Article

General access to cubanes as benzene bioisosteres

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The replacement of benzene rings with sp^3-hybridized bioisosteres in drug candidates generally improves pharmacokinetic properties while retaining biological activity[1–5]. Rigid, strained frameworks such as bicyclo[1.1.1]pentane and cubane are particularly well suited as the ring strain imparts high bond strength and thus metabolic stability on their C–H bonds. Cubane is the ideal bioisostere as it provides the closest geometric match to benzene[6,7]. At present, however, all cubanes in drug design, like almost all benzene bioisosteres, act solely as substitutes for mono- or *para*-substituted benzene rings[1–7]. This is owing to the difficulty of accessing 1,3- and 1,2-disubstituted cubane precursors. The adoption of cubane in drug design has been further hindered by the poor compatibility of cross-coupling reactions with the cubane scaffold, owing to a competing metal-catalysed valence isomerization[8–11]. Here we report expedient routes to 1,3- and 1,2-disubstituted cubane building blocks using a convenient cyclobutadiene precursor and a photolytic C–H carboxylation reaction, respectively. Moreover, we leverage the slow oxidative addition and rapid reductive elimination of copper to develop C–N, C–C(sp^3), C–C(sp^2) and C–CF_3 cross-coupling protocols[12,13]. Our research enables facile elaboration of all cubane isomers into drug candidates, thus enabling ideal bioisosteric replacement of *ortho*-, *meta*- and *para*-substituted benzenes.

The substitution of a benzene group with an sp^3-hybridized bioisostere can produce drug candidates with improved compound properties[1,2]. Suitable bioisosteres emulate the size and the rigid steric relationship between substituents in the parent benzene unit, thus maintaining the activity while reducing the overall C(sp^2) character, which generally improves key pharmacokinetic properties such as solubility and metabolic stability[14]. Bicyclo[1.1.1]pentanes and cubanes are particularly privileged, as they are rigid and because their strained nature imparts high *s* character and thus bond strength on their C–H bonds[15]. Although bicyclo[1.1.1]pentanes are now routinely used in drug discovery, cubanes remain less explored despite being a better geometric match to benzene[6,7] (Fig. 1a). Furthermore, all cubanes in drug candidates, like most benzene bioisosteres, are either mono-substituted or bear linear exit vectors 180° apart, acting solely as substitutes for terminal or *para*-substituted phenyl rings. Although several bicycloalkanes have recently been explored as nonlinear benzene isosteres[16–23], their scarcity is a severe limitation for drug design given that over 170 approved drugs contain *ortho*- or *meta*-substituted benzene rings. 1,3-Disubstituted and 1,2-disubstituted cubanes are ideally suited to bridge this gap as they most closely emulate the size and spatial arrangement of the substituents in the parent benzenes.

Access to these nonlinear cubanes is hampered by protracted sequences towards the respective precursors (Fig. 1b). Eaton's linear dimethyl cubane-1,4-dicarboxylate, the most commercially available cubane-containing fragment, can be synthesized in eight steps on a laboratory scale and has been scaled up to the kilogram scale via a flow photoreactor[24–26]. By contrast, the nonlinear 1,3- and 1,2-dicarboxylate isomers both require eight additional steps, starting from the expensive 1,4-diester[27].

Moreover, the adoption of cubanes in medicinal chemistry is limited by the lack of cross-coupling reactions. All cubane-containing drug candidates have been synthesized by traditional carboxylic acid reactivity, such as amide couplings and heterocycle syntheses[28–30]. Despite recent progress on the arylation of cubane[11,31,32], a general, fragment-based cross-coupling of cubanes and challenging bond formations such as cubane–N, cubane–C(sp^3) and cubane–CF_3 remain elusive owing to the metal-catalysed strain-releasing valence isomerization of cubanes (Fig. 1c)[8–11]. With the goal of increasing the adoption of cubanes in medicinal chemistry, we set out to develop expedient routes to cubane-1,3- and 1,2-diesters and a general platform for cubane cross-coupling.

Cubane-1,3-dicarboxylate ester synthesis

We were inspired by an isolated report on the synthesis of cubane-1,3-dicarboxylic acid published by the Pettit group in 1966[33]. Under this protocol, a Diels–Alder reaction between cyclobutadiene, generated in situ from cyclobutadieneiron tricarbonyl, and

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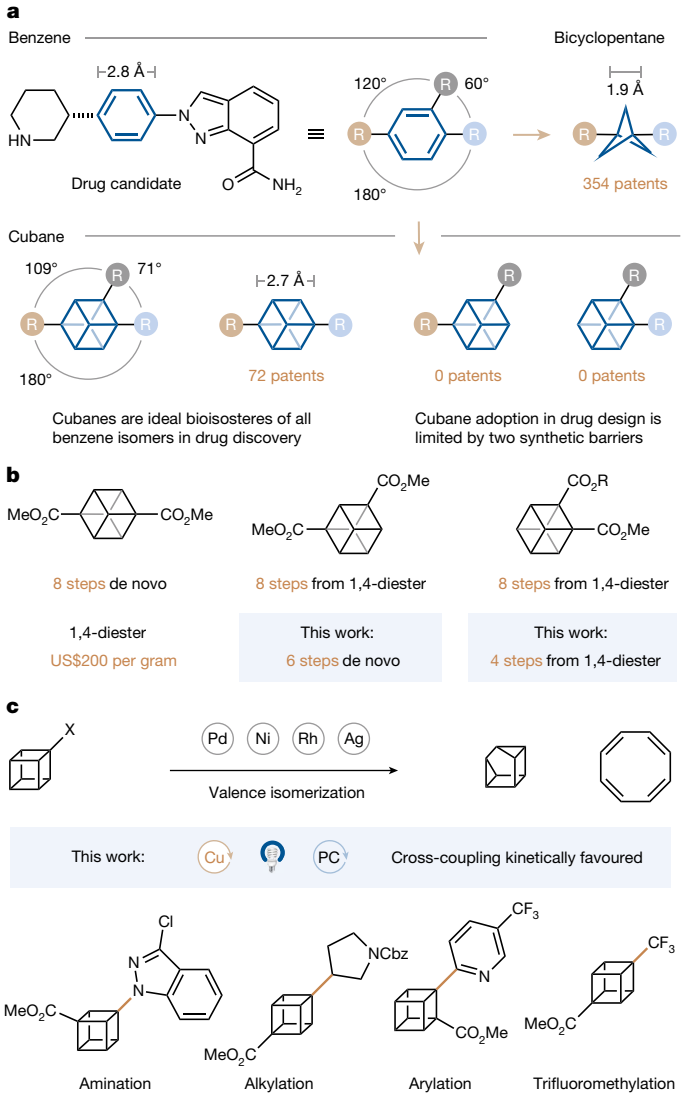


Fig. 1 | Cubanes in medicinal chemistry. a, Cubane closely resembles benzene in spacer size and exit vector orientation but remains underutilized in drug discovery—especially as bioisosteres of nonlinear benzenes. **b**,**c**, Our concise syntheses of 1,3- and 1,2-cubane precursors and copper photoredox-catalysed cross-coupling reactions remove the major barriers for cubane adoption in medicinal chemistry: the long synthesis of nonlinear precursors (**b**) and the poor compatibility of cubane with cross-coupling reactions (**c**). The number of patents was determined by a SciFinder search conducted on 12 January 2023 at 13:00 CET. All patents with at least one spectroscopically characterized drug candidate were counted. See Supplementary Information for details. PC, photocatalyst; Me, methyl; Cbz, carbobenzyloxy.

2,5-dibromobenzoquinone served to construct the cubane framework in only three steps. So far, this synthesis has seen no application in medicinal chemistry, probably owing to the arduous synthesis of the cyclobutadiene precursor cyclobutadieneiron tricarbonyl, which involves 4 steps (9% overall yield[34,35]) and requires inconvenient reagents such as chlorine gas, benzene and highly toxic diiron nonacarbonyl. Convenient access to 1,3-cubane precursors would thus require the development of a readily accessible cyclobutadiene precursor.

As a key design principle, this precursor would be required to liberate cyclobutadiene under mild, oxidative conditions, as the quinone coupling partner is itself an oxidant, and because the key bisalkene intermediate **2** is unstable (Fig. 2a). Drawing inspiration from a 1975 study by the Masamune group[36], we reasoned that 1,2-dihydropyridazine **1**, which is readily available from commercial material (75% yield over 2 steps)[37], could be a suitable candidate. We developed an improved route to cyclobutadiene (**7**) commencing with light-mediated, endocyclic 4-π-cyclization of dihydropyridazine **1** followed by deprotection to generate diazetidine **5**[38,39]. Oxidation to diazine **6** by the mild oxidant 2,5-dibromoquinone followed by nitrogen extrusion releases cyclobutadiene (**7**), which can undergo [4+2] cycloaddition with a second equivalent of the quinone to form bisalkene **2** thus intercepting the key intermediate of Pettit's synthesis[33]. Following optimization, the sequence was telescoped and proceeded in 80% analytical yield. The quinone was removed by a reductive work-up before the internal [2+2] cycloaddition to diketone **3** to prevent decomposition by sensitization. This work-up enabled us to circumvent the highly challenging recrystallization of the unstable bisalkene **2** used in Pettit's synthesis. Finally, Favorskii ring contraction and esterification provided dimethyl cubane-1,3-dicarboxylate (**4**). The entire synthesis requires 4 steps from dihydropyridazine **1** (6 from commercial material), proceeds in 35% isolated yield on a 1-mmol scale (26% from commercial material), requires only one chromatographic purification, and can be conducted in 3 days, thus rapidly providing sufficient quantities for medicinal chemistry projects (see Supplementary Information for details).

Cubane-1,2-dicarboxylate ester synthesis

However, a similar strategy proved unsuitable for the synthesis of the corresponding cubane-1,2-diester owing to a competing Haller–Bauer cleavage (see Supplementary Information for details). We speculated that C–H functionalization could provide a workaround to access this valuable substitution pattern (Fig. 2b). To avoid laborious installation and removal of a directing group, we decided to start with the symmetrical, commercially available dimethyl cubane-1,4-dicarboxylate (**8**). Inspired by a cubane C–H carboxylation reported by Bashir-Hashemi[40,41], we utilized a light-mediated one-pot C–H carboxylation/esterification sequence. Deprotection of the sterically exposed methyl ester of **9** yielded the monoacid **10**. Photoredox-mediated decarboxylation in presence of 1,4-cyclohexadiene was achieved via the redox-active ester. Overall, cubane 1,2-diester **11** was obtained in 21% isolated yield over 4 steps from commercially available cubane **8**.

Copper-mediated amination of cubanes

With facile routes to the cubane diesters in hand, we set out to develop a general and modular cross-coupling platform en route to a wide array of functionalized cubane isomers. We intended to utilize the carboxylic acid handles introduced by the cubane-forming Favorskii reaction for metallaphotoredox-mediated decarboxylative cross-coupling[42,43]. Crucially, the metal must be compatible with the highly strained cubane framework. Typical cross-coupling catalysts, such as nickel and palladium complexes, are known to facilitate cubane decomposition by strain-releasing valence bond isomerization to generate products such as cuneane (**12**) and cyclooctatetraene (**13**)[8–11]. Several decomposition pathways have been proposed, including oxidative insertion into the cubane framework (to **14**; Fig. 3)[9] and decomposition of metal–cubane complexes (**15**)[10]. We realized that both of these undesirable pathways would be suppressed under a copper catalytic manifold as copper is known to undergo slow oxidative addition and rapid reductive elimination[12]. The former property should prevent it from decomposing cubane via oxidative insertion while the latter should ensure that reductive elimination outcompetes valence isomerization.

Given the importance of C–N cross-coupling reactions in pharmaceutical research[44,45], we tested our hypothesis by adopting our laboratory's protocol for the decarboxylative amination of alkyl carboxylic acids[13] to cubane functionalization starting from commercially available 1,4-disubstituted cubane **16** (Fig. 3). An optimized procedure enabled C(sp^3)–N bond formation for a wide range of products in good yields.

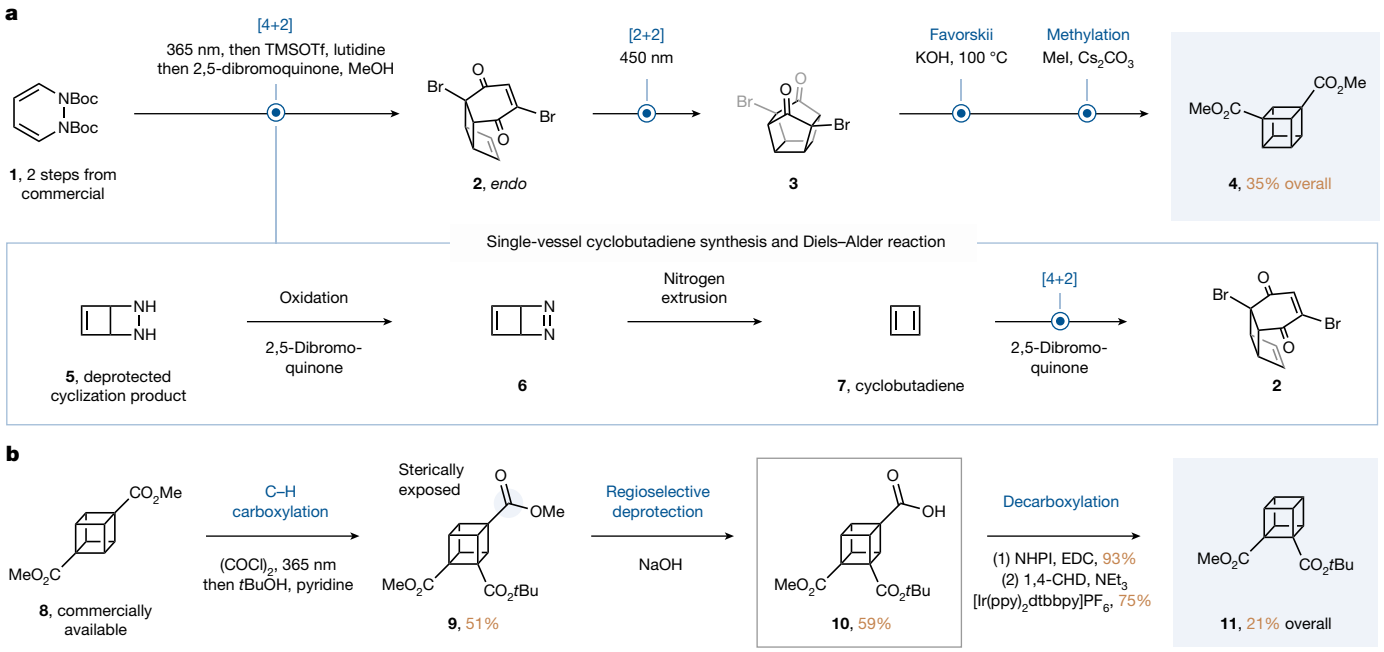


Fig. 2 | Synthetic strategies towards nonlinear cubane precursors. a, De novo synthesis of dimethyl 1,3-cubanedicarboxylate (**4**) using dihydropyridazine **1** as precursor of cyclobutadiene (**7**). **b**, Synthesis of *tert*-butylmethyl 1,2-cubanedicarboxylate (**11**) by C–H carboxylation. Boc, *tert*-butylcarbonyl; TMS, trimethylsilyl; Tf, trifluoromethylsulfonyl; *t*Bu, *tert*-butyl; NHPI, *N*-hydroyphthalimide; EDC, 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride; CHD, cyclohexadiene; Et, ethyl; ppy, 2-phenylpyridine; dtbbpy, 4,4′-di*tert*-butyl-2,2′-bipyridine.

The scope included heteroaromatic amines (**18**–**27**) as well as amide functionalities (**28** and **29**). Multifunctional substrates such as triazole and benzotriazole were alkylated with complete regioselectivity (**22** and **26**). Many functional groups including ketones (**19**), aryl halides (for example, **24**), esters (**18**–**29**) and ethers (**21**) were tolerated, thus enabling orthogonal functionalization of the products. This method is therefore a direct, convenient and general alternative to the Curtius rearrangement[46] for the synthesis of aminated cubanes. Such motifs are desirable as they can act as bioisosteres of anilines, which are structural alerts for drug discovery owing to their tendency for oxidative arene metabolism leading to adverse idiosyncratic drug reactions[47,48].

C–C cross-coupling of cubanes

To develop C–C cross-coupling reaction of cubanes, we designed a unified mechanistic platform that utilizes copper to couple cubyl radicals with alkyl and aryl radicals. Before our work, no general copper-mediated alkylation or arylation reactions of alkyl radicals were known. To be able to utilize the widely available alkyl and aryl halides as coupling partners, we planned to utilize silyl radical-mediated halide abstraction from the broadly available bromides to generate alkyl and aryl radicals[12,49]. We sought to pair this oxidative activation mode with a reductively generated cubyl radical derived from a redox-active ester (**30**). Both radicals could then undergo radical cross-coupling via copper catalysis (see Supplementary Information for a detailed design plan). To prevent decomposition of the electrophilic redox-active ester, we developed a non-nucleophilic tertiary aminosilane (**32**; see Supplementary Information for details). Under the optimized conditions, primary, secondary and benzylic alkyl bromides were coupled with the tertiary cubane in good yields (Fig. 3, **33**–**38**). Moreover, many functional groups, including the metal-sensitive isoxazole moiety (**33**), were tolerated, demonstrating the mildness of the reaction.

Under slightly modified conditions, aryl and heteroaryl bromides were also coupled with cubane (**39**–**46**) and synthetically useful functional groups such as cyanides (**39**) and aryl chlorides (**42** and **44**) were preserved. Of note is the tolerance of an *ortho*-substituent in the coupling with the sterically hindered, tertiary cubyl radical (**43**).

Given the prevalence of trifluoromethylated benzenes in drug candidates, we next sought to extend our copper-mediated radical–radical coupling manifold to the trifluoromethylation of cubanes. We intended to generate trifluoromethyl radical reductively using a modified version of Umemoto's reagent previously developed by our group[12], while generating the cubyl radical oxidatively starting directly from the cubane carboxylic acid **16**. We found that this challenging tertiary C(sp^3)–CF_3 cross-coupling proceeded in good yield (to **47**). We have thus achieved a general platform for the amination, arylation, alkylation and trifluoromethylation of cubanes.

Cross-coupling of new cubane isomers

We proceeded to explore the cross-coupling of the newly synthesized 1,3- and 1,2-disubstituted cubane isomers (see Supplementary Information for the synthesis of the free acids and redox-active esters). Both cubane isomers underwent amination and alkylation in yields comparable to the 1,4-isomers (Fig. 4a, **48**–**51**). The arylation reactions proceeded in lower, yet still synthetically useful yields (**52** and **53**).

Synthesis of pharmaceutical analogues

Finally, we demonstrated that our streamlined synthetic routes and cross-coupling protocols enable the rapid synthesis of cubane analogues of benzene-containing drugs (Fig. 4b, **56** and **58**). Cuba-lumacaftor (**56**) was synthesized starting from our mono-hydrolysed 1,3-disubstituted cubane precursor **54**, with our new copper-mediated arylation reaction with a complex aryl bromide as the key step. Cuba-acecainide (**58**) was synthesized from 1,4-monoacid **16** using our copper-catalysed cubane amination. Biological studies were conducted for the cubane-containing drug analogues **56** and **58**, and both compounds were found to be metabolically stable (in vitro intrinsic clearance (CL_{int}) <7 μl min^{-1} per 10^6 cells; see Supplementary Information for details).

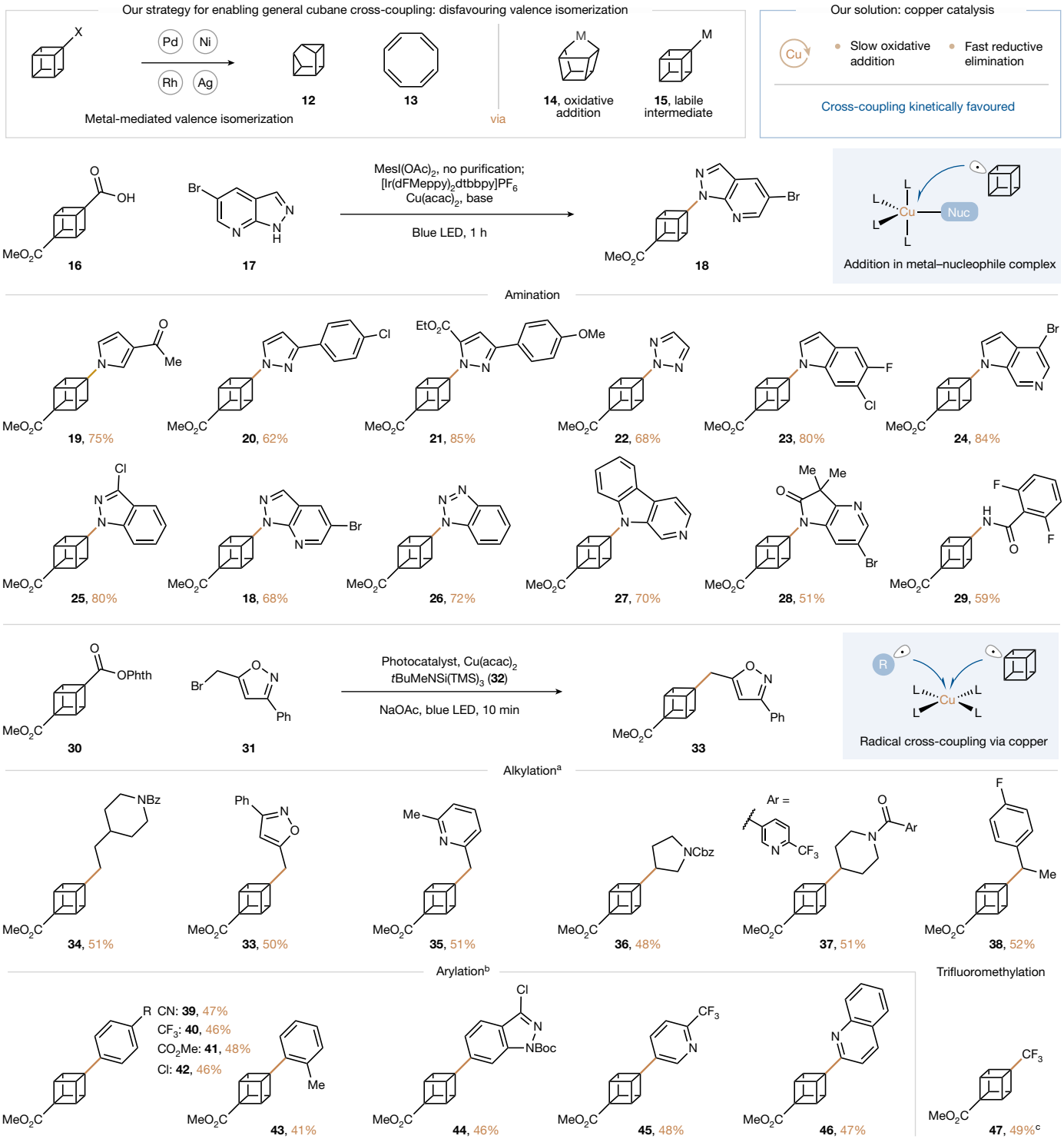
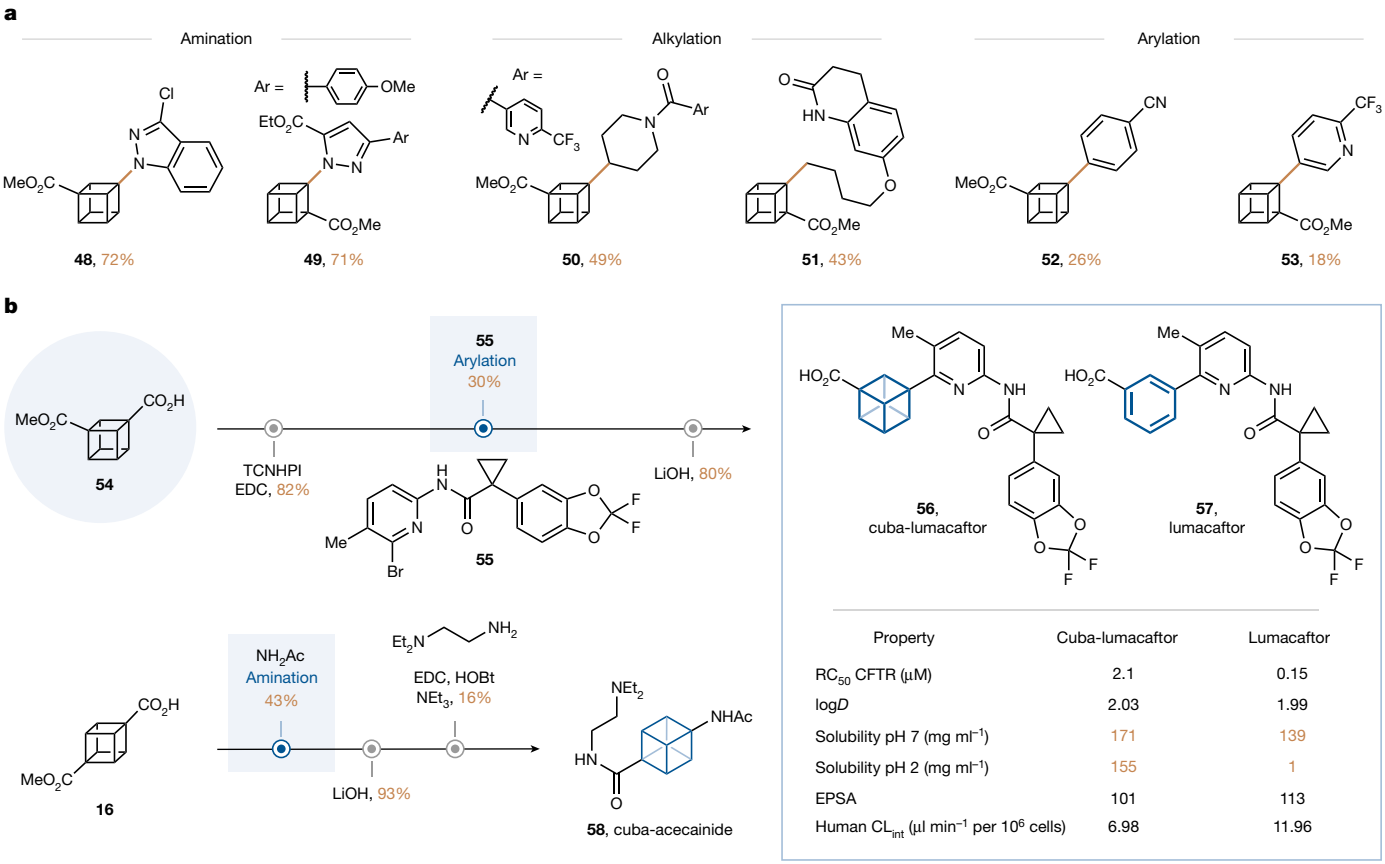


Fig. 3 | Copper-mediated cross-coupling of cubane. See Supplementary Sections 4 and 5 for additional examples. Isolated yields. [a]Photocatalyst: 2,4,5,6-tetrakis(9H-carbazol-9-yl) isophthalonitrile (4-CzIPN). [b]Tetrachlorophthalimidyl used instead of phthalimidyl (Phth). Photocatalyst: $[Ru(4,4'\text{-dClbpy})_3](PF_6)_2$ for aryl bromides and $[Ir(dFCF_3ppy)_2(4,4'\text{-d}(CF_3)bpy)]PF_6$ for heteroaryl bromides. [c]^{19}F NMR yield versus 1,4-difluorobenzene. X, cross-coupling handle; Mes, 1,3,5-trimethylphenyl; Ac, acetyl; dFMebpy, 2-(2,4-difluorophenyl)-5-methylpyridine; acac, acetylacetone; LED, light-emitting diode; L, ligand; Nuc, nucleophile; Bz, benzoyl; Ph, phenyl; bpy, bipyridine.

Furthermore, cuba-lumacaftor (**56**) still showed high activity (see half-maximal rescue concentration) despite the structural change near a binding moiety of the original, optimized drug (**57**). Interestingly, the cuba-lumacaftor (**58**) has an improved solubility compared with the parent benzene-containing drug at all measured pH values. This pH-independent high solubility would allow for improved compound absorption throughout the gastrointestinal tract. Moreover, bioisosteric replacement of the benzene ring with a cubane showed increased metabolic stability (CL_{int} = 6.98 µl min^{-1} per 10^6 cells) compared with the parent benzene-containing drug (CL_{int} = 11.96 µl min^{-1} per 10^6 cells) thus further demonstrating the positive influence of bioisosteric replacement on the physicochemical and pharmacokinetic properties.



Property	Cuba-lumacaftor	Lumacaftor
RC_{50} CFTR (μM)	2.1	0.15
log*D*	2.03	1.99
Solubility pH 7 (mg ml^{-1})	171	139
Solubility pH 2 (mg ml^{-1})	155	1
EPSA	101	113
Human CL_{int} (μl min^{-1} per 10^6 cells)	6.98	11.96

Fig. 4 | Synthetic and medicinal applications of novel cubane isosteres. **a**, Cross-couplings of 1,3- and 1,2-cubane isomers. **b**, Synthesis of cubane-containing analogues of drug candidates via the developed protocols. See Supplementary information for experimental details. HOBt, hydroxybenzotriazole; TCNHPI, tetrachloro *N*-hydroyphthalimide; CFTR, cystic fibrosis transmembrane conductance regulator; *D*, octanol–water partition coefficient; EPSA, experimental polar surface area; RC_{50}, half-maximal rescue concentration.

Conclusions

We report laboratory-scale syntheses of the sought-after 1,3- and 1,2-disubstituted cubanes. Furthermore, we demonstrate general copper photoredox-catalysed decarboxylative amination, arylation, alkylation and trifluoromethylation reactions of cubanes. In the process, we developed a practical means to access the highly reactive cyclobutadiene in situ and a copper-mediated alkyl radical cross-coupling manifold. Altogether, we expect that this work will expedite the use of cubanes as bioisosteres of *ortho*-, *meta*- and *para*-substituted benzenes in drug design. Moreover, we anticipate that our strategy of accessing cyclobutadiene by mild oxidation of a readily accessible dihydropyridazine and the cross-coupling manifold will find further application in synthetic organic chemistry.

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/s41586-023-06021-8.

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Data availability

All data are available in the main text or in the Supplementary information.

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Additional information

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