Rapid Access to 2-Substituted Bicyclo[1.1.1]pentanes

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ABSTRACT: The replacement of aryl rings with C(sp^3)-rich structures has garnered significant interest in drug discovery due to the potential for improved pharmacokinetic properties upon substitution. In particular, 1,3-difunctionalized bicyclo[1.1.1]pentanes (BCPs) have been widely adopted as bioisosteres for *para*-substituted arene rings, appearing in a number of lead pharmaceutical candidates. Due to their medicinal importance, multiple methods have been developed to efficiently synthesize these 1,3-difunctionalized BCPs. However, despite the pharmaceutical value of 2-substituted BCPs as replacements for *ortho*- or *meta*-substituted arene rings, general and rapid syntheses of these scaffolds remain elusive. Current approaches to 2-substituted BCPs rely on installation of the bridge substituent prior to BCP core construction, leading to lengthy step counts and often non-modular sequences. While challenging, direct functionalization of the strong bridge BCP C–H bonds would offer a more streamlined pathway to diverse 2-substituted BCPs. Here we report a generalizable synthetic linchpin strategy for bridge functionalization via radical C–H abstraction of the BCP core. Through mild generation of a strong hydrogen atom abstractor, we rapidly synthesize novel 2-substituted BCP synthetic linchpins in one pot. These synthetic linchpins then serve as common precursors to complex 2-substituted BCPs, allowing one step access to a number of previously inaccessible electrophile and nucleophile fragments at the 2-position via two new metallaphotoredox protocols. Altogether, this platform enables the expedient synthesis of four pharmaceutical analogs, all of which show similar or improved properties compared to their aryl-containing equivalents, demonstrating the potential of these 2-substituted BCPs in drug development.

The substitution of arene rings with BCPs in pharmaceutical candidates often leads to improved properties, including increased solubility, greater metabolic stability and decreased non-specific binding.[1–4] Given these advantages and the synthetic accessibility of bridgehead-substituted BCP cores (i.e. BCPs substituted at the 1(,3)-position) from [1.1.1]propellane,[5–9] 1,3-disubstituted BCPs have been investigated in a number of lead candidates as replacements for *para*-substituted aryl rings, appearing in over 700 patents to date (Figure 1A).[10,11] However, despite the wide adoption of 1(,3)-substituted BCPs in medicinal chemistry programs, the corresponding 2-substituted BCPs are virtually non-existent in the patent literature. While there is substantial interest in synthesizing these bridge-substituted BCPs (i.e. BCPs substituted at the 2-position) as a means to access novel chemical space and replace *ortho*- or *meta*-substituted arene rings in bioactive molecules,[12–14] no methods exist that allow the direct preparation of complex 2-substituted BCP scaffolds. Although current approaches have enabled the introduction of some drug-like substituents at the bridge position, they suffer from long step counts and often lack modularity as they require pre-installation of the desired 2-substitutent prior to BCP core construction.[15–18] Conversely, direct functionalization of the bridge BCP C–H bonds would dramatically streamline the synthesis of these 2-substituted BCP scaffolds, enabling rapid library generation of these sought-after structures for drug development. While appealing, BCP C–H activation represents a significant synthetic challenge due to the high BDEs (bond dissociation energies) of the methylene C–H bonds (estimated BDE ~ 106 kcal mol^{-1}),[19] meaning no general methods exist to convert these strong bonds to useful functional handles in good efficiency.[20,21] Furthermore, selectivity for the mono- functionalized bridge BCP is difficult given that past BCP C–H functionalization strategies all favor the difunctionalization or bridgehead-substituted product over the desired bridge-functionalized BCP.[21–24] A third challenge to modular bridge functionalization is the lack of cross-coupling procedures that can elaborate 2-substituted BCPs, which are hindered by the high s character of the bridge C–X bonds, and corresponding intermediates, compared to typical alkyl systems (hybridization of bridge C–H ~$sp^{2.5}$)[25]. To overcome these long-standing issues, we hypothesized a programmable platform for 2-substituted BCP synthesis could be achieved through radical-mediated C–H functionalization and metallaphotoredox cross coupling (Figure 1B). First, we would directly access linchpin 2-monosubstituted BCPs by selective radical abstraction of the strong bridge BCP C–H bonds under mild visible light conditions, to minimize multifunctionalization and/or ring opened products. Importantly, these intermediates would have orthogonal functional handles at the bridgehead- and bridge-position, enabling modular elaboration. Following synthesis of these linchpin BCPs, we hypothesized that new metallaphotoredox cross-coupling procedures could transform our common intermediates to an unprecedented array of drug-like 2-substituted BCP scaffolds in only one step (Figure 1C). Overall, this strategy would considerably expand the number of obtainable bridge-substituted BCPs, allowing their wide application in the pharmaceutical sector across various therapeutic areas.

To enable installation of diverse functionality at the bridge and bridgehead positions of the BCP scaffold, we targeted a previously unreported 1(,3)-carboxylated, 2-brominated BCP. To access this intermediate, we hypothesized that a hydrogen atom transfer (HAT) mechanism could selectively activate the strong bridge C–H bonds of the commercially available mono- and di-substituted carboxylated BCPs, leading to brominated products in one step (Figure 2A). Within the field of radical-mediated HAT, a range of regioselective strong C–H bond functionalizations have been developed using polarity-matched hydrogen-atom abstraction by electrophilic radicals, such as quinuclidinium or halogen radicals, followed by radical trapping by an appropriate radical acceptor or metal catalyst.[26] Considering the thermodynamic dependence of HAT rates and the high BDE of H–Cl (103 kcal mol^{-1}),[27] we postulated that chlorine radicals could be suitable to accomplish this difficult BCP bridge C–H abstraction. In particular, we were inspired by studies demonstrating that chlorine gas could activate the strong methylene C–H bonds of BCPs to generate di- and trisubstituted

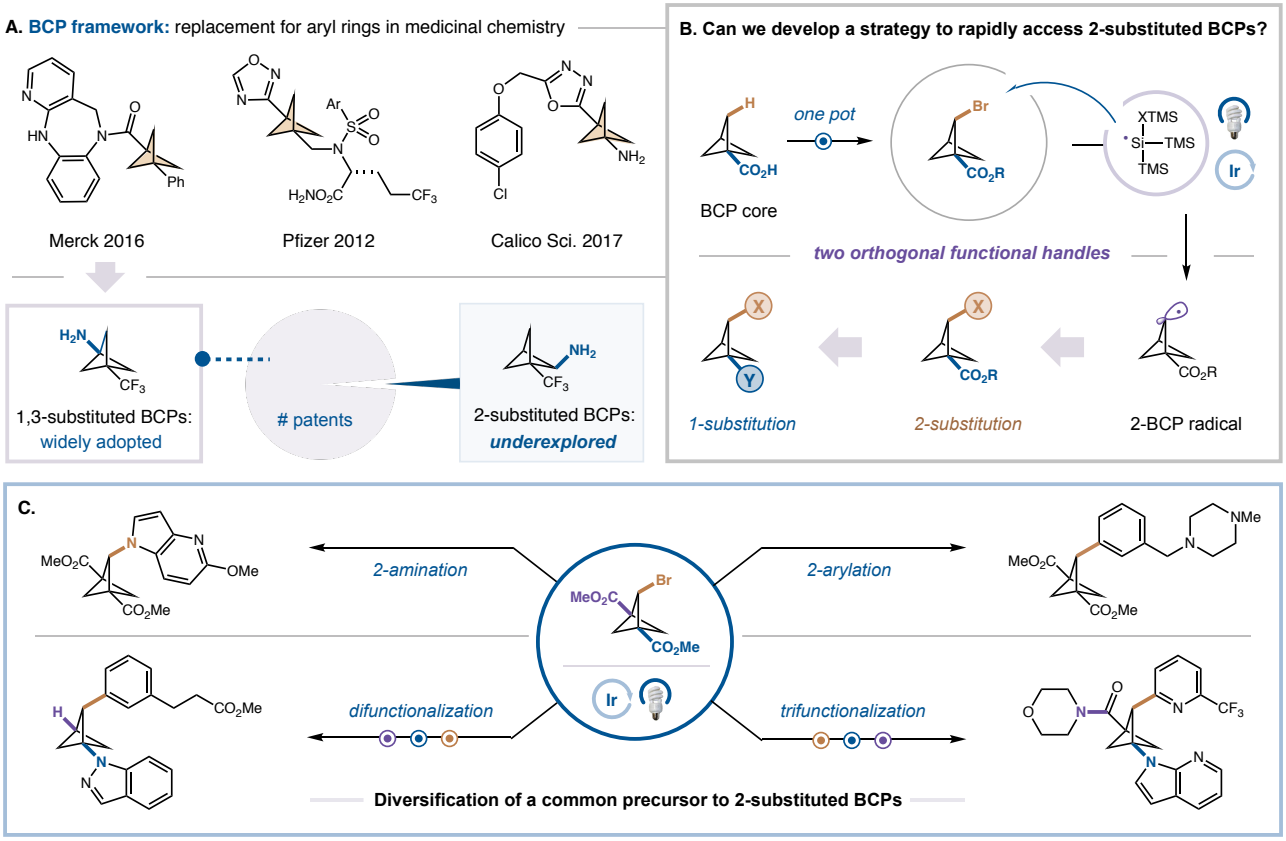


Figure 1. Rapid synthesis of 2-substituted bicyclo[1.1.1]pentanes. A, Examples of the BCP framework in pharmaceutical compounds. Relative number of patents containing 1,3- and 1,2-disubstituted BCPs. B, A one pot C–H functionalization to access a key disubstituted BCP intermediate with orthogonal functional handles. Functionalization of this intermediate via photoredox catalysis to access diverse 1,2-disubstituted BCPs. **C**, Photoredox catalysis enables diversification of a common 1,2,3-trisubstituted BCP intermediate to 2-aminated, 2-arylated, difunctionalized and trifunctionalized BCPs.

chlorinated products in moderate yield under photochemical conditions.[22–24] In our proposed monobromination protocol, we would generate high energy radicals by photolysis of *N*-chlorosuccinimide (NCS) under visible light conditions, which would then abstract the BCP bridge C–H bonds of **1** leading to a BCP bridge radical **2**. This radical would then abstract a bromine atom from a brominating agent to give our desired 2-brominated BCP **3**. Overall, we speculated these milder conditions would favor bridge monofunctionalization over multifunctionalization and/or ring opened products which are traditionally favored in BCP C–H bridge functionalization protocols.[13]

We first examined this bromination protocol with the commercially available 1,3-dicarboxylic acid BCP **1**. Pleasingly, exposure of 1,3-dicarboxylic acid BCP and NCS to visible light (450 nm) conditions, in the presence of brominating agent bromotrichloromethane, led to the formation of 2-brominated-1,3-dicarboxylic acid BCP **3** in moderate yield (Table S1–4). Control reactions omitting NCS, light or brominating agent proved that each component was necessary for efficient bromination (Table S5). Noting our desired use of these brominated BCPs in cross-coupling reactions and sequential functionalization sequences, we next targeted a one-pot bromination/esterification sequence to place linchpin functionality at the bridgehead positions that would be tolerated in further metal-catalyzed procedures (Figure 2B). The desired esterification could be achieved following bromination through a solvent swap to the desired alcohol and addition of EDC and DMAP as activator and base, respectively, to yield a range of BCP esters in synthetically useful yields (**4**–**8**). Flow conditions enabled excellent yield of the brominated BCP **4** on a 25 g scale, meaning this synthetic linchpin can be rapidly accessed for library generation. To avoid volatility, the monosubstituted carboxylic acid BCP was esterified with propanol, yielding building block **9** in decent yield on an 8 g scale.

Given the ubiquity of aryl groups and amine functionality in pharmaceuticals, we next targeted 2-amination and 2-arylation reactions on our newly synthesized brominated BCP intermediates To the best of our knowledge, there are presently no cross-coupling methods to aminate the bridge-position of BCPs; consequently, very few 2-heteroamine BCPs have been synthesized to date. Furthermore, current cross-coupling methods to arylate the 2-position of BCPs are limited in arene scope, and do not couple nitrogen-containing heterocycles,[15] which are present in the majority of approved drug molecules.

To activate the 2-bromine handle of our BCPs, we aimed to use silyl-radical chemistry developed by our group over the last several years (see Figure 1B).[28–31] In 2016, our laboratory established that alkyl halides could be activated by photocatalytically generated silyl radicals to produce the corresponding alkyl radical under visible light conditions.[28] These open shell intermediates have been engaged in a number of copper- and nickel- cross-coupling pathways, yielding a number of valuable transformations, such as C(sp^3)-arylation, -alkylation, -trifluoromethylation and -amination.[28–31] Using these silyl-radical-

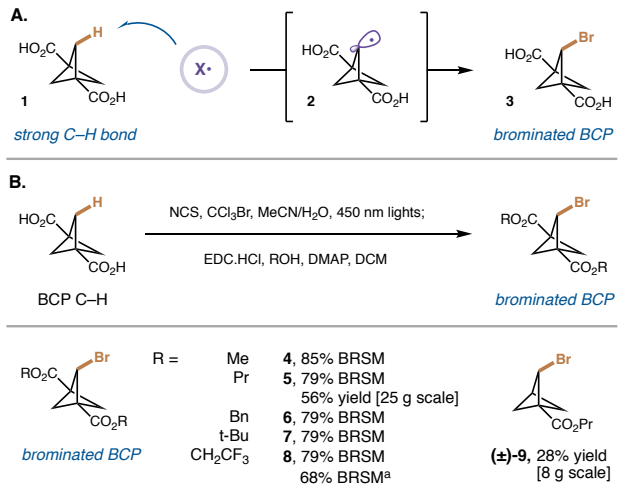


Figure 2. Synthesis of C–H bridge-brominated BCP intermediates. A. Proposed mechanism for bromination. B. A range of 2-brominated BCPs can be synthesized**.** All yields are isolated. Standard conditions: BCP acid (1 equiv.) NCS (1.1 equiv.), CCl_3Br (5.0 equiv.), MeCN/H_2O (9:1); EDC•HCl (6 equiv.), ROH (10 equiv.), DMAP (4 equiv.), DCM; NaOH, THF/H_2O. See SI for full experimental details. BRSM, based on recovered starting material. DMAP, 4-dimethylaminopyridine; EDC, *N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide; NCS, *N*-chlorosuccinimide.

mediated technologies, we anticipated that under photocatalytic conditions we could form BCP radicals at the bridge position from our 2-brominated BCPs, which could engage in subsequent cross-coupling with an aryl bromide or amine via a nickel or copper metal catalyst, respectively.

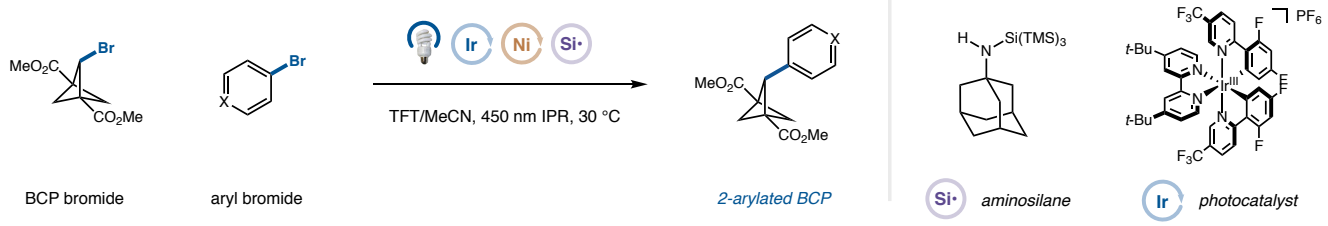
From the outset, we recognized that a fundamental challenge to high product yield would be the high s character of the proposed BCP radical intermediate (see Figure 1B).[19,25] In contrast to typical alkyl radicals, we anticipated the more electrophilic character of this BCP radical and the high BDE of the corresponding bridge C–H bonds would likely favor the protodehalogenation product over the desired cross-coupling product. Indeed, initial attempts at silyl-radical-mediated C(sp^3)-arylation[28] and -amination[31] using our previously published conditions gave only minimal yield (<10%) of the desired cross-coupling product, instead leading to solvent-coupled products, dimer formation and/or protodehalogenated BCP.[25] To prevent this byproduct formation, we found that solvents lacking weaker, hydridic C–H bonds, combined with rigorous control of the reaction temperature, as well as slow addition of aryl bromide and use of a different silane source, enabled efficient formation of the arylated product (see SI for more details). Conversely, for the amination reaction, use of more electron-rich bipyridine (bipy) ligands, a copper(I) source and organic bases, such as DBN, led to high yields of 2-aminated BCP in preference to protodehalogenated BCP and detrimental BCP hydrolysis side products (see SI for more details).

Following optimization, we turned to evaluate the scope of the arylation reaction for a range of BCP bromides and aryl bromide coupling partners (Figure 3). Pleasingly, both disubstituted and monosubstituted BCP bromides could be successfully coupled (**10**–**15**). A wide range of aryl bromides were also found to serve as productive coupling partners: *para*-substituted electron-deficient and electron-rich substituents could be coupled in excellent yield (**16**–**21**). Furthermore, *ortho*-, *meta*- and *para*-substituents on the aryl ring were amenable to our reaction conditions (**16, 22, 23**). The conditions were applicable to a range of potentially sensitive functional groups and useful synthetic handles, such as tertiary amines (**24**), carbamates (**20** and **25**), nitriles (**26**) and aryl chlorides (**19** and **27**). Notably, acidic functionality such as NH bonds, which are commonly problematic in transition-metal catalyzed reactions,[14] could also be accommodated in this reaction (**25**).

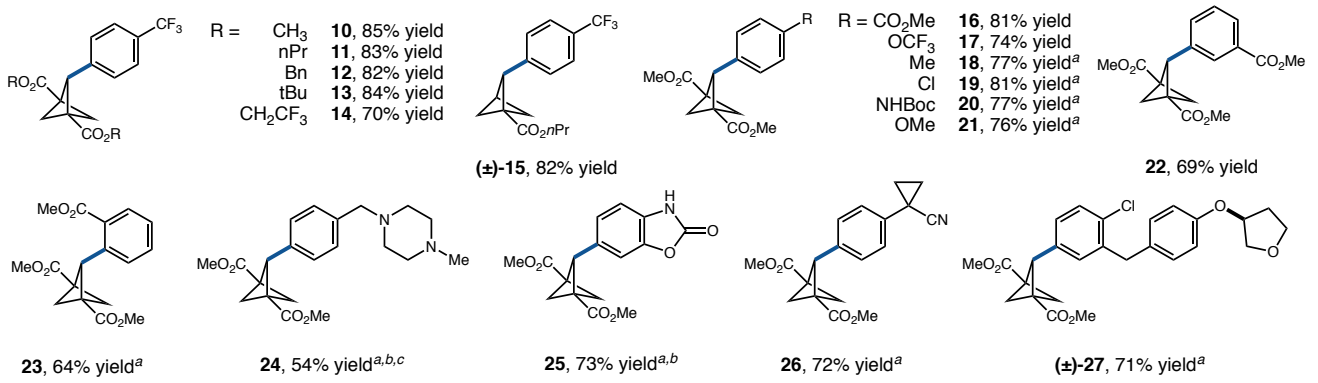
Given the prevalence of heteroaryl moieties in pharmaceutical molecules, we were pleased to find that a number of heteroaryl bromides could also be successfully coupled in this reaction. A range of 2-, 3-, and 4-pyridyl bromides bearing electronically diverse substituents all served as competent coupling partners (**28**–**33**). Heteroaryl bromides with extended pi systems, such as quinolines and quinoxalines, performed well under these reaction conditions (**34**–**38**). Pleasingly, excellent yields were still observed for heterocyclic systems containing multiple nitrogen atoms, including pyrazines (**39**), triazolopyridines (**40**) and imidazopyridazines (**41**). Furthermore, traditional heterocycles such as indoles (**42** and **43**), azaindoles (**44**) and indazoles (**45** and **46**) were all well-tolerated in this reaction. Notably, a number of 5-membered ring heteroaryl bromides, compounds that are notoriously challenging for transition-metal cross coupling procedures, were also effective substrates albeit in modest yields (**47–50**).

Our optimized amination conditions also proved highly general: over 10 classes of amines were capable nucleophiles in our procedure (Figure 4). These results are particularly notable, given that these bridge-substituted heteroamines have been scarcely synthesized. A variety of indazoles (**51**–**53**) pyrazoles (**54**–**56**) and azaindazoles (**57** and **58**) were coupled in excellent yields and regioselectivities, with reaction only at the designated nitrogen site. Amines with only one reactive nitrogen site, such as azaindoles (**59–61**), benzophenone imine (**62**), carbazoles (**63**–**65**), azacarbazole (**66**), pyrroles (**67** and **68**) and indoles (**69** and **70**) were all competent reaction partners. Notably, a number of substrates containing heteroaryl chloride substituents, which can be easily elaborated in further transition-metal catalyzed protocols, were successful partners in this reaction (**51**, **55**, **59**, **60**, **63, 70**). Furthermore, heteroamines that are traditionally challenging in these silyl-radical-mediated copper-catalyzed aliphatic aminations, such as imidazoles (**71**) and triazoles (**72** and **73**), could be coupled in synthetically useful yield. Both trisubstituted and disubstituted BCPs (**55**, **60**, **75**) were amenable to these reaction conditions. Finally, to determine the necessity of employing metal cross-coupling procedures for installation of nucleophiles at the bridge position, we evaluated basic and/or thermal S_N2 conditions for a variety of amines and iodide sources—no reaction was observed under these alternate conditions (Table S6, Figure S1– see SI for more details).

With optimized protocols in hand, we next sought to apply these photoredox transformations in sequential functionalization reactions (Figure 5A). In these sequences, we hoped to employ our previously published decarboxylative amination chemistry at the bridgehead carboxylic acid,[32] followed by a metallaphotoredox silyl-radical cross-electrophile coupling reaction to yield difunctionalized 1-amine, 2-aryl BCP cores. Pleasingly, using the forementioned amination conditions, we were able to couple indazoles (**S11**, 84% yield), azaindoles (**S14**, 73% yield) and azaoxindoles (**S15**, 46% yield) at the bridgehead position of our brominated BCPs in excellent yield. Furthermore, the subsequent silyl-radical-mediated arylation reaction



aryl bromide scope



hetero(aryl) bromide scope

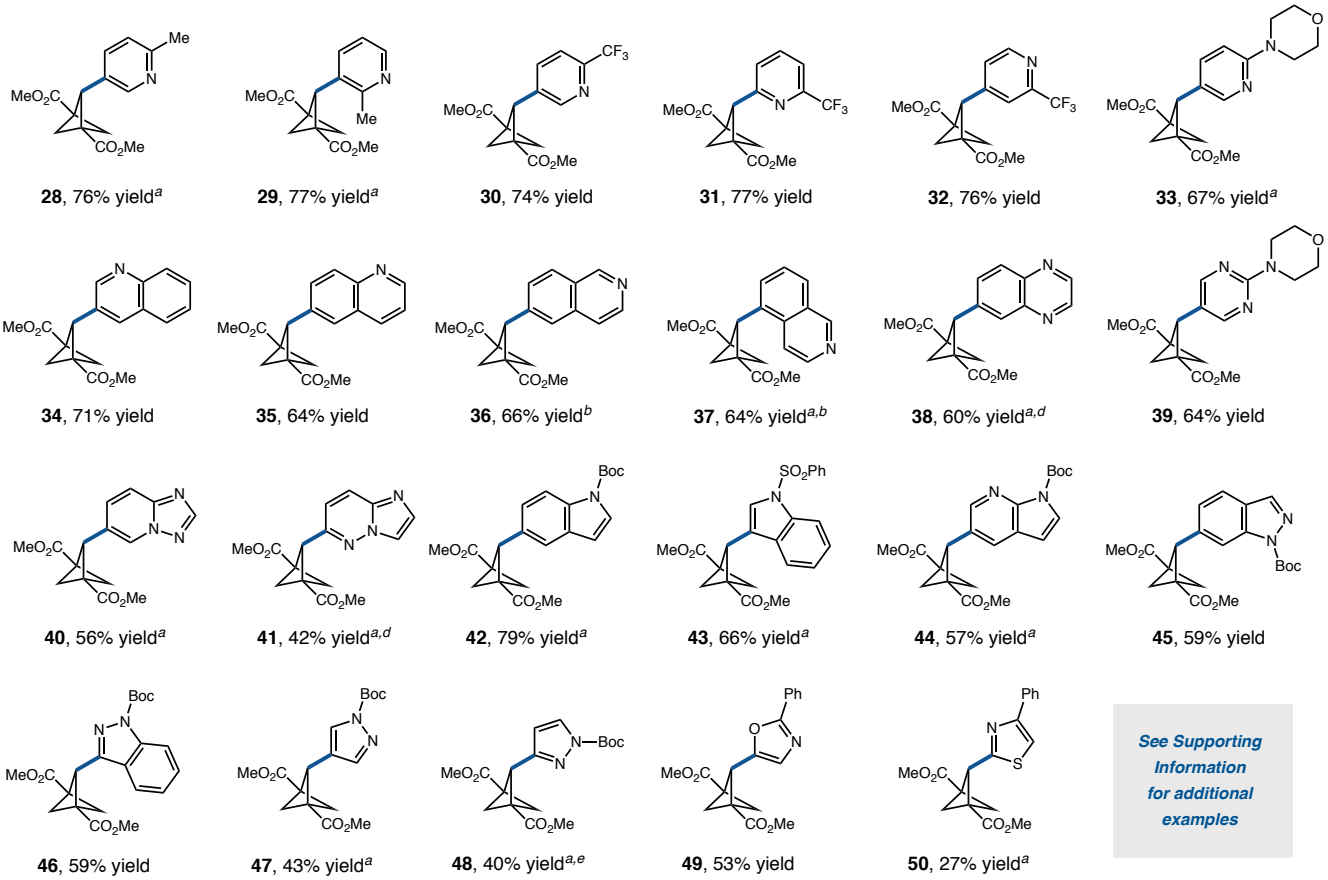


Figure 3. Scope for silyl-radical-mediated BCP 2-arylation. A range of hetero(aryl) bromides can be used as aryl coupling partners. All yields are isolated. Standard conditions: Aryl bromide (0.5 mmol, 1 equiv.), BCP bromide (2 equiv.), Aminosilane (1.6 equiv.), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (2 mol%), $Ni(dtbbpy)Br_2$ (5 mol%), Cs_2CO_3 (2 equiv.), TFT (0.05 M), IPR 450 nm (100% intensity) for 2 hours. See SI for full experimental details. [a]10 mol% $Ni(dtbbpy)Br_2$. [b]Reaction performed in TFT/tBuOH (v/v = 3/1). [c]Isolated as the dihydrochloride. [d]Reaction performed in TFT/tBuOH (v/v = 1/1). [e]Irradiation for 240 min. Boc, *tert*-butyloxycarbonyl; Bn, benzyl; IPR, integrated photoreactor; TFT, trifluorotoluene TMS, trimethylsilane.

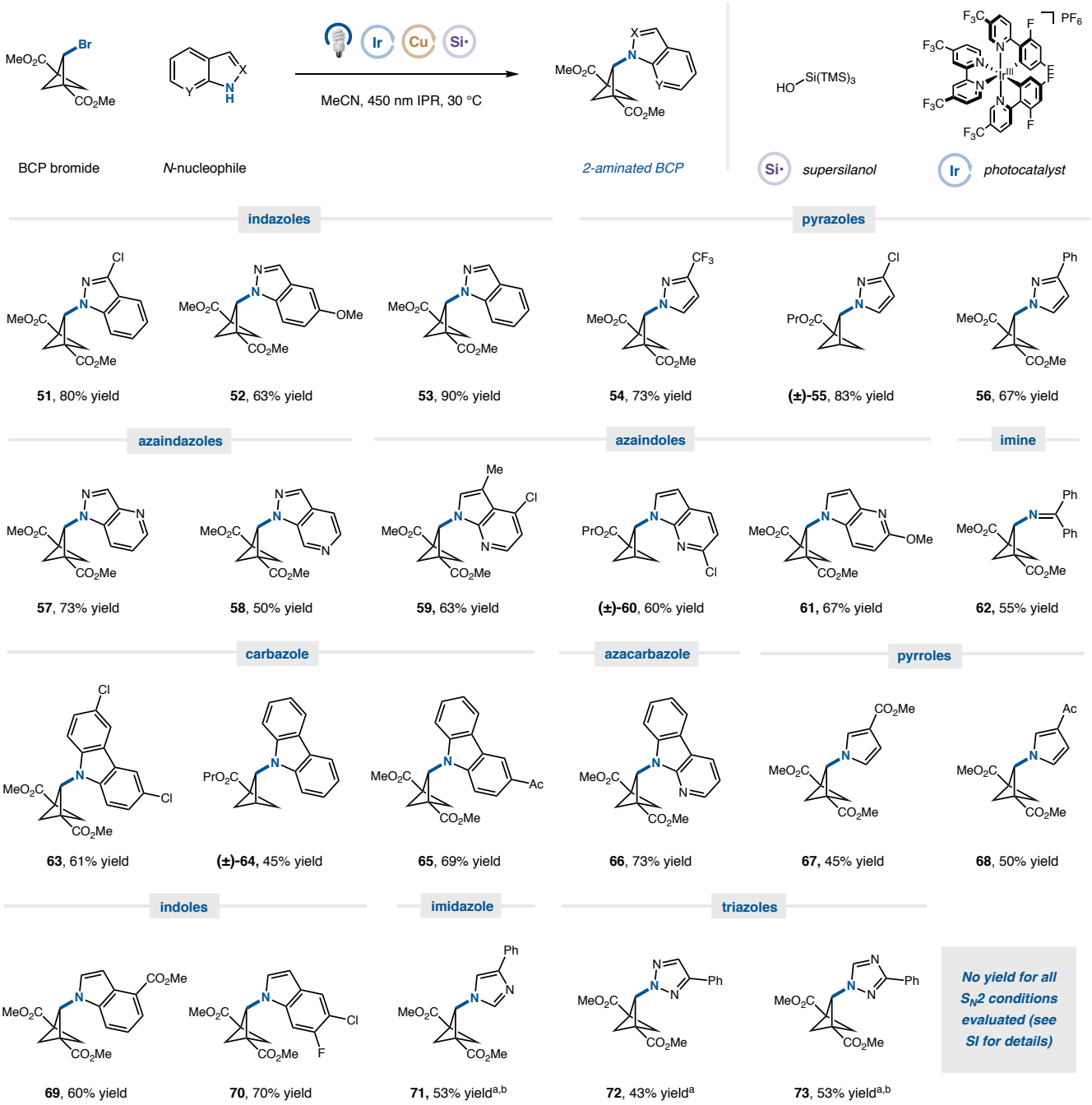
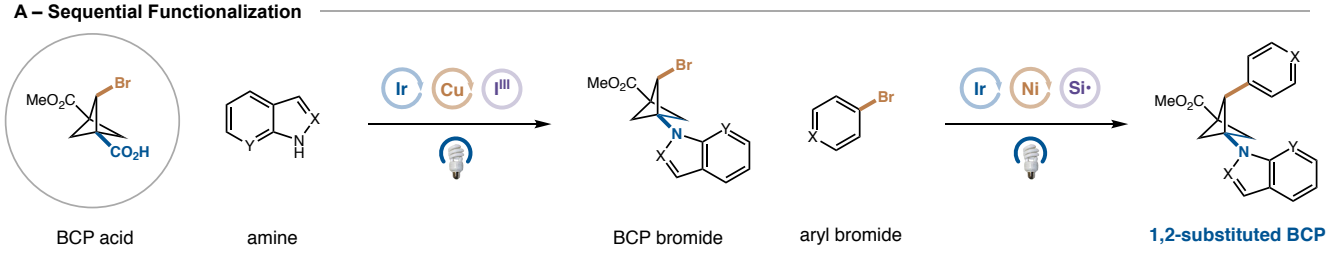
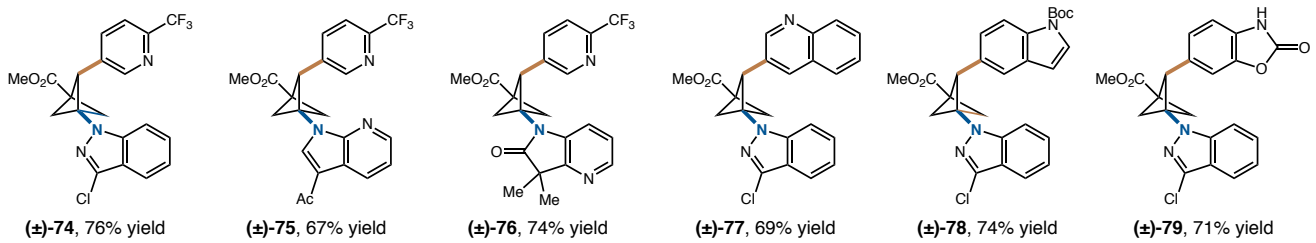


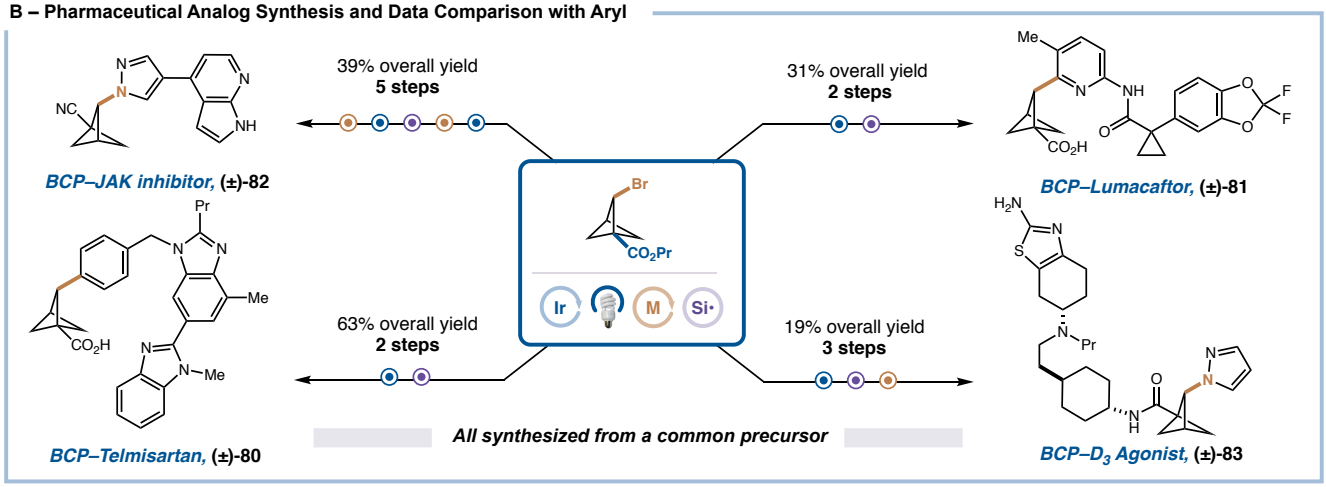
Figure 4. Scope for silyl-radical-mediated BCP 2-amination. Numerous (hetero)amine classes can be used in this transformation. All yields are isolated. Standard conditions: Amine (0.25 mmol, 1 equiv.), BCP bromide (2 equiv.), Silanol (2.5 equiv.), Ir(dF(CF$_3$)ppy)$_2$(4,4'-dCF$_3$bpy)PF$_6$ (0.8–1.6 mol%), CuTC (50 mol%), 4,4'-dOMebpy (50 mol%), DBN (2 equiv.), MeCN, 25 equiv. H_2O, IPR 450 nm (25–30% intensity) for 2 hours. See SI for full experimental details. [a]5 mol% 4CzIPN. [b]5 x 0.5 mmol. Ac, acetyl. CuTC, copper(I)-thiophene-2-carboxylate. DBN, 1,5-diazabicyclo(4.3.0)non-5-ene.

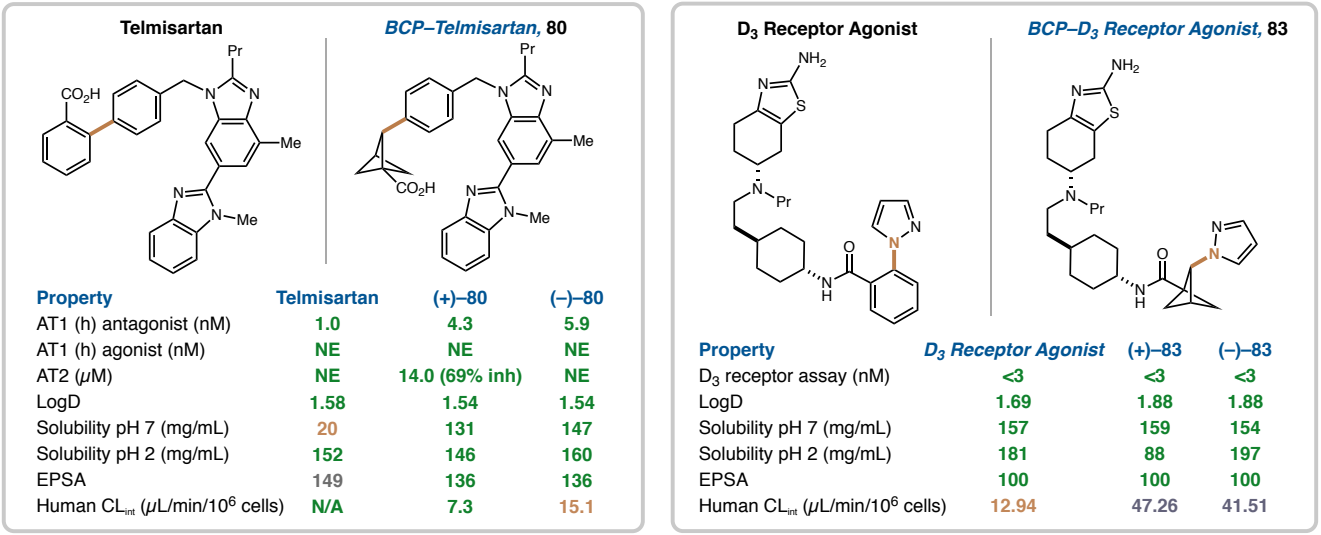
could tolerate all of this amine functionality (**74**–**76**) and utilize diverse hetero(aryl) bromides, including pyridines (**74**), quinolines (**77**), indoles (**78**) and unprotected carbamates (**79**) in high yields. To showcase our platform for the synthesis of densely functionalized BCP cores with three exit vectors, we took BCP **74**, and, following hydrolysis, installed a morpholine substituent through an amide coupling (**S13**, 45% overall yield over 5 steps). Alternatively, the third bridgehead substituent can be decarboxylated through a photoredox decarboxylation procedure from the redox active ester to yield 1,2-difunctionalized BCP scaffolds (see SI for details).

To demonstrate the potential of these 1,2-difunctionalized BCP cores as *ortho*- or *meta*-disubstituted aryl bioisosteres, and the applicability of our procedures to drug discovery settings, we next applied our new metallaphotoredox coupling reactions to the synthesis of four pharmaceutical analogs (Figure 5B).









Property	Telmisartan	(+)–80	(–)–80
AT1 (h) antagonist (nM)	1.0	4.3	5.9
AT1 (h) agonist (nM)	NE	NE	NE
AT2 (μM)	NE	14.0 (69% inh)	NE
LogD	1.58	1.54	1.54
Solubility pH 7 (mg/mL)	20	131	147
Solubility pH 2 (mg/mL)	152	146	160
EPSA	149	136	136
Human CL_{int} (μL/min/10^6 cells)	N/A	7.3	15.1

Property	D_3 Receptor Agonist	(+)–83	(–)–83
D_3 receptor assay (nM)	<3	<3	<3
LogD	1.69	1.88	1.88
Solubility pH 7 (mg/mL)	157	159	154
Solubility pH 2 (mg/mL)	181	88	197
EPSA	100	100	100
Human CL_{int} (μL/min/10^6 cells)	12.94	47.26	41.51

See supporting information for data on all synthesized bicyclo[1.1.1]pentanes

Figure 5. Sequential functionalization and drug analogs. A, A 2-brominated, 1-carboxylic acid BCP can be leveraged in sequential photoredox-catalyzed decarboxylative coupling followed by silyl-radical-mediated 2-arylation. Reported yield is for the silyl-radical-mediated 2-arylation. All yields are isolated. Standard conditions: Aryl bromide (0.3 mmol, 1 equiv.), BCP bromide (2 equiv.), Aminosilane (1.6 equiv.), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (2 mol%), $Ni(dtbbpy)Br_2$ (5 mol%), Cs_2CO_3 (2 equiv.), TFT (0.05 M), IPR 450 nm (100% intensity) for 2 hours. See SI for full experimental details. B, These silyl-radical-mediated 2-arylation and 2-amination procedures can be applied to the rapid preparation of pharmaceutical analogs and bioactive molecules. Data comparison with aryl compound. All yields are isolated. See SI for full experimental details. inh, Inhibition; NE, No significant effect.

Toward this end, BCP–Telmisartan **80** was synthesized in just two steps and 63% overall yield from our common BCP precursor and the corresponding aryl bromide (previous best: 10 steps, 10% overall yield)[15]. This approach was also applied to the synthesis of BCP–Lumacaftor **81** from the corresponding aryl bromide and the BCP intermediate in 2 steps and 31% overall yield. To test our amination chemistry in pharmaceutically relevant contexts, we targeted the BCP analogs of a JAK inhibitor (**82**) and D_3-dopamine agonist (**83**). Excitingly, we could synthesize BCP–JAK inhibitor analog **82** in 5 steps and 39% overall yield, through coupling of the appropriate protected azaindole-pyrazole followed by amidation of the bridgehead ester, and subsequent dehydration to the nitrile. Furthermore, BCP–Dopamide D_3 agonist **83** could be prepared by coupling of pyrazole followed by hydrolysis and amide coupling of a complex amine (3 steps, 19% overall yield).

We next tested these BCP pharmaceutical analogs in comparison to their aryl-containing counterparts (Figure 5B, Figure S3). Most notably, three out of four of the BCP compounds retained potency when moving from the arene ring to BCP scaffold. In addition, all BCP compounds tested showed improved or similar lipophilicity, solubility and EPSA over the corresponding 2-arylated and 2-aminated BCP drug molecule, with most retaining or improving the metabolic profile. Altogether, these results demonstrate the high potential of 2-substituted BCPs for improving the pharmacological properties of drug candidates containing *ortho*- or *meta*-substituted aryl rings.

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