Rapid Construction of Tetralin, Chromane, and Indane Motifs via Cyclative C−H/C−H Coupling: Four-Step Total Synthesis of (±)-Russujaponol F

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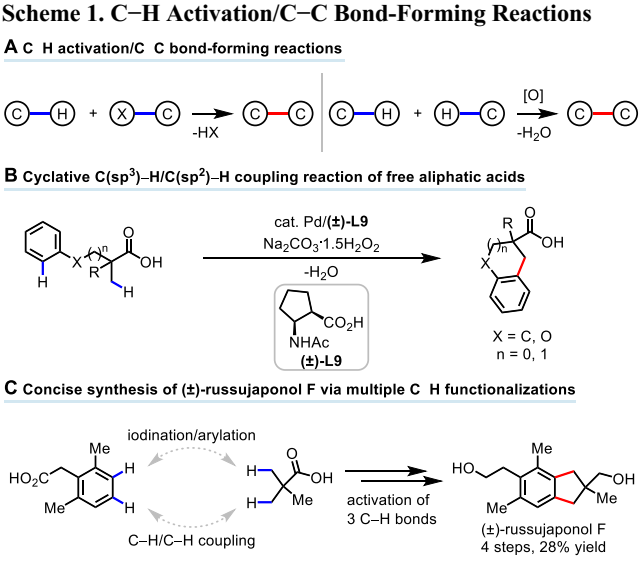
Supporting Information Placeholder

ABSTRACT: The development of practical C−H/C−H coupling reactions remains a challenging yet appealing synthetic venture because it circumvents the need to prefunctionalize both coupling partners for the generation of C−C bonds. Herein, we report a cyclative C(sp^3)−H/C(sp^2)−H coupling reaction of free aliphatic acids enabled by a cyclopentane-based mono-*N*-protected β-amino acid ligand. This reaction uses inexpensive sodium percarbonate ($Na_2CO_3·1.5H_2O_2$) as the sole oxidant, generating water as the only byproduct. A range of biologically important scaffolds, including tetralins, chromanes, and indanes, could be easily prepared by this protocol. Finally, the synthetic application of this methodology is demonstrated by the concise total synthesis of (±)-russujaponol F in a four-step sequence starting from readily available phenylacetic acid and pivalic acid through the sequential functionalizations of four C−H bonds.

Carbon-carbon (C−C) bond formation constitutes one of the most important classes of reactions in organic synthesis. Owing to its potential to shorten synthesis, the past two decades have witnessed rapid developments in using C−H activation strategies for the construction of C−C bonds.[1] While most coupling methods require prefunctionalized coupling partners (e.g. organoborons and organohalides), C−H/C−H coupling reactions offer a complementary strategy to construct a C−C bond directly from two simple C−H bonds (Scheme 1A).[2] Compared to traditional coupling methods, this green and atom-economical approach is highly attractive because water is potentially the sole stoichiometric byproduct of this process (Scheme 1A). To date, extensive studies have focused on the coupling of two relatively reactive C(sp^2)−H bonds for biaryl synthesis,[3] whereas only a few reactions have been reported for the construction of more challenging C(sp^3)−C(sp^2) bonds. Because these existing reaction protocols require exogenous directing groups (DGs) to promote cyclometallation, additional steps to install and remove the DG are necessary.[5,6] Additionally, reported methods pose practical limitations, such as the stoichiometric use of precious silver salts[4b,c,5,6b,c] and harsh conditions[4b,c,5a,b,6] — with temperatures as high as 160 °C being reported. Moreover, current methods for C(sp^3)−H/C(sp^2)−H coupling initiated by C(sp^3)−H activation are largely limited to more reactive heterocyclic C(sp^2)−H bonds.[5a,b,6] Despite the great value that C−H/C−H coupling reactions might have for organic synthesis, the development of C(sp^3)−H/C(sp^2)−H coupling reactions that use both a practical oxidant and native substrates remains a significant challenge.

Scheme 1. C−H Activation/C−C Bond-Forming Reactions



Recent advances in C−H functionalization have provided chemists with creative and strategic retrosynthetic disconnections that are otherwise difficult to achieve using traditional methods.[7] However, for C−H functionalization strategies to truly improve the overall efficiency of synthesis, three criteria should be met: (1) the ability to use a wide range of simple starting materials to enable the synthesis of diverse natural product families; (2) the use of native functionalities as the DG; (3) the site-selectivity of C−H functionalization reactions should be precisely controllable. Given the ubiquitous nature of C−H bonds in organic molecules, synthetic sequences that incorporate multiple C−H functionalizations are particularly attractive for the efficient synthesis of natural products. However, approaches that meet these aforementioned criteria are challenging to execute and so uncommon in literature.[7a,8]

To address these challenges, we herein report a cyclative C(sp^3)−H/C(sp^2)−H coupling reaction using a native free carboxylic acid as the DG (Scheme 1B). The use of a cyclopentane-based mono-*N*-protected β-amino acid ligand and a practical and inexpensive oxidant sodium percarbonate ($Na_2CO_3·1.5H_2O_2$) proved crucial to the success of this reaction. Tetralins, chromanes, or indanes, common frameworks in natural products could be readily prepared by this protocol (Figure 1). The synthetic application of this methodology is further demonstrated by a concise total synthesis of (±)-russujaponol F (the shortest and highest yielding to date) via multiple C−H functionalizations in four steps from readily available

phenylacetic acid and pivalic acid (Scheme 1C), demonstrating the potential of C−H activation disconnections to enhance the ideality of synthesis[9].

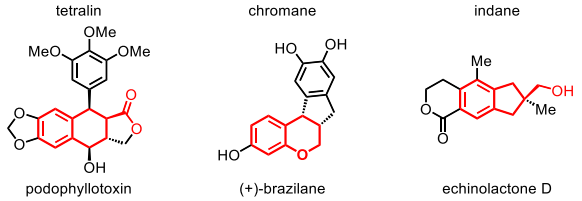
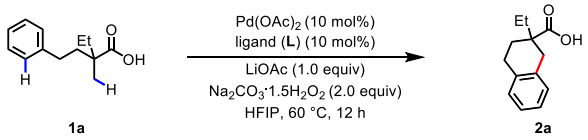


Figure 1. Biologically significant natural products containing tetralin, chromane, or indane frameworks.

Table 1. Ligand Investigation for the Cyclative C(sp^3)−H/C(sp^2)−H Coupling Reaction[a,b]

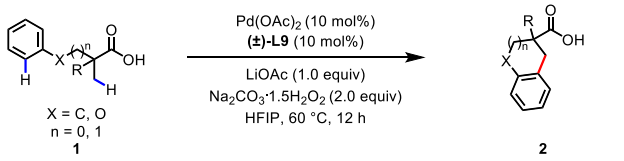


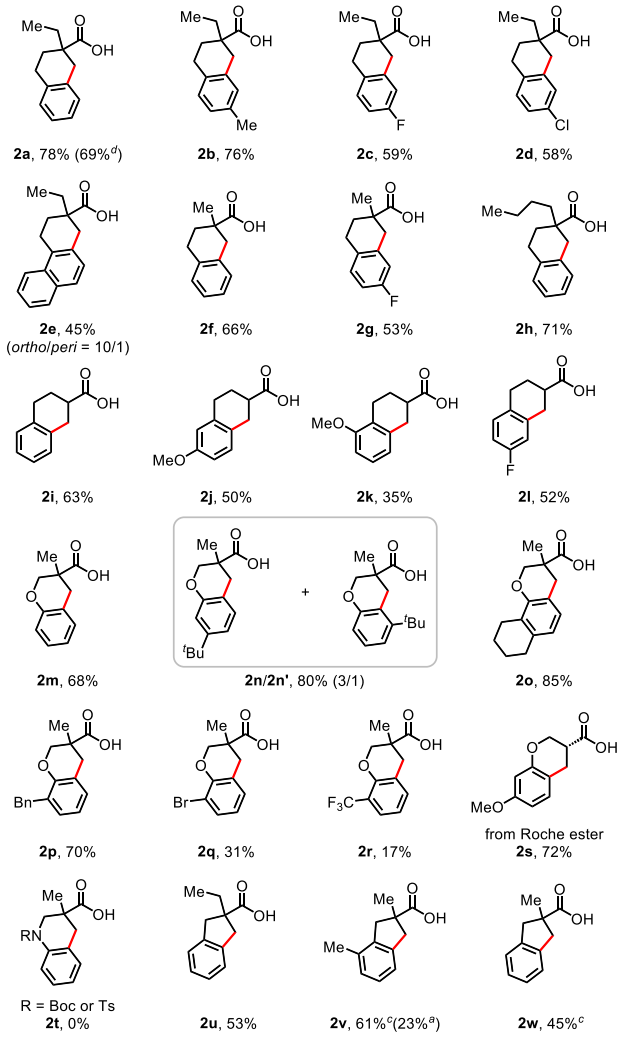
w/o ligand(**L**)	**L1**, 19%	**L2**, 45%	**L3**, 39%
23%			
L4, 57%	**L5**, 53%	**L6**, 62%	**L7**, 63%
L8, 54%	**(±)-L9**, 75%(78%[c])	**(±)-L10**, 63%	**L11**, 20%

[a]Conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), ligand (**L**) (10 mol%), LiOAc (1.0 equiv), $Na_2CO_3·1.5H_2O_2$ (2.0 equiv), HFIP (1.0 mL), 60 °C, 12 h. [b]The yields were determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]Isolated yield.

Aliphatic carboxylic acids are ubiquitous and synthetically versatile motifs and are often inexpensive reagents in organic chemistry; as such, they are privileged substrates for C−H activation reactions.[10] Following our recent disclosure of the β-C(sp^3)−H lactonization[10i] and acyloxylation[10j] of free carboxylic acids using *tert*-butyl hydrogen peroxide (TBHP) as the sole oxidant, we initiated our investigation of cyclative C(sp^3)−H/C(sp^2)−H coupling reactions by selecting TBHP as the bystanding oxidant and aliphatic acid **1a** as a model substrate. Under the optimal conditions of the aforementioned β-acyloxylation reaction[10j], we were delighted to observe a 50% ^{1}H NMR yield of the desired product **2a** without forming competing reductive elimination products, such as the β-lactone or β-hydroxy acid (see Supporting Information, Table S1). Further investigation of the bystanding oxidants and bases revealed that the combination of $Na_2CO_3·1.5H_2O_2$ and LiOAc could further improve the yield to 57% (see Supporting Information, Table S1−S2). The yields using LiOAc are generally better than those using NaOAc as the metal additives under the optimized conditions (see Supporting Information, Table S4). The use of sodium percarbonate, one of the cheapest and most easily handled oxidants,[11] potentially renders this protocol practical and scalable. In light of recent advances in ligand-accelerated Pd(II)-catalyzed C−H activation,[12] we next searched for ligands that could substantially improve the reactivity of the catalyst. Guided by mono-*N*-protected amino acid (MPAA) ligand-enabled C(sp^3)−H activation reactions of free carboxylic acids[10c,d,g,i,j], we tested a series of commercially available MPAA ligands (**L1**−**L4**): β-amino acid ligand **L4** showed superior reactivity over α-amino acid ligands **L1**−**L3** (57% vs. 19−45%), as was also observed in other C(sp^3)−H functionalization reactions of free acids via Pd(II)/Pd(IV) catalytic cycles[10d,i,j]. Through systematic modifications to the backbone of the β-amino acid ligand (**L5**−**L10**), we found that *cis*-cyclopentane-based ligand **(±)-L9** gave the optimal reactivity (78% isolated yield). The superior reactivity of **(±)-L9** might be attributed to the more rigid conformation enforced by the cyclopentane linkage. Control experiments showed that the yields were low in the absence of the ligand or in the presence of the γ-amino acid ligand (**L11**) (23% or 20%, respectively), indicating the importance of six-membered chelation by the ligand for reactivity.

Table 2. Substrate Scope of the Cyclative C(sp^3)−H/C(sp^2)−H Coupling Reaction[a,b]



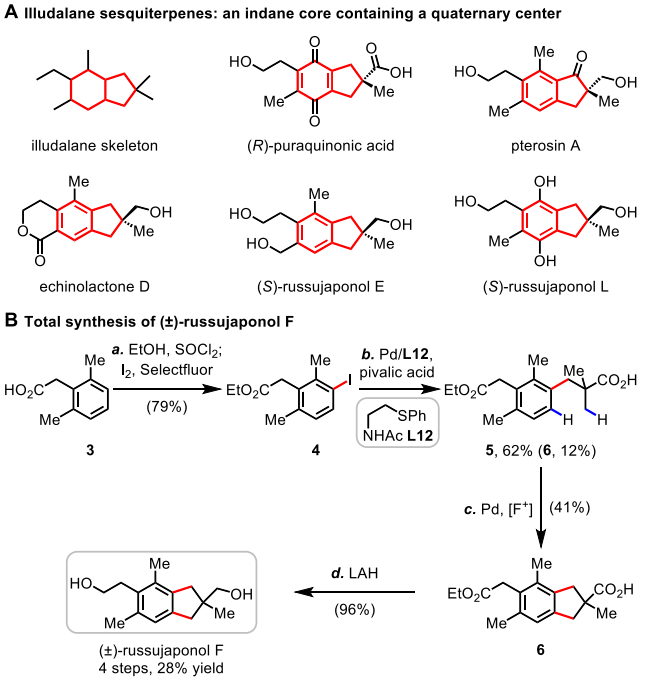


[a]Conditions A: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **(±)-L9** (10 mol%), LiOAc (1.0 equiv), $Na_2CO_3·1.5H_2O_2$ (2.0 equiv), HFIP (1.0 mL), 60 °C, 12 h. [b]Isolated yields. [c]Conditions B: **1** (0.1 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), Ag_2CO_3 (1.0 equiv), 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (2.0 equiv), HFIP (1.0 mL), 90 °C, 12 h. [d]On 2.0 mmol scale.

With the optimal ligand and reaction conditions in hand, we evaluated the scope of the cyclative C(sp^3)−H/C(sp^2)−H coupling reaction (Table 2). A wide range of tertiary aliphatic acids bearing a

single α-methyl group (**1a**–**1e** and **1h**) or an α-gem-dimethyl group (**1f** and **1g**) were all compatible, affording the tetralin products in moderate to good yields (52–78%). The reaction could also be conducted on a 2.0 mmol scale, delivering **2a** in 69% yield. The attempted desymmetrization of the α-gem-dimethyl group of **1f** using enantioenriched **L9** resulted in racemic product. Less reactive free carboxylic acids containing α-hydrogens (**1i**–**1l**) also reacted in synthetically useful yields (35–65%). Among these, a variety of functionalities on the aryl rings such as methyl (**2b**), methoxy (**2j** and **2k**), fluoro (**2c**, **2g**, and **2l**), and chloro (**2d**) as well as naphthyl (**2e**) were tolerated, with the halogen moiety (**2d**) serving as a useful synthetic handle for subsequent derivatization. This protocol could also be successfully extended to the synthesis of biologically important chromane products. β-Phenoxy carboxylic acids containing an α-gem-dimethyl group (**1m**–**1r**) or α-hydrogens (**1s**, from Roche ester) were all reactive substrates. While a range of electron-donating (methoxy, *tert*-butyl, cyclohexyl, and benzyl) (**2s** and **2n**–**2p**) groups on the aryl ring were well tolerated to afford the desired products in good yields (70–85%), aliphatic acids containing electron-withdrawing (bromo and trifluoromethyl) groups (**2q** and **2r**) showed comparatively low reactivity (31% and 23%), likely due to the sluggish nature of C(sp^2)–H activations of electron-deficient arenes. Although intermolecular KIE experiments of electron-rich **1m** and **1m**-d_5 (k_H/k_D = 1.1) suggest that C(sp^2)–H activation is not the rate-determining step (see Supporting Information, KIE experiments section), the possibility of C(sp^2)–H activation with electron-deficient substrates as the rate-determining step cannot be ruled out. It is noteworthy that high regioselectivity was observed for the aliphatic acids containing *meta*-methoxy groups (**1j** and **1s**), while the substrate bearing a *tert*-butyl group (**1n**) afforded a mixture of regioisomers (**2n**/**2n'** = 3/1). Considering the previously observed high *para*-selectivity of Pd(IV)-mediated C–H coupling reactions of anisoles[3g,5c,22], it is likely that the alkyl-Pd(II) intermediate is oxidized to Pd(IV) prior to C–H activation. Under the present conditions, the carboxylic acid **1t** containing either NBoc or NTs groups failed to deliver tetrahydroisoquinoline (THIQ) product **2t**. This cyclative C–H/C–H coupling reaction was also amenable to the syntheses of indane scaffolds (**2u**–**2w**). Notably, an [F^+] oxidant[3g,13] (1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate) showed superior reactivity for tertiary aliphatic acids containing an α-gem-dimethyl group (**2v** and **2w**) (see Supporting Information, Table S5).

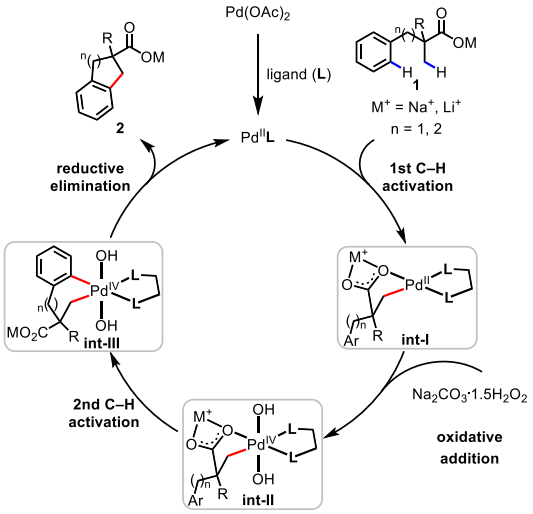
Scheme 2. Total Synthesis of (±)-Russujaponol F[a]



[a]Conditions: (**a**) $SOCl_2$, EtOH, reflux, overnight; I_2 (0.5 equiv), Selectfluor (0.5 equiv), CH_3CN, 60 °C, 3 h. (**b**) $Pd(OAc)_2$ (10 mol%), **L12** (10 mol%), pivalic acid (3.0 equiv), CsOAc (1.0 equiv), Ag_2CO_3 (2.0 equiv), HFIP, 80 °C, 12 h. (**c**) $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), Ag_2CO_3 (1.0 equiv), 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (2.0 equiv), HFIP, 90 °C, 12 h. (**d**) LAH (3.0 equiv), THF, 0 °C to rt, overnight.

Illudalane sesquiterpenes comprise a large family of natural products, which typically feature an indane core (for which various oxidation states are possible) bearing a challenging all-carbon quaternary center (Scheme 2A).[14] Owing to their promising biological activities, tremendous efforts have been devoted to the total syntheses of these targets.[15,16] Given the power of this methodology for the construction of indane scaffolds, we embarked on the total synthesis of (±)-russujaponol F via multiple C–H functionalizations (Scheme 2B). Baudoin's group reported the first total synthesis of russujaponol F in racemic and enantioselective forms based on a C(sp^3)–H arylation strategy in 13 steps (26% yield) and 15 steps (12% yield) respectively.[15] Beginning with phenylacetic acid **3** that is commercially available or synthesized through *ortho*-C–H methylation[17], we were able to prepare aryl iodide **4** by esterification and subsequent mono-iodination[18] of **3** using I_2 and Selectfluor in 79% yield. Investigation of the C–H arylation of pivalic acid indicated that, with ligand **L12**[10f,19], the mono-arylated product **5** could be obtained in 62% yield, along with 12% of the cyclative C–H/C–H coupling product **6** (see Supporting Information, Table S6). The formation of **6** under these conditions might be attributed to a second arylation of **5** with additional aryl iodide serving as the bystanding oxidant.[20] The cyclative C–H/C–H coupling was then performed under the standard conditions using an [F^+] oxidant to give the desired product **6** in 41% yield. Finally, global reduction of **6** using LAH cleanly delivered (±)-russujaponol F in 96% yield, completing the total synthesis in four steps and 28% overall yield: the shortest and highest yielding total synthesis of russujaponol F to date.

Scheme 3. Proposed Mechanism for Cyclative C(sp^3)–H/C(sp^2)–H Coupling Reaction



On the basis of literature precedents[3–5] and our recent work on the C−H activation of free acids[10i,j], we propose that this cyclative C(sp^3)−H/C(sp^2)−H coupling reaction proceeds via a Pd(II)/Pd(IV) catalytic cycle as outlined in Scheme 3. First, coordination of $Pd(OAc)_2$ to an MPAA ligand generates the active **L**Pd(II) species. After coordination of the acid substrate **1** to Pd, both the counter-cation Na^+ or Li^+ and the MPAA ligand accelerate the cyclopalladation of the β-C(sp^3)−H bond to form **int-I**. Next, oxidative addition of the hydrogen peroxide occurs to produce **int-II**, a process established in previous studies on the oxidation of Pd(II) to Pd(IV) by benzoyl peroxide[21a], *tert*-butyl peroxyacetate[21b], or hydrogen peroxide[21c,d]. In the previously reported β-lactonization[10i] or acetoxylation[10j] reactions, selective reductive elimination yields β-lactone or β-acetoxylated carboxylic acid. In this case, a reactive phenyl group on the side chain of the substrate undergoes a second C(sp^2)−H activation of **int-II** to deliver **int-III** via a seven or six-membered palladacycle, enabled by the facile dissociation of the weakly coordinating free acid.[22] However, it is also possible that the Pd(II) intermediate **int-I** performs the second C−H activation prior to the oxidative addition of hydrogen peroxide that generates **int-III**. Finally, reductive elimination of **int-III** generates the cyclative C−H/C−H coupling product **2** and regenerates the **L**Pd(II) species.

In summary, we have realized a Pd(II)-catalyzed cyclative C(sp^3)−H/C(sp^2)−H coupling reaction enabled by a cyclopentane-based mono-*N*-protected β-amino acid ligand. The use of inexpensive sodium percarbonate as the sole oxidant and native free carboxylic acids as the directing group renders this reaction highly practical and potentially amenable to large-scale manufacturing. A range of biologically significant scaffolds, including tetralins, chromanes, and indanes, could be readily prepared by this protocol. The synthetic application of this methodology was demonstrated by a concise total synthesis of (±)-russujaponol F via multiple C−H functionalizations in four steps from readily available phenylacetic acid and pivalic acid.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full experimental details and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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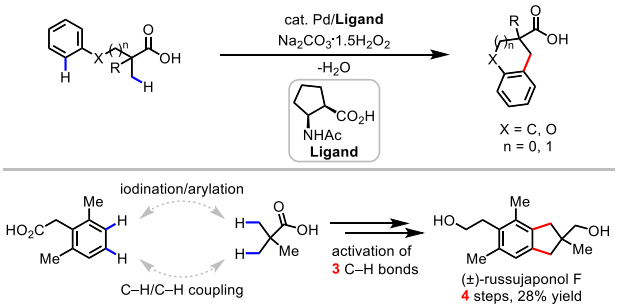
cat. Pd/Ligand
Na2CO3·1.5H2O2
-H2O
CO2H
NHAc
Ligand
X = C, O
n = 0, 1
iodination/arylation
C–H/C–H coupling
activation of
3 C–H bonds
(±)-russujaponol F
4 steps, 28% yield