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Formal γ–C–H Functionalization of Cyclobutyl Ketones: Synthesis of *cis*-1,3-Difunctionalized Cyclobutanes

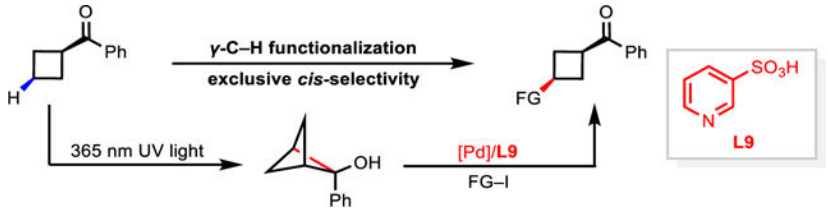
Zhoulong Fan[a,+], **Daniel A. Strassfeld**[a,+], **Han Seul Park**[a], **Kevin Wu**[a], **Jin-Quan Yu**[a]

[a]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)

Abstract

1,3-Difunctionalized cyclobutanes are an emerging scaffold in medicinal chemistry that can confer beneficial pharmacological properties to small-molecule drug candidates. However, the diastereocontrolled synthesis of these compounds typically requires complicated synthetic routes, indicating a need for novel methods. Here, we report a sequential C–H/C–C functionalization strategy for the stereospecific synthesis of *cis*-γ-functionalized cyclobutyl ketones from readily available cyclobutyl aryl ketones. Specifically, a bicyclo[1.1.1]pentan-2-ol intermediate is generated from the parent cyclobutyl ketone via an optimized Norrish-Yang procedure. This intermediate then undergoes a ligand-enabled, palladium-catalyzed C–C cleavage/functionalization to produce valuable *cis*-γ-(hetero)arylated, alkenylated, and alkynylated cyclobutyl aryl ketones, the benzoyl moiety of which can subsequently be converted to a wide range of functional groups including amides and esters.

Graphical Abstract



A sequential C–H/C–C functionalization strategy was reported to effect the otherwise challenging synthesis of 1,3-disubstituted cyclobutane building blocks. Numerous aryl, heteroaryl, alkenyl, and alkynyl groups can be installed at the 3-position of the cyclobutane ring with exclusive *cis*-selectivity.

Keywords

C–H functionalization; cyclobutanes; palladium; diastereocontrol; ligand

yu200@scripps.edu .

[+]These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.

Conflict of interest

The authors declare no conflict of interest.

Cyclobutanes have recently become the focus of increased interest in medicinal chemistry due to their unique shape and rigidity, which can enhance pharmacological properties such as metabolic stability and binding efficiency.[1] Particular attention has been directed towards 1,3-disubstituted cyclobutanes because they adopt a puckered linear geometry that can serve as a conformationally restricted alternative to ethyl or propyl linkers or as an aryl isostere with decreased planarity.[1,2] Multiple small molecules containing 1,3-disubstituted cyclobutanes have entered the clinic, including PF-03654746, a histamine H_3 antagonist for the treatment of cognitive disorders,[3] and TAK-828F, a retinoic acid-related orphan receptor (RORγt) inverse agonist for the treatment of autoimmune diseases (Figure 1A),[4] highlighting the value of this unique motif in drug design. Accordingly, a variety of synthetic strategies have been developed for accessing 1,3-difunctionalized cyclobutanes, including: (i) intermolecular [2+2][5] and [3+1][6] cycloadditions; (ii) strain-release-driven C–C cleavage/functionalization of bicyclo[1.1.0]butanes;[7] and (iii) the direct radical C–H chlorination of cyclobutanes (Figure 1B).[8] Unfortunately, these strategies typically provide little control over *cis*- vs. *trans*-selectivity, and most rely on specialized precursors (activated alkenes, 1,1-diborylalkanes, or bicyclo[1.1.0]butanes), which can be difficult to access efficiently. Thus, there remains a need for efficient synthetic methods that enable diastereocontrolled syntheses of 1,3-disubstituted cyclobutanes containing versatile synthetic handles.

Our research group is guided by the long-term goal of developing catalytic strategies to enable molecular editing of C–H bonds at any site and in any order.[9] In accord with this goal, we hypothesized that C–H bond functionalization could provide an efficient solution for accessing diverse 1,3-difunctionalized cyclobutanes from readily available cyclobutane substrates. Given the well-established preference for C–H activation at the more proximal β-position of cyclobutanes,[10] we turned to alternative strategies for selectively cleaving the γ-C–H bond. Norrish type II reactivity—which reliably cleaves γ-C–H bonds via hydrogen atom transfer to a photochemically excited carbonyl—seemed particularly promising, as it would complement existing methods for transient-directing-group-enabled β-arylations of cyclobutyl ketones.[10a,c,d]

Recently, Sarpong, Yeung, Baik, Musaev and coworkers have successfully exploited Norrish Type II reactivity for sequential C–H/C–C functionalization of the α-position in piperidine derivatives (Figure 1C, limited examples of β-functionalization were also demonstrated via chain walking).[11] Palladium-catalyzed C–C bond cleavage of cyclobutanols and other strained alcohols to access linear ketones have also been extensively investigated,[12] and a strain-release-driven C–C cleavage process has been used to synthesize 3,3-disubstituted cyclobutanones from bicyclo[1.1.1]pentan-1-ol via established Pd(0)/Pd(II) catalysis (Figure 1D).[13] Inspired by these examples, we envisioned that Pd-catalyzed C–C bond cleavage of the isomeric bicyclo[1.1.1]pentan-2-ol followed by functionalization of the resulting organopalladium intermediate could provide access to *cis*-1,3-disubstituted cyclobutanes. Since the key bicyclo[1.1.1]pentan-2-ol intermediate can be accessed by a UV-light promoted Norrish-Yang cyclization of the corresponding cyclobutyl ketone,[14] the proposed two-step sequence would amount to a formal γ-C–H functionalization of cyclobutyl ketones (Figure 1E). Herein we report the successful development of this two-

step route to afford 1,3-disubstituted cyclobutane building blocks—valuable products which are otherwise challenging to access—from readily available aryl cyclobutyl ketone starting materials. A range of aryl, heteroaryl, alkenyl, and alkynyl substituents can be installed at the 3-position of cyclobutyl ketones with exclusive selectivity for the *cis*-isomer. The benzoyl motif used to enable the reactivity can then be converted to an amide, ester, or other functional groups.

To test the feasibility of the C–H/C–C functionalization strategy, we first investigated the Norrish-Yang cyclization of cyclobutyl phenyl ketone **1a** to afford key intermediate 2-phenylbicyclo[1.1.1]pentan-2-ol **2a**. Prior studies have reported 15–38% yield accompanied by pinacol and ring-opened pentenone side-products when a 450-W Hanovia mercury arc lamp was employed.[14] Gratifyingly, we found that replacing the mercury lamp with a milder 365 nm UV source simplified reaction setup, significantly reduced the generation of side-products, and improved the yield of **2a** up to 45%. Electron-withdrawing aryl cyclobutyl ketones worked well and gave moderate yields. However, electron-rich aryl cyclobutyl ketones failed to form the corresponding bicyclic products (Scheme 1).

Having established a practical route to intermediate **2**, we next sought to investigate the Pd-catalyzed C–C cleavage/arylation of 2-phenylbicyclo[1.1.1]pentan-2-ol **2a** with methyl 4-iodobenzoate **3a** (Table 1). In the absence of ligand, $Pd(OAc)_2$ was found to afford the desired arylation product **4a** in 21% yield along with side-product **1a** in 12% yield. Varying reaction parameters based on this initial lead did not afford any improvement. Guided by our lab's work on the development of ligand-enabled C–H functionalization reactions,[15] we examined the effect of mono-*N*-protected amino acid (MPAA) and amino-acid-derived ligands (**L1-L5**). However, these ligands failed to increase the yield of **4a** to synthetically useful levels. Next, we screened a series of 2-pyridone, pyridine, and quinoline ligands (**L6-L15**).[16] Pyridine 3-sulfonic acid ligand **L9** was found to be optimal for the C–C cleavage/arylation step, affording **4a** in 75% yield.

With the optimized ligand and reaction conditions in hand, we next examined the scope of the transformation. A variety of *ortho*-, *meta*-, and *para*-substituted iodobenzene coupling partners were tested, providing corresponding products **4b-4p** in good to excellent yields (Scheme 2, aryl bromides led to reduced yield and aryl chlorides and sulfonates were unreactive, *vide infra*). In addition, multiply substituted and fused polycyclic aryl iodides were found to be viable coupling partners, reacting with 2-phenylbicyclo[1.1.1]pentan-2-ol **2a** to afford γ-arylated products **4q-4t** in good yields. Notably, heteroaryl iodides containing pyridyl and indolyl functionality—which are typically challenging for palladium catalysis due to inhibitory coordination by the nitrogen atom—also performed well under the standard conditions, affording moderate yields of products **4u-4ad**. Alkenyl and alkynyl iodides were also found to be effective coupling partners, providing the γ-functionalized products **4ae-4ai** in satisfactory yields, though alkyl iodides proved to be incompatible with the reaction (see Table S7 in the Supporting Information). In addition, the pharmaceutically important cyclobutyl *C*-glycoside **4ah** can be accessed in 31% yield via coupling with TIPS-protected 1-iodoglucal.[17]

To further examine the scope of this method, a range of other aryl bicyclo[1.1.1]pentan-2-ols were prepared via Norrish-Yang cyclization of the corresponding cyclobutyl ketones (see Scheme 1). 2-Arylbicyclo[1.1.1]pentan-2-ols containing electron-deficient arenes proved effective in the reaction, affording the corresponding products **4aj**-**4ar** in high yields when subjected to the C–C cleavage/arylation process (Scheme 3). Electron deficient heteroaromatic bicyclo[1.1.1]pentan-2-ols were also effective substrates, affording **4as-4au** in good to excellent yields. Electron-rich aryl cyclobutyl ketones failed to undergo the Norrish-Yang cyclization,[18] and thus, could not be tested in the arylation reaction.

To demonstrate the possibility of performing the two-step sequence in a one-pot procedure, we performed the sequential Norrish-Yang/C-C arylation of cyclobutyl phenyl ketone **1a** with only a solvent swap in between the two steps, affording γ-arylated product **4a** in 25% overall yield (Scheme 4A). The synthetic versatility of the γ-arylated cyclobutane products was demonstrated by elaboration of representative product **4** to give diverse 1,3-difunctionalized cyclobutanes, including a pharmaceutical analogue. Notably, the product can be epimerized to a roughly 1:1 mixture of *cis*- and *trans*-isomers, which are separable on silica, allowing access to the epimerized product **5** in a 41% isolated yield. The ketone motif readily participates in standard carbonyl chemistry, including reduction to afford alkane **6** and Knoevenagel condensation with malononitrile to form an alkene derivative **7**. Moreover, the aryl ketone can be converted into cyclobutane carboxylic anilide **8**[19] through a Beckmann rearrangement or acyl cyclobutanol **9** via Baeyer-Villiger oxidation. Critically, the regioselectivity of the migration step differs in the two reactions, allowing for selective cleavage of either the cyclobutyl-acyl or aryl-acyl bond. In addition, the *p*-methoxyphenyl substituent of product **4j** can undergo ruthenium-catalyzed oxidation[20] to afford a carboxylic acid, providing a versatile functional group handle for a wide range of further elaborations (Scheme 4B). The utility of the *cis*-γ-arylation methodology is exemplified in a simple synthesis of compound **14**, a conformationally restricted analogue of the hyperparathyroidism drug Cinacalcet, in 4 steps from product **4h** (Scheme 4C).

Mechanistic experiments were performed to examine the proposed C–C activation/C–C coupling pathway (Scheme 5). First, subjecting the observed side product **1a** to the standard reaction conditions did not produce the desired product, ruling out a ketone-directed γ-C–H activation pathway and supporting the direct functionalization of an alkyl palladium intermediate formed via C–C cleavage (Scheme 6A). A radical process was also excluded based on the observation that superstoichiometric loadings of TEMPO did not significantly inhibit the reaction (Scheme 6B). Next, we performed the reaction in the presence of 20 equivalents of acetic acid-d_4 to check for deuterium incorporation. Under these conditions, product **4a** was obtained in 14% yield with no measurable deuterium incorporation into the cyclobutane along with 25% yield of **1a** containing 24% deuterium incorporation into the *cis*-γ-position (Scheme 6C). The latter result supports the intermediacy of γ-palladated species **C** (Scheme 5), while the former excludes mechanisms proceeding via desaturation to a β,γ-unsaturated cyclobutene intermediate followed by carbopalladation. Lastly, alternate phenyl (pseudo)halide coupling partners were examined to probe the nature of the arylation step. While phenyl bromide afforded product **4b** in moderately reduced yields, phenyl triflate, tosylate, and chloride were unreactive (Scheme 6D).

The ligand system, oxidizing reaction conditions, critical role of silver salts (see Table S4 in the Supporting Information, the silver salt likely serves as an iodide scavenger to help regenerate the active catalyst from inactive Pd–I species, and it may participate in other steps of the reaction such as oxidative addition or reductive elimination),[21] and the reactivity pattern with alternate arylating reagents are more characteristic of Pd(II)/Pd(IV) catalysis —as is well precedented in C–H activation chemistry occurring under similar reaction conditions[22]—than a Pd(0)/Pd(II) cycle, though the latter cannot be conclusively excluded. A plausible catalytic cycle is depicted in Scheme 5 wherein hydroxyl coordination to Pd(II) (intermediate **B**) is followed by strain-release-driven β-carbon elimination to access key organopalladium(II) intermediate **C**. The oxidation of intermediate **C** by an equivalent of the aryl iodide could afford aryl-alkyl Pd(IV) intermediate **D**, which could then undergo C–C bond forming reductive elimination to afford the desired product.

In conclusion, we have developed a two-step approach to access *cis*-1,3-difunctionalized cyclobutanes from readily available aryl-cyclobutyl ketones. The procedure relies on an improved UV-light promoted Norrish-Yang cyclization to access aryl bicyclo[1.1.1]pentan-2-ol intermediates, which then undergo Pd(II)-catalyzed stereospecific C–C bond functionalizations with diverse coupling partners including aryl, heteroaryl, alkenyl, and alkynyl iodides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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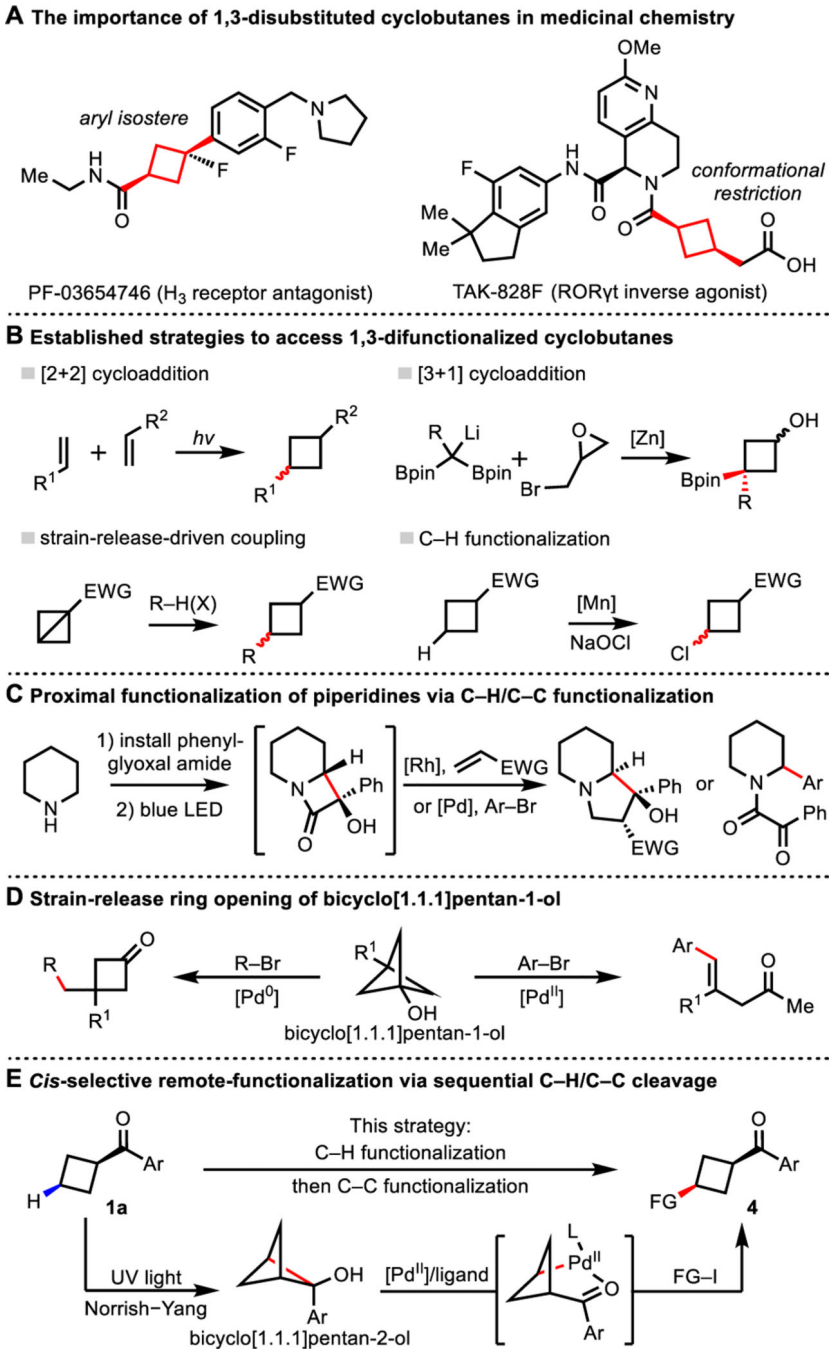
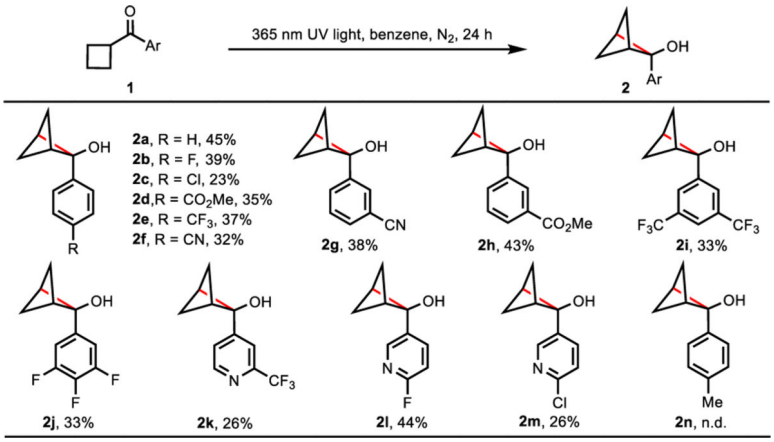


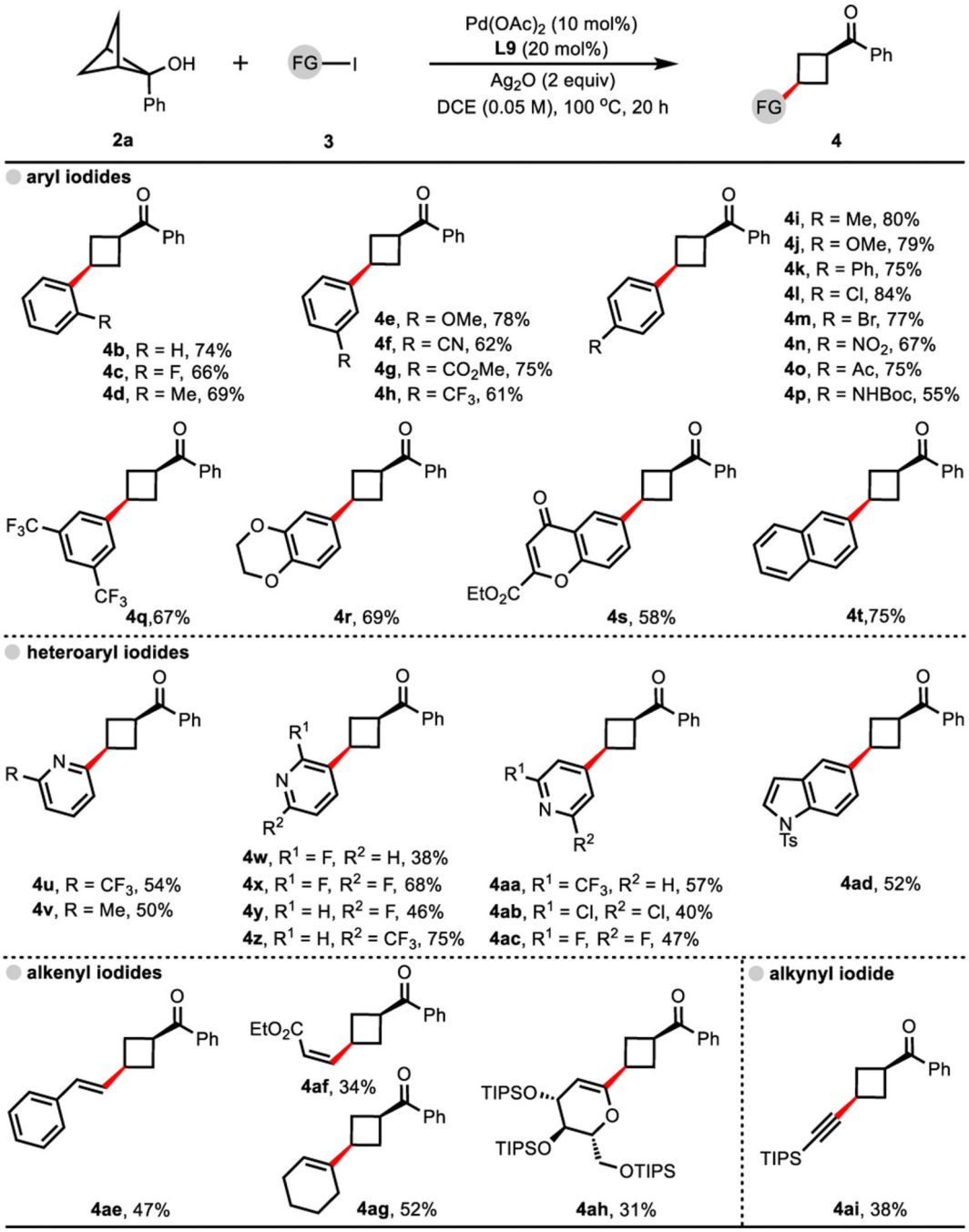
Figure 1.

(A) Pharmaceutical importance. (B) Synthetic strategies for 1,3-difunctionalized cyclobutanes. (C) Application of sequential Norrish-Yang/C–C cleavage for the functionalization of piperidines (Ref. 11). (D) Strain-release-driven ring-opening of bicyclo[1.1.1]pentan-1-ols (Ref. 13). (E) This work. EWG, electron-withdrawing group; FG, functional group.



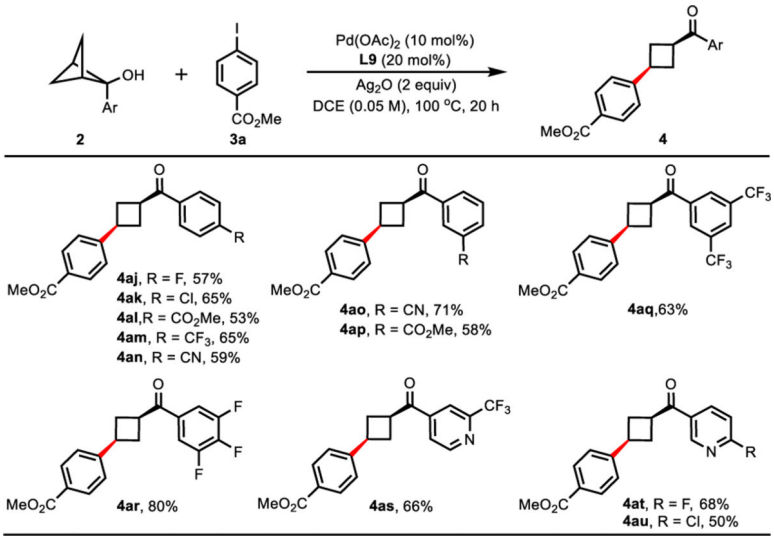
Scheme 1.

Synthesis of bicyclo[1.1.1]pentan-2-ol intermediates. Reaction scale: 0.3 mmol. Isolated yields were reported. n.d., not detected.



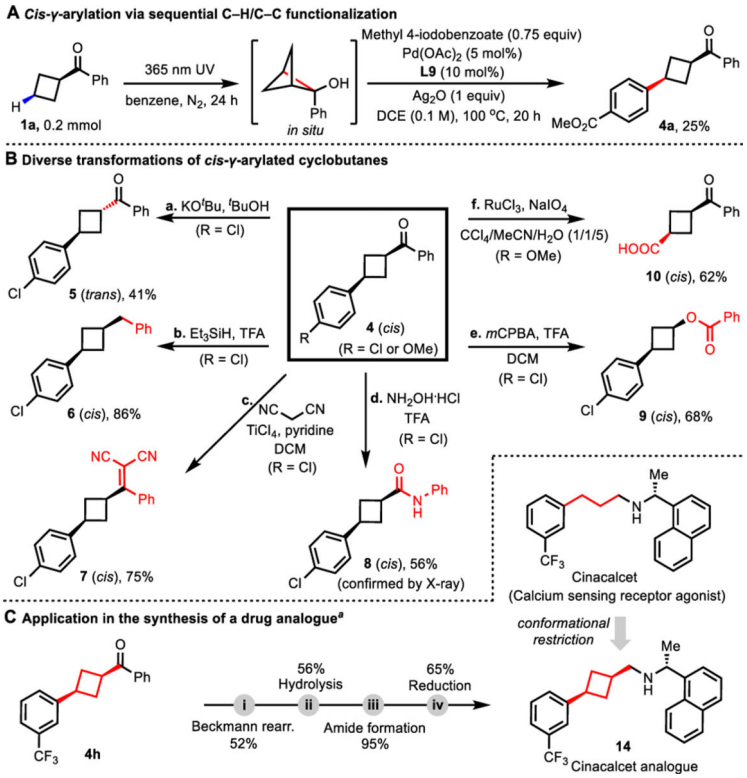
Scheme 2.

Substrate scope of coupling partners. Reaction conditions: **2a** (0.1 mmol), **3** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), **L9** (20 mol%), Ag_2O (2.0 equiv.), DCE (2.0 mL), 100 °C, 20 h. Isolated yields were reported.



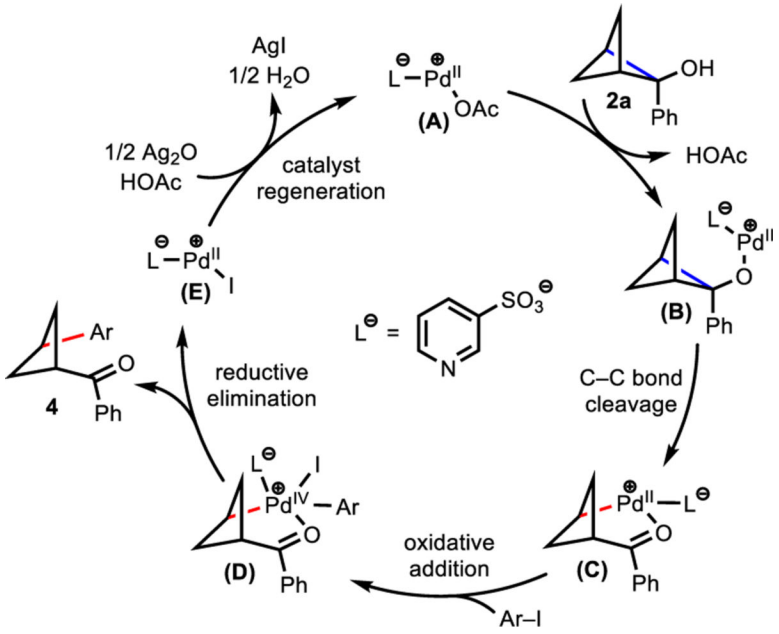
Scheme 3.

Substrate scope of 2-arylbicyclo[1.1.1]pentan-2-ols. Reaction conditions: **2** (0.1 mmol), **3a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), **L9** (20 mol %), Ag_2O (2.0 equiv.), DCE (2.0 mL), 100 °C, 20 h. Isolated yields were reported.

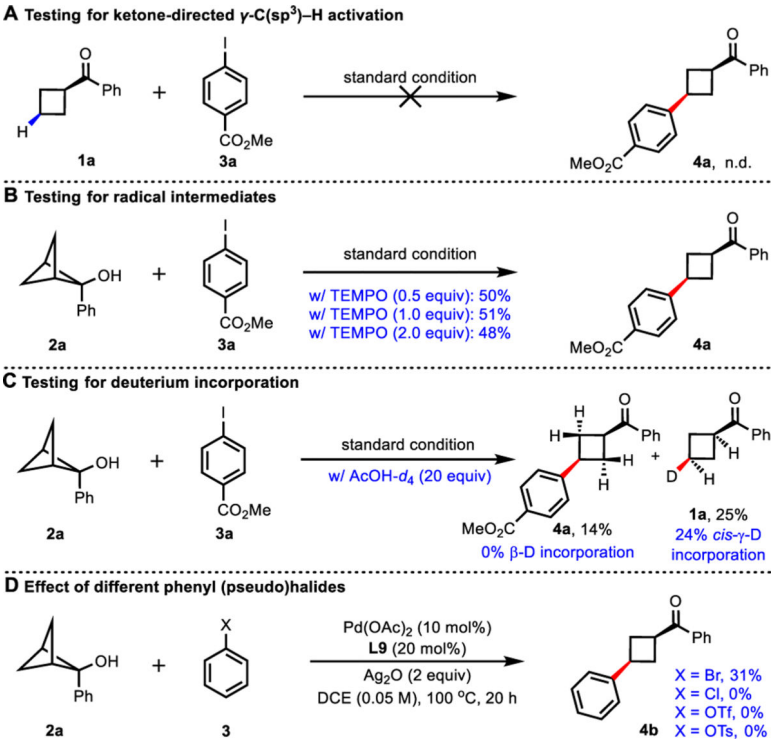


Scheme 4.

Synthetic applications. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$ (3 equiv.), TFA, 60 °C, 12 h. (ii) *conc.* HCl, 100 °C, 15 h. (iii) (*R*)-1-(1-naphthyl)ethylamine (1.5 equiv.), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equiv.), DMAP (0.1 equiv.), DCM, r.t., 12 h. (iv) $LiAlH_4$ (10 equiv.), Et_2O, 60 °C, 5 h.



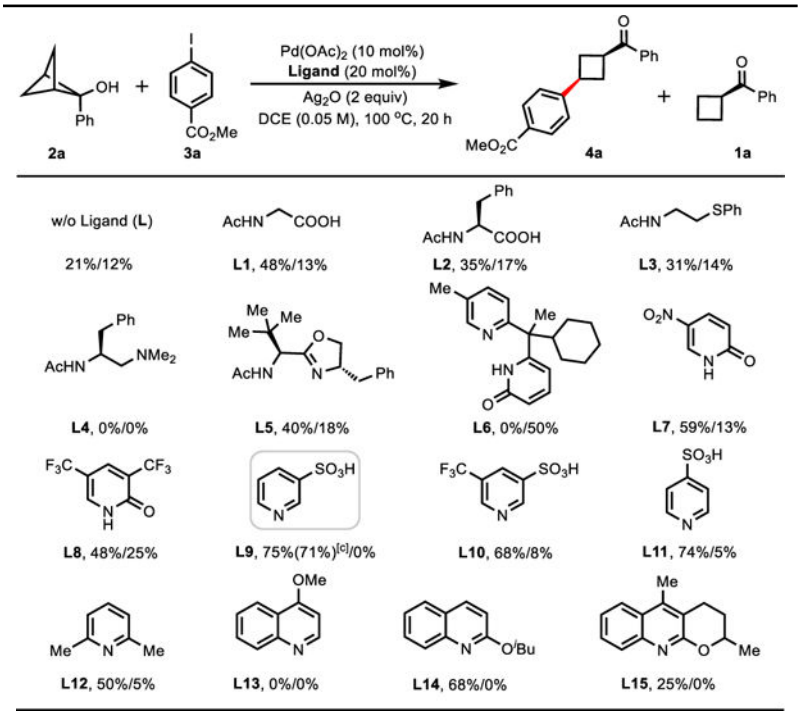
Scheme 5.
Plausible catalytic cycle.



Scheme 6.
Preliminary mechanistic experiments.

Table 1.

Ligand investigation for C–C cleavage/arylation of bicyclo[1.1.1]pentan-2-ol.[a,b]



[a]Conditions: **2a** (0.1 mmol), **3a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), Ligand (20 mol%), Ag_2O (2.0 equiv.), DCE (2.0 mL), 100 °C, 20 h.

[b]The yields of **4a**/**1a** were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

[c]Isolated yield.