nature synthesis

Article

https://doi.org/10.1038/s44160-023-00277-8

O-, *N*- and *C*-bicyclopentylation using thianthrenium reagents

Received: 9 June 2022

Accepted: 23 February 2023

Published online: 30 March 2023

Check for updates

Eva Maria Alvarez[1,2,3], Zibo Bai[1,3], Saikat Pandit[1,2], Nils Frank[1], Luca Torkowski[1] & Tobias Ritter[1]

Rigid 1,3-disubstituted bicyclo[1.1.1]pentanes (BCPs) are linear bioisosteres for *para*-substituted benzene rings in drug development and can lead to an improved pharmacokinetic profile. The construction of BCPs commonly requires the cumbersome use of labile [1.1.1]propellane in solution, and more stable reagents do not show the versatile reactivity of propellane itself. Here we report stable thianthrenium-based BCP reagents for practical *O*-, *N*- and *C*-alkylation reactions that expand the scope of bicyclopentylation beyond that of any other reagent, including [1.1.1]propellane. The redox and stereoelectronic properties of the thianthrene scaffold are relevant for both the synthesis of the BCP-thianthrenium reagents via strain release as well as their subsequent reactivity. The weak exocyclic C–S bond can undergo selective mesolytic cleavage upon single-electron reduction to produce BCP radicals that engage in transition metal-mediated C–O, C–N and C–C bond formations, even at a late stage of multistep reactions with a wide variety of functional groups present.

Bicyclo[1.1.1]pentanes (BCPs) are three-dimensional isosteres of phenyl rings and, when 1,3-disubstituted, provide two exit vectors that are opposite each other, as in 1,4-disubstituted arenes[1]. About 45% of marketed small-molecule drugs contain phenyl substituents[2]. The replacement of aryl substituents with 1,3-disubstituted bicyclopentanes can improve the metabolic and pharmacokinetic properties of drug candidates[3]. For example, the replacement of the fluorobenzene motif with BCP in the γ-secretase inhibitor BMS-708163 led to an increase in aqueous solubility and metabolic stability compared with the parent compound, as revealed using in vivo mouse models[1]. Currently, there are two main approaches to accessing 1,3-disubstituted BCPs in molecules of interest: the difunctionalization of highly reactive [1.1.1]propellane[4], which must be prepared before use because it has limited shelf stability even at −20 °C (ref. 5), and alkylation using functionalized BCP reagents[6,7]. Several impressive examples of the use of [1.1.1]propellane in, for example, *N*-alkylation[8] or even difunctionalization[7,9–13] reactions, have been advanced recently. Despite the large synthetic utility of the products, all the synthetic routes have in common [1.1.1]propellane, which is not suitable for central production and distribution, and therefore is of attenuated utility for practitioners. A more practical reagent of similar or greater utility could increase the incorporation of BCP substituents to benefit from their desirable properties, but such a reagent has not yet been reported. Several useful BCP-based reagents, such as Grignard reagents[14], iodides[6,15,16], boronates[7,12,17] and redox-active esters[18], have been developed. Although most of these reagents can successfully engage in C–C bond formations, none has yet reached the generality in reactivity of [1.1.1]propellane[4], and they often lack stability for storage[19] or require multiple steps for preparation[18]. Furthermore, neither BCP-based reagents nor [1.1.1]propellane are yet available for the synthesis of aryl bicyclo[1.1.1]pentyl ethers.

Sulfonium salts can act in nature as efficient alkylation reagents[20]. Similarly, chemists have used sulfonium salts in alkylation reactions, but the transfer of tertiary alkyl groups, such as bicyclopentyl, remains unknown. We have previously reported on the reactivity of arylthianthrenium salts, which can expand the chemical space of (pseudo)halides, and attributed their unusual properties to the thianthrene scaffold[21–26]. Based on single electron reactivity, a high reduction potential, and the ability to function as a good leaving group and readily engage in radical chemistry, we have devised a strategy for the synthesis of BCP-thianthrenium salts that function

[1]Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany. [2]Institute of Organic Chemistry, RWTH Aachen University, Aachen, Germany. [3]These authors contributed equally: Eva Maria Alvarez, Zibo Bai. e-mail: ritter@kofo.mpg.de

https://doi.org/10.1038/s44160-023-00277-8

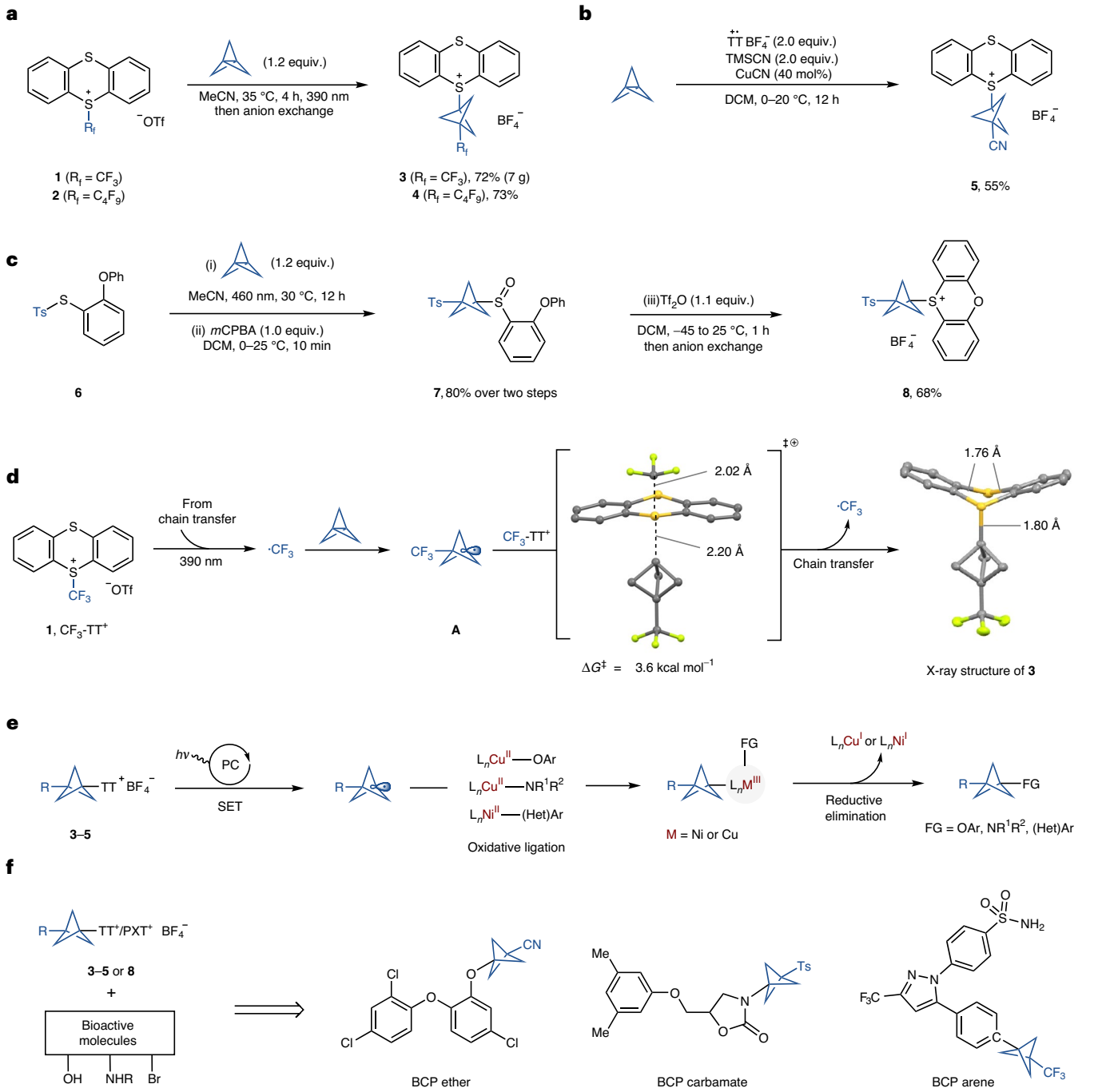

Fig. 1 | Synthesis of cyclo[1.1.1]pentylthianthrenium salts. a, Synthesis of CF_3BCP-TT$^+$ BF_4^- (**3**) and *n*-C_4F_9BCP-TT$^+$ BF_4^- (**4**). General reaction conditions: CF_3-TT$^+$ $^-$OTf (1.0 equiv.), [1.1.1]propellane (1.2 equiv.), MeCN (0.14 M), purple LED (390 nm), 35 °C, 4 h, then anion exchange by aqueous work-up with $NaBF_4$ (10% w/w). **b**, Synthesis of CNBCP-TT$^+$ BF_4^- (**5**). Reagents and conditions: [1.1.1] propellane (1.0 equiv.), TT$^{+\cdot}$ BF_4^- (2.0 equiv.), TMSCN (2.0 equiv.), CuCN (40 mol%), DCM (0.20 M), 0–20 °C, 12 h. **c**, Synthesis of TsBCP-PXT$^+$ BF_4^- (**8**). Reagents and conditions: (i) **6** (1.0 equiv.), [1.1.1]propellane (1.2 equiv.), MeCN (0.12 M), blue LEDs (460 nm), 30 °C, 12 h; (ii) *m*CPBA (1.0 equiv), DCM (0.3 M), 0–25 °C, 10 min; (iii) Tf_2O (1.1 equiv.), DCM (0.12 M), –45 to 25 °C, 1 h, then anion exchange by aqueous work-up with $NaBF_4$ (10% w/w). **d**, Proposed mechanism for the formation of **3** proceeding by radical chain propagation. The crystal structure of **3** is shown. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms and the counterion have been omitted for clarity. **e**, Proposed mechanism for the cross-coupling of BCP-TT$^+$ salts enabled by photoredox catalysis and transition metal catalysis. **f**, Synthetic utility of BCP-TT$^+$ and BCP-PXT$^+$ salts. TMS, trimethylsilyl; DCM, dichloromethane; Ts, 4-toluenesulfonyl; *m*CPBA, 3-chloroperbenzoic acid; Tf, trifluoromethanesulfonyl; PXT, phenoxathiine; PC, photoredox catalyst; L, ligand; hv, the energy of a photon; h, Planck's constant; v, photon frequency; FG, functional group; Ar, aryl; Het, hetero.

as stable and versatile alkylating reagents. Distinct from conventional alkylsulfonium salts, thianthrenium-substituted BCPs can engage in radical chemistry that productively combines photoredox catalysis with transition metal-mediated bond formation. Although copper catalysis has been used successfully in thianthrene (TT)[27] and BCP[10] chemistry, we also introduce here a previously unreported photoredox-mediated nickel-catalysed cross-coupling reaction with alkylthianthrenium salts.

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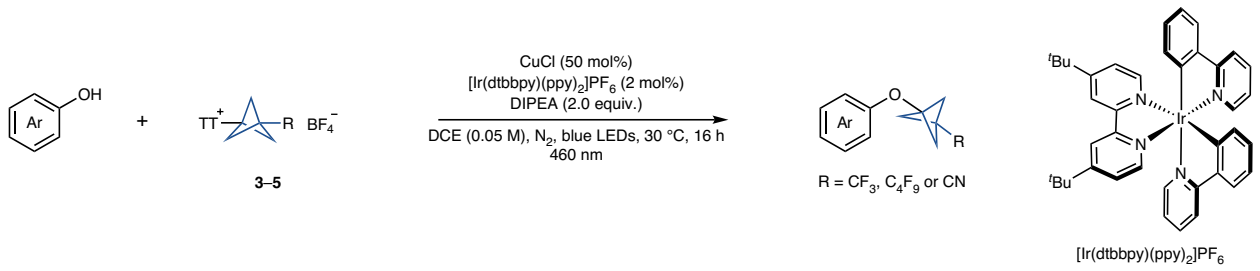
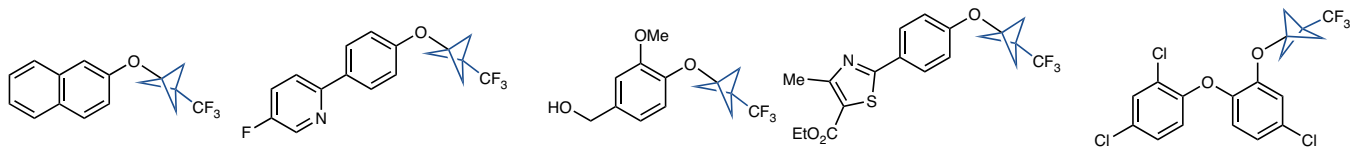
Table 1 | Substrate scope for Cu-catalysed C–O cross-coupling of 3–5 with phenols





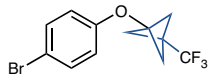
9, 78%

10, 82%[a]

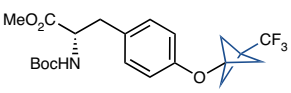
From vanillyl alcohol
11, 84%

From febuxostat intermediate
12, 60%

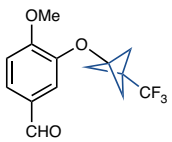
From triclosan
13, 83%



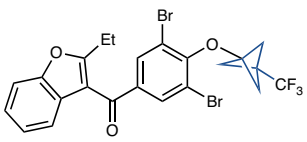
14, 71%



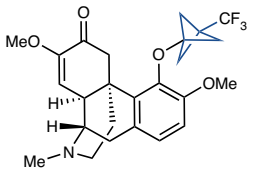
15, 69%



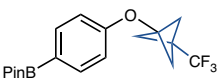
From isovanillin
16, 91%



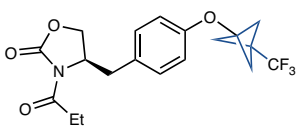
From benzbromaron
17, 80%[b]



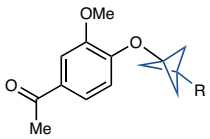
From sinomenine
18, 41%[b]



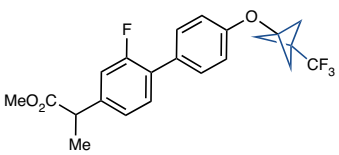
19, 62%



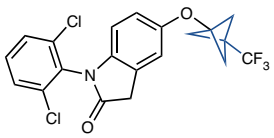
20, 90%



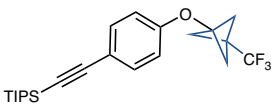
From apocynin
21 (R = CF_3), 81%
22 (R = C_4F_9), 84%



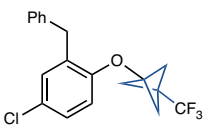
From hydroxyflurbiprofen methyl ester
23, 70%[a]



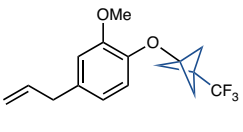
From hydroxydiclofenac amide
24, 61%



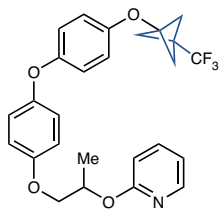
25, 95%



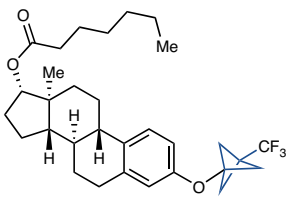
From chlorophene
26, 96%



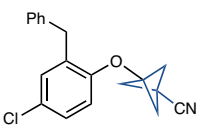
From eugenol
27, 62%



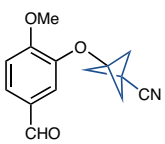
From (±)-hydroxypyriproxyfen
28, 64%



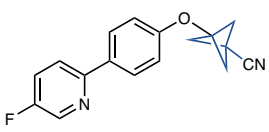
From estradiol
29, 72%



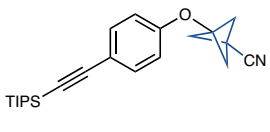
From chlorophene
30, 78%



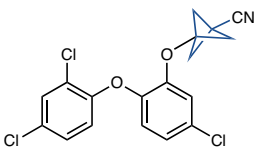
From isovanillin
31, 82%



32, 86%[a]



33, 75%



From triclosan
34, 77%

General reaction conditions: phenol (0.15 mmol, 1.0 equiv.), **3**–**5** (2.0 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (2 mol%), CuCl (50 mol%), DIPEA (2.0 equiv.), DCE (0.05 M), N_2, blue LEDs (460 nm, 40 W), 30 °C, 16 h. [a]DCM (0.05 M) was used instead of DCE. [b]Compounds **3**–**5** (3.0 equiv.) and CuCl (100 mol%) were used. DIPEA, *N*,*N*-diisopropylethylamine; DCE, 1,2-dichloroethane; pin, pinacolato; TIPS, triisopropylsilyl; Boc, *tert*-butoxycarbonyl.

Results and discussion

Development of stable thianthrenium-based BCP reagents

The CF_3BCP-TT$^+$ salt **3** was synthesized by the addition reaction between the trifluoromethylthianthrenium reagent **1** (ref. [28]) and [1.1.1]propellane (Fig. 1a). All the experimental observations (Supplementary Figs. 12 and 13) were consistent with a radical chain transfer mechanism initiated by the irradiation of **1** with purple light-emitting diodes (LEDs) at a wavelength transparent to **3** to induce homolytic

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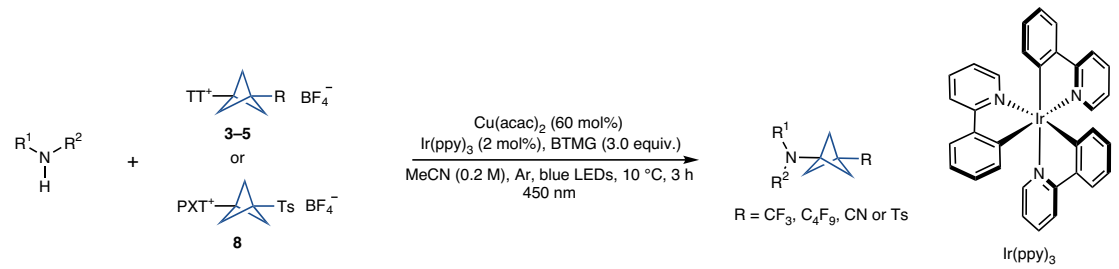
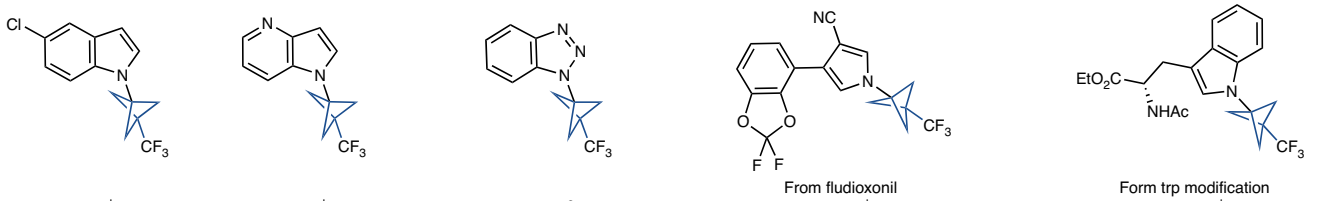
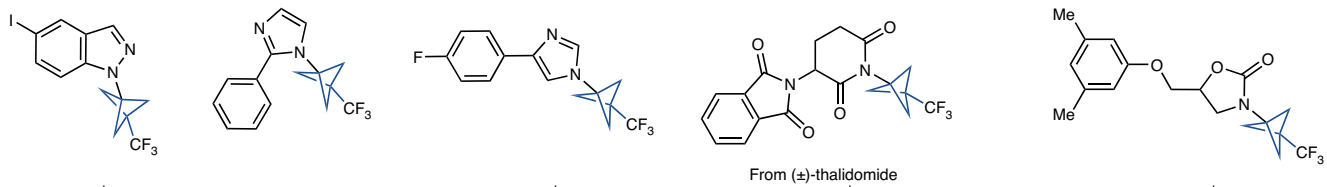
Table 2 | Substrate scope for C–N cross-coupling of 3–5 and 8 with N-nucleophiles

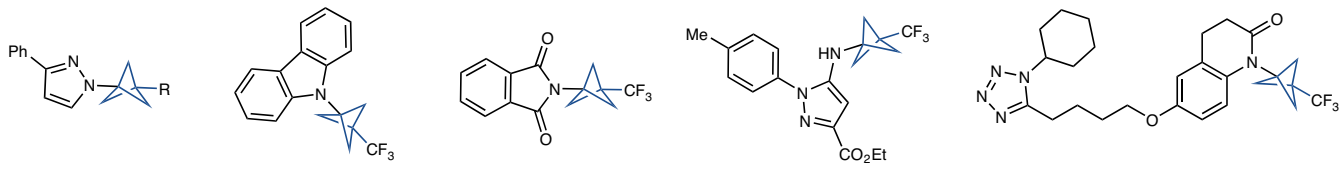




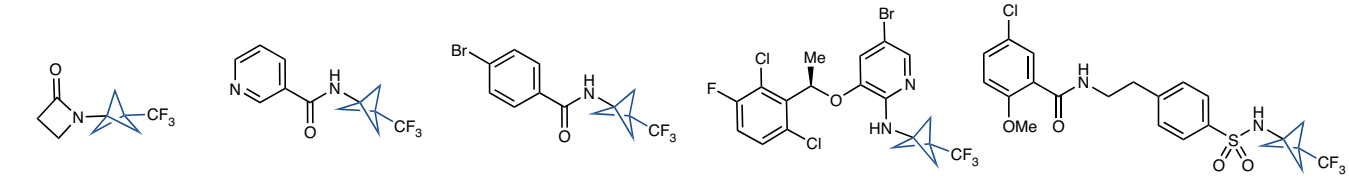
35, 61%[b] | **36**, 97%[b] | **37**, 60%[a] | From fludioxonil **38**, 44%[b] | Form trp modification **39**, 86%[b]



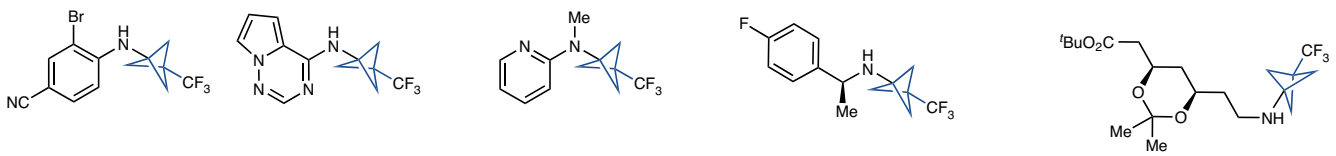
40, 61%[b] | **41**, 53%[a] | **42**, 78%[b] | From (±)-thalidomide **43**, 33%[b] | **44**, 93%[b]



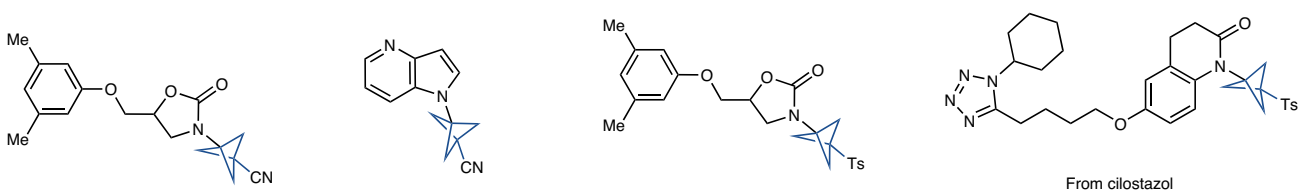
45 (R = CF_3), 92%[b]
46 (R = C_4F_9), 89%[b]
47, 60%[a] | **48**, 59%[a] | **49**, 82%[b] | From cilostazol **50**, 94%[b]



51, 88%[b] | **52**, 78%[a] | **53**, 53%[a] | From crizotinib **54**, 84%[b] | From glimenclamide **55**, 79%[b]



56, 83%[b] | **57**, 87%[a] | **58**, 64%[a,d] | **59**, 51%[b,c] | **60**, 24%[a,c]

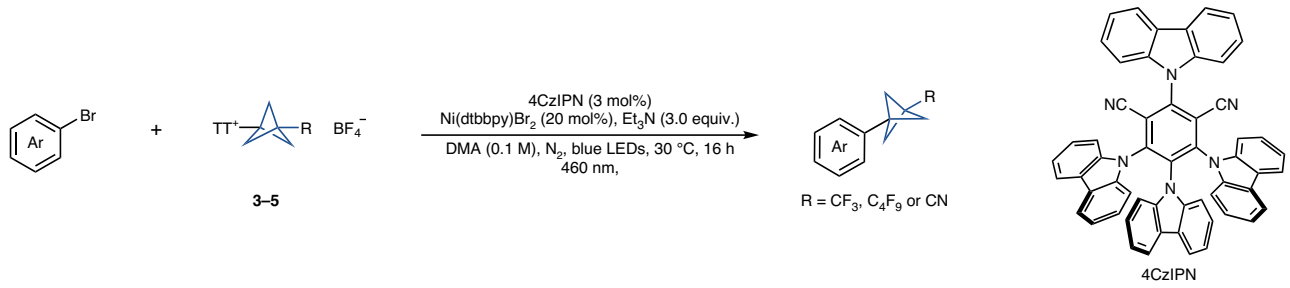


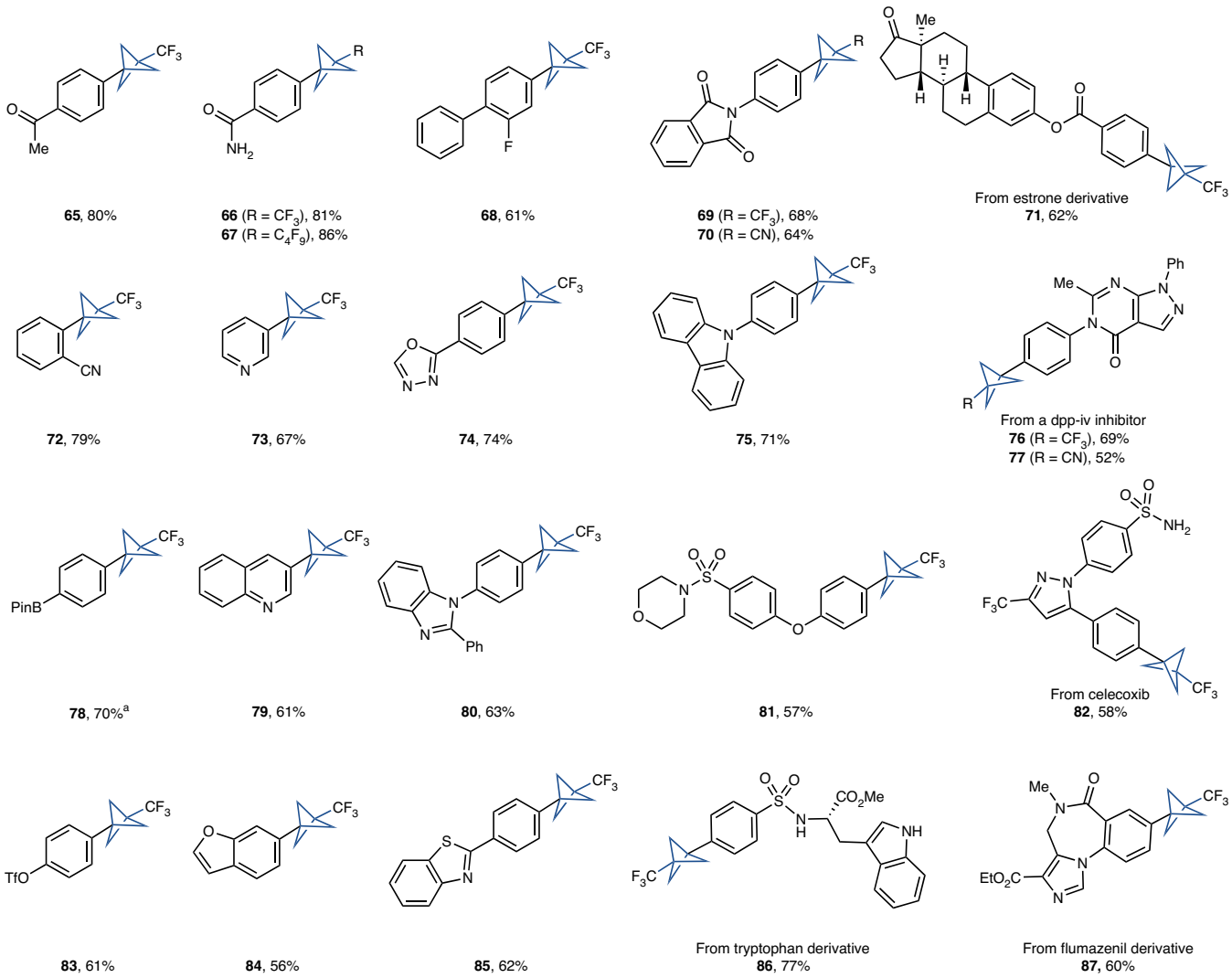
61, 89%[b] | **62**, 72%[b] | **63**, 60%[b] | From cilostazol **64**, 60%[b]

General reaction conditions: N-nucleophile (0.25 mmol, 1.0 equiv.), **3**–**5** or **8** (1.3 equiv.), $Ir(ppy)_3$ (2 mol%), $Cu(acac)_2$ (60 mol%), BTMG (3.0 equiv.), MeCN (0.2 M), Ar, blue LEDs (450 nm, 60 W), 10 °C, 3 h. [a]Compounds **3**–**5** (1.0 equiv.) and N-nucleophile (1.50–1.80 equiv.) were used. [b]N-Nucleophile (1.0 equiv.) and **3**–**5** or **8** (1.30–2.00 equiv.) were used. [c]$[Cu(MeCN)_4]BF_4$ (1.0 equiv.) was used as catalyst and K_2CO_3 (2.0 equiv.) was used as base. [d]K_2CO_3 (2.0 equiv.) was used as base. acac, acetylacetonate; BTMG, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine; trp, tryptophan.

https://doi.org/10.1038/s44160-023-00277-8

Table 3 | Substrate scope for Ni-catalysed reductive C–C cross-coupling of 3–5 with (hetero)aryl bromides





General reaction conditions: aryl halide (0.20 mmol, 1.0 equiv.), **3**–**5** (1.5 equiv.), 4CzIPN (3 mol%), Ni(dtbbpy)Br_2 (20 mol%), Et_3N (3.0 equiv.), DMA (0.1 M), N_2, blue LEDs (460 nm, 40 W), 30 °C, 16 h. [a]Ni(dtbbpy)Cl_2 (20 mol%) was used as catalyst. 4CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; DMA, *N*,*N*-dimethylacetamide; dpp-iv, dipeptidyl peptidase-iv.

S–CF_3 cleavage, followed by radical addition of the CF_3 radical to [1.1.1]propellane to form the putative BCP radical **A**. Subsequent chain propagation by abstraction of a thianthrenium radical cation from **1** by **A** via a low-lying transition state is supported by density functional theory (DFT) calculations (Supplementary Tables 15–18) and consistent with a measured quantum yield of $\Phi = 16$ (Fig. 1d). The stability of the thianthrenium radical cation sets TT apart from conventional sulfides. In contrast to volatile and thermally unstable propellane[29], compound **3** is a non-hygroscopic, free-flowing powder with a melting point of 150 °C that can be stored under ambient conditions without observable decomposition for at least 1 year. Differential scanning calorimetry analysis confirmed that heating **3** to 170 °C did not lead to exothermic decomposition, which attests to its favourable safety properties. Although compound **3** is synthesized from [1.1.1]propellane, the practitioner interested in BCP substitution would not be required to handle the unstable reagent if **3** were produced centrally and distributed. Based on the same strategy, we prepared nonafluorobutyl-BCP-TT^+ salt **4** from **2** in 73% yield (Fig. 1a). In addition, this class of compound can be accessed by an alternative mechanism from *S*-substituted TT-based reagents, as shown by the reaction of a persistent thianthrenium radical cation with [1.1.1]propellane to afford the cyano-substituted BCP reagent **5** (Fig. 1b),

https://doi.org/10.1038/s44160-023-00277-8

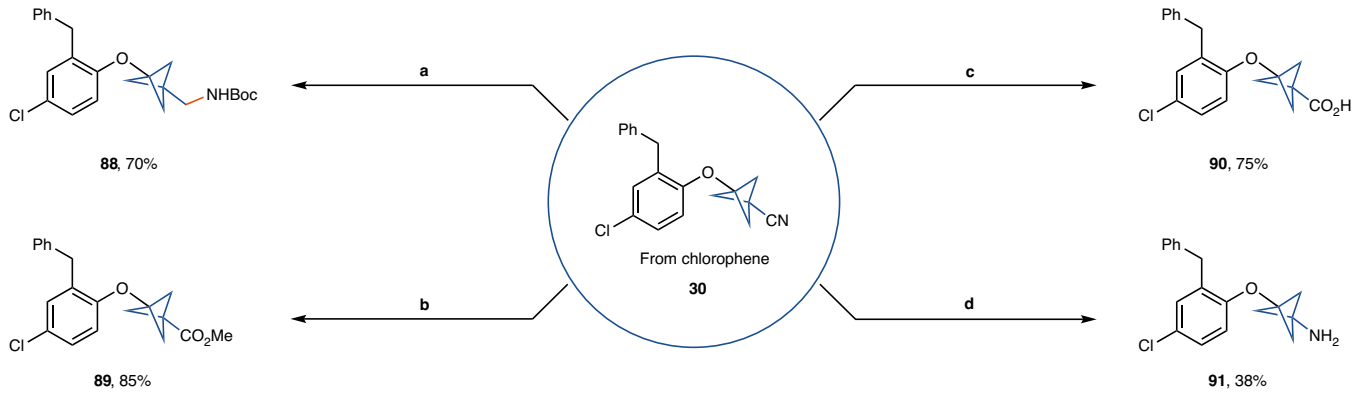


Fig. 2 | Synthetic transformations of cyanobicyclo[1.1.1]pentyl ether 30. Reagents and conditions: **a**, $NiCl_2$, $NaBH_4$, Boc_2O, MeOH, 25 °C, 6 h. **b**, H_2SO_4, MeOH, 65 °C, 12 h. **c**(i), H_2SO_4, MeOH, 65 °C, 12 h; (ii) $LiOH{\cdot}H_2O$, THF–H_2O, 25 °C, 3 h. **d**(i) H_2SO_4, MeOH, 65 °C, 12 h; (ii) $LiOH{\cdot}H_2O$, THF–H_2O, 25 °C, 3 h; (iii) DPPA, Et_3N, toluene, 25–105 °C, 6 h, then 1 M HCl, 60 °C, 12 h. See the Supplementary Information for detailed experimental conditions. DPPA, diphenylphosphoryl azide.

and the stepwise synthesis of 4-toluenesulfonyl-BCP-phenoxathiine salt **8** starting from thiosulfonate **6** (Fig. 1c)[30].

It was expected that the cationic BCP-TT$^+$ salts **3**–**5** would be easily reduced by single electron transfer (SET)[22] from the excited state of a photoredox catalyst or a reduced photoredox catalyst obtained by reductive quenching of the excited state. We observed reductive quenching of the excited photocatalyst $[Ir(dtbbpy)ppy_2]PF_6$ (dtbbpy, 4,4′-di-*tert*-butyl-2,2′-dipyridyl; ppy, 2-phenylpyridine) in Stern–Volmer quenching studies, for example, in the presence of copper(I), to generate putative Ir(II) for SET reduction of **3** (half-wave potential ($E_{1/2}$) = −1.4 V for **3**; Ir^{III}/Ir^{II} = −1.5 V (ref. 31), both versus the saturated calomel electrode in MeCN; Supplementary Figs. 16–21). The ensuing chemoselective mesolytic cleavage of the exocyclic BCP-thianthrene C–S bond can be rationalized by both a notably longer exocyclic C–S bond compared with the endocyclic C–S bonds within the TT scaffold, as determined by X-ray crystallographic analysis of **3** (Fig. 1d), and barrierless homolysis of the exocyclic C–S bond upon single electron reduction of **3**, as supported by DFT calculations (Supplementary Figs. 14 and 15). The resulting synthetically useful BCP radical is thus readily generated in situ by functional group-tolerant photoredox-mediated SET. Oxidative ligation of the BCP radical to transition metals in medium oxidation states, such as Cu(II), obtained by reductive quenching of the excited photocatalyst, or Ni(II), obtained by oxidative addition to aryl halides, can provide high-valent transition metal–BCP complexes. Ensuing facile reductive elimination reactions in which the BCP scaffold attaches to functional groups should be achievable from such high-valent complexes (Fig. 1e).

Scope of *O*-bicyclopentylation

Aryl bicyclo[1.1.1]pentyl ethers have potential as bioisosteres of diaryl ether derivatives, which are common structural motifs in pharmaceutically important natural and synthetic compounds[32]. However, no synthetic procedure towards aryl bicyclo[1.1.1]pentyl ethers is currently documented. Reagents **3**–**5** can successfully be used in the metallaphotoredox-catalysed alkylation of phenols with substoichiometric amounts of copper salts to access the previously unknown class of aryl bicyclo[1.1.1]pentyl ethers (Table 1). The reaction exhibits broad scope and proceeds efficiently with phenols bearing electron-neutral, -rich and -poor substituents (for example, **9**, **11** and **17**, respectively), as well as *ortho*-substituted phenols (for example, **13**, **16** and **18**). Synthetically useful functional groups, such as hydroxy (**11**), ester (**12**, **15**, **23** and **29**), amide (**15**), aldehyde (**16**), 2-oxazolidone (**20**), ketone (**21**), lactam (**24**), alkynyl (**25**), alkenyl (**27**) and even tertiary amines (**18**) are tolerated, highlighting the mildness of the reaction conditions. Aryl chlorides (**13**, **24** and **26**) and bromides (**14** and **17**) are also tolerated, resulting in potential reactive sites for functional group conversion. Similarly, pinacolboranyl (Bpin; **19**) and triisopropylsilyl (**25**) groups are tolerated, which are well known nucleophilic coupling partners for Suzuki and Hiyama cross-coupling reactions, respectively. In addition, Lewis basic heterocycles, including pyridine (**10**) and thiazole (**12**), which can be a liability in transition metal-catalysed coupling reactions, do not inhibit the desired cross-coupling reactions. The reaction is also chemoselective with respect to N-nucleophiles (for example, **15**; vide infra). Due to the broad functional group compatibility, late-stage functionalization of drug molecules, such as triclosan (**13**), benzbromaron (**17**), sinomenine (**18**) and chlorophene (**26**), is viable. Combined with TT-mediated late-stage aromatic C–H hydroxylation[25], we have realized a multistep site-selective C–H bicyclopentyloxylation of small-molecule pharmaceuticals and pesticides, such as flurbiprofen methyl ester (**23**), diclofenac amide (**24**) and pyriproxyfen (**28**).

Scope of *N*-bicyclopentylation

An analogous strategy was successful for the bicyclopentylation of N-nucleophiles (Table 2). Compared with the published *N*-alkylation reactions with propellane[8,10,33–36], *N*-bicyclopentylation with **3**–**5** and **8** has much greater scope. Medicinally relevant substructures, such as indoles (**35** and **39**) and pyrrole (**38**), are compatible with our protocol, as are 4-azaindole (**36**), benzotriazole (**37**), indazole (**40**), imidazoles (**41** and **42**), pyrazoles (**45** and **46**) and carbazole (**47**). Moreover, the methodology is not limited to N-heterocycles, as phthalimide (**48**), dihydroquinolinone (**50**), β-lactam (**51**), amides (**52** and **53**) and sulfonamide (**55**) also work well in this transformation. Aniline (**56**), 2-aminopyridines (**54** and **58**) and 5-aminopyrazole (**49**) also undergo C–N coupling in good yields. Notably, 2-aminopyrrolo[2,1-*f*][1,2,4]triazine (**57**), which is found in the structure of remdesivir[37] (an antiviral agent against COVID-19), can be functionalized efficiently. By slightly modifying the conditions, the scope of the reaction could be further extended to benzylamines (**59**) and alkylamines (**60**). As in the corresponding ether bond formation, broad functional group tolerance, even for redox-active aryl iodides (**40**), enables late-stage modification of various pharmaceutically relevant molecules in the drug discovery process (**38**, **39**, **43**, **50**, **54**, and **55**), as shown in Table 2. Basic, electron-rich tertiary amines are not tolerated, potentially a consequence of their single electron oxidation by excited photoredox catalysts. When more than one N-nucleophile is present, functionalization of the more acidic position proceeds chemoselectively (for example, **55**). Both C–O and C–N bond-forming reactions are, in principle, catalytic in the transition metal, yet the use of about half

an equivalent of copper afforded higher yields. Although a lower copper loading is possible, the reduced yield is, in our opinion, not justifiable given the low cost of simple copper salts compared with the cost of the other complex starting materials employed in these transformations.

Scope of *C*-bicyclopentylation

Reagents **3**–**5** can, beyond C–heteroatom cross-coupling with copper, also participate in metallophotoredox catalysis with nickel catalysts for reductive C–C cross-coupling reactions with (hetero) aryl bromides (Table 3). The synergistic cooperation of nickel and photoredox catalysis with thianthrenium salts has not been reported before. Carbon–carbon cross-coupling reactions of iodo-BCPs[9], BCP Grignard reagents[14], BCP-boronates[7,12,17] and BCP redox-active esters[18] have been developed previously, but not with reagents as synthetically convenient as **3**–**5**. The mechanism from **3**–**5** could proceed through a Ni(0)–Ni(II)–Ni(III)–Ni(I) cycle with oxidative ligation of the BCP radical to a Ni(II)–aryl complex obtained by the oxidative addition of Ni(0) to an aryl bromide, with ensuing reductive C–C elimination from a putative high-valent Ni(III) complex[38]. The cross-coupling of electron-poor arenes (**65**, **66**, **72** and **83**) was successful, while engaging electron-rich arenes resulted in lower yields (**81**). Under the current reaction conditions, a variety of functional groups are tolerated, such as ketones (**65**), amides (**66** and **67**), esters (**71**, **86** and **87**), nitriles (**72**), heteroarenes (**74**, **76**, **80**, **82** and **85**–**87**), and primary, secondary and tertiary sulfonamides (**81**, **82** and **86**). The reactive functional groups Bpin (**78**) and triflate (**83**) are also well tolerated. The synthetic utility of the strategy is further exemplified by the functionalization of heteroaromatic bromides (**73**, **79** and **84**) and pharmaceuticals (**77, 82** and **87**). The most prominent side reaction for electron-rich aryl bromides is protodebromination.

Synthetic applications

To highlight the synthetic utility of the methodology, we performed several transformations on cyanobicyclo[1.1.1]pentyl ether **30** (Fig. 2). For example, the reduction of **30** with $NiCl_2$ and $NaBH_4$ afforded alkylamine **88** in 70% yield. In addition, the cyano group was converted into BCP ester **89** and BCP carboxylic acid **90**. Finally, BCP amine **91** was prepared from **30** by Curtius rearrangement.

Conclusion

We have reported here a storable, thianthrenium-based class of BCP transfer reagents that can afford valuable small molecules that are in part currently inaccessible by other methods. We anticipate that the commercial availability of a stable and readily employed reagent would enable practitioners, for example, in the pharmaceutical industry, to introduce the promising BCP substituent substantially more easily into small molecules of interest than is possible today.

Methods

General procedure for Cu-catalysed C–O coupling of 3–5 with phenols

Under nitrogen atmosphere, a 4-ml borosilicate vial equipped with a magnetic stirring bar was charged with phenol (0.150 mmol, 1.00 equiv.), **3**–**5** (0.300 mmol, 2.00 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (3 mg, 3 µmol, 2 mol%), CuCl (7.4 mg, 75 µmol, 50 mol%), anhydrous DCE (3.0 ml, c = 50 mM) and DIPEA (52 µl, 39 mg, 0.30 mmol, 2.0 equiv.). The vial was sealed with a septum cap. The mixture was then stirred for 10 min at 25 °C, placed 5 cm away from two blue LEDs (Kessil A160WE Tuna Blue (460 nm), LED lighting, 40 W) and irradiated for 16 h while maintaining the temperature at approximately 30 °C by cooling with a fan. After irradiation, the mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel to afford the desired product.

General procedure A for Cu-catalysed C–N coupling of 3–5 and 8 with N-nucleophiles

Under air, a 4-ml borosilicate vial equipped with a magnetic stirring bar was charged with the N-nucleophile (0.300 mmol, 1.00 equiv.), **3**–**5** or **8** (1.30–2.00 equiv.), $Ir(ppy)_3$ (4 mg, 6 µmol, 2 mol%) and $Cu(acac)_2$ (47 mg, 0.18 mmol, 60 mol%). The vial was sealed with a septum cap, evacuated and flushed with argon three times using Schlenk techniques. Under a positive pressure of 0.1 bar argon, BTMG (0.18 ml, 0.15 g, 0.90 mmol, 3.0 equiv.) was added, followed by anhydrous MeCN (1.5 ml, c = 0.20 M). The mixture was irradiated for 3 h at 10 °C using a photoreactor equipped with a blue LED module (KT-Elektronik, '100 W Power LED blau 450 nm Aquarium', 450 nm, 60 W), cooled with two Peltier elements (TEC1-12706). After irradiation, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the desired product.

General procedure B for Cu-catalysed C–N coupling of 3–5 and 8 with N-nucleophiles

Under air, a 4-ml borosilicate vial equipped with a magnetic stirring bar was charged with **3**–**5** or **8** (0.250 mmol, 1.00 equiv.), the N-nucleophile (1.50–1.80 equiv.), $Ir(ppy)_3$ (3.3 mg, 5.0 µmol, 2 mol%) and $Cu(acac)_2$ (39.3 mg, 0.150 mmol, 60 mol%). The vial was sealed with a septum cap, evacuated and flushed with argon three times using Schlenk techniques. Under a positive pressure of 0.1 bar argon, BTMG (0.15 ml, 0.13 g, 0.75 mmol, 3.0 equiv.) was added, followed by anhydrous MeCN (1.3 ml, c = 0.20 M). The mixture was irradiated for 3 h at 10 °C using a photoreactor equipped with a blue LED module (KT-Elektronik, '100 W Power LED blau 450 nm Aquarium', 450 nm, 60 W), cooled with two Peltier elements (TEC1-12706). After irradiation, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the desired product.

General procedure for Ni-catalysed reductive C–C coupling of 3–5 with aryl bromides

Under nitrogen atmosphere, a 4-ml borosilicate vial equipped with a magnetic stirring bar was charged with the aryl bromide (0.200 mmol, 1.00 equiv.), **3**–**5** (0.300 mmol, 1.50 equiv.), 4CzIPN (5 mg, 6 µmol, 3 mol%), $Ni(dtbbpy)Br_2$ (19.4 mg, 40.0 µmol, 20.0 mol%), anhydrous DMA (2.0 ml, c = 0.10 M) and Et_3N (83 µl, 61 mg, 0.60 mmol, 3.0 equiv.). The vial was sealed with a septum cap. The mixture was then stirred for 10 min at 25 °C, placed 5 cm away from two blue LEDs (Kessil A160WE Tuna Blue (460 nm), LED lighting, 40 W) and irradiated for 16 h while maintaining the temperature at approximately 30 °C by cooling with a fan. After irradiation, EtOAc (6 ml) was added to the mixture, which was then washed with brine (2 × 3 ml). The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product.

Data availability

The data reported in this paper are available in the main text or the Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2075820 (compound **3**) and 2172887 (compound **5**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Acknowledgements

We thank S. Marcus, D. Margold, F. Köhler, N. Haupt and D. Kampen for mass spectrometric analysis, M. Kochius, M. Leutzsch and C. Wirtz for NMR spectroscopic analysis, J. Rust for X-ray crystallographic analysis, H. Jia for the synthesis of reagent **2**, and F. Berger, H. Jia, S. Lin and L. Zhang (all MPI für Kohlenforschung) for helpful scientific discussions. Z.B. acknowledges the Alexander von Humboldt Foundation for a Humboldt Research Fellowship. N.F. thanks the Studienstiftung des Deutschen Volkes for a scholarship. We thank the MPI für Kohlenforschung for funding.

Author contributions

E.M.A. initiated the project, developed the synthesis of reagent **3** and C–N bond formation, initiated the C–O bond formation and conducted mechanistic experiments. Z.B. developed the synthesis of reagents **5** and **8**, the C–O bond formation and the synthetic transformations of **30**. Z.B. and S.P. developed the C–C bond formation. E.M.A., Z.B., S.P. and L.T. synthesized the compounds presented in Tables 1–3. N.F. executed DFT calculations. E.M.A., Z.B. and T.R. wrote the paper. T.R. directed the project.

Funding

Open access funding provided by Max Planck Society.

Competing interests

E.M.A., Z.B. and T.R. are listed as inventors for a patent application (*A Bicyclopentyl Thianthrenium Compound, Process for Preparing the Same and the Use Thereof*, application no. EP22181685.3; filing year, 2022, status, pending) filed by SGK in Germany for compounds **3** and **5** and their use. The remaining authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44160-023-00277-8.

Correspondence and requests for materials should be addressed to Tobias Ritter.

Peer review information *Nature Synthesis* thanks Christophe Aissa, Masanobu Uchiyama and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Thomas West, in collaboration with the *Nature Synthesis* team.

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