nature

https://doi.org/10.1038/s41586-020-2060-z

Accelerated Article Preview

Copper-mediated synthesis of drug-like bicyclopentanes

Received: 25 November 2019

Accepted: 29 January 2020

Accelerated Article Preview Published online 17 February 2020

Cite this article as: Zhang, X. et al. Copper-mediated synthesis of drug-like bicyclopentanes. *Nature* https://doi.org/10.1038/s41586-020-2060-z (2020).

Xiaheng Zhang, Russell T. Smith, Chip Le, Stefan J. McCarver, Brock T. Shireman, Nicholas I. Carruthers & David W. C. MacMillan

Copper-mediated synthesis of drug-like bicyclopentanes

https://doi.org/10.1038/s41586-020-2060-z

Received: 25 November 2019

Accepted: 29 January 2020

Published online: 17 February 2020

Xiaheng Zhang[1,3], Russell T. Smith[1,3], Chip Le[1], Stefan J. McCarver[2], Brock T. Shireman[2], Nicholas I. Carruthers[2] & David W. C. MacMillan[1]✉

Multicomponent reactions have become a mainstay in both academic and industrial synthetic organic chemistry owing to their step- and atom-economy advantages over traditional synthetic sequences[1]. Recently, bicyclo[1.1.1]pentane (BCP) motifs have come to the fore as valuable pharmaceutical bioisosteres of benzene rings, and, in particular, 1,3-disubstituted BCP moieties have become widely adopted in medicinal chemistry as *para*-phenyl ring replacements[2]. Often these structures are generated from [1.1.1]propellane via opening of the internal C–C bond, through the addition of either radicals or metal-based nucleophiles[3–13]. The resulting propellane-addition adducts are subsequently transformed to the requisite polysubstituted BCP compounds via a range of synthetic sequences that traditionally involve multiple chemical steps. While this approach has been effective so far, it is clear that a multicomponent reaction that enables single-step access to complex and diverse polysubstituted BCP products would be synthetically advantageous over the current stepwise approaches. Here we report a one-step three-component radical coupling of [1.1.1]propellane to afford diverse functionalized bicycles using various radical precursors and heteroatom nucleophiles via a metallaphotoredox catalysis protocol. The reaction operates on short timescales (five minutes to one hour) across multiple (>10) nucleophile classes and can accommodate a diverse array of radical precursors, including those which generate alkyl, α-acyl, trifluoromethyl, and sulfonyl radicals. This method has been used to rapidly prepare BCP analogues of known pharmaceuticals, one of which has pharmacokinetic properties substantially different to those of its commercial progenitor.

It has been shown that replacement of an aromatic ring with the BCP scaffold can improve the pharmacokinetic profile of many pharmaceutical candidates while providing similar levels of potency (typically via the reduction of metabolic susceptibility and increases in solubility and membrane permeability). It is not surprising, therefore, that the pharmaceutical sector has begun to extensively investigate BCP-containing leads in recent years (Fig. 1a)[14–17]. From a synthetic standpoint, these compounds have largely been prepared by opening of [1.1.1]propellane, most often via multi-step chemical sequences to install and manipulate functional handles at the BCP bridgehead positions (Fig. 1b)[18]. Radical addition to [1.1.1]propellane is well-established and perhaps the most widely leveraged mechanism of BCP functionalization, with numerous examples of chain reactions being reported[13]. However, it has also been demonstrated that strong nucleophiles, such as turbo Grignard and turbo amide reagents, can be employed to open the internal propellane bond, leading to BCP-organometallic reagents that can be subsequently utilized in transition metal-catalyzed cross-coupling reactions (via a two-step difunctionalization protocol)[11,12]. While these multi-step approaches have been leveraged to furnish BCP targets with varying levels of synthetic utility, new reaction designs that would enable one-step access to complex and drug-like BCPs would be of significant value to medicinal and process chemists on a community-wide basis. Furthermore, while pioneering work by Uchiyama and coworkers enables a single-step carboamination multicomponent reaction (MCR) of [1.1.1]propellane via radical addition to azodicarboxylates[4], a modular MCR approach to [1.1.1]propellane difunctionalization that is amenable to a diverse series of structural inputs would allow generic adoption and application across a range of therapeutic areas.

Metallaphotoredox catalysis has recently become a valuable platform for the facile generation of radicals from native organic functional groups and their subsequent capture and cross-coupling via a transition metal co-catalyst[19–22]. Recently, our lab and others have demonstrated that activated carboxylic acids can be leveraged in a photoredox/copper catalysis platform to enable decarboxylative alkylation of *N*-nucleophiles[23–25]. These reactions proceed via reductive generation of an alkyl radical that can be subsequently trapped by a copper catalyst, which upon reductive elimination generates the desired C–N fragment-coupled product. Given the susceptibility of [1.1.1]propellane to radical opening with numerous classes of organic radicals[13], we recently wondered whether it might be possible to intercept the

[1]Merck Center for Catalysis at Princeton University, Princeton, NJ, USA. [2]Janssen Research and Development, San Diego, CA, USA. [3]These authors contributed equally: Xiaheng Zhang, Russell T. Smith. ✉e-mail: dmacmill@princeton.edu

strained propellane system with photoredox-derived alkyl radicals. Thereafter, subsequent copper-BCP radical trapping/reductive elimination might enable a three-component coupling to yield complex bicyclo[1.1.1]pentane products (Fig. 1b). A critical factor to the success of this new MCR pathway would be selective addition of the photogenerated alkyl radical to [1.1.1]propellane in lieu of direct addition to the copper center, which would result in a known, two-component coupling that omits the bicyclopentane framework (Fig. 1c). A further complication is the potential for the resultant BCP radical intermediate to add into a second equivalent of the strained [1.1.1]propellane substrate, leading to BCP oligomerization. Although the rates of these elementary steps are not known in the literature, we recognized that the markedly different reactivity of BCP radicals compared to alkyl radicals[26] might enable differential reactivity with respect to both [1.1.1] propellane capture (desired in the first bond-forming step, but not the second) and capture of the copper catalyst (desired of the BCP radical but not the photo-generated alkyl radical). Importantly, if selectivity could be achieved, the radicophilic nature of [1.1.1]propellane might enable the use of numerous classes of radical precursors, while the copper catalyst might simultaneously allow several types of *N*-, *P*- and *S*-nucleophiles to be employed, thereby demonstrating the synthetic utility of the transformation to access a diverse array of molecular architectures (Fig. 1d).

A plausible mechanism for the proposed three-component coupling is shown in Fig. 2a. Excitation of photocatalyst $Ir(ppy)_3$ (**1**) (ppy = 2-phenylpyridinato) is known to generate the long-lived triplet excited state $^*Ir^{III}$ complex **2** (lifetime $\tau = 1.9$ μs)[27]. This excited-state complex is a strong reductant ($E_{1/2}^{red}[Ir^{IV}/^*Ir^{III}] = -1.81$ V vs. SCE in acetonitrile)[28] and should readily reduce iodonium dicarboxylate **3** ($E_{pc}[\mathbf{3}/\mathbf{3}^{\bullet-}] = -0.82$ V vs. SCE in acetonitrile) to generate alkyl radical **4** upon CO_2 extrusion[29]. This species would then undergo subsequent radical addition to [1.1.1]propellane (**5**) to generate the resultant BCP radical **6**. Radical interception with nucleophile-ligated copper complex **7** would thereafter generate the formal Cu^{III} complex **8**, which is poised to undergo reductive elimination[22,25] to forge the desired product **9**. However, we recognize that the exact electronic configuration of complex **8** may be somewhat more complicated than depicted above based on recent work from Lancaster and coworkers[30]. Nevertheless, reductive elimination by this complex should still be facile given its electron deficiency. Finally, ligation of another equivalent of *N*-nucleophile **10** would generate a new Cu^{I} species **11**, which upon oxidation by the Ir^{IV} form of the photocatalyst ($E_{1/2}^{red}[Ir^{IV}/Ir^{III}] = +0.77$ V vs SCE in acetonitrile)[28] would simultaneously complete both catalytic cycles.

From the outset, we recognized that controlling the relative rates of radical addition to [1.1.1]propellane versus the copper catalyst would be necessary to enable the desired three-component C–N coupling while minimizing the amount of two-component coupling and/or propellane oligomerization. To this end, we began our studies by evaluating a number of copper salts and ligands (Fig. 2b, also see Supplementary Information). To our delight, we found that the use of diketonate ligands, such as acetylacetonate (acac), enabled efficient formation of the desired three-component product with minimal quantities of the two-component decarboxylative C–N coupled product observed. Interestingly, oligomerization does not appear to be a major side reaction in this three-component coupling, with again, only trace amounts of poly-BCP products being observed. The differential reactivity of BCP radical **6** compared to the substrate alkyl radicals (such as **4**), which is critical to ensuring this three-component coupling, has been previously documented and might be attributed to the substantial *s*-character of this and other alkyl bridgehead radicals[31–33]. To probe this hypothesis, we examined radical precursors that generate alkyl radicals with similar *s*-character (Fig. 2c, also see Supplementary Information). Interestingly, a clear trend is observed demonstrating that as the *s*-character of the radical increases, the proportion of two-component coupling concomitantly increases (see refs. [31–33] for a discussion of radical *s*-character in pertinent systems). As a corollary, it would further appear that an increase in *s*-character favors radical addition to copper instead of [1.1.1] propellane. This interesting trend has not, to the best of our knowledge, been documented in the realm of copper catalysis and is under further investigation in our lab.

Following our initial optimization studies, we began to evaluate the scope of this three-component coupling for a range of carboxylic acids (via iodonium dicarboxylates, generated without purification) as radical precursors with 7-bromo-4-azaindole as the prototypical *N*-nucleophile. As can be seen in Fig. 3, we found that a variety of alkyl acid structural inputs were amenable to this decarboxylative multi-component coupling, including primary (**13**, 50% yield) and acyclic secondary (**14** and **15**, 60% and 77% yield, respectively) substrates, as well as secondary carboxylates appended to cyclic frameworks (4–7 membered rings, **16**–**22**, 45–72% yield). Furthermore, we have found that tertiary carboxylates readily undergo addition to [1.1.1] propellane to give the desired three-component products that bear vicinal quaternary substituted centers in good yields (**23**–**30**, 50–80% yield). Notably, this decarboxylative coupling platform enables access to structures bearing pharmaceutically relevant aliphatic heterocycles, such as oxetanes (**24**), azetidines (**13**, **16**, and **25**), pyrrolidines (**19**), and piperidines (**20** and **28**). Having established that a wide array of carboxylic acid structural formats are suitable electrophiles for this transformation, we next sought to expand the scope of radical precursors beyond that of carboxylic acids. In so doing, we found that activated alkyl bromides, such as α-bromo carbonyls and benzylic bromides, were viable radical precursors, providing functionalized BCP products in modest to excellent yields (**31**–**34**, 46–85% yield), in line with results obtained by both the Anderson[5] and Aggarwal[34] groups in similar radical additions to strained sigma bonds. Furthermore, we also found that amino-trifluoromethylation of [1.1.1]propellane can be efficiently achieved using commercially available Togni reagent II (**35**, 68% yield). Notably, while control experiments with other radical precursors revealed that both light and photocatalyst were necessary for efficient product formation, 1,3-amino-trifluoromethylation is achieved efficiently in the dark with the desired product formed in only a matter of minutes (see Supplementary Information for details). Finally, thiosulfonates were also found to be viable electrophiles, generating the amino-sulfone adduct **36** with useful efficiency (41% yield). It is important to consider that the capacity to implement multiple classes of radical precursors should render this three-component coupling protocol valuable across a number of areas of chemical synthesis and medicinal chemistry.

We next turned our attention to the scope of the *N*-nucleophile component in this new BCP-MCR protocol (Fig. 4). To our delight, nearly every class of medicinally relevant *N*-heterocycles, including azaindoles (**37**–**39**, 60–75% yield), indazoles (**40** and **41**, 72% and 64% yield, respectively), benzimidazoles (**42**, 81% yield), azaindazoles (**43** and **44**, 54% and 46% yield, respectively), indoles (**45** and **46**, 68% and 55% yield, respectively), carbazoles (**47** and **48**, 70% and 69% yield, respectively), pyrroles (**49** and **50**, 53% and 62% yield, respectively), pyrazoles (**51**, 55% yield), and oxazaindoles (**52**, 65% yield) can be successfully employed to deliver the desired products in good to excellent efficiency. As further shown in Fig. 4, this three-component C–N coupling method is not limited to the cross-coupling of *N*-heterocycles. Under standard or slightly modified conditions, a variety of other *N*-nucleophiles, including amides (**53** and **54**, 52% and 60%, respectively), anilines (**55**–**57**, 62–80% yield), imines (**58**, 80% yield), and sulfonamides (**59** and **60**, 48% and 50% yield, respectively) were found to participate readily in this multi-component reaction. Notably, functional groups including nitriles (**46**, 55% yield), aryl bromides (**37**, 75% yield) and ketones (**50**, 62% yield) were readily tolerated, a useful feature with respect to further synthetic manipulation. Furthermore, regioselectivity could be achieved for a substrate bearing multiple nucleophilic nitrogen sites (see Supplementary Information, substrate S5). Remarkably, we were

also able to demonstrate that *P*- and *S*-nucleophiles were competent in this three-component platform, allowing access to a broad array of chemical diversity under a single reactivity platform (**61**–**63**, 33%–67% yield. See Supplementary Information for further examples).

To demonstrate the synthetic utility of this new MCR, we sought to apply it to the late-stage modification of several readily available natural products and pharmaceuticals. As can be seen in Fig. 5a, direct installation of an azaindole-bearing BCP unit onto several commercial steroid systems was possible in this context, enabling single-step access to vicinal quaternary centers within multicyclic products in synthetically useful yields (**64** and **65**, 39 and 52% yield, respectively). Furthermore, modification of the pharmaceutical gemfibrozil was also possible, giving product **66** in 70% yield.

Carbocyclic aryl rings are major sites of metabolic action by cytochrome P450 (CYP) enzymes, and therefore isosteric replacement of such motifs with BCPs, which are less susceptible to oxidative degradation, has the potential to drastically reduce compound clearance and increase metabolic half-life[14]. With this in mind, we sought to synthesize and test the in vitro metabolic stability of MCR products **67** and **69**, which constitute two bicyclo[1.1.1]pentane analogues of the known pharmaceutical agents, indoprofen and leflunomide respectively. To this end, indoprofen analogue **67** was prepared via our three-component coupling protocol, followed by an ester hydrolysis step to generate the desired carboxylic acid in excellent overall yield (86% yield over two steps). Next, we applied our conditions for amino-trifluoromethylation using *tert*-butyl carbamate as the nucleophile to enable gram-scale synthesis of trifluoromethyl bicyclo[1.1.1]pentylamine hydrochloride **68** in only two steps and good yield (60% combined yield). Acylation of the amine using a commercially available acid chloride then gave leflunomide analogue **69** in short order, demonstrating the practicality of **68** as a molecular building block. We next assessed the in vitro metabolic stability of analogues **67** and **69** for comparison to their parent pharmaceuticals. Intriguingly, we found that compound **67** has similar pharmacokinetic properties to indoprofen. Remarkably, however, the corresponding leflunomide analogue **69** was found to exhibit markedly improved metabolic stability, with the BCP-variant demonstrating significantly longer half-life in both rat and human liver microsomes than the parent leflunomide.

This methodology is amenable to a variety of radical precursors as well as multiple classes of *N*-, *P*-, and *S*-nucleophiles, allowing single-step access to a diverse array of products. Analogues of known drugs have been prepared in short order and their properties measured in comparison to their aromatic counterparts, demonstrating marked improvements in metabolic stability in the case of leflunomide.

Data availability

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

Online content

Any methods, additional references, Nature Research 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/s41586-020-2060-z.

1. Dömling, A., Wang, W. & Wang, K. Chemistry and biology of multicomponent reactions. *Chem. Rev.* **112**, 3083–3135 (2012).
2. Mykhailiuk, P. K. Saturated bioisosteres of benzene: where to go next? *Org. Biomol. Chem.* **17**, 2839–2849 (2019).
3. Kanazawa, J. & Uchiyama, M. Recent advances in the synthetic chemistry of bicyclo[1.1.1] pentane. *Synlett* **30**, 1–11 (2019).
4. Kanazawa, J., Maeda, K. & Uchiyama, M. Radical multicomponent carboamination of [1.1.1] propellane. *J. Am. Chem. Soc.* **139**, 17791–17794 (2017).
5. Nugent, J., Arroniz, C., Shire, B. R., Sterling, A. J., Pickford, H. D., Wong, M. L. J., Mansfield, S. J., Caputo, D. F. J., Owen, B., Mousseau, J. J., Duarte, F. & Anderson, E. A. A general route to bicyclo[1.1.1]pentanes through photoredox catalysis. *ACS Catal.* **9**, 9568–9574 (2019).
6. Kondo, M., Kanazawa, J., Ichikawa, T., Shimokawa, T., Nagashima, Y., Miyamoto, K. & Uchiyama, M. Silaboration of [1.1.1]propellane to provide a storable feedstock for bicyclo[1.1.1]pentane derivatives. *Angew. Chem. Int. Ed.* (2019) Accepted Author Manuscript. https://doi.org/10.1002/anie.201909655.
7. Kaszynski, P. & Michl, J. A practical photochemical synthesis of bicyclo[1.1.1]pentane-l,3-dicarboxylic acid *J. Org. Chem.* **53**, 4593–4594 (1988).
8. Caputo, D. F. J., Arroniz, C., Dürr, A. B., Mousseau, J. J., Stepan, A. F., Mansfield, S. J. & Anderson, E. A. Synthesis and applications of highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes. *Chem. Sci.* **9**, 5295–5300 (2018).
9. Trongsiriwat, N., Pu, Y., Nieves-Quinones, Y., Shelp, R. A., Kozlowski, M. C. & Walsh, P. J. Reactions of 2-aryl-1,3-dithianes and [1.1.1]propellane. *Angew. Chem. Int. Ed.* **58**, 13416–13420 (2019).
10. Gianatassio, R., Lopchuk, J. M., Wang, J., Pan, C.-M., Malins, L. R., Prieto, L., Brandt, T. A., Collins, M. R., Gallego, G. M., Sach, N. W., Spangler, J. E., Zhu, H., Zhu, J. & Baran, P. S. Strain-release amination. *Science* **351**, 241–246 (2016).
11. Makarov, I. S., Brocklehurst, C. E., Karaghiosoff, K., Koch, G. & Knochel, P. Synthesis of bicyclo[1.1.1]pentane bioisosteres of internal alkynes and *para*-disubstituted benzenes from [1.1.1]propellane. *Angew. Chem. Int. Ed.* **56**, 12774–12777 (2017).
12. Hughes, J. M. E., Scarlata, D. A., Chen, A. C.-Y., Burch, J. D. & Gleason, J. L. Aminoalkylation of [1.1.1]propellane enables direct access to high-value 3-alkylbicyclo[1.1.1]pentan-1-amines. *Org. Lett.* **21**, 6800–6804 (2019).
13. Wiberg, K. B. & Waddell, S. T. Reactions of [1.1.1]propellane. *J. Am. Chem. Soc.* **112**, 2194–2216 (1990).
14. Stepan, A. F. et al. Application of the bicyclo[1.1.1]pentane motif as a nonclassical phenyl ring bioisostere in the design of a potent and orally active γ-secretase inhibitor. *J. Med. Chem.* **55**, 3414–3424 (2012).
15. Measom, N. D., Down, K. D., Hirst, D. J., Jamieson, C., Manas, E. S., Patel, V. K. & Somers, D. O. Investigation of a bicyclo[1.1.1]pentane as a phenyl replacement within an $LpPLA_2$ inhibitor. *ACS Med. Chem. Lett.* **8**, 43–48 (2017).
16. Fischer, C., Bogen, S., Childers, M. L., Llinas, F. X. F., Ellis, J. M., Esposite, S., Hoffman D. M., Huang, C., Kattar, S., Kim, A. J., Lampe, J. W., Machacek, M. R., Mcmasters, D. R., Parker, D. L. Jr, Reutershan, M., Sciammetta, N., Shao, P. P., Sloman, D. L., Sun, W., Ujjainwalla, F., Wu, Z., Gibeau, C. Patent WO/2016/089830 A1 (2016).
17. Sidrauski, C., Pliushchev, M., Frost, J. M., Black, L. A., Xu, X., Sweis, R. F., Shi, L., Zhang, Q. I., Tong, Y., Hutchins, C. W., Chung, S., Dart, M. J. Patent WO/2017/193030 A1 (2017).
18. Kaszynski, P., McMurdie, N. D. & Michl, J. Synthesis of doubly bridgehead substituted bicyclo[1.1.1]pentanes. Radical transformations of bridgehead halides and carboxylic acids. *J. Org. Chem.* **56**, 307–316 (1991).
19. Twilton, J., Le, C., Zhang, P., Shaw, M. H., Evans, R. W. & MacMillan, D. W. C. The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **1**, 0052 (2017).
20. Kalyani, D., McMurtrey, K. B., Neufeldt, S. R. & Sanford, M. S. Room-temperature C–H arylation: merger of Pd-catalyzed C–H functionalization and visible-light photocatalysis *J. Am. Chem. Soc.* **133**, 18566–18569 (2011).
21. Primer, D. N. & Molander, G. A. Enabling the cross-coupling of tertiary organoboron nucleophiles through radical-mediated alkyl transfer *J. Am. Chem. Soc.* **139**, 9847-9850 (2017).
22. Le, C., Chen, T. Q., Liang, T., Zhang, P. & MacMillan, D. W. C. A radical approach to the copper oxidative addition problem: trifluoromethylation of bromoarenes. *Science* **360**, 1010–1014 (2018).
23. Mao, R., Frey, A., Balon, J. & Hu, X. Decarboxylative C(sp^3)–N cross-coupling via synergetic photoredox and copper catalysis. *Nat. Catal.* **1**, 120–126 (2018).
24. Zhao, W., Wurz, R. P., Peters, J. C., & Fu, G. C. Photoinduced, copper-catalyzed decarboxylative C–N coupling to generate protected amines: an alternative to the Curtius rearrangement. *J. Am. Chem. Soc.* **139**, 12153–12156 (2017).
25. Liang, Y., Zhang, X. & MacMillan, D. W. C. Decarboxylative sp^3 C–N coupling via dual copper and photoredox catalysis. *Nature* **559**, 83–88 (2018).
26. Banks, J. T., Ingold, K. U., Della, E. W. & Walton, J. C. Bicyclo[1.1.1]pent-1-yl: a tertiary radical with enhanced reactivity. *Tetrahedron Lett.* **37**, 8059–8060 (1996).
27. Dixon, I. M., Collin, J., Sauvage, J., Flamigni, L., Encinas, S. & Barigelletti, F. A family of luminescent coordination compounds: iridium(III) polyimine complexes. *Chem. Soc. Rev.* **29**, 385–391 (2000).
28. Nacsa, E. D. & MacMillan, D. W. C. Spin-center shift-enabled direct enantioselective α-benzylation of aldehydes with alcohols *J. Am. Chem. Soc.* **140**, 3322–3330 (2018).
29. Minisci, F., Vismara, E., Fontana, F. & Barbosa, M. C. N. A new general method of homolytic alkylation of protonated heteroaromatic bases by carboxylic acids and iodosobenzene diacetate. *Tetrahedron Lett.* **30**, 4569–4572 (1989).
30. DiMucci, I. M., Lukens, J. T., Chatterjee, S., Carsch, K. M., Titus, C. J., Lee, S. J., Nordlund, D., Betley, T. A., MacMillan, S. N. & Lancaster, K. M. The myth of d^8 copper(III) *J. Am. Chem. Soc.* **141**, 18508–18520 (2019).
31. Walton, J. C. Bridgehead radicals. *Chem. Soc. Rev.* **21**, 105–112 (1992).
32. Fiorentino, M., Testaferri, L., Tiecco, M. & Troisi, L. Structural effects on the reactivity of carbon radicals in homolytic aromatic substitution. Part 4. The nucleophilicity of bridgehead radicals. *J. Chem. Soc., Perkin Trans.* **2**, 87–93 (1977).
33. Della, E. W., Cotsaris, E., Hine, P. T., & Pigou, P. E. ^{13}C Spectral parameters of some polycyclic hydrocarbons. II Bicyclo[3,1,1]heptane, tricyclo[3,1,1,$0^{3,6}$]heptane, tricyclo[3,3,0,$0^{2,6}$]octane and bicyclo[1,1,1]pentane *Aust. J. Chem.* **34**, 913–916 (1981).
34. Silvi, M. & Aggarwal, V. K. Radical addition to strained σ-bonds enables the stereocontrolled synthesis of cyclobutyl boronic esters *J. Am. Chem. Soc.* **141**, 9511–9515 (2019).

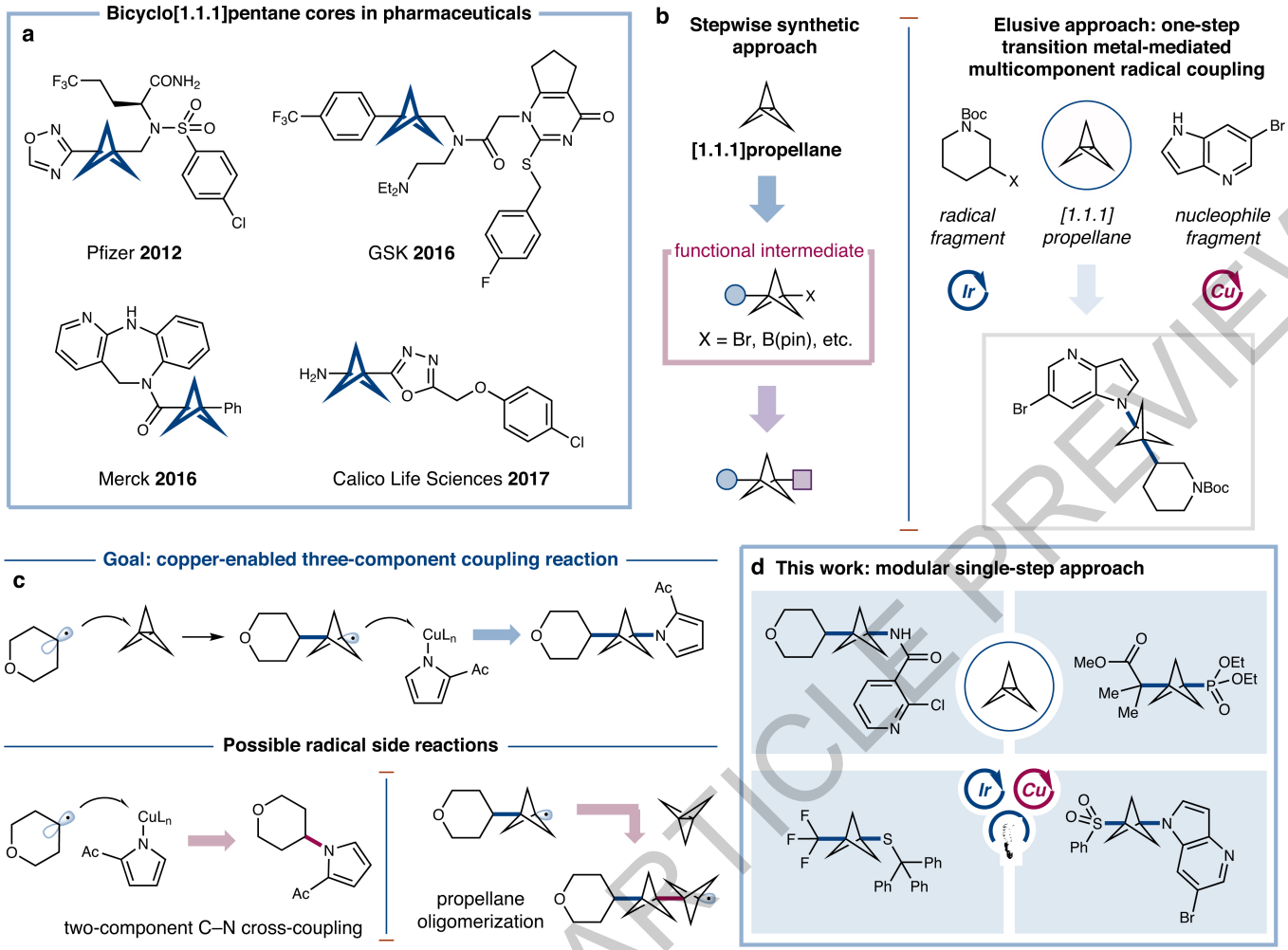
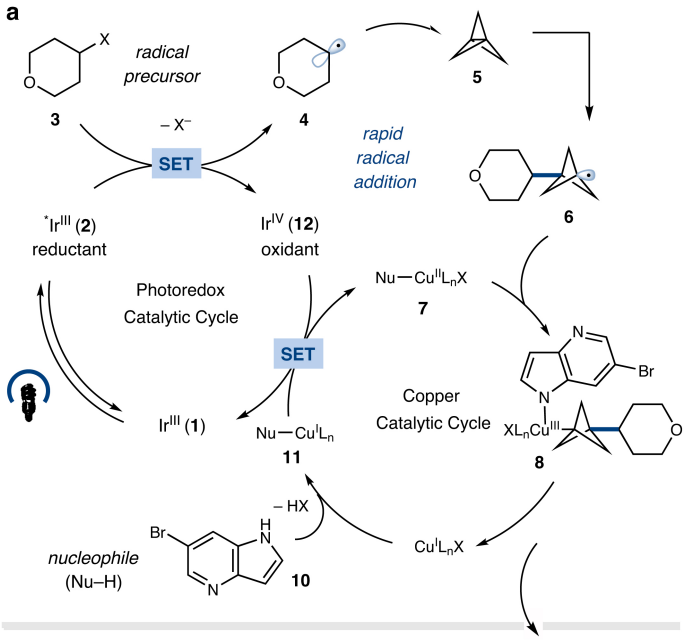
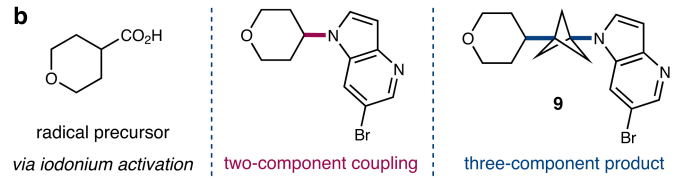


Fig. 1 | Direct three-component coupling of [1.1.1]propellane. a, Examples of the BCP core appearing in bioactive compounds. **b**, Typical approaches to BCP structures require stepwise synthetic sequences. In contrast, a multicomponent approach might enable single-step access to complex BCP molecules. **c**, A three-component coupling enabled by a sequence of radical addition and BCP radical capture could be synthetically powerful if selectivity over two-component coupling and oligomerization could be achieved. **d**, A photoredox-copper platform enables single-step access to an array of diverse products. Ph, phenyl; Et, ethyl; (pin), pinacolato; Boc, *tert*-butoxycarbonyl; Ac, acetyl; L, ligand; Me, methyl.





copper source[a]	ligand[a]	two-component coupling[b]	three-component product[b]
CuTC	BPhen	10%	8%
$Cu(OAc)_2$	BPhen	10%	10%
$Cu(acac)_2$	BPhen	trace	58%
$Cu(acac)_2$	none	trace	64%
$Cu(OAc)_2$	acetylacetone	trace	56%
$Cu(acac)_2$[c]	none	trace	**80%**

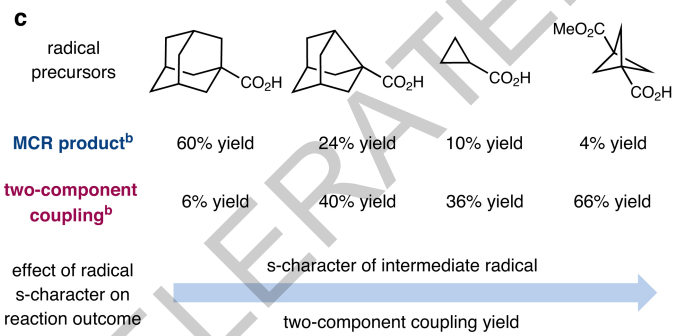
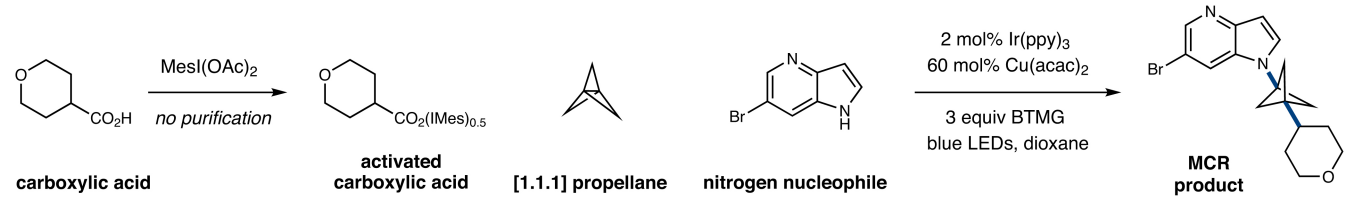
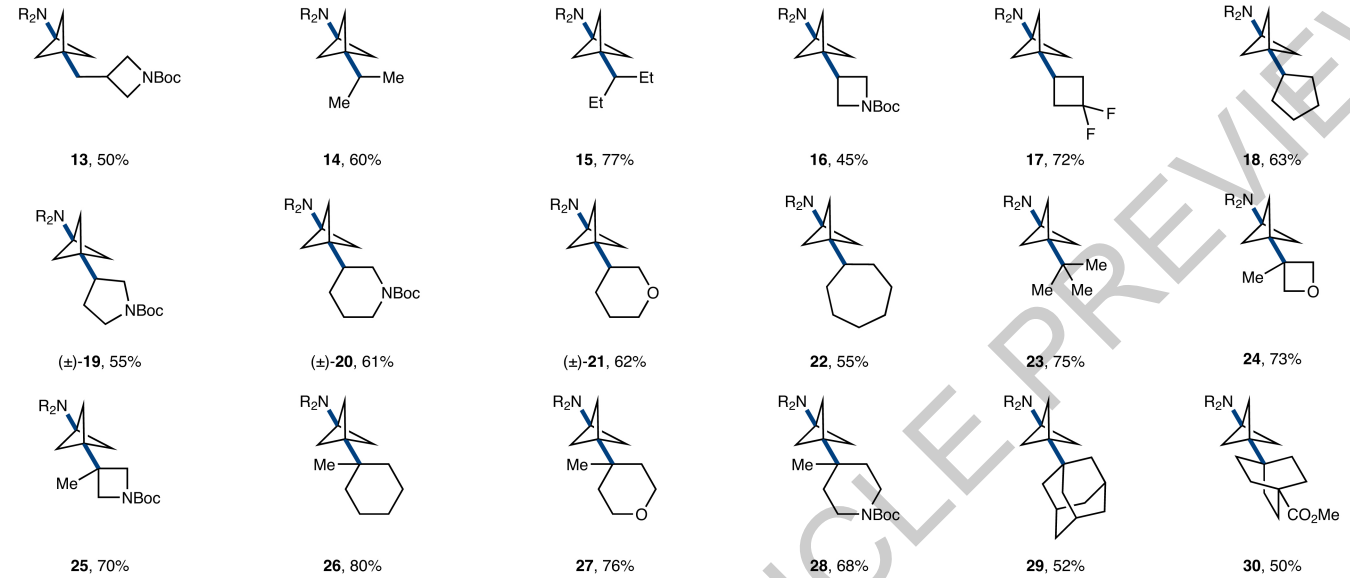


Fig. 2 | Plausible mechanism and catalyst evaluation for three-component coupling. a, Reductive radical generation gives an alkyl radical (**4**) which can be intercepted by [1.1.1]propellane (**5**) to give BCP radical **6**. Trapping by an appropriate copper species, such as **7**, followed by reductive elimination would give the desired three-component BCP product **9**. **b**, Evaluation of copper salts and ligands to achieve the desired reactivity revealed that copper (II) acetoacetonate (acac) is the optimal catalyst. **c**, Studies on the effect of radical *s*-character reveal that selectivity trends with this characteristic. [a]30 mol% of each copper salt and ligand was used unless otherwise specified. [b]^{1}H-NMR yields. [c]60 mol% $Cu(acac)_2$ used. SET, single-electron transfer; Nu, *N*-nucleophile; TC, thiophene-2-carboxylate; BPhen, bathophenanthroline.



carboxylic acid scope



alternative radical precursors[a]

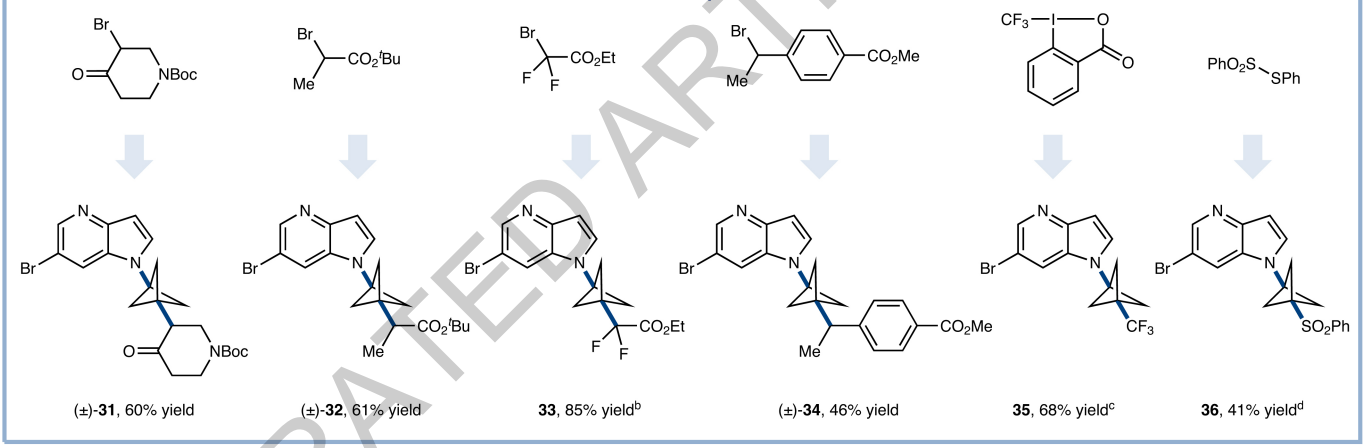


Fig. 3 | Radical precursor scope for three-component coupling. Numerous radical precursors can be utilized in this transformation. All yields are isolated unless otherwise noted. Experiments typically run with 1 eq. of nucleophile, 1.5 eq. of [1.1.1]propellane, and 2 eq. of iodonium dicarboxylate; however, alternative stoichiometry is optimal in some cases. See Supplementary Information for exact experimental conditions. [a]Conditions vary slightly for each class of radical precursor. See Supplementary Information for exact reaction conditions. [b]^{1}H-NMR yield. [c]30 mol% $Cu(acac)_2$, no light (see SI). [d]THF as solvent. NR_2, 6-bromo-4-azaindole; Mes, mesityl; BTMG, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine; ^{t}Bu, *tert*-butyl.

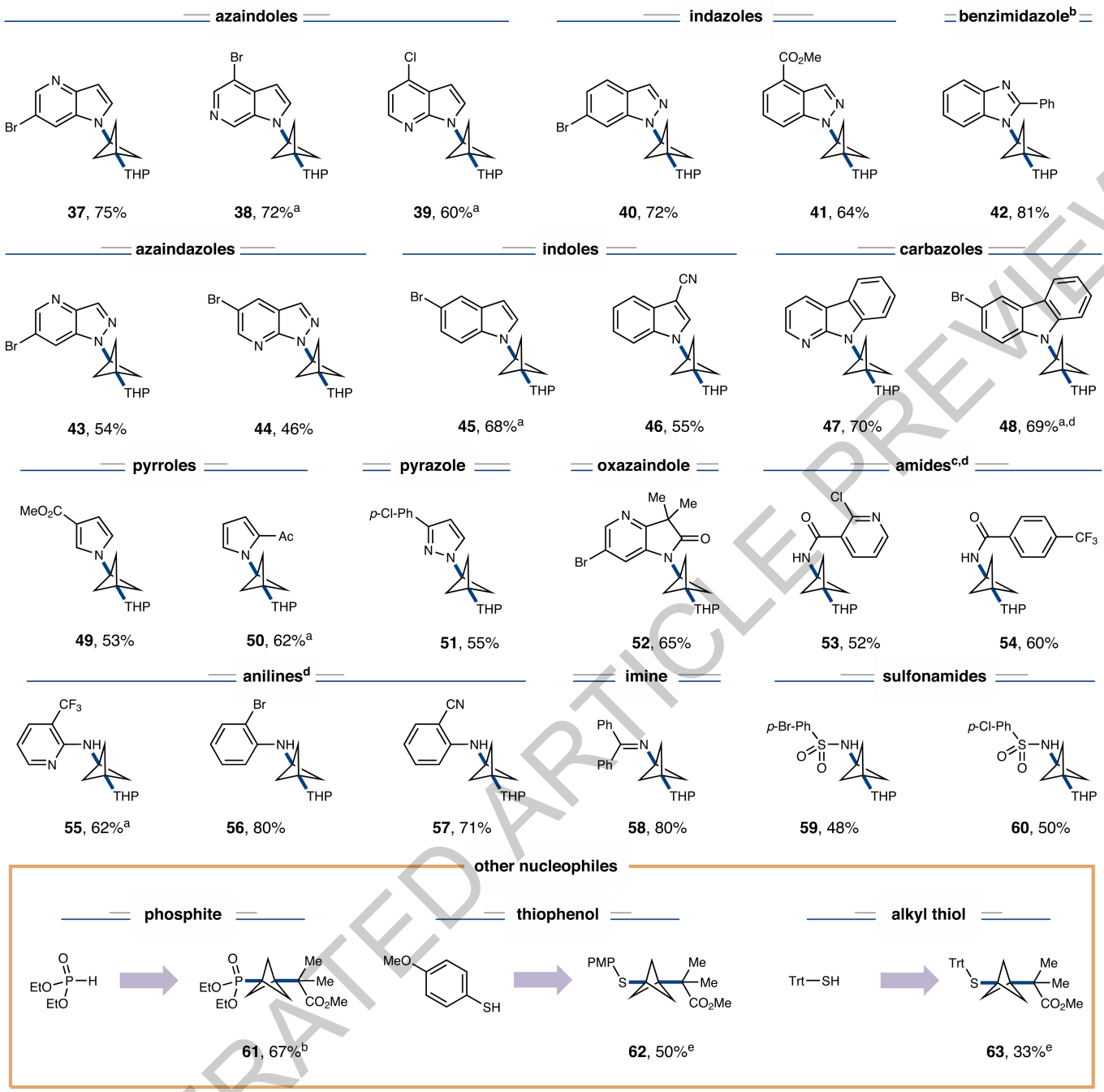


Fig. 4 | Nucleophile scope of three-component coupling. All yields are isolated, and conditions are similar to those in Fig. 3 unless otherwise noted. [a] ^{1}H-NMR yields. Isolated yields for these compounds typically 10–15% lower, see Supplementary Information for details. [b]$Cu(TMHD)_2$ used instead of $Cu(acac)_2$. [c]Cu(II) *bis*-(2-isobutyrylcyclohexanone) complex used instead of $Cu(acac)_2$. [d]BTTP used as base instead of BTMG. [e]UPLC yields. THP, 4-tetrahydropyranyl; Trt, trityl; TMHD, 2,2,6,6-tetramethyl-3,5-heptanedionate; BTTP, *tert*-butylimino-tri(pyrrolidino)phosphorane.

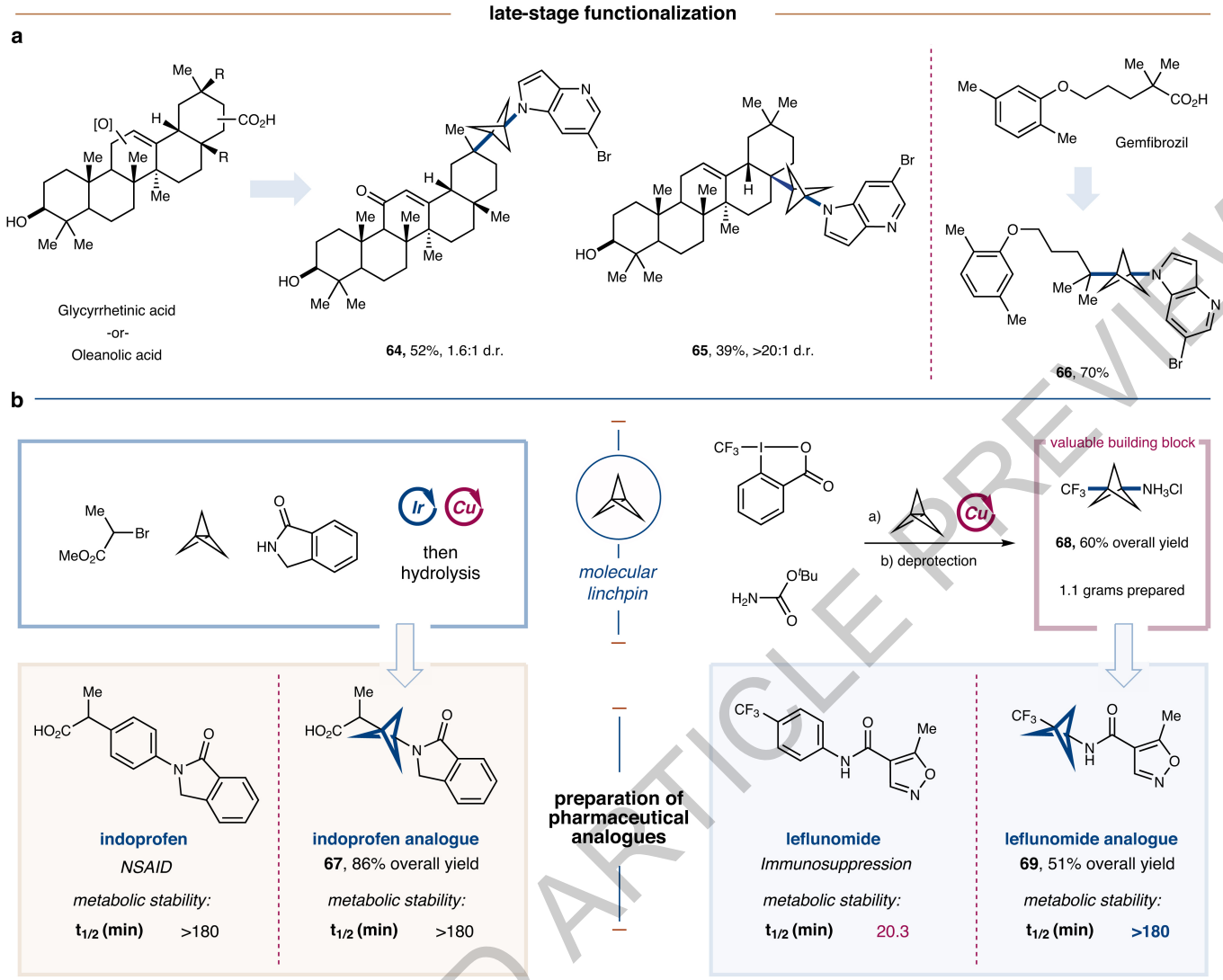


Fig. 5 | Rapid functionalization of drugs and natural products and preparation of pharmaceutical analogues. a, Drug and natural product carboxylic acids can be leveraged in this three-component coupling for rapid diversification. **b**, This protocol can also be applied to the rapid preparation of pharmaceutical analogues, such as compounds **67** and **69**. All yields are isolated, see Supplementary Information for exact conditions.

Data availability

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

Acknowledgements Research reported in this publication was supported by the NIH National Institute of General Medical Sciences (1R35GM134897-01) and gifts from Merck, Bristol-Myers Squibb, Eli Lilly, and Janssen Research and Development LLC. We acknowledge Y. Liang for discussions.

Author contributions X.Z., R.T.S., C.L., and S.J.M. performed and analysed the experiments. X.Z., R.T.S., C.L. and D.W.C.M. designed the experiments. S.J.M., B.T.S. and N.I.C. provided intellectual contributions. R.T.S., X.Z., and D.W.C.M. prepared this manuscript.

Competing interests The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41586-020-2060-z.

Correspondence and requests for materials should be addressed to D.W.C.M.