Copper-mediated synthesis of drug-like bicyclopentanes

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Multicomponent reactions are relied on 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 become valuable as 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]. These structures are often 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 then transformed to the requisite polysubstituted BCP compounds via a range of synthetic sequences that traditionally involve multiple chemical steps. Although this approach has been effective so far, a multicomponent reaction that enables single-step access to complex and diverse polysubstituted drug-like BCP products would be more time efficient compared to current stepwise approaches. Here we report a one-step three-component radical coupling of [1.1.1]propellane to afford diverse functionalized bicyclopentanes using various radical precursors and heteroatom nucleophiles via a metallaphotoredox catalysis protocol. This copper-mediated reaction operates on short timescales (five minutes to one hour) across multiple (more than ten) nucleophile classes and can accommodate a diverse array of radical precursors, including those that generate alkyl, α-acyl, trifluoromethyl and sulfonyl radicals. This method has been used to rapidly prepare BCP analogues of known pharmaceuticals, one of which is substantially more metabolically stable than 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). Therefore it is not surprising that the pharmaceutical sector has begun to extensively investigate BCP-containing leads in recent years[14–17] (Fig. 1a). From a synthetic standpoint, these compounds have largely been prepared by the opening of [1.1.1] propellane, most often via multi-step chemical sequences, to install and manipulate functional handles at the BCP bridgehead positions[18] (Fig. 1b). Radical addition to [1.1.1]propellane is well established and perhaps the most widely used mechanism of BCP functionalization; numerous examples of chain reactions are reported[13]. However, it has also been demonstrated that strong nucleophiles—such as turbo Grignard and turbo amide reagents—can be used to open the internal propellane bond, leading to BCP-organometallic reagents that can be subsequently used in transition-metal-catalysed cross-coupling reactions (via a two-step difunctionalization protocol)[11,12]. Although these multi-step approaches have been used 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 considerable value to medicinal and process chemists in various industries. Furthermore, although previous work demonstrated a single-step carboamination multicomponent reaction of [1.1.1]propellane via radical addition to azodicarboxylates[4], a modular multicomponent reaction approach to [1.1.1]propellane difunctionalization that is amenable to a diverse series of structural inputs could be generically adopted and applied 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 laboratory 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 by numerous classes of organic radicals[13], we recently wondered whether it might be possible

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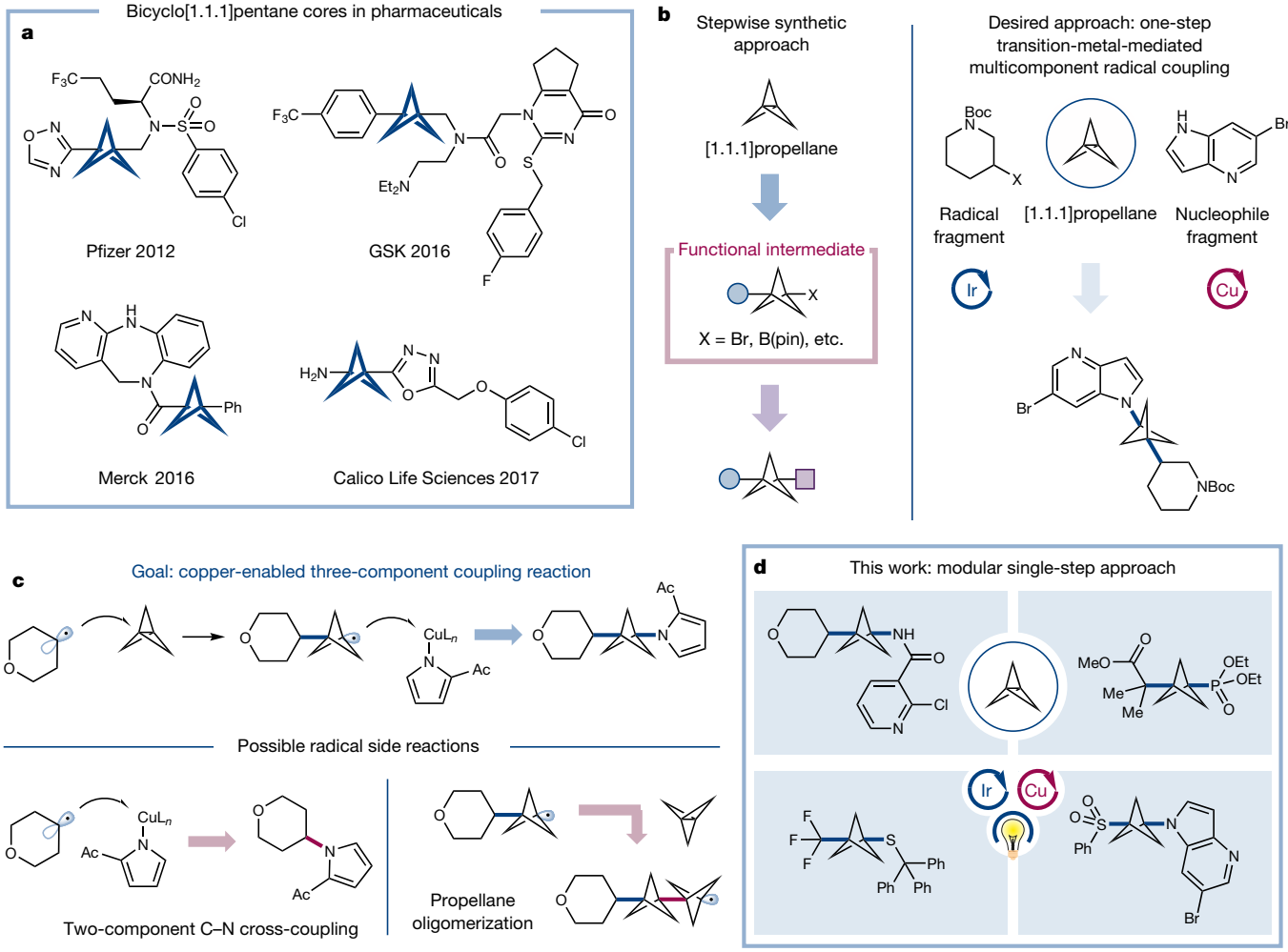
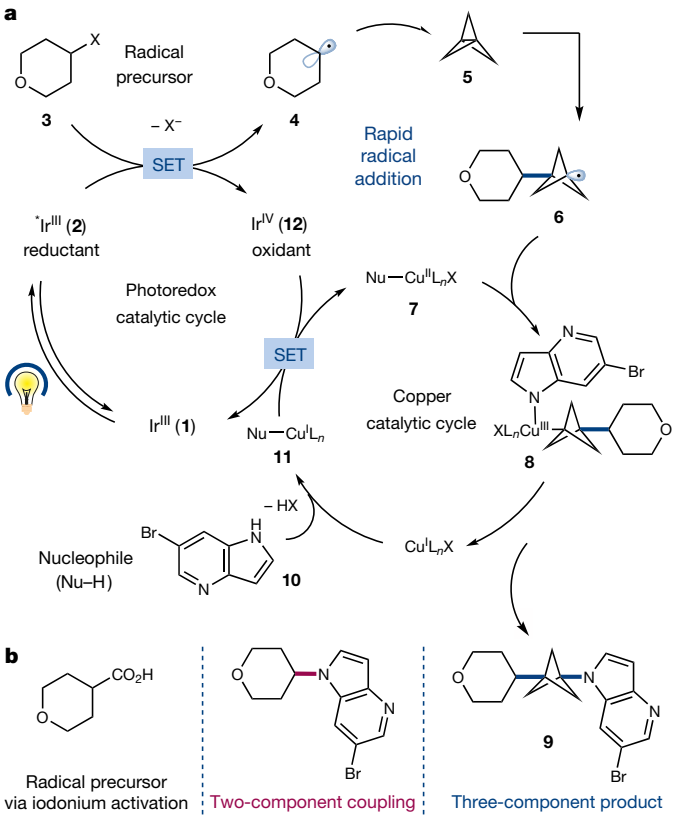


Fig. 1 | Direct three-component coupling of [1.1.1]propellane. a, Examples of the BCP core appearing in bioactive compounds from Pfizer (2012), GSK (2016), Merck (2016) and Calico Life Sciences (2017); dates indicate year of publication or patent registration. **b**, Typical approaches to BCP structures require stepwise synthetic sequences. By 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. The blue shapes are *p* orbitals containing alkyl radicals. **d**, A photoredox-copper platform enables single-step access to an array of diverse products. Ac, acetyl; Boc, *tert*-butoxycarbonyl; Et, ethyl; L_n, ligand (where *n* is an integer); Me, methyl; Ph, phenyl; pin, pinacolato.

to intercept the 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 key to the success of this multicomponent reaction pathway would be the selective addition of the photo-generated alkyl radical to [1.1.1]propellane instead of its direct addition to the copper centre, which would thus 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 be added to 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, whereas 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 the 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 (the half-wave potential is $E_{1/2}^{red}[Ir^{IV}/^*Ir^{III}] = -1.81$ V versus the saturated calomel electrode (SCE) in acetonitrile)[28] and should readily reduce iodonium dicarboxylate **3** (the cathodic peak potential is $E_{pc}[\mathbf{3}/\mathbf{3}^{\bullet-}] = -0.82$ V versus 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, on the basis of recent work[30] we recognize that the exact electronic configuration of complex **8** may be more complicated than depicted above. 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 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



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%**

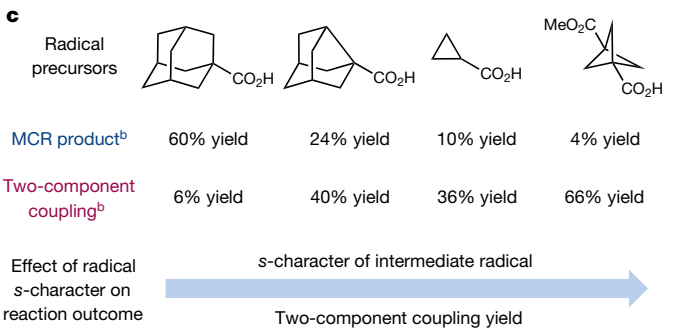


Fig. 2 | Plausible mechanism and catalyst evaluation for three-component coupling. a, Reductive radical generation gives an alkyl radical (**4**) which can be intercepted by [1.1.1]propellane (**5**) to give BCP radical **6**. Trapping by an appropriate copper species, such as **7**, followed by reductive 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. BPhen, bathophenanthroline; Nu, N-nucleophile; SET, single-electron transfer; TC, thiophene-2-carboxylate.

versus 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 or propellane oligomerization. To this end, we began our studies by evaluating several copper salts and ligands (Fig. 2b; see also Supplementary Information). We found that the use of diketonate ligands such as acetylacetonate (acac) enabled efficient formation of the desired three-component product, and minimal quantities of the two-component decarboxylative C–N coupled product were observed. Interestingly, oligomerization does not appear to be a major side reaction in this three-component coupling; again, only trace amounts of poly-BCP products were 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; see also 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 favours radical addition to copper instead of [1.1.1]propellane. This trend has not, to the best of our knowledge, been documented in the realm of copper catalysis and is under further investigation in our laboratory.

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 various alkyl acid structural inputs were amenable to this decarboxylative multicomponent 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 centres 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**). After establishing 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 doing so, 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[5,34] obtained 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, although control experiments with other radical precursors revealed that both light and a photocatalyst were necessary for efficient product formation, 1,3-amino-trifluoromethylation was 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.

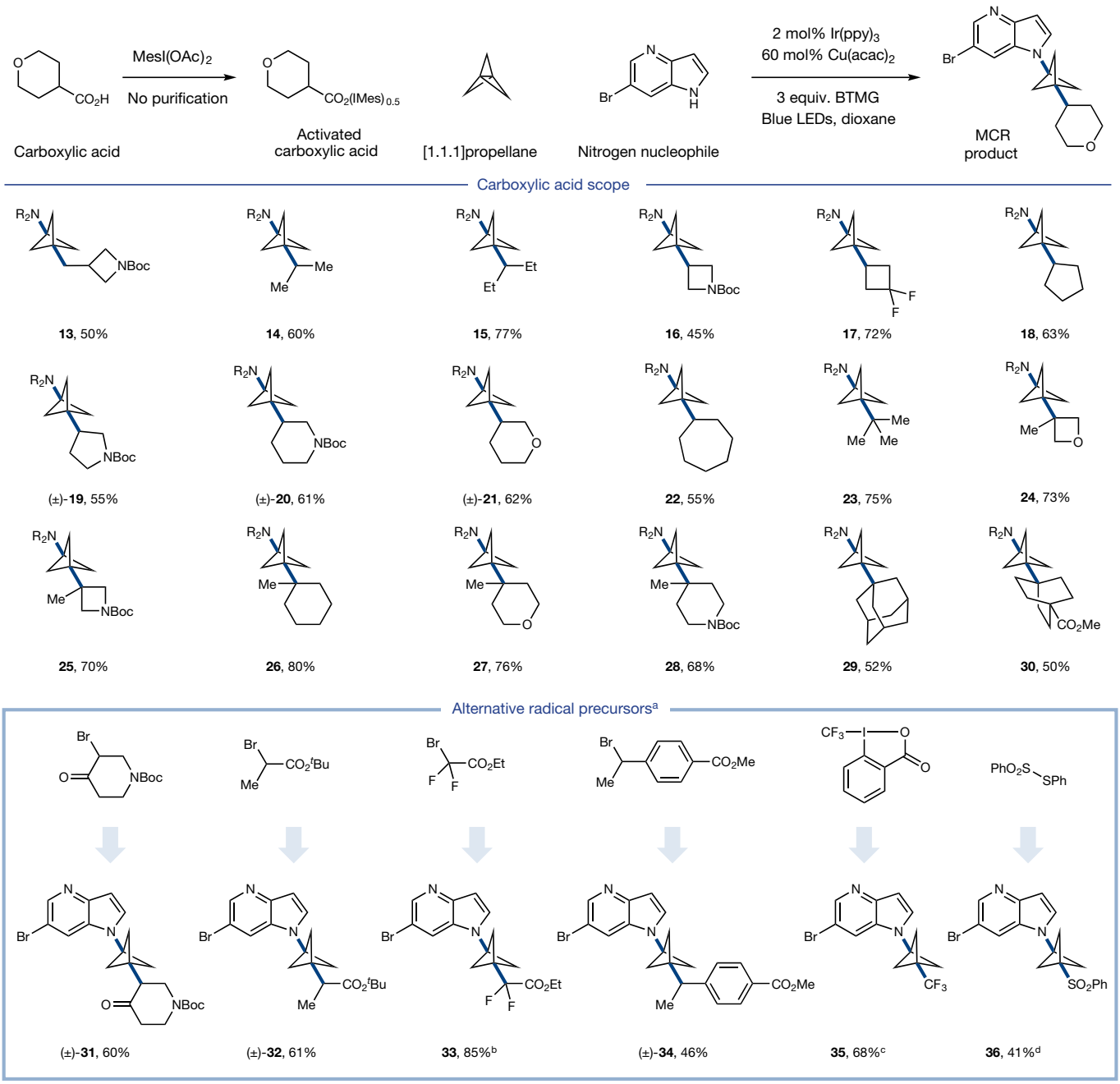


Fig. 3 | Radical precursor scope for three-component coupling. Numerous radical precursors can be used in this transformation. All yields (given as a percentage) are isolated unless otherwise noted. Experiments were typically run with 1 equiv. of nucleophile, 1.5 equiv. of [1.1.1]propellane and 2 equiv. 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]Yield by ^{1}H NMR. [c]30 mol% $Cu(acac)_2$, no light (see Supplementary Information). [d]THF as solvent. BTMG, 2-*tert*-butyl-1,1,3,3- tetramethylguanidine; Mes, mesityl; R_2N, 6-bromo-4-azaindole; ^{t}Bu, *tert*-butyl.

We next turned our attention to the scope of the N-nucleophile component in this BCP-multicomponent reaction protocol (Fig. 4). We found that 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 successfully 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, various 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 multicomponent 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

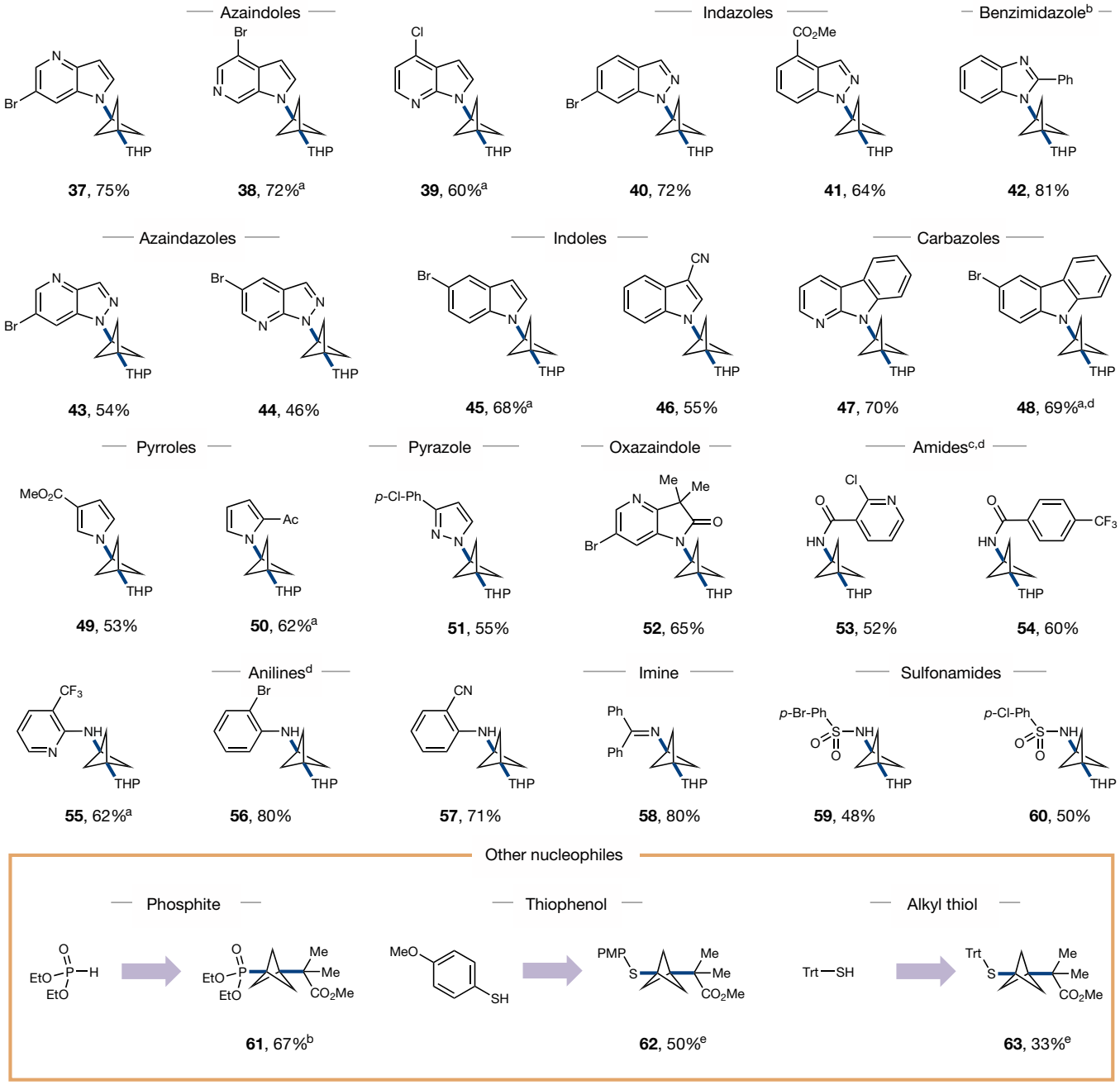


Fig. 4 | Nucleophile scope of three-component coupling. All yields are isolated, and conditions are similar to those in Fig. 3 unless otherwise noted. [a]Yields by ^{1}H NMR. Isolated yields for these compounds are typically 10–15% lower; see Supplementary Information for details. [b]$Cu(TMHD)_2$ used 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]Yields obtained from ultra performance liquid chromatography. BTTP, *tert*-butylimino-tri(pyrrolidino)phosphorene; PMP, *p*-methoxyphenyl; THP, 4-tetrahydropyranyl; TMHD, 2,2,6,6-tetramethyl-3,5-heptanedionate; Trt, trityl.

substrate bearing multiple nucleophilic nitrogen sites (see Supplementary Information, section 9). 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 multicomponent reaction, 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 centres 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 enzymes, and therefore isosteric replacement of such motifs with BCPs—which are less susceptible to oxidative degradation—has the potential to substantially reduce compound clearance and increase their metabolic half-life[14]. With this in mind, we sought to synthesize and test the in vitro metabolic stability of multicomponent reaction products **67** and **69**, which constitute bicyclo[1.1.1]pentane analogues of the known pharmaceutical agents indoprofen and leflunomide, respectively. To this end, the indoprofen analogue

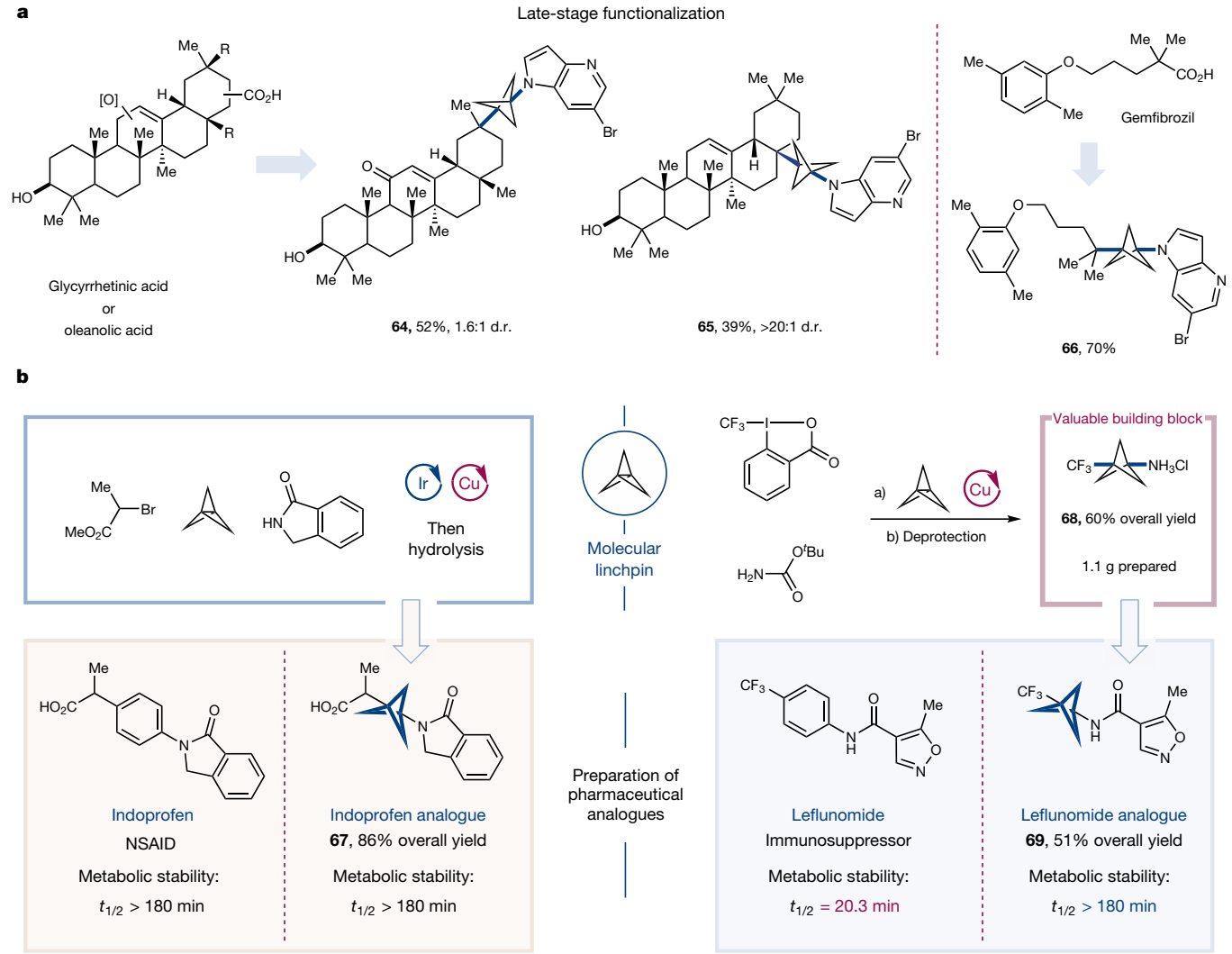


Fig. 5 | Rapid functionalization of drugs and natural products and preparation of pharmaceutical analogues. a, Drug and steroid natural product carboxylic acids can be leveraged for rapid diversification in this three-component coupling. **b**, This protocol can also be applied to the rapid preparation of pharmaceutical analogues, such as compounds **67** and **69**. Compound **68** was generated via a two-step sequence involving: a) our standard conditions for amino-trifluoromethylation; then b) acid deprotection of the Boc protecting group. All yields are isolated; see Supplementary Information for exact conditions. $t_{1/2}$, compound half-life.

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 the leflunomide analogue **69**, 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, and 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 a substantially longer half-life in both rat and human liver microsomes than the parent leflunomide.

This methodology is amenable to various radical precursors as well as multiple classes of N-, P- and S-nucleophiles, enabling single-step access to a diverse array of products. Analogues of known drugs were prepared and their properties measured in comparison to their aromatic counterparts, and in the case of leflunomide, demonstrated marked improvements in metabolic stability.

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.

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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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Competing interests The authors declare no competing interests.

Additional information

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