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Regio-controllable [2+2] benzannulation with two adjacent C(sp³)–H bonds

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Abstract

Regiocontrol in traditional cycloaddition reactions between unsaturated carbon compounds is often challenging The increasing focus in modern medicinal chemistry on scaffolds speaks to the need for alternative, more selective routes to diverse rigid carbocycles rich in C(sp^3) character. Here we report a Pd-catalyzed double C–H activation of two adjacent methylene units in carboxylic acids, enabled by bidentate amide-pyridone ligands, to achieve a regio-controllable synthesis of BCBs through a formal [2+2] cycloaddition involving σ-bonds only (two C–H bonds and two aryl–halogen bonds). A wide range of cyclic and acyclic aliphatic acids, as well as dihaloheteroarenes, are compatible, generating diversely functionalized BCBs and hetero-BCBs present in drug molecules and bioactive natural products.

One Sentence Summary:

Twofold β,γ-methylene C(sp^3)−H activation/C−C bond formation was realized using a Pd(II) catalyst bound to amide-pyridone ligands, leading to regio-controllable [2+2] annulation between aliphatic acids and dihaloarenes.

Benzocyclobutenes (BCBs) represent an important class of rigid four-membered carbocycles found in natural products (1, 2) that have demonstrated great potential as therapeutical molecular scaffolds (3, 4), versatile synthons (5), and functional motifs in material science and mechanochemistry (6, 7) (Fig.1A). BCB-based rigid and three-dimensional pharmacophores have led to the discovery of Ivabradine, an FDA-approved drug for the

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Author contributions: J.-Q. Y. conceived the concept. J.-M. Y. discovered and developed the [2+2] benzannulation reaction. Y.-K. L. developed the amide-pyridone ligands, completed the benzannulation of the acyclic acids and proposed the mechanism. J.-M. Y. and Y.-K. L. conducted preliminary mechanistic studies, and the transformations of BCB products. T. S., L. H., and X.-P. C. participated in substrate scope survey. J.-M. Y., Y.-K. L., and J.-Q. Y. wrote the manuscript. J.-Q. Y. directed the project.

Competing interests: J.-Q. Y., J.-M. Y. and Y.-K. L. are inventors on a patent application related to this work (US Patent application 63/487,381) filed by The Scripps Research Institute. The authors declare no other competing interests.

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treatment of heart failure and heart-related chest pain (3). In addition, the BCB-analogue of the psychoactive 2C-B (4-Bromo-2,5-dimethoxyphenethylamine) was found to show superior affinity for the human 5-HT_{2A} receptor compared with the conformationally flexible parent compound and the benzocyclopentane analogue (Fig. 1A) (8). Currently, the [2+2] cycloaddition of alkenes and benzynes is one of the most common synthetic routes to BCBs (9). However, controlling the regioselectivity of this cycloaddition reaction is an unsolved problem. As illustrated in Fig. 1B, the [2+2] cycloadditions between a substituted alkene and benzyne typically lead to mixtures of head-to-head and head-to-tail regioisomers as well as multiple diastereoisomers. A number of alternative intramolecular processes, such as cyclization of *o*-quinodimethane (10), cyclative C−H arylations (11–14), visible-light induced radical processes (15) and others (16) have been developed. A modular two-component intermolecular synthesis of BCBs has recently been reported using an elegant Pd-catalyzed [2+2] annulation of alkenes bearing an amide directing group and arylboronic acids (17); however, this method does not allow regiocontrol. In addition, existing methods for BCB synthesis suffer from scope and efficiency limitations due to the requirement of preinstallation of reactive functional groups such as double or triple bonds. Notably, the synthesis of medicinally important heterocyclic BCBs using these reactions is challenging (18, 19). Our recently demonstrated Pd-catalyzed activation of β- or γ-C−H bonds of aliphatic acids (20–22) inspired us to explore a formal [2+2] annulation of aliphatic acids with dihaloarenes through a dual sequential methylene C−H activation at the β- and γ-positions. The state of the art of dual functionalization of two adjacent methylene C−H bonds is limited to allylic and benzylic positions, or sites α- to a heteroatom (23–26). Here we report successful palladium-catalyzed BCB synthesis through the annulation of aliphatic acids with dihaloarenes enabled by amide-pyridone ligands, in which the exclusive regiocontrol is achieved through the differentiation between the aryl iodide and bromide sites. The direct use of abundant and structurally varied acyclic and cyclic acids as substrates without pre-functionalization substantially expands access to diverse BCBs, including heterocyclic BCB scaffolds (Fig.1C).

Reaction development.

During our mechanistic investigations of the methylene C–H lactonization of dicarboxylic acids, we observed the β,γ-C–H deuteration of 7-ethoxy-7-oxoheptanoic acid (20). This observation prompted us to wonder whether a sequential twofold C–H coupling process with ortho-dihaloarenes could be developed to construct BCB scaffolds. Using 1-propyl-1-cyclopentanecarboxylic acid **1a** and dihaloarene coupling partner 1-bromo-4-chloro-2-iodobenzene **2a** with Ag_2CO_3 as a scavenger for halides, we began to test the feasibility of this transformation with a series of pyridine-pyridone ligands recently developed in our laboratory (Table S1). Encouragingly, the desired BCB **3a** was indeed formed as a single isomer (Figure S1). However, attempts to improve the reaction yield using pyridine-pyridone ligands and other known ligand scaffolds (**L27** to **L36**) under various conditions proved unsuccessful (≤ 22% yield).

These initial results with pyridine-pyridone ligands, while promising, pointed to the need for more effective ligands. Since the 2-pyridone serves a critical role as the internal base for C–H cleavage (27), we focused on developing alternatives for the pyridine arm of

the scaffold. Inspired by the superior reactivity of the electron-deficient amide motif as a directing group for Pd(II) in C(sp^3)−H activation (28), we synthesized a class of bidentate ligands bearing both a pyridone and an electron-deficient amide derived from perfluorinated anilines. Amide-pyridone ligand **L1**, posited to coordinate to Pd(II) as five-membered chelate, afforded significantly improved yield in the annulation reaction (38%). Through extensive structural tuning, we identified ligand **L7** as optimal, providing BCB **3a** in 90% isolated yield.

Cyclic acids substrate scope.

Under these optimized conditions, we subsequently evaluated the substrate scope of the [2+2] annulation reaction (Fig. 2). A wide range of cyclic aliphatic acids including five- (**1a-l**), six- (**1m-t**), seven- (**1u-v**), and eight-membered (**1w**) rings were compatible to afford *cis*-BCB products as single regioisomers (**3a-3w**). Larger cyclic aliphatic acids including 11- (**1x**), 12- (**1y**) and 15-membered (**1z**) rings produced *trans*-BCB products as major isomers. Remaining unreacted aliphatic acid reactants were recovered when the yields are relatively low. Notably, ligand **L7** allowed us to reduce Pd loading from 10% to 5% or 1% while maintaining synthetically useful yields for the [2+2] annulation between dihaloarene **2a** and acids (**1a-1i**) as selected examples. Various substitutions at the α-position of carboxylic acid were tested in the reaction. Alkyl groups (**3a-3f**, **3l-q**, **3s**, **3u**) and aryl groups (**3g-3j**, **3r**) with electronically diverse substituents were compatible with this protocol despite the presence of reactive methyl and aryl C−H bonds. Functionalities such as methoxy (**3f**), OTBS (**3q**), phenyl (**3d-e**, **3p**) were well-tolerated. Bicyclic aliphatic acid (**1l**) was converted to the corresponding fused 6-5-4-6 ring (**3l**) in 32% yield. Cyclohexanecarboxylic acid bearing substitutions at the 3-position (**1s**) consistently provided the corresponding product (**3s**) in moderate yield. In addition to the aliphatic acids containing an α-quaternary center, aliphatic acids containing an α-hydrogen (**1k**, **1t**, **1v-1z**) afforded the products (**3k**,**3t**,**3v-3z**) in 20%−52% yield. Quinoline-pyridone ligand **L28** was more suitable for 8–15-membered rings (**1w-1z**). The structures of **3h** and *trans*-**3y** were confirmed by single-crystal x-ray diffraction analysis. We also investigated the scalability of this [2+2] annulation reaction, in which 1.05 gram of the desired product **3a** could be obtained in 88% isolated yield (see supplementary materials for experimental details).

Acyclic acids substrate scope.

Acyclic aliphatic acid **4a** only gave low yield with **L7** (2%) (Table S6). We found that six-membered chelating amide-pyridone ligand **L12** emerged as the most effective ligand for these linear substrates, affording diverse *trans*-BCBs (Fig. 3). A wide range of functional groups, such as methoxy (**5d**), chloro (**5e-5f**), phosphonate (**5g**), and substituted aryl groups (**5h-l**) were compatible. Aliphatic acids bearing α-*gem*-dimethyl groups (**4a-l**) or a single methyl group (**4n-o**) were also compatible despite the presence of the typically more accessible α-methyl C−H bonds. In addition to the substrates containing an α-quaternary center (**4a-o**), aliphatic acids containing an α-hydrogen (**4p-q**) were also found to be viable, as exemplified with products **5p** and **5q**, generated in moderate yields. A number of synthetic elaborations of benzocyclobutyl acid products were also demonstrated.

Heating a solution of **5a** as an *o*-quinodimethane precursor with *N*-methylmaleimide in *o*-dichlorobenzene at 180 °C provided Diels-Alder adduct **6** in 60% yield. **5a** could be readily transformed to medicinally important amine **7**. The benzocyclobutyl amide **11**, a patented bioactive molecule for crop protection (29), could be rapidly synthesized by [2+2] annulation of aliphatic acid **4a** and *N*-dihaloaryl amide **10** in a two-step sequence.

Dihaloarenes substrate scope.

The broad scope of bromoiodoarenes further expands the diversity of BCBs (**12b**-**12u**) (Fig. 4A). Substituents at various positions were compatible with this catalytic system (**12c**-**12f**). Halogens such as fluorine (**12g**), chlorine (**12h**), and bromine (**12i**-**j**) were compatible, providing the desired BCBs in good yields. Arenes bearing electron-donating (**12k-l**) and electron-withdrawing (**12m-t**) groups were also tested, affording the products in good to excellent yields. The amide (**12s-t**) and carboxylic acid (**12u**) groups, widely used in C–H activations as directing groups, were also viable for this protocol. An aryl triflate, a highly reactive site in Pd cross-coupling chemistry, was also tolerated (**12m**). Moreover, dibromoarenes (**2b**$^{\mathbf{Br}}$, **2v**-**y**) and diiodoarene (**2b**$^{\mathbf{I}}$) were amenable to the standard conditions, generating the desired BCBs in moderate to good yields (Fig. 4B). As expected, reaction of **1b** with 2,3-dibromotoluene (**2c**$^{\mathbf{Br}}$) afforded a mixture of two regioisomers (**12c** and **12d**, rr = 2.5 : 1), indicating that bromoiodoarenes with two different active sites are vital for controlling regioselectivity.

Heteroaromatics and complex molecules.

Modular synthesis of hetero-BCBs has been a longstanding challenge using various methods (22, 23). Gratifyingly, pyridine (**13a-b**, **13j-l**), quinoline (**13c-d**), quinoxaline (**13e**), and indole (**13f**) derivatives were also competent in this process, affording the desired hetero-BCBs in 25–59% yield (Fig. 4C). Heterocycles such as pyrrole (**13g**), thiophene (**13h**) and furan (**13i**) were well tolerated, providing the desired products in good to excellent yields. Dihaloarenes bearing bioactive structures such as celecoxib (**13m**), pregnenolone (**13n**), galactose (**13o**), and menthol (**13p**) were also compatible. This protocol could also be applied in late-stage modification of bioactive molecules, such as gemfibrozil and isosteviol, leading to products **13q** and **13r**.

Mechanistic study.

The sequential activation of two C–H and two aryl halide bonds in surprisingly exclusive regioselectivity calls for mechanistic investigation into this complex catalytic cycle.Reactivity of various possible intermediates (Fig. S2–3) is consistent with a highly complex Pd(II)/Pd(0)/Pd(II)/Pd(IV) catalytic reaction pathways (Fig. S4). β,γ-dehydrogenation occurred via ligand enabled β- or γ-C−H bond activation accompanied by the formation of Pd(0) species. Oxidative addition of the more reactive aryl iodide with Pd(0) species followed by directed carbopalladation afforded a key intermediate bearing the aryl on the γ-position with all regioselectivity defined. Next, intramolecular oxidative addition of the aryl bromide with the alkyl Pd(II) led to Pd(IV) intermediate, which underwent reductive elimination to afford the desired BCB product and Pd(II) catalyst.

The plausibility of the dehydrogenation pathway is supported by the catalytic formation of the desired BCB product using β,γ-unsaturated aliphatic acid **S5a** as substrate (For various control experiments see Fig. S4A–G). Notably, the following two elementary steps must be exclusively regioselective to form a single regioisomer of BCB: oxidative addition with Pd(0) occurs preferentially with the more reactive aryl iodide bond; the subsequent carbopalladation step is then governed by the directing effect to place the aryl on the γ-position and Pd(II) on the β-position.

Beyond the realization of regioselective functionalization of two adjacent methylene C–H bonds, the modular synthesis of diverse BCBs with exclusive regioselectivity is applicable to pharmaceuticals, material science and mechanochemistry, as well as natural product synthesis. Further studies on the reaction mechanism are under way.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data and materials availability:

All data are in the supplementary materials. Crystallographic data for compounds **3h** and trans-**3y** are available from the CambridgeCrystallographic Data Center under reference numbers CCDC 2220709 and 2246693.

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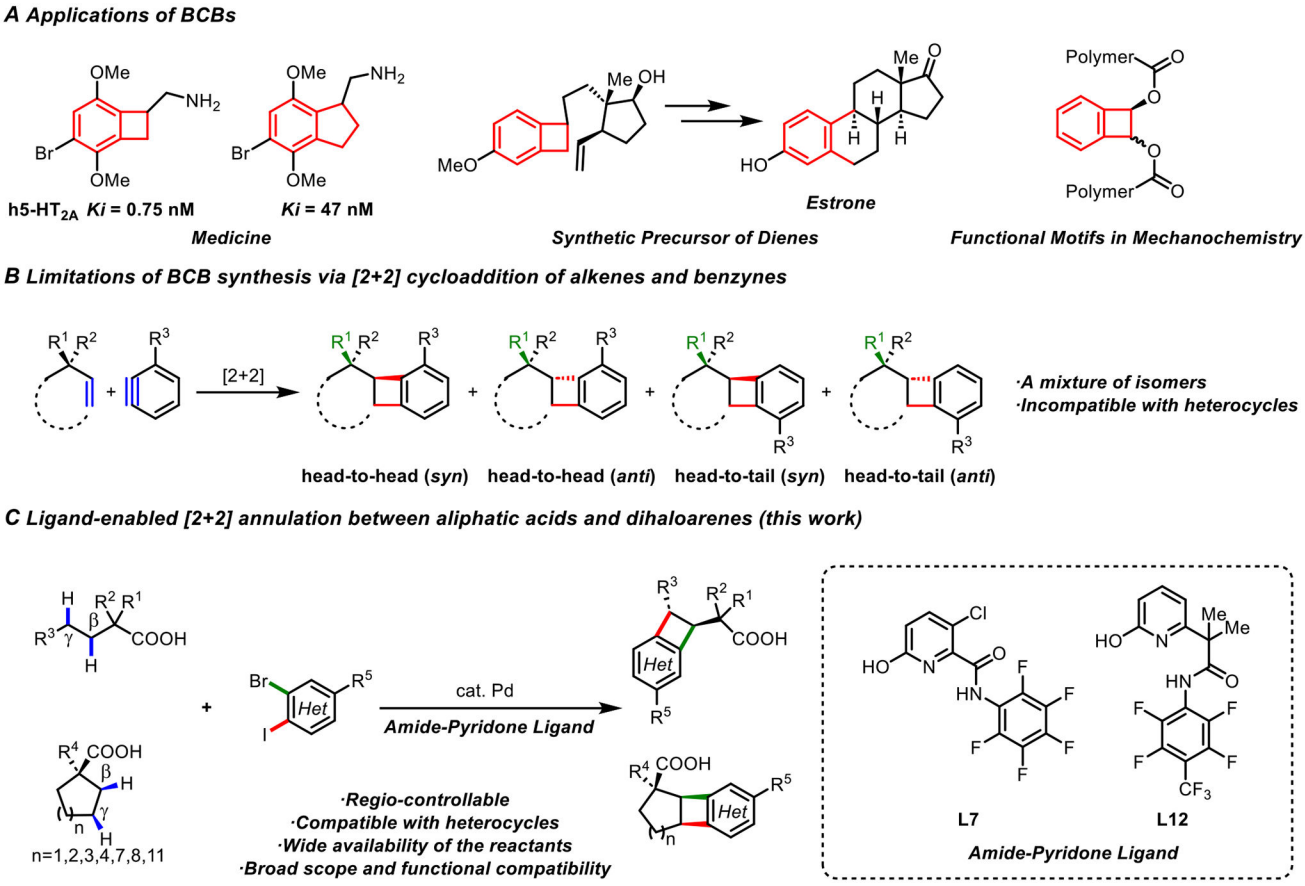

Fig. 1. [2+2] Annulation Reaction via Dual Methylene C−H Bond Functionalization.

(**A**) Applications of BCBs. *Ki* is the inhibitor constant. (**B**) Limitations of BCB synthesis via [2+2] cycloaddition of alkenes and benzynes. *Syn*, *anti* refers to the conformation of R^1 group and the adjacent aryl group. (**C**) Ligand-enabled [2+2] annulation between aliphatic acids and dihaloarenes (this work).

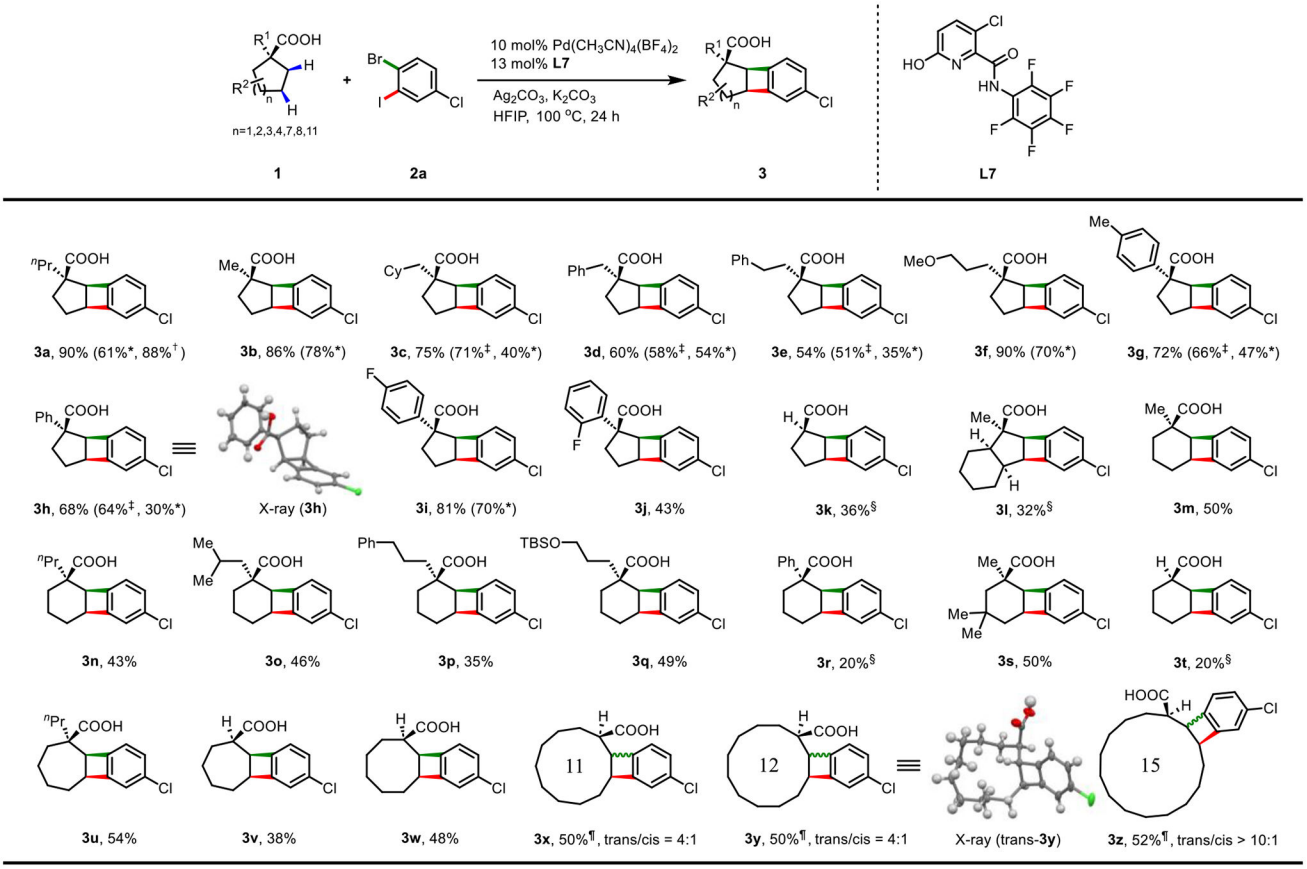

Fig. 2. Cyclic aliphatic acid scope for the [2+2] annulation reaction.

Reaction conditions: aliphatic acid (0.1 mmol), **2a** (0.2 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), **L7** (13 mol%), K_2CO_3 (2.5 equiv), Ag_2CO_3 (2.0 equiv), HFIP (1.0 ml), at 100 °C for 20 hours. Isolated yields are reported. Relative configurations are shown, as the synthesis is racemic. See supplementary materials for details. *$Pd(CH_3CN)_4(BF_4)_2$ (1 mol%) was used, reaction time 56 hours. †Reaction conducted with of aliphatic acid **1a** (4.5 mmol), 1.05 g of **3a** was obtained. ‡ $Pd(CH_3CN)_4(BF_4)_2$ (5 mol%) was used, reaction time 40 hours. §Aliphatic acid (0.2 mmol), **2a** (0.1 mmol), K_2CO_3 (3.5 equiv).¶**L28** instead of **L7**, $KHCO_3$ instead of K_2CO_3.

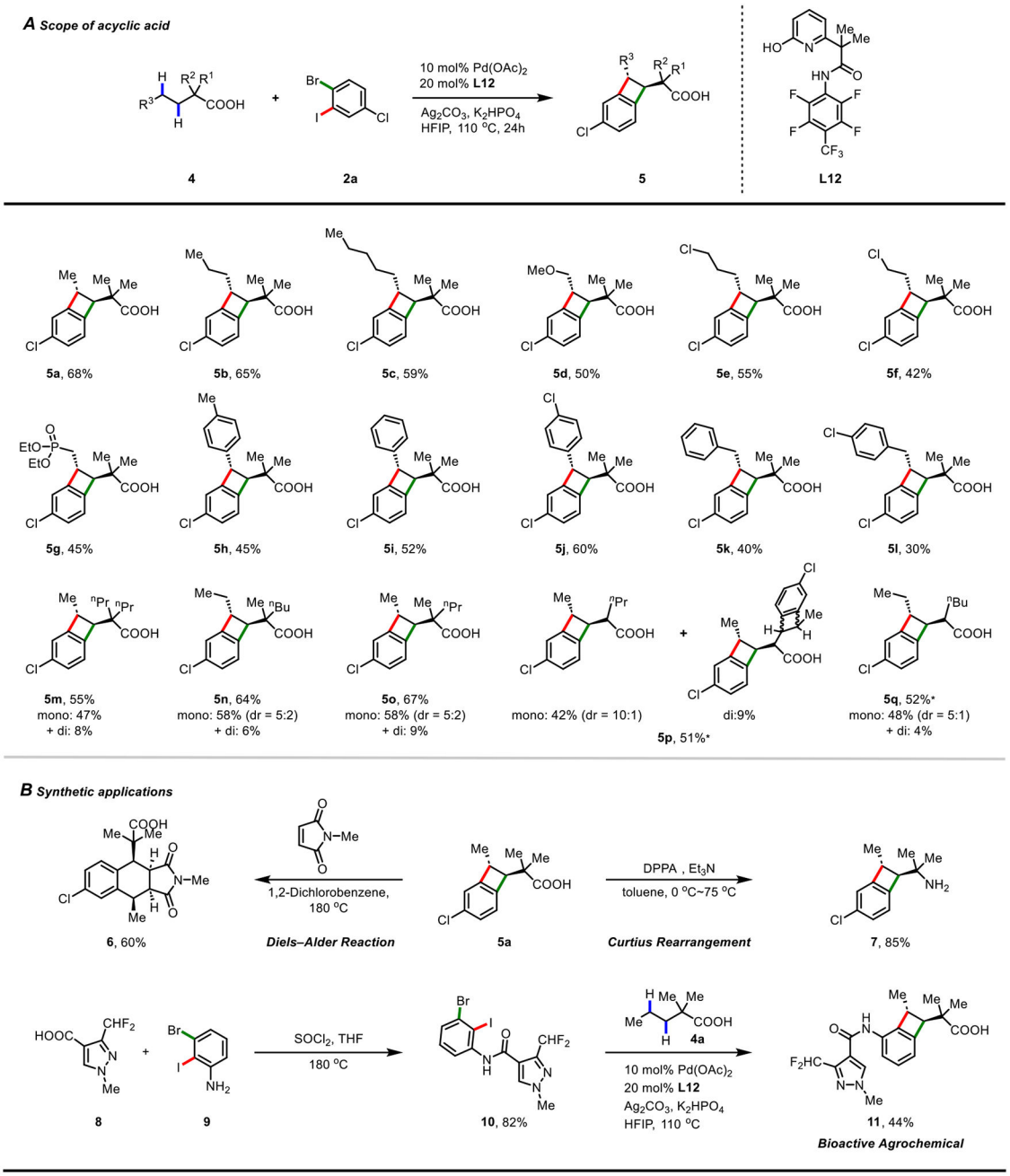

Fig. 3. Acyclic aliphatic acids scope for the [2+2] annulation reaction and transformations of the products.

(**A**) Acyclic aliphatic acid scope. Reaction conditions: aliphatic acid (0.1 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), K_2HPO_4 (3.5 equiv), Ag_2CO_3 (2.0 equiv), HFIP (1.2 ml), at 110 °C for 24 hours. Isolated yields are reported. Relative configurations are shown, as the synthesis is racemic. Di-**5p** was isolated and drawn as a representative of di-BCB products. ***2a** (0.35 mmol), K_2HPO_4 (3.0 equiv), HFIP (1.8 ml) as a replacement. (**B**) Synthetic applications. DPPA = Diphenylphosphoryl azide.

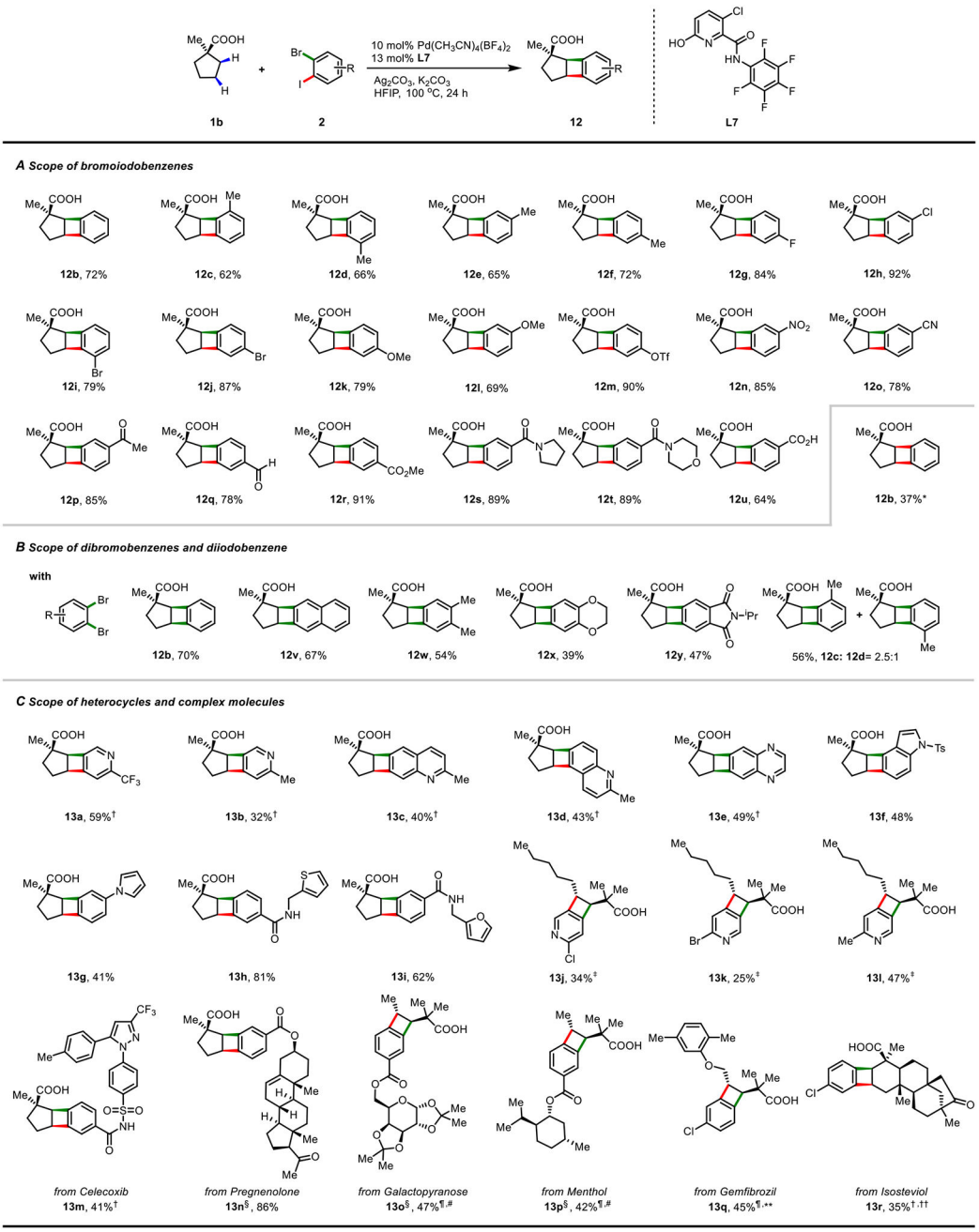

Fig. 4. Dihaloarenes scope for the [2+2] annulation reaction.

(**A**) Scope of bromoiodobenzenes; (**B**) Scope of dibromobenzenes and diiodobenzene; (**C**) Scope of heterocycles and complex molecules. Reaction conditions: aliphatic acid (0.1 mmol), dihaloarene (0.2 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), **L7** (13 mol%), K_2CO_3 (2.5 equiv), Ag_2CO_3 (2.0 equiv), HFIP (1.0 ml), at 100°C for 20 hours. Isolated yields are reported. Relative configurations are shown, as the synthesis is racemic. *1,2-diiodobenzene (**2b^{I}**) as substrate. †Aliphatic acid (0.2 mmol), dihaloarene (0.1 mmol), K_2CO_3 (3.5 equiv). ‡**L28** instead of **L7**, **4c** instead of **1b**, $KHCO_3$ instead of K_2CO_3. §Diastereoisomers. ¶Dihaloarene (0.3 mmol), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), K_2HPO_4 (3.5 equiv),

Ag_2CO_3 (2.0 equiv), HFIP (1.2 ml), at 110 °C for 24 hours. #**4a** instead of **1b**. **Gemfibrozil instead of **1b**. ††Isosteviol instead of **1b**.