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Transannular C–H Functionalization of Cycloalkane Carboxylic Acids

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Abstract

Cyclic structures are ubiquitous among natural products and pharmaceuticals[1,2]. Thus, new methods for the direct site- and diastereoselective synthesis of functionalized carbocycles are highly desirable. In principle, molecular editing via native-functional-group-directed C–H activation offers an idea route to these compounds. However, the γ-C–H functionalization of cycloalkanes remains a significant challenge due to the strain encountered in transannular C–H palladation. Here we report that two classes of ligands—quinuclidine-pyridones (QuinNuPyridones **L1**, **L2**) and sulfonamide-pyridones (SulfonaPyridone **L3**)—enable transannular γ-methylene C–H arylation of small to medium sized cycloalkane carboxylic acids, with ring sizes ranging from cyclobutane to cyclooctane. Excellent γ-regioselectivity was observed in the presence of multiple β-C–H bonds. This advance marks a significant step towards achieving molecular editing of saturated carbocycles: a class of scaffolds that are important in synthetic and medicinal chemistry[3–5]. The utility of this protocol was demonstrated by two-step formal syntheses of a series of patented biologically active small molecules, prior syntheses of which required up to eleven steps[6].

Cyclic structures are important in medicinal chemistry since they provide control over molecular shape and reduce the number of rotatable bonds, often increasing oral bioavailability while providing enhanced control over the activity, specificity, and physical properties of drug candidates[3–5]. Consequently, the overwhelming majority of small-molecule pharmaceuticals contain at least one ring system[1]. Likewise, rings are ubiquitous among natural products[2], highlighting the importance of cyclic systems in biology. Organic chemists have often relied on cycloadditions, typified by the Diels-Alder reaction, or intramolecular cyclizations to assemble ring systems from acyclic precursors[7]. However, the synthesis of those precursors frequently requires multiple steps, and the cyclization reactions themselves can be challenging to promote and control[8]. As an

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alternative, complex carbocycles can be constructed through the modification of pre-formed cyclic starting materials, such as cycloalkanones or terpenoid chiral pool compounds[9]. However, elaboration of these starting materials by classical methods can necessitate lengthy synthetic sequences to relay reactivity from pre-existing functionality to the desired site of functionalization. C–H activation offers an alternative disconnection that could bypass this limitation and enable rapid and efficient access to a diverse range of functionalized (poly)cyclic scaffolds, but the general applicability of this approach is predicated on the development of methods for the site-selective functionalizations of both proximal and remote C–H bonds (Fig. 1A). The former are typically far more reactive[10], so achieving selectivity for the functionalization of remote positions in the presence of competing proximal C–H bonds remains a major challenge. This is particularly true for cyclic systems, where the activation of remote sites requires transannular C–H cleavage resulting in strained, bicyclic palladacycles. Recent advances in macrocyclophane-based directing templates have provided a solution for controlling remote C(sp^2)–H activation of (hetero)aromatic rings[11–12]. However, methods for the C–H functionalization of saturated compounds—a focus of modern drug discovery efforts[13]—have largely been limited to the activation of proximal sites in cyclic systems[14–16]. Some transannular C–H activations have been reported[10,17–31], but the vast majority of these proceed via 5-membered palladacycles[17,19,20,22,23,25–30], necessitating the presence of a nitrogen atom within or directly attached to the ring to be able to reach remote C–H bonds (Fig. 1B). Functionalization via 6-membered palladacycles would provide a much more general solution, however, only a few such examples have been reported[10,18,21,24,31], often with modest site-selectivity or specialized bicyclic substrates. Moreover, because of the challenging nature of methylene C–H activation, nearly all previous reports of transannular functionalizations employ pre-installed bidentate directing groups[10,17–19,21,23–26,28–30], limiting the scope of these transformations and the opportunities for downstream derivatization of the products. Hence, it is imperative to develop a general and native-functional-group-directed method for the transannular functionalizations of simple, monocyclic substrates.

Here we report a first step towards realizing the vision of ultimate molecular editing of saturated carbocyclic scaffolds: the development of γ-selective transannular C–H arylation of a wide range of small to medium-sized cycloalkane carboxylic acids (Fig. 1D). A quinuclidine-pyridone ligand enables the transannular γ-arylation of carboxylic acid substrates ranging from cyclopentane to cyclooctane rings. Transannular arylation of cyclobutane carboxylic acids was realized via double C–H activation of the acid substrate and simple arene coupling partners. These transformations display excellent selectivity for transannular arylation of the γ-position in the presence of typically more reactive β-C–H bonds[10,32], providing expedient access to a valuable family of compounds that previously necessitated lengthy synthetic sequences, sometimes exceeding ten steps[6]. Notably, γ-arylated cycloalkane acids and acid derivatives can display important biological activity[6,33–39], rendering this transformation especially valuable for medicinal chemistry (Fig. 1C).

Our investigation of transannular C–H arylation was initiated using α-propyl-cyclopentane carboxylic acid **1a** as a model substate. Ligands were found to play a crucial role in this transformation (see table S1). While ligands known to promote β-C(sp^3)–H activation,

such as mono-protected aminoethyl phenyl thioether (MPAThio), monoprotected amino acid (MPAA), and monoprotected aminoethyl amine (MPAAm)[40] failed to provide any of the desired product, we observed that quinoline-pyridone ligands, which have been demonstrated to enable β-and γ-methylene C–H activation of free acids[31,41], afforded the desired γ-arylated product in 30% yield. Similar yields were also observed with a tertiary amine-pyridone ligand, confirming the importance of the pyridone moiety. We hypothesized that replacing the tertiary amine in that scaffold with a quinuclidine might have a profound effect on the reactivity of the catalyst due to the special character of the quinuclidine motif, which is more Lewis basic and more rigid than typical tertiary amines[42]. Gratifyingly, we found that quinuclidine-pyridone ligand **L1** is uniquely effective in promoting the transannular γ-arylation, providing product **3a** in 69% yield. The structure of **L1** was confirmed by X-ray crystallographic analysis (a crystal structure of a dimeric **L1**-Pd(II) complex was also obtained to gain insight into the coordination mode of the key binding motifs. For details, see the Supporting Information). After further optimization of the reaction conditions (see tables S2–S8), we were able to obtain the desired γ-arylated product in 87% isolated yield.

The generality of the transannular C–H functionalization was investigated by varying the structure and ring size of the cycloalkane carboxylic acid and the identity of the (hetero)aryl iodide coupling partner. We first examined the substrate scope of α-quaternary cyclopentane carboxylic acids (Fig. 2). Substrates with α-aryl substituents, which contain γ-C(sp^2)–H bonds that could compete with the desired site of functionalization, all provided the transannular γ-C(sp^3)–H arylation products in good to excellent yields regardless of the electronic properties on the aryl ring (**3b-3h**). No γ-C(sp^2)–H or β-C(sp^3)–H arylation products were observed, demonstrating the exquisite regioselectivity of the reaction. The reaction also proved to be scalable, with only a modest reduction in the yield of **3e** from 85% to 71% observed when the arylation was performed on 1 g scale. Carboxylic acids with α-Me and α-Et substituents also performed well, affording the transannular γ-arylation products with 69% and 80% yield respectively (**3i, 3j**). Other α-alkyl substituents including those with additional functional groups, such as an ester, chloride, or ether substituent (**3l, 3o-3p**), were also compatible with our methodology. In addition, modest yields were obtainable with bicyclic systems such as **3q** and **3r**. Notably, transannular γ-arylation of α-tertiary cyclopentane carboxylic acid also proceeded smoothly to give the target product **3s** in good yield. However, α-heteroatom-substituted carboxylic acids proved to be poor substrates for the reaction (see Supporting Information Table S9). X-ray crystallographic characterization of representative α-aryl (**3c**), α-tertiary (**3s**), and α-alkyl (**4ac**) cyclopentane carboxylic acid products confirmed that the aryl group is installed *cis* to the carboxylic acid directing group (see Supporting Information).

Next, we examined the scope of the ArI coupling partner using α-propyl cyclopentane carboxylic acid as a model substrate (Fig. 3A, aryl bromides and aryl chlorides performed poorly in the reaction, see Supporting Information Table S10). A wide range of electronically varied *para*-substituted aryl iodides were compatible with this protocol, providing the transannular arylation products in 55% to 85% yield (**4a-4i**). In general, electron deficient aryl iodides gave slightly higher yields than those with electron donating

groups (e.g., **4e** vs **4g**). *Meta*- and *ortho*-substituted aryl iodides also performed well in the reaction (**4j-4p**). Heteroarylation with heteroaryl iodides was then investigated (Fig. 3B). A variety of 2-substituted-4-iodopyridines reacted smoothly to provide the target products (**4s-4v**). 2,6-and 2,3-disubstituted-4-iodopyridines and 2-substituted-5-iodopyridines were also viable coupling partners for the transannular reaction, leading to moderate to excellent yields of the corresponding γ-arylated products (**4w-4aa**). Notably, thiophene, benzothiazole, quinazoline, quinoline, pyrimidine and indole based heteroaryl iodides were all successful coupling partners in the γ-arylation reaction, with 2-acetyl-5-iodothiophene leading to the highest yield (**4ae**) (78%). 2,4-dimethoxy-5-iodopyrimidine only provided the product with 38% yield, presumably due to the strong electron donating effect of the dimethoxy group (**4ai**). Aryl iodides containing acidic functionality such as phenols, anilines, and free carboxylic acids performed poorly in the reaction (see Supporting Information Table S10).

The potential of this protocol for medicinal chemistry was demonstrated through the preparation of several reported histone deacetylase (HDAC) inhibitor precursors (Fig. 3C.-i), the synthesis of which previously required up to ten steps and proceeded in low overall yields[6]. For example, a patented procedure details a 10-step synthesis of **4ak** as a mixture of diastereomers at the benzylic position, which were subsequently separated to access either diastereomer as an enantiopure compound. Employing our transannular γ-C–H arylation, racemic **4ak** and its analogues **4al-4an** can be easily accessed as single diastereomers in 49% to 65% yield in just one step from the commercially available α-aryl cyclopentane carboxylic acid. Notably, amidation of α-arylated cyclopentane carboxylic acid **4am** affords potent histone deacetylase (HDAC) inhibitors with IC_{50} values as low as 0.062 μm[6] (Fig. 1 C). Heterocyclic analogues were also prepared using indole and thiophene based aryl iodides (**4ao-4ap**). Inhibitors for AKR1C1 and AKR1C3 are promising scaffolds for the treatment of hormone-dependent cancers and other diseases[33]. Transannular C–H arylation of simple α-tertiary cyclopentane carboxylic acid provides a one-step synthesis of reported AKR1C1 and AKR1C3 inhibitor **4as** and a series of analogues (**4aq-4aw**) in 37% to 70% yield (Fig. 3C-ii). In contrast to the previously reported route, our transannular C–H activation chemistry provides diastereocontrol and allows for easy variation of the aryl substituent.

Next, we investigated the transannular γ-C–H arylation of larger and smaller cycloalkane carboxylic acids (Fig. 4). Applying the optimal conditions identified for the arylation of cyclopentane carboxylic acids to α-propyl cyclohexane carboxylic acid only resulted in a 35% yield of the γ-arylated product. Fortunately, after a brief optimization of the ligands and the reaction conditions, we found that **L2** could provide the desired product (**5a**) in 65% isolated yield (see tables S11–S16 for details). Next, we examined the substrate scope of the transannular γ-arylations of cyclohexane carboxylic acids (Fig. 4A). Excellent regioselectivity was observed with substrates containing multiple potential reaction sites, such as α-methyl and α-ethyl cyclohexane carboxylic acids (**5b-5c**). α-Aryl substituted cyclohexane acids were also effective substrates (**5i-5k**). A substrate with geminal dimethyl substitution at the γ'-position was also reactive, albeit with a modest yield, possibly due to the 1,3-diaxial strain between the axial methyl substituent and the transannular palladacycle (**5l**). Notably, transannular arylation of a tetrahydropyran-

containing substrate (**5m**) proceeded smoothly, indicating that this methodology can be applied to the functionalization of some saturated heterocycles (6-membered heterocyclic carboxylic acid substrates with heteroatoms in the 2- or 3-position failed to undergo arylation, see Supporting Information Table S17). In addition, our protocol proved effective in complex settings such as late-stage functionalizations, as demonstrated through the arylation of the natural product isosteviol in 63% yield (**5n**). The structure and relative stereochemistry of the cyclohexane products was confirmed by X-ray crystallographic analysis of representative α-alkyl (**5b**) and α-aryl (**5k**) cyclohexane carboxylic acids (see Supporting Information for crystallographic data). Transannular γ-C–H arylation of seven and eight membered cycloalkane carboxylic acids were also achieved, providing the corresponding products with moderate to good yields (**6a-6j**, Fig. 4B) (see tables S18–S21 for optimization details). The structure of representative cycloheptane carboxylic acid product **6a** was confirmed by X-ray crystallographic analysis, and the structure of the cyclooctane carboxylic acids were assigned based on the observation of an NOE cross peak between the benzylic hydrogen and the α-methyl group in **6j** (see Supporting Information).

We anticipated transannular arylation of cyclobutane carboxylic acids would be most challenging due to the rigidity of the small ring. Moreover, it would be necessary to override the established selectivity for functionalization of the β-C–H bonds of cyclobutane acids[43–46]. Indeed, when α-ethylcyclobutane carboxylic acid was subjected to the reaction conditions developed for cyclopentane carboxylic acids, only the undesired β-arylated product was formed. (See Table S22). Using **L3**, a ligand developed by our lab for alcohol-directed chemistry,[47] we were able to identify reaction conditions that could afford a mixture of the β- and γ-arylated products, but the undesired β-product was always favoured (a crystal structure of **L3** bound to a Pd(ethylenediamine) complex was also obtained, revealing an X, X- binding mode. For details, see the Supporting Information). The ratio of γ- to β-arylation varied as a function of the electronic properties of the aryl iodide coupling partner (ρ=0.41 vs σ_{para}, R^2=0.98, see Table S23 for details), suggesting that the arylation step might be selectivity determining, and thus, that an alternate arylation mechanism might provide enhanced site selectivity. A particularly intriguing possibility was that the aryl iodide could be replaced with an aryl palladium species generated *in situ* via non-directed C(sp^2)–H activation, resulting in the net cross coupling of two C–H bonds[48]. Gratifyingly, we found that a combination of **L3** and **L4**—the latter of which may facilitate the non-directed C–H functionalization of the arene (see Tables S34–S36, notably, the addition of the monodentate ligand altered the *meta*- vs. *para*-selectivity of the transformation, which is consistent with the proposed role of **L4**)[49]—can promote the arylation of cyclobutane carboxylic acids with benzene with exclusive selectivity for the γ-position of the cyclobutane. (Fig. 4C, see Tables S24–S33 for optimization and discussion. Of particular note is the observation that portion-wise addition of the $Pd(OAc)_2$ by adding 10 mol% at the start of the reaction and an additional 5 mol% after 2.5 days affords optimal yields, see Tables S32 and S33). The structure and relative stereochemistry of **8a** were confirmed by X-ray crystallographic analysis (see Supporting Information).

We next sought to examine the scope of the cyclobutane carboxylic acid γ-arylation reaction. The reaction of the model α-ethylcyclobutane substrate proved effective with a

range of electronically neutral to electron rich arenes (**8a**-**8d**). Electron deficient arene coupling partners resulted in somewhat reduced yields (**8e**-**8f**). There was only modest selectivity between alkylation of the *meta*- and *para*-positions of the arene, but *ortho*-functionalization was strongly disfavoured except with electronically biased arenes as in **8b** and **8e**. Additionally, variation of the α-substituent on the cyclobutane carboxylic acid was tolerated (**8h-8j**), though methyl substation led to reduced yields (**8i**). Simple, non-quaternized cyclobutane carboxylic acid was also found to undergo arylation to afford **8k** in moderate yields. While $Cu(OAc)_2$ was found to be the optimal oxidant for α-quaternary carboxylic acids, AgOAc proved optimal for substrate **7k** (using $Cu(OAc)_2$ as the oxidant resulted in a 19% yield of **8k**. See Tables S31 and S32 for oxidant screening data).

In conclusion, we have achieved transannular γ-methylene C–H arylation of cycloalkane carboxylic acids with QuinNuPyridone ligands (**L1** and **L2**) and through double C–H activation with a SulfonaPyridone ligand (**L3**) and a monodentate pyridone (**L4**). A wide range of cycloalkane carboxylic acids with ring sizes ranging from four to eight were effective substrates in reactions with a diverse array of (hetero)aryl iodide/arene coupling partners. Excellent regioselectivity was demonstrated with substrates containing multiple potential sites for C–H activation. Thus, these reactions provide general and straightforward access to γ-arylated cycloalkane acids, which are versatile synthetic building blocks, and in some cases, exhibit biological activity even without further elaboration. The utility of this protocol was demonstrated through the concise preparation of a series of biologically active compounds, previous syntheses of which required lengthy sequences. We anticipate that this methodology will simplify the synthesis of γ-arylated cycloalkanes, helping to fuel the design and discovery of novel therapeutics.

Supplementary Material

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Data availability:

The data supporting the findings of this study are available within the article and its Supplementary Information files.

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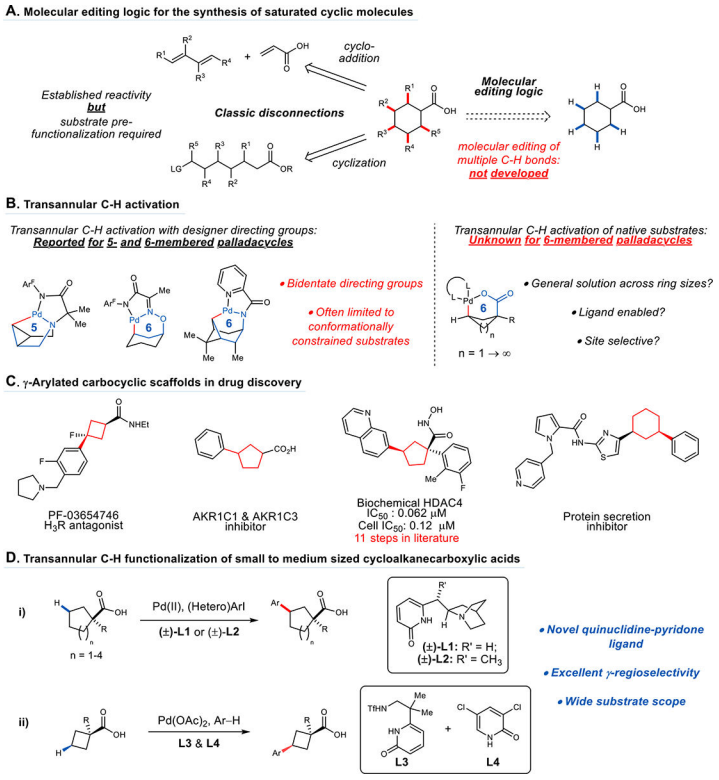

Fig. 1. Transannular C–H arylation via activation of methylene C–H bonds

a, Molecular editing logic for the synthesis of complex carbocycles. **b,** Transannular C–H activation reactions. **c,** γ-Arylated carbocycle containing bioactive molecules. **d,** (this work) Transannular C–H functionalization of small to medium sized cycloalkane carboxylic acids. **H_3R**: Histamine H3 receptor. **AKR1C1**: Aldo-keto reductase family 1 member C1; **AKR1C3:** Aldo-keto reductase family 1 member C3; **HDAC4**: Histone deacetylase 4.

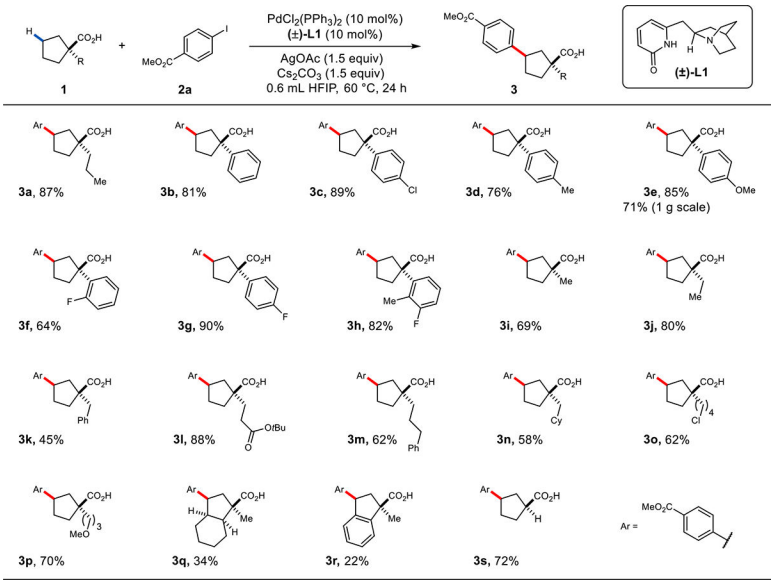

Fig. 2. Substrate scope of cyclopentane carboxylic acids.

Bolded bonds indicate relative stereochemistry. Reaction conditions: Substrate (0.1 mmol), $PdCl_2(PPh_3)_2$ 10 mol%, ArI **2a** (2.0 equiv.), Ligand **L1** (10 mol%), AgOAc (1.5 equiv.), Cs_2CO_3 (1.5 equiv.), HFIP (0.6 mL), 60 °C, 24 h. Isolated yields are reported.

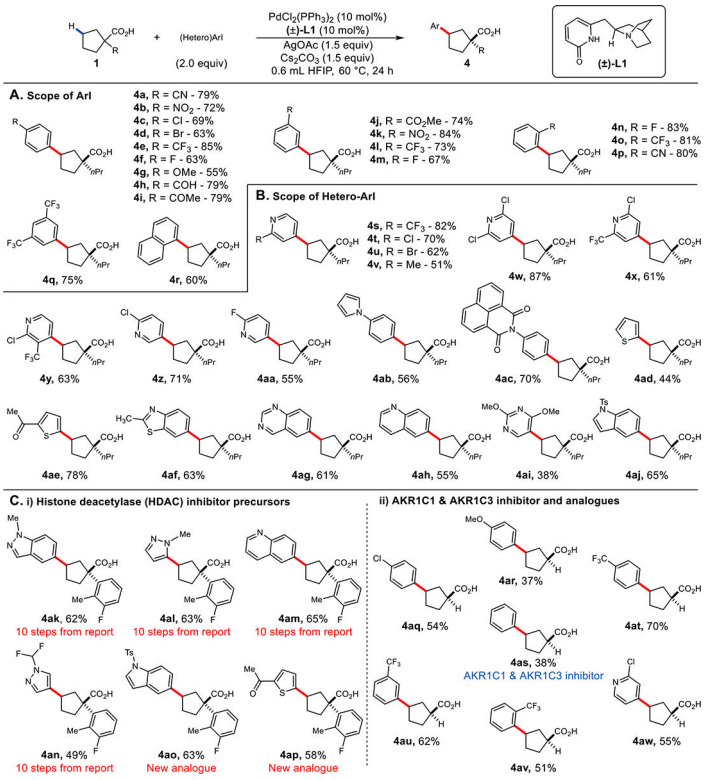

Fig. 3. Transannular γ-C–H arylation:

Bolded bonds indicate relative stereochemistry. **a,** Substrate scope of aryl iodide. **b,** Substrate scope of heteroaryl iodide. **c,** i) Precursors to reported histone deacetylase (HDAC) inhibitors (see Fig. 1C for a representative HDAC inhibitor structure). ii) AKR1C1 & AKR1C3 inhibitor and analogues. Reaction conditions: Substrate (0.1 mmol), $PdCl_2(PPh_3)_2$ (10 mol%), (hetero)ArI (2.0 equiv.), Ligand **L1** (10 mol%), AgOAc (1.5 equiv.), Cs_2CO_3 (1.5 equiv.), HFIP (0.6 mL), 60 °C, 24 h. Isolated yields are reported.

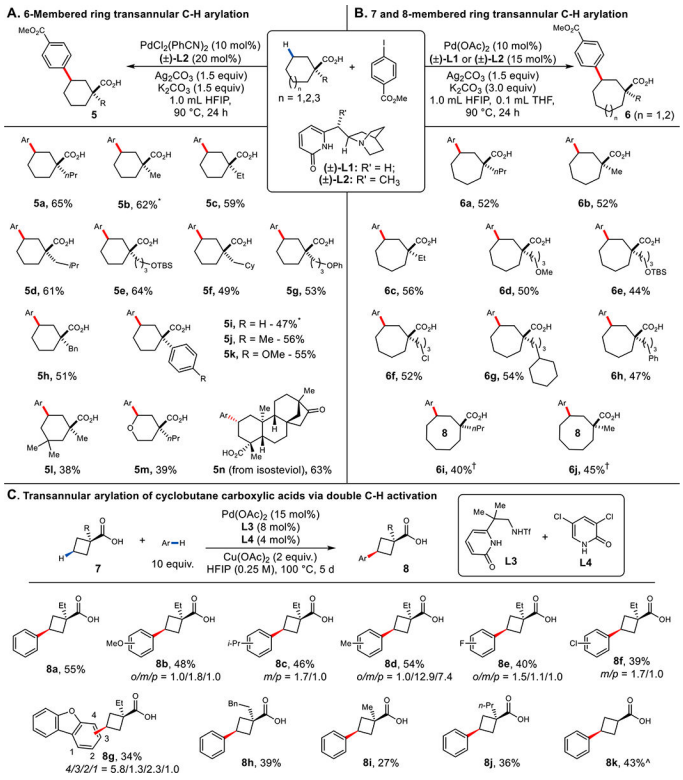

Fig. 4. Transannular C–H arylation of cycloalkane carboxylic acids.

Bolded bonds indicate relative stereochemistry **(A)** 6-membered ring transannular C–H arylation. Reaction conditions: Substrate (0.1 mmol), $PdCl_2(PhCN)_2$ 10 mol%, Ligand **L2** (20 mol%), ArI (2.0 equiv.), Ag_2CO_3 (1.5 equiv.), K_2CO_3 (1.5 equiv.), HFIP (1.0 mL), 90 °C, 24 h. Isolated yields are reported. *0.1 mL CH_3CN was added. **(B)** 7- and 8-membered ring transannular C–H arylation. Reaction conditions: Substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol%), Ligand **L2** (15 mol%), ArI (2.0 equiv.), $AgCO_3$ (1.5 equiv.), K_2CO_3 (3.0 equiv.), HFIP (1.0 mL) and THF (0.1 mL), 90 °C, 24 h. †Substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol%), Ligand **L1** (15 mol%), ArI (2.0 equiv.), $AgCO_3$ (1.5 equiv.), Na_3PO_4 (1.5 equiv.), HFIP (0.6 mL), 120 °C, 48 h. (C) 4-membered ring transannular C–H arylation. Reaction conditions: substrate (0.1 mmol), arene (1 mmol), $Pd(OAc)_2$ 10 mol% + 5 mol% after 2.5 days, ligand **L3** (8 mol%), ligand **L4** (4 mol%), $Cu(OAc)_2$ (2.0 equiv.), HFIP (400 μL), 100 °C, 5 days. Isolated yields are reported. ^AgOAc (4.0 equiv.) was used in place of $Cu(OAc)_2$.