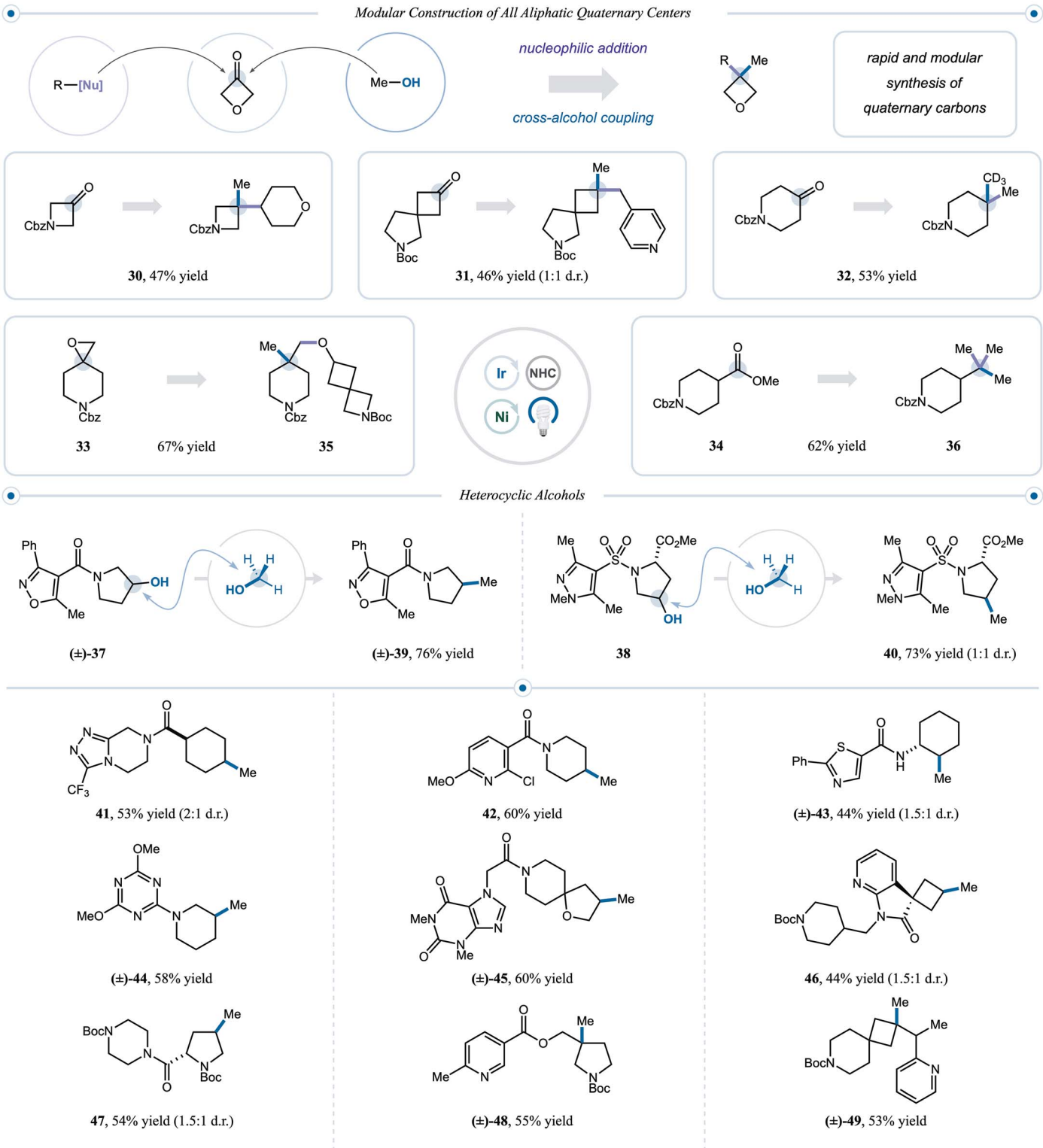

Fig. 3. Modular construction of all-carbon quaternary centers and heterocyclic alcohols. All yields are isolated. See the supplementary materials for full detailed experimental conditions.

with the common nuclear magnetic resonance (NMR) solvent CD_3OD, obviating the need for lengthy de novo synthesis (*40*). Additionally, homobenzylic alcohols and alcohols appended to anilinic ring systems could be directly methylated in 56 and 68% yields, respectively (**18** and **19**).

All-carbon quaternary centers are among the most difficult motifs to construct in organic chemistry but are highly desirable because they can impart beneficial effects on biologically active molecules (*41*). Historically, transition metal–catalyzed cross-coupling has struggled to form this important motif in a mild and generic fashion, typically proceeding through

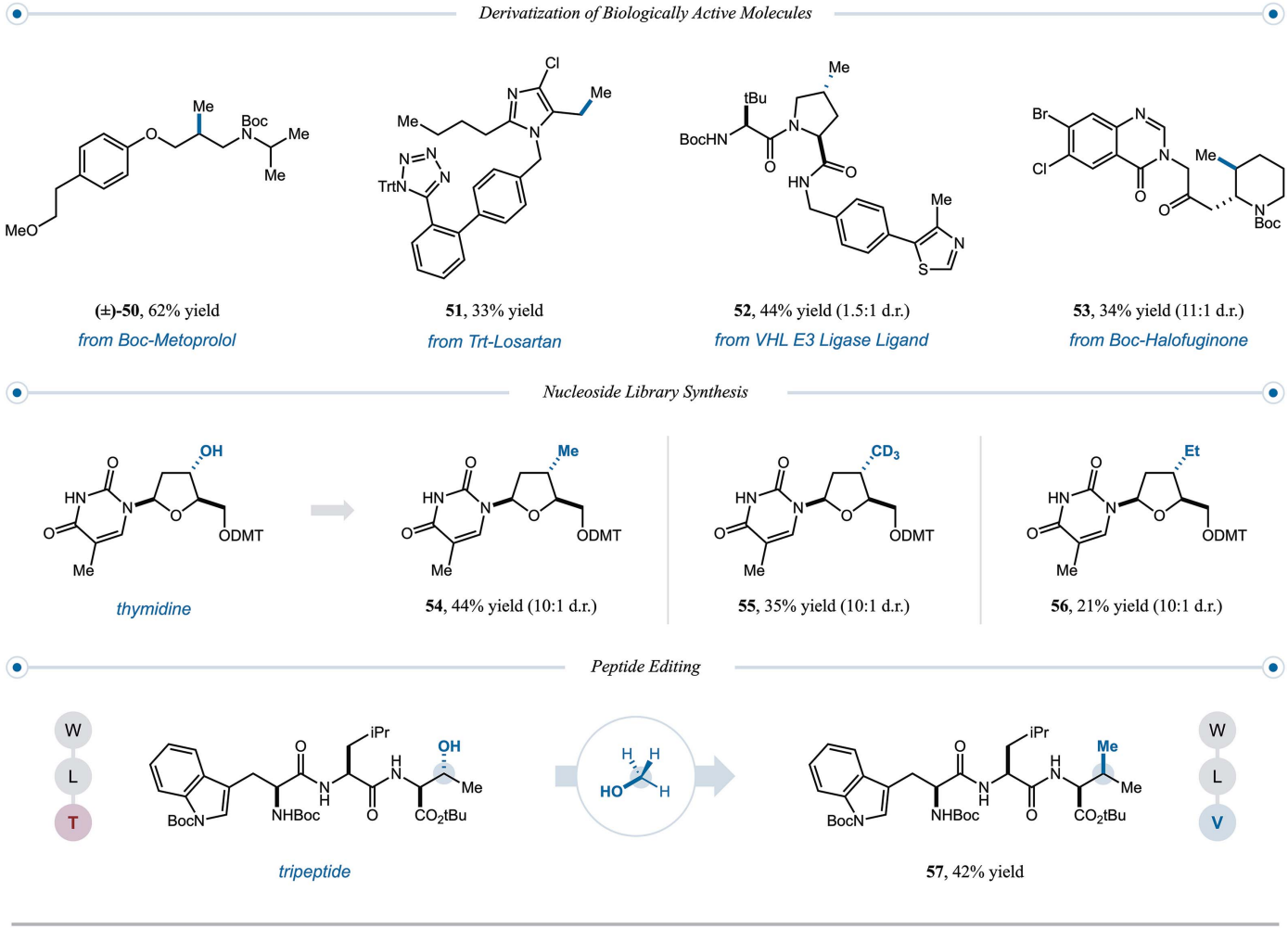

Fig. 4. Complex molecule applications. All yields are isolated. See the supplementary materials for detailed reaction conditions.

the intermediacy of unstable dialkyl-metal complexes (*4*).

Despite progress in recent years by our laboratory and others (*12*, *21*, *31*, *42*, *43*), we recognized a critical unmet need for a mild and general method to form all aliphatic quaternary carbons from abundant and bench-stable precursors. Despite their broad availability and synthetic accessibility, tertiary alcohols remain underused for quaternary center formation (*44*, *45*). We wondered whether we could leverage cross-alcohol coupling to form all aliphatic quaternary carbons from 3° alcohol building blocks and methanol. To this end, we subjected a range of tertiary alcohols to a modified set of reaction conditions using a more-electrophilic, trifluoromethylated NHC activator (NHC–CF_3; see the supplementary materials for experimental details) and 2 equiv of methanol. We found that a series of structurally diverse quaternary carbons could be constructed. In this case, the use of Tp*Ni(acac) as an S_H2 catalyst proved far superior to $Ni(acac)_2$ alone. This observation is consistent with previous studies from our laboratory that have shown that Tp*Ni(acac) is a privileged catalyst for the methylation of tertiary radicals through S_H2 (*12*).

Cyclic tertiary alcohols present on saturated heterocycles of four, five, six, and seven members were all converted to quaternary methylated products in synthetically useful to excellent yields (**21** to **25** and **28**, 40 to 71% yields). Additionally, spirocyclic and bicyclic ring systems bearing tertiary alcohols could also be cross-coupled to deliver methylated products in 62% yield (**20**) and 63% yield (**26**), respectively. Oxygen heteroatoms adjacent to tertiary alcohols were well tolerated, resulting in good yields of quaternary carbon formation (**27**, 57% yield). Finally, arylated quaternary carbons could be constructed through cross-alcohol coupling with methanol in synthetically useful yields (**29**, 34% yield).

Given that tertiary alcohols are widely accessible through simple nucleophilic addition to native electrophilic functional groups, we recognized an opportunity to convert ketones, esters, and epoxides to quaternary carbons in two synthetic steps (Fig. 3). To this end, we subjected a series of ketones to structurally diverse organometallic nucleophiles, converting them to the corresponding 3° alcohols, which could participate in cross-alcohol coupling with methanol or CD_3OD to deliver quaternary carbons **30**, **31**, and **32** in good yields (47, 47, and 53% yields, respectively). Furthermore, nucleophilic addition to epoxide **33** and methyl ester **34** followed by methylation of the resulting tertiary alcohol provided quaternary products **35** and **36** in good yields (67 and 62% yields, respectively).

We next turned our attention to the methylation of alcohols bearing medicinally relevant heterocycles (Fig. 3). To this end, we subjected isoxazole **37** and pyrazole sulfonamide **38** to our reaction conditions, which delivered the desired methylated product in excellent yields (**39**, 76% yield, and **40**, 73% yield, respectively). Furthermore, triazolopiperazine **41**, thiazole **43**, triazine **44**, and piperazine **47** could all be converted to the corresponding methylated

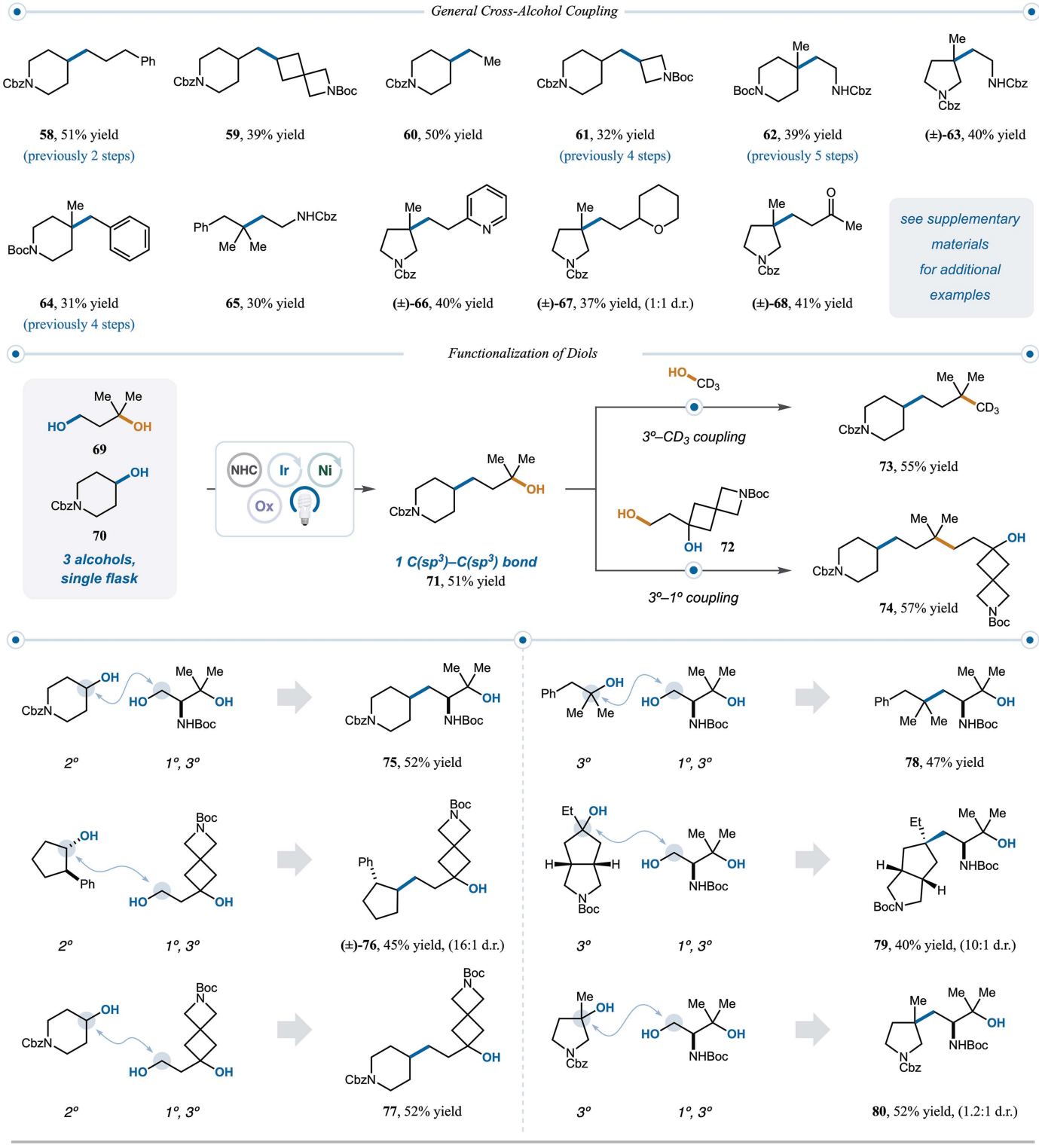

Fig. 5. General cross-alcohol coupling. All yields are isolated. See the supplementary materials for detailed reaction conditions.

product in synthetically useful to good yields (44 to 58% yields).

Heterocycles, such as pyridine **42**, purine **45**, and azaoxindole **46**, can pose a challenge for net oxidative, open-shell cross-coupling because of their propensity to accept radicals in a Minisci-type reaction (*46*). Under our optimal conditions, however, alcohols bearing all such heterocycles underwent methylation in good yields (43 to 60% yields). Moreover, we demonstrated the ability to form quaternary centers from pyridines **48** and **49** (55 and 53% yields, respectively).

At this stage, we explored the late-stage functionalization of biologically active molecules

(Fig. 4). To this end, we considered the alcohols present in metoprolol, losartan, a von Hippel–Lindau (VHL) E3 ligase binder, and halofuginone as points of functionalization. Synthesis of the methylated analogs of these complex molecules would typically represent a substantial synthetic burden, requiring lengthy de novo synthesis. Alternatively, cross-alcohol coupling with methanol could provide each methylated product in a single synthetic operation. We found that methylated analogs of metoprolol (**50**), losartan (**51**), VHL E3 ligase binder (**52**), and halofuginone (**53**) could all be synthesized at a late stage in synthetically useful to good yields (33 to 62% yields), circumventing the time and resources otherwise required to access these analogs through multistep synthesis.

A key goal within the field of late-stage functionalization is to access multiple structural analogs from a single complex molecule (*33*). Historically, the installation of small alkyl groups at the 3′ position of nucleosides has posed a substantial challenge, requiring that each analog be synthesized independently in a lengthy multistep sequence (*47*). We sought to circumvent this barrier by using our cross-alcohol coupling protocol to rapidly synthesize a small library of 3′-functionalized nucleosides. To this end, we subjected thymidine to cross-alcohol coupling with methanol, CD_3OD, and ethanol. The desired methyl, CD_3, and ethyl analogs were accessed in 44% yield (**54**), 35% yield (**55**), and 21% yield (**56**), respectively.

Finally, we explored our cross-alcohol coupling in the context of late-stage peptide modification. Traditional peptide modification technologies are dominated by methods to derivatize reactive side chains such as cysteine, serine, lysine, and tryptophan (*48*). Consequently, methods to derivatize less-reactive residues, such as threonine, remain underdeveloped. To address this disparity, we subjected a tryptophan-leucine-threonine tripeptide to cross-alcohol methylation conditions. In this instance, exchange of the secondary hydroxyl group in the threonine side chain for a methyl group would constitute an amino acid interconversion to a valine residue. Valine product **57** was formed in 42% yield, representing the successful editing of a tripeptide from W–L–T to W–L–V in one simple synthetic operation. Having thoroughly explored cross-alcohol coupling between a variety of alcohols and methanol, we next explored general $C(sp^3)$–$C(sp^3)$ bond formation through cross-coupling between any two differentially substituted alcohols.

General cross-alcohol coupling

In recent years, drug candidates rich in sp^3-character have demonstrated a higher success rate in clinical trials (*49*). As a result, medicinal chemists require the means to rapidly synthesize and evaluate a range of $C(sp^3)$-rich frameworks as potential therapeutics. Oftentimes, such aliphatic linkages must first be constructed as $C(sp^2)$–$C(sp^3)$ bonds before being exhaustively reduced during downstream oxidation state manipulations (*50*). We wondered whether general cross-alcohol coupling could enable rapid exploration of aliphatic chemical matter in one synthetic step.

We found that highly modular $C(sp^3)$–$C(sp^3)$ fragment coupling could be readily achieved under our optimal reaction conditions (Fig. 5). Thus, 2° and 1° alcohols of varying ring sizes were coupled with synthetically useful to good efficiency (**58** to **61**, 32 to 51% yields). Notably, cross-alcohol coupling between 3° and 1° alcohols led to the construction of quaternary carbons in a modular and user-friendly fashion. Both cyclic and acyclic tertiary alcohols were coupled in one synthetic operation, delivering all-aliphatic quaternary carbon products in synthetically useful yields (**62** to **68**, 30 to 41% yields).

Although modest yields were obtained with certain substrates, control experiments indicate that radical sorting remains operative and delivers significantly higher yields than can be achieved through stochastic radical-radical recombination. Even in the case of a 1:1 stoichiometric ratio between alcohol partners, the addition of $Ni(acac)_2$ effectively increases the yield of cross product by 2.6-fold (22 to 57%) and increases the ratio of cross product to 2°–2° dimer by approximately fivefold when compared with the nickel-free control (see fig. S16 for details). Furthermore, general cross-alcohol coupling significantly reduces the time, resources, and step count required to access these valuable core structures (*50*–*53*).

We next investigated iterative functionalization of diols as a means to rapidly access complex, $C(sp^3)$-rich structures. The rate of condensation between an alcohol and a NHC salt is governed by sterics (MeOH > 1° > 2° >> 3°). On the basis of this trend, we anticipated that differentially substituted diols would represent orthogonal functional handles for cross-coupling. To this end, we subjected a 1°, 3° diol (**69**) to condensation in the same flask as 2° alcohol **70**. We anticipated that the 1° and 2° alcohols would rapidly condense with NHC–**1** while leaving the 3° alcohol in **69** unaltered. Upon subjection of these substrates to our optimized reaction conditions, we found that **71** was formed in 51% yield through selective deoxygenation of the 1° and 2° alcohols. At this stage, the remaining 3° alcohol in **71** could be subjected to another round of cross-alcohol coupling with CD_3OD or **72** to deliver complex quaternary carbon products **73** and **74** in 55 and 57% yields, respectively. The first step of this iterative functionalization proved very robust, enabling high material throughput and producing more than 700 mg of intermediate alcohol **71** in a single pass. Functionalization of 1°, 3° diols proved highly successful, delivering a series of complex 2°–1° coupling products (**75** to **77**, 45 to 52% yields) as well as 3°–1° coupling products (**78** to **80**, 40 to 52% yields) (*54*).

Outlook

Over the past several decades, modern synthetic organic chemistry has experienced a paradigm shift in retrosynthetic analysis. New synthetic methods have replaced harsh conditions or bespoke coupling partners with abundant and bench-stable alkyl fragments. In this era of chemical synthesis, practitioners seek disconnections enabled by robust and operationally simple protocols (*1*). In this work, we report a cross-coupling technology that constructs five distinct classes of $C(sp^3)$–$C(sp^3)$ bonds from the most abundant and diverse alkyl fragments in a single, robust, and user-friendly step. We anticipate that the cross-alcohol coupling technology described here will have immediate implications in the applied chemical sciences.

REFERENCES AND NOTES

1. D. C. Blakemore *et al*., *Nat. Chem.* **10**, 383–394 (2018).
2. W. P. Walters, J. Green, J. R. Weiss, M. A. Murcko, *J. Med. Chem.* **54**, 6405–6416 (2011).
3. Y. Wang, I. Haight, R. Gupta, A. Vasudevan, *J. Med. Chem.* **64**, 17115–17122 (2021).
4. J. Choi, G. C. Fu, *Science* **356**, eaaf7230 (2017).
5. J.-P. Corbet, G. Mignani, *Chem. Rev.* **106**, 2651–2710 (2006).
6. R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **41**, 1461–1473 (2008).
7. S. B. Beil, T. Q. Chen, N. E. Intermaggio, D. W. C. MacMillan, *Acc. Chem. Res.* **55**, 3481–3494 (2022).
8. G. Laudadio, M. D. Palkowitz, T. El-Hayek Ewing, P. S. Baran, *ACS Med. Chem. Lett.* **13**, 1413–1420 (2022).
9. A. Y. Chan *et al*., *Chem. Rev.* **122**, 1485–1542 (2022).
10. S. J. Connon, S. Blechert, *Angew. Chem. Int. Ed.* **42**, 1900–1923 (2003).
11. R. T. Smith *et al*., *J. Am. Chem. Soc.* **140**, 17433–17438 (2018).
12. A. V. Tsymbal, L. D. Bizzini, D. W. C. MacMillan, *J. Am. Chem. Soc.* **144**, 21278–21286 (2022).
13. Y. Gao, B. Zhang, J. He, P. S. Baran, *J. Am. Chem. Soc.* **145**, 11518–11523 (2023).
14. Y. Hioki *et al*., *Science* **380**, 81–87 (2023).
15. B. Zhang *et al*., *Nature* **606**, 313–318 (2022).
16. P. Ertl, T. Schuhmann, *J. Nat. Prod.* **82**, 1258–1263 (2019).
17. T. Henkel, R. M. Brunne, H. Müller, F. Reichel, *Angew. Chem. Int. Ed.* **38**, 643–647 (1999).
18. Reaxys search from October 2023 of commercially available fragments: alcohols (634,160), carboxylic acids (287,463), alkenes (472,916), and alkyl bromides (55,073).
19. Z. Dong, D. W. C. MacMillan, *Nature* **598**, 451–456 (2021).
20. W. L. Lyon, D. W. C. MacMillan, *J. Am. Chem. Soc.* **145**, 7736–7742 (2023).
21. H. A. Sakai, D. W. C. MacMillan, *J. Am. Chem. Soc.* **144**, 6185–6192 (2022).
22. W. P. Carson II, P. J. Sarver, N. S. Goudy, D. W. C. MacMillan, *J. Am. Chem. Soc.* **145**, 20767–20774 (2023).
23. N. B. Bissonnette, N. Bisballe, A. V. Tran, J. A. Rossi-Ashton, D. W. C. MacMillan, ChemRxiv [Preprint] (2023); https://doi.org/10.26434/chemrxiv-2023-65m0v.
24. C. Chatgilialoglu, D. Griller, M. Lesage, *J. Org. Chem.* **54**, 2492–2494 (1989).
25. K. Suga, K. Ohkubo, S. Fukuzumi, *J. Phys. Chem. A* **110**, 3860–3867 (2006).
26. M. J. Gibian, R. C. Corley, *Chem. Rev.* **73**, 441–464 (1973).
27. Q. Lin, E. H. Spielvogel, T. Diao, *Chem* **9**, 1295–1308 (2023).
28. M. Yuan, Z. Song, S. O. Badir, G. A. Molander, O. Gutierrez, *J. Am. Chem. Soc.* **142**, 7225–7234 (2020).

29. C. G. Riordan, J. Halpern, . *Inorg. Chim. Acta* **243**, 19–24 (1996).
30. J. Halpern, *Polyhedron* **7**, 1483–1490 (1988).
31. W. Liu, M. N. Lavagnino, C. A. Gould, J. Alcázar, D. W. C. MacMillan, *Science* **374**, 1258–1263 (2021).
32. H. Schönherr, T. Cernak, *Angew. Chem. Int. Ed.* **52**, 12256–12267 (2013).
33. T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **45**, 546–576 (2016).
34. L. F. T. Novaes *et al*., *J. Am. Chem. Soc.* **144**, 1187–1197 (2022).
35. N. Sarki, V. Goyal, K. Natte, R. V. Jagadeesh, *Adv. Synth. Catal.* **363**, 5028–5046 (2021).
36. Tp*Ni(acac) is generated in situ by adding $Ni(acac)_2$ and potassium tris(3,5-dimethyl-1-pyrazol)borate (KTp*) to the reaction mixture in a 1:1 molar ratio. No premixing is required.
37. Previous studies from our laboratory have shown that nickel diketonate complexes can mediate selective C–C bond formation from two alkyl radicals. Although inner sphere pathways remain possible, both outer sphere reductive elimination and S_H2-type C–C bond formation have been demonstrated from related nickel complexes.
38. J. R. Bour, D. M. Ferguson, E. J. McClain, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **141**, 8914–8920 (2019).
39. An ~10:1 molar ratio based off 5% yield of 1°–1° dimer with maximum dimer yield set to 50%.
40. D. J. Aberhart, L. J. Lin, *J. Am. Chem. Soc.* **95**, 7859–7860 (1973).
41. T. T. Talele, *J. Med. Chem.* **63**, 13291–13315 (2020).
42. X. C. Gan *et al*., *J. Am. Chem. Soc.* **145**, 15714–15720 (2023).
43. S. A. Green, T. R. Huffman, R. O. McCourt, V. van der Puyl, R. A. Shenvi, *J. Am. Chem. Soc.* **141**, 7709–7714 (2019).
44. C. A. Gould, A. L. Pace, D. W. C. MacMillan, *J. Am. Chem. Soc.* **145**, 16330–16336 (2023).
45. H. Xie *et al*., *J. Am. Chem. Soc.* **142**, 16787–16794 (2020).
46. R. Gianatassio *et al*., *Angew. Chem. Int. Ed.* **53**, 9851–9855 (2014).
47. M. Aljarah, S. Couturier, C. Mathé, C. Périgaud, *Bioorg. Med. Chem.* **16**, 7436–7442 (2008).
48. J. N. deGruyter, L. R. Malins, P. S. Baran, *Biochemistry* **56**, 3863–3873 (2017).
49. F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **52**, 6752–6756 (2009).
50. M. T. Rudd, D. J. Bennett, J. Wai, Z. Meng, International Patent Application Publication No. WO 2017/095758 (2017).
51. M. Balestera *et al*., International Patent Application Publication No. WO 2006/071730A1 (2006).
52. K. R. Dahnke *et al*., International Patent Application Publication No. WO 2007/092095A2 (2007).
53. E. Holson *et al*., International Patent Application Publication No. WO 2016/100940A1 (2016).
54. In the case of coupling a 3° alcohol with a 1°, 3° diol (**74**, **78**, **79**, and **80**), the activation of these two alcohol partners is carried out in parallel and in separate vessels. This is done to avoid competition between two 3° alcohols in the same flask. See the supplementary materials for representative procedure.

ACKNOWLEDGMENTS

The authors thank Z. Dong, C. N. Prieto-Küllmer, B. T. Boyle, E. Mao, A. Long, W. Lyon, and J. Wang for helpful discussions. The authors thank R. Lambert for assistance in preparing this manuscript. **Funding:** The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS) (R35GM134897-04); the Princeton Catalysis Initiative; Janssen R&D; and gifts from Merck, Bristol Myers Squibb, GenMab, Genentech, and Pfizer. R.C. thanks the William G. Bowden Merit Fellowship for a graduate fellowship. N.E.I. thanks the Ted Taylor family for a graduate fellowship. C.A.G. thanks the Beckman Foundation for a postdoctoral fellowship. R.T.M. thanks the National Science Foundation for financial support through the MPS-Ascend Postdoctoral Research Fellowship (grant no. 2316541). **Author contributions:** J.A.R.-A. and D.W.C.M. conceived of the work. All authors designed the experiments. R.C., J.X., N.E.I., J.A.R.-A., C.A.G., and R.T.M. performed the experiments. N.E.I., J.X., R.C., and D.W.C.M. prepared the manuscript. **Competing interests:** D.W.C.M. declares a financial interest with respect to the integrated photoreactor. The authors declare no other competing interests. **Data and materials availability:** Data are available in the supplementary materials.

SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.adl5890
Supplementary Text
Figs. S1 to S5
Tables S1 to S17
NMR Spectra
References (*55*–*66*)

Submitted 31 October 2023; accepted 15 February 2024
10.1126/science.adl5890