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General Access to Cubanes as Benzene Bioisosteres

Mario P. Wiesenfeldt^{1,4}, James A. Rossi-Ashton^{1,4}, Ian B. Perry^{1,4}, Johannes Diesel¹, Olivia L. Garry¹, Florian Bartels¹, Susannah C. Coote², Xiaoshen Ma³, Charles S. Yeung³, David J. Bennett³, David W. C. MacMillan^{1,*}

¹Merck Center for Catalysis at Princeton University, Princeton, NJ, USA.

²Lancaster University, Bailrigg, Lancaster, LA1 4YB, United Kingdom.

³Department of Discovery Chemistry, Merck & Co., Inc., Boston, MA, USA.

⁴These authors contributed equally: Mario P. Wiesenfeldt, James Rossi-Ashton, Ian B. Perry.

Abstract

The replacement of benzene rings with sp³-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 since the ring strain imparts high bond strength and thus metabolic stability on its C–H bonds. Cubane is the ideal bioisostere since 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 due 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-catalyzed valence isomerization^{8–11}. Herein, we disclose 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(sp³), C–C(sp²), and C–CF₃ 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.

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*Correspondence and requests for materials should be addressed to D.W.C.M. (dmacmill@princeton.edu).

Author contributions M.P.W. and I.B.P. developed the route towards dimethyl cubane-1,3-dicarboxylate. O.L.G., M.P.W., and J.A.R.-A. developed the route towards 1-*tert*-butyl-2-methyl cubane-1,2-dicarboxylate. J.A.R.-A. and I.B.P. developed the amination reaction, J.D. and M.P.W. developed the alkylation reaction, M.P.W., F.B., and J.D. developed the arylation reaction, and J.A.R.-A. and F. B. developed the trifluoromethylation reaction. J.A.R.-A. applied the reactions to new cubane isomers and synthesized the drug analogues. Biological testing was conducted by X.M., C.S.Y., and D.J.B.. D.W.C.M., S.C.C., X.M., C.S.Y., and D.J.B. provided advise. D.W.C.M., M.P.W., J.A.R.-A., I.B.P., and J.D. wrote the manuscript with contributions by all authors. D.W.C.M. directed the project.

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The substitution of a benzene group with an sp³-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(sp²)-character, which generally improves key pharmacokinetic properties like solubility and metabolic stability¹⁴. Bicyclo[1.1.1]pentanes (BCPs) and cubanes are particularly privileged, since they are rigid, and because their strained nature imparts high s-character and thus bond strength on their C–H bonds¹⁵. While BCPs are now routinely employed in drug discovery, cubanes remain less explored despite being a better geometric match to benzene (Fig. 1a)^{6,7,16}. 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. While several bicycloalkanes have recently been explored as nonlinear benzene isosteres^{17–24}, their scarcity is a severe limitation for drug design given that over 170 approved drugs contain *ortho*- or *meta*-substituted benzene rings. 1,2- and 1,3-disubstituted cubanes are ideally suited to bridge this gap since 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 8 steps on a laboratory scale and has been scaled up to a kilogram scale via a flow photoreactor^{25–27}. By contrast, the nonlinear 1,3- and 1,2-dicarboxylate isomers both require 8 additional steps, starting from the expensive 1,4-diester²⁸.

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^{29–31}. Despite recent progress on the arylation of cubane^{11,32,33}, a general, fragment-based cross-coupling of cubanes and challenging bond formations such as cubane–N, cubane–C(sp³) and cubane–CF₃ remain elusive due to the metal-catalyzed 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-diester and a general platform for cubane cross-coupling.

Results and discussion

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 1966³⁴. Under this protocol, a Diels-Alder reaction between cyclobutadiene, generated in situ from cyclobutadieneiron tricarbonyl, and 2,5-dibromobenzoquinone, served to construct the cubane framework in only 3 steps. To date, this synthesis has seen no application in medicinal chemistry, likely owing to the arduous synthesis of the cyclobutadiene precursor cyclobutadieneiron tricarbonyl, which involves 4 steps (9% overall yield^{35,36}) 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 new, readily accessible cyclobutadiene precursor.

As a key design principle, this new precursor would be required to liberate cyclobutadiene under mild, oxidative conditions, since the quinone coupling partner is itself an oxidant, and because the key bisalkene intermediate **2** is unstable (Fig. 2, a). Drawing inspiration from a 1975 study by the Masamune group³⁷, we reasoned that 1,2-dihydropyridazine **1**, which is readily available from commercial material (75% yield over 2 steps)³⁸, 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**^{39,40}. Oxidation to diazine **6** by the mild oxidant 2,5-dibromoquinone followed by nitrogen extrusion releases cyclobutadiene, 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 synthesis³⁴. Following optimization, the sequence was telescoped and proceeded in 80% analytical yield. The quinone was removed by a reductive workup prior to the internal [2+2] cycloaddition to diketone **3** to prevent decomposition by sensitization. This workup 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 SI for details).

Cubane-1,2-dicarboxylate ester synthesis

However, a similar strategy proved unsuitable for the synthesis of the corresponding cubane-1,2-diester due to a competing Haller-Bauer cleavage (see SI for details). We speculated that C–H functionalization could provide a workaround to access this valuable substitution pattern (Fig. 2b). In order 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^{41,42}, 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^{43,44}. 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 since copper is known to undergo slow oxidative addition and rapid reductive elimination¹². 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^{45,46}, we tested our hypothesis by adopting our laboratory's protocol for the decarboxylative amination of alkyl carboxylic acids¹³ to cubane functionalization starting from commercially available 1,4-disubstituted cubane **16** (Fig. 3). To our delight, an optimized procedure enabled C(sp³)–N Bond formation for a wide range of products in good yields. The scope included heteroaromatic amines (**18–27**) as well as amide functionalities (**28**, **29**). Multifunctional substrates such as triazole and benzotriazole were alkylated with complete regioselectivity (**22**, **26**). Many functional groups including ketones (**19**), aryl halides (e.g., **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 rearrangement⁴⁷ for the synthesis of aminated cubanes. Such motifs are desirable since they can act as bioisosteres of anilines, which are structural alerts for drug discovery due to their tendency for oxidative arene metabolism leading to adverse idiosyncratic drug reactions^{48,49}.

C–C cross coupling of cubanes

In order to develop C–C cross-coupling reaction of cubanes, we designed a new, unified mechanistic platform that utilizes copper to couple cubyl radicals with alkyl and aryl radicals. Prior to our work, no general copper-mediated alkylation or arylation reactions of alkyl radicals were known. In order 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^{12,50}. 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 SI for a detailed design plan). To prevent decomposition of the electrophilic redox-active ester, we developed a new, non-nucleophilic tertiary aminosilane (**32**, see SI 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**, **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 new 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 group¹², while generating the cubyl radical oxidatively starting directly from the cubane carboxylic acid **16**. We were pleased to find that this challenging tertiary C(sp³)-CF₃ 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 SI 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, 53**).

Synthesis of pharmaceutical analogs

Finally, we demonstrated that our streamlined synthetic routes and cross-coupling protocols enable the rapid synthesis of cubane analogs of benzene containing drugs (Fig. 4b, **56, 58**). Cuba-Lumacaftor (**56**) was synthesized starting from our new, monohydrolyzed 1,3-disubstituted cubane precursor **54**, with our new copper-mediated arylation reaction with a complex aryl bromide as the key step. Cuba-Acecaïnide (**58**) was synthesized from 1,4-monoacid **16** using our copper-catalyzed cubane amination. Biological studies were conducted for the cubane-containing drug analogs **56** and **58**, and both compounds were found to be metabolically stable (in vitro intrinsic clearance (CL_{int}) <7 μL/min/10⁶ cells, see SI for details). Furthermore, Cuba-Lumacaftor (**56**) still showed high activity (see half-maximal rescue concentration (RC₅₀)) despite the structural change near a binding moiety of the original, optimized drug (**57**). Interestingly, the Cuba-Lumacaftor (**58**) has an improved solubility compared to 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/10⁶ cells) compared to the parent benzene-containing drug (CL_{int} = 11.96 μL/min/10⁶ cells) thus further demonstrating the positive influence of bioisosteric replacement on the physicochemical and pharmacokinetic properties.

Conclusions

In conclusion, we disclose laboratory-scale syntheses of sought-after 1,3- and 1,2-disubstituted cubanes. Furthermore, we demonstrate general copper photoredox-catalyzed 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 new cross-coupling manifold will find further application in synthetic organic chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

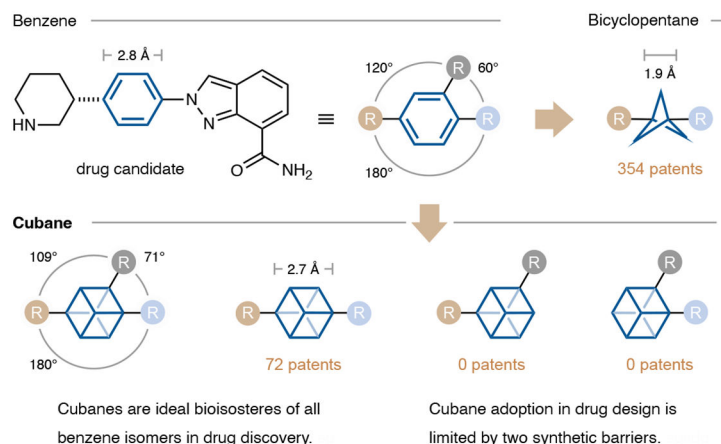
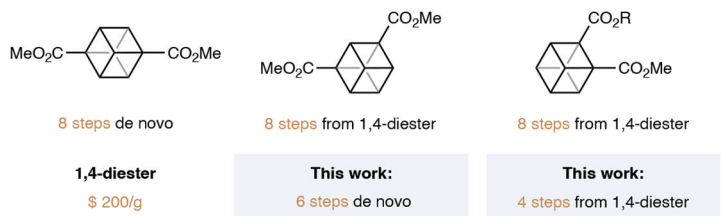
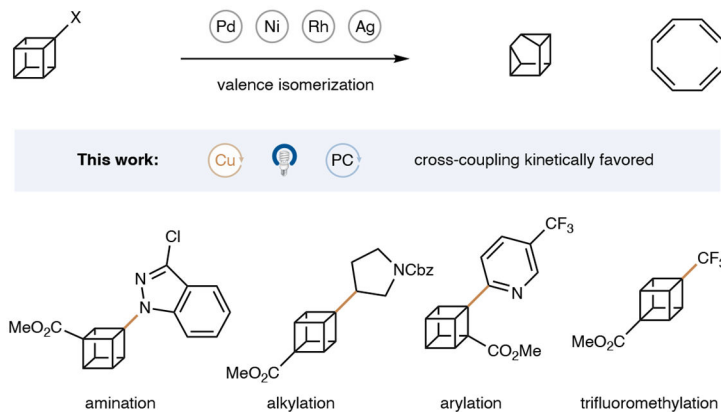
All data are available in the main text or in the supplementary information.

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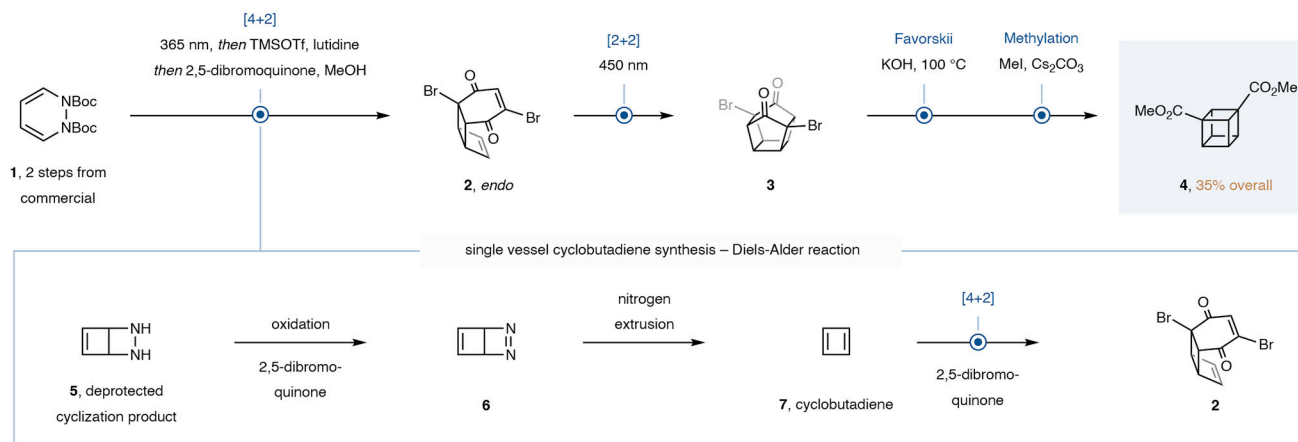
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a Cubane: ideal but underutilized benzene bioisostere**b** Barrier 1 for cubane adoption: long synthesis of nonlinear precursors**c** Barrier 2: cubane poorly compatible with cross-coupling reactions**Figure 1 |. Cubanes in medicinal chemistry.**

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-catalyzed cross-coupling reactions remove the major barriers for cubane adoption in medicinal chemistry. Me, methyl; Cbz, carbobenzyloxy.

a De novo synthesis of dimethyl cubane-1,3-dicarboxylate (**4**) via cyclobutadiene (**7**)



b Synthesis of 1-*tert*-butyl-2-methyl cubane-1,2-dicarboxylate (**11**) by C–H carboxylation

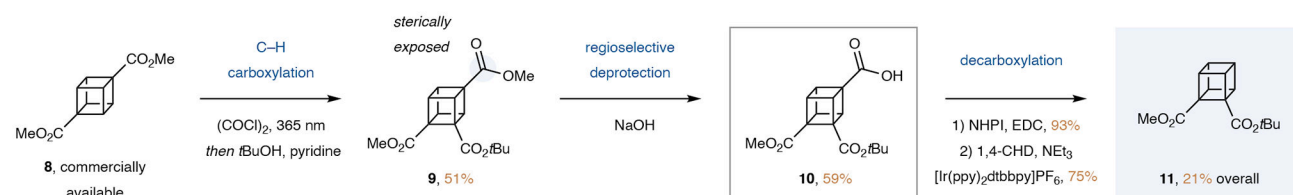


Figure 2 |. Synthetic strategies towards non-linear cubane precursors.

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. Me, methyl; Boc, *tert*-butylcarbonyl; TMS, trimethylsilyl; Tf, trifluoromethylsulfonyl; *t*Bu, *tert*-butyl; NHPI, *N*-hydroxyphthalimide; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; CHD, cyclohexadiene; Et, ethyl; ppy, 2-phenylpyridine; dtbbpy, 4,4'-di-*tert*-butyl-2,2'-bipyridine.

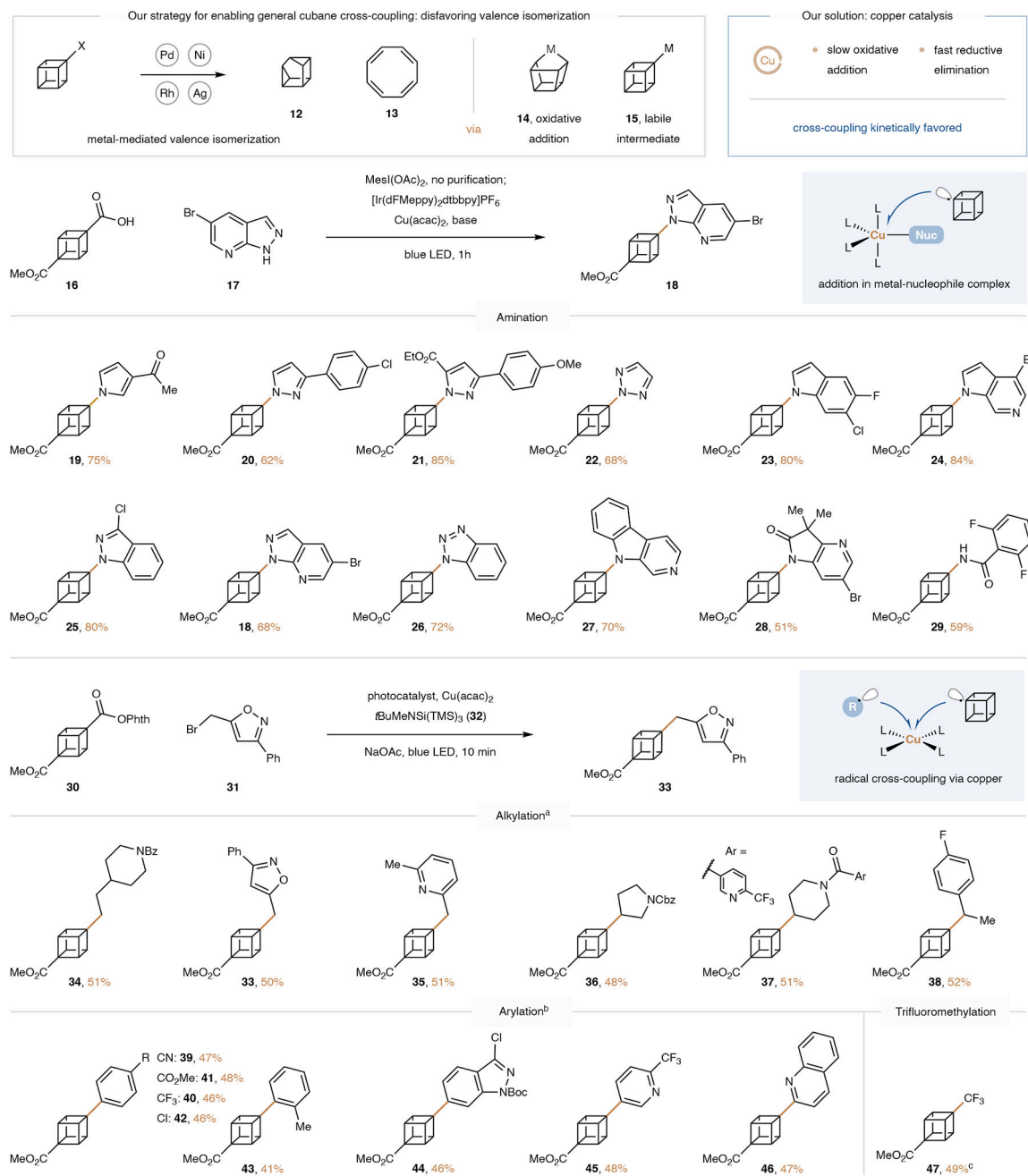


Figure 3 | Copper-mediated cross-coupling of cubane.

See SI sections 4 and 5 for additional examples. Isolated yields. ^aPhotocatalyst: 4-CzIPN. ^bTetrachlorophthalimidyl used instead of Phth. Photocatalyst: [Ru(4,4'-dClbpy)₃](PF₆)₂ for aryl bromides and [Ir(dFCF₃ppy)₂(4,4'-d(CF₃)bpy)]PF₆ for heteroaryl bromides. ^c¹⁹F NMR yield vs 1,4-difluorobenzene. Me, methyl; Mes, 1,3,5-trimethylphenyl; Ac, acetyl; dFMeppy, 2-(2,4-difluorophenyl)-5-methylpyridine; dtbbpy, 4,4'-di-*tert*-butyl-2,2'-bipyridine; acac, acetylacetonate; LED, light-emitting diode; Nuc, nucleophile *t*Bu, *tert*-butyl; TMS: trimethylsilyl; Bz, benzoyl; Ph, phenyl, Phth, phthalimidyl; Cbz, carbobenzyloxy;

Boc, *tert*-butylcarboxyl; SI, supplementary information; 4-CzIPN, 2,4,5,6-Tetrakis(9H-carbazol-9-yl) isophthalonitrile.

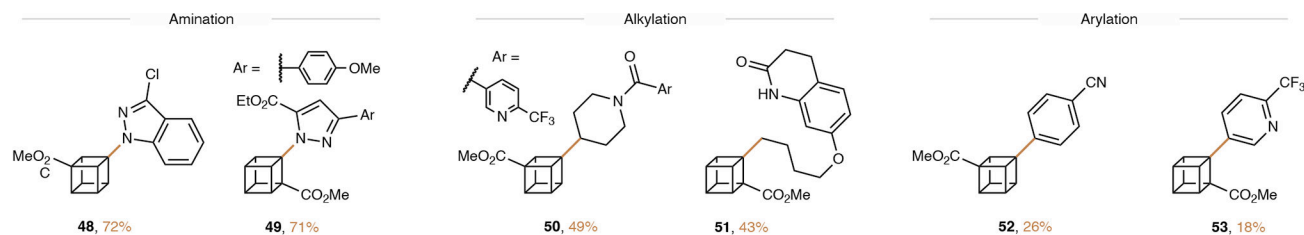
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a Cross-coupling of new cubane isomers



b Synthesis of pharmaceutical analogs

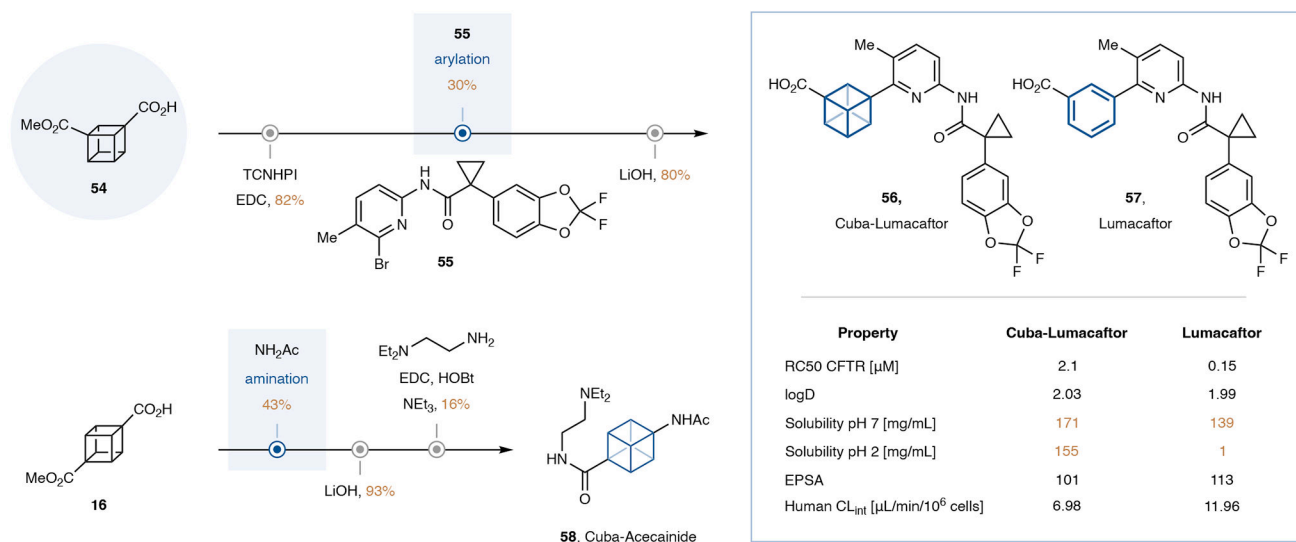


Figure 4 | Synthetic and medicinal applications of novel cubane isosteres.

a, Cross-couplings of 1,3- and 1,2-cubane isomers. **b**, Synthesis of cubane-containing analogues of drug candidates via the newly developed protocols. See supplementary information for experimental details. Me, methyl; Ac, acetyl; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; HOBt, hydroxybenzotriazole; Et, ethyl; TCNHPI, tetrachloro *N*-hydroxyphthalimide; RC50, half-maximal rescue concentration; CFTR, cystic fibrosis transmembrane conductance regulator; CL_{int}, in vitro intrinsic clearance.