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C–C bond activation enabled by dyotropic rearrangement of Pd(IV) species

Jian Cao[#1,2], **Hua Wu**[#1], **Qian Wang**[1], **Jieping Zhu**[1,*]

[1]Laboratory of Synthesis and Natural Products, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH5304, CH-1015 Lausanne, Switzerland [2]Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou 311121, P. R. China

[#] These authors contributed equally to this work.

Abstract

The weak carbon–metal bond combined with the kinetic inertness of carbon–carbon bond renders the metal catalyzed C–C bond activation to be highly challenging. Most of the reported C–C bond activation methodologies involve the strain-releasing cleavage of small rings to compensate the unfavorable kinetic and thermodynamic penalties associated with the C–C bond cleavage. Here we report that the 1,2-positional interchange of vicinal C–C and C–Pd(IV) bonds (dyotropic rearrangement) can be realized in a stereospecific manner under mild conditions, giving access to quaternary carbon-palladium bonds. An enantioselective synthesis of medicinally relevant fluorinated cyclopentanes, featuring this rearrangement as a key step, has been developed. We anticipate that implementing a Pd-based dyotropic rearrangement in reaction design could provide a new dimension in the development of Pd-catalyzed transformations.

Dyotropic rearrangement, coined by Reetz in 1972,[1,2] is a class of pericyclic valence isomerization reactions in which two σ-bonds simultaneously migrate intramolecularly.[3] Dyotropic rearrangements involving metal are known,[4] most of them being stoichiometric in metal with the carbon-metal bond as stationary scaffold as exemplified in Fig. 1a.[5] 1,2-Pd shifts proceeding through a sequence of β-H elimination followed by re-insertion are well established and elegantly exploited in organic synthesis.[6,7] On the other hand, 1,2-Pd migration[8] and Wagner-Meerwein rearrangement[9–11] implicating Pd as leaving group have also been reported. However, the 1,2-alkyl(aryl)/Pd dyotropic rearrangement has, to the best of our knowledge, never been recognized as a viable mechanistic pathway. As depicted in Fig. 1b, we thought that the realization of such transformation is of high synthetic value as it

[*]Correspondence and requests for materials should be addressed to J.Z. jieping.zhu@epfl.ch.

Author Contributions
J.C., H.W., Q.W. and J.Z. conceived the work, designed the experiments and analyzed the data. J.C. and H.W. optimized the reaction conditions, performed the experiments, J.C., H.W., Q.W. and J.Z. co-wrote the paper.

Competing interests
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represents a conceptually unprecedented C–C bond activation methodology.[12] Indeed, the process breaks formally an unactivated C–C σ-bond with concurrent formation of a new C–C σ-bond and a new C–Pd bond ready for the subsequent functionalization (Fig. 1b). It is important to note that the mechanistic picture of this reaction is completely different from that of the *syn*-β-carbon elimination/carbopalladation sequence (Fig.1c).[13]

The palladium-catalyzed enantioselective 1,2-[14] and 1,1-[15] arylative fluorinations of alkenes involving Pd(IV) intermediate[16,17] have been reported. Merging the carbopalladation with palladium walking strategy, a 1,3-arylative fluorination of chromenes[18] has also been developed.[19–24] Due to the difficulties associated with the generation of quaternary C(sp^3)–Pd species, all these methods create a C–F containing tertiary stereocenter. We hypothesized that a domino process implicating a 1,2-aryl(alkyl)/Pd dyotropic rearrangement could be an interesting pathway to the quaternary C(sp^3)–Pd species, hence the quaternary C–F stereocenter.[25] Towards this end, a reaction sequence featuring this key elementary reaction is designed as depicted in Fig. 1d. The amide group-directed arylpalladation of **1** with an in situ generated ArPdX species would afford intermediate **A** which could isomerize to **B** via a β-hydride elimination and reinsertion sequence. The formation of 5-membered chelate between Pd and amide group in **B**could provide a driving force to this Pd-walking process. Oxidation of Pd(II) to Pd(IV) species **C** followed by dyotropic rearrangement would afford **D** which could exist as an η^3-complex **E**. A C–F bond forming reductive elimination of Pd–complex **D** would then furnish product **2**. Since enantioselective construction of C–F bond via C–C bond activation remains unknown, we chose F^+ donor as both oxidant and fluorine donor for the final reductive elimination step. The whole catalytic process merging the carbopalladation with the C(sp^3)–H and the C–C bond activation would create three stereocenters including one quaternary C–F bond from a prochiral substrate. As the Pd walking in a cyclic system and concerted dyotropic rearrangement proceed with high stereochemical fidelity, the whole sequence would be diastereoselective should the initial carbopalladation be effectively directed. Here we show the realization of this endeavor, employing arylboronic acids **3** as coupling partner and Selectfluor® (**4**) as both oxidant and fluorine source.

Results and discussion

Reaction development

To streamline the designed sequence, the following competitive reactions – a) the β-hydride elimination of intermediates **A** and **B** to alkene **5** (Heck reaction); b) the premature oxidation of Pd(II) intermediate **A**; and c) C(sp^3)–F reductive elimination of Pd(IV) species **C** to 1,3-fluoroarylation product **6** – would have to be overcome. With these considerations in mind, we initially examined the feasibility of our hypothesis in its racemic version. After much experimentation (Supplementary Table S1), we found that reaction of prochiral cyclopentene **1a** (R = R^1 = Ph) with 3-methoxyphenylboronic acid (**3a**) and Selectfluor® (**4**) in dichloroethane (DCE) in the presence of a catalytic amount of $Pd(OAc)_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (**L1**) afforded indeed the desired product (±)-**2a** in 70% yield as a single diastereomer. We then turned our attention to the enantioselective version. After a survey of various reaction parameters including the chiral ligands (Supplementary Table S2),

the palladium sources, the bases, the solvents, the additives and the F^+ sources, the optimum conditions found consisted of heating a DCE solution of **1a**, **3a** and **4** at 50 °C in the presence of $Pd(AdCO_2)_2$ (10 mol%), pyrox ligand **L2** (12 mol%), Na_2CO_3 (3.0 equiv.) and $AdCO_2H$ (1.0 equiv.). Under these conditions, compound **2a** was isolated in 70% yield with 92% e.e. (Table 1). We note that using bulky adamantane-1-carboxylate ($AdCOO^-$) as the Pd(II) counterion is important to ensure the good yield of **2a**. The same reaction using $Pd(OAc)_2$ as pre-catalyst under otherwise standard conditions provided **2a** with similar e.e., but with much reduced yield (47%, Supplementary Table S3).

The substrate scope

We then investigated the substrate scope of this bisarylative fluorination reaction under the optimized conditions (Table 1). Aryl boronic acids bearing both electron-donating and -withdrawing groups, regardless of their positions, participated in the reaction efficiently to afford the desired products (Table 1, **2a**-**2m**). The relative and absolute stereochemistry of **2a** and **2d** were determined by X-ray crystallographic analysis. Functional groups including methoxy, ketone, ester, lactone, cyano and halogens (F, Cl, Br) were well tolerated. Naphthalene was also easily introduced into the product (**2f**). Heterocycle such as isobenzofuranone derived boronic acid participated in the reaction to afford **2m** in 51% yield with 92% e.e.. However, electron-rich indole and benzofuran are incompatible with the reaction conditions due probably to their interference with electrophilic Selectfluor® reagent. Amides derived from functionalized anilines were also compatible with the reaction conditions (Table 1, **2n**-**2r**), although 2-methylaniline derived amide afforded the product (**2p**) with reduced enantiomeric excess. As expected, the migrating groups exerted dramatic effect on the reaction outcome, especially on the yield of the product (Table 1, **2s**-**2z**). Interestingly, methyl and methoxy groups also participated in the migration process to afford products **2y** and **2z**, albeit with low yields. It should be noted that only one diastereoisomer was isolated from all these reactions. Performing the reaction of **1a** with **3a** and Selectfluor® (**4**) at one mmol scale afforded **2a** in 61% yield and 93% e.e., indicating the practicability of this protocol.

Mechanistic considerations

The formation of alkene **5** was not observed under optimized conditions. On the other hand, the 1,3-fluoroarylation product **6** was formed as a byproduct in most of the cases. Compounds **6s**, **6y** and **6z** were isolated and fully characterized in the reactions leading to **2s**, **2y** and **2z**, respectively (Fig. 2a). The isolation of both **2s** and **6s** from the same reaction has important stereochemical and mechanistic implications. Two pathways, namely, reductive elimination of Pd^{IV} species **C** (Fig. 2b, Path a) and regioselective ring opening of phenonium **F** by fluoride at C_β (Fig. 2b, Path b),[26] could lead to the side product **6s**. Although nucleophilic attack of fluoride at C_α of the intermediate **F** could in principle also explain the formation of product **2s**, we assumed that this wouldn't be the preferred pathway since attack on C_β leading to **6s** would be favored by both the steric and the electronic effects.[27] The fact that the yield of **2a** resulting from phenyl migration is higher than **2s** involving the shift of 4-methoxyphenyl group was against the notion that the phenonium intermediate is involved in the formation of these compounds. Overall, we think that the

type-I dyotropic rearrangement of **C** to **D** via transition state **G** would be more plausible (Fig 2b, Path c). The participation of the d orbital of Pd might render the $[_{\sigma}2_s + _{\sigma}2_s]$, an otherwise thermally symmetry forbidden process, operational. Whereas the **π**-electron is involved in the phenonium formation, the C–C_{sp} ^{2} **σ** bond, not the **π**-cloud would be engaged in the concerted dyotropic rearrangement. The 4-aryl group in compound **6** is *cis* to the amide substituent as a result of amide-directed carbopalladation step. However, the relative stereochemistry of these two groups became *trans* in compound **2** in accordance with the *trans*-selective dyotropic rearrangement of intermediate **C**.

Gratefully, we were able to isolate two Pd(II) complexes (±)-**7a** and (±)-**7b** by reaction of **1a** with arylboronic acids **3** in the presence of a stoichiometric amount of $Pd(OAc)_2$ and ligand **L1** (Fig. 3a). Both of the complexes are sufficiently stable to be isolated by flash column chromatograph and are fully characterized including X-ray diffraction analysis of (±)-**7b**. Heating a solution of (±)-**7a** in DCE at 50 °C in the presence of Selectfluor® and Na_2CO_3 afforded (±)-**2l** and (±)-**6l** in yields of 38% and 21%, respectively (Fig. 3b). Attempt to monitor the reaction course by ^{19}F NMR spectroscopy failed to observe the formation of either $PdF(IV)^+$ **8a** or **9a** species[28,29] nor the PdF(II) complex.[30,31] However, the presence of $PdF(IV)^+$ intermediate **8a** or **9a** was detected by HRMS analysis (ESI/QTOF) of the reaction mixture (Supplementary Fig. S1). These results indicate that both the dyotropic rearrangement and the reductive elimination of the Pd(IV) $^+$ species are kinetically fast process. This is unusual as C–F reductive elimination is known to be reluctant.[32] Alternative C–N reductive elimination from **8a** leading to fused β-lactam was not observed.[21,33] Since adding external fluoride source, such as NaF, TBAF (tetrabutylammonium fluoride, 2.0 equiv.), or TBAT (tetrabutylammonium difluorotriphenylsilicate, 2.0 equiv.) had no impact on the reaction outcome (Supplementary Fig. S2), we inferred that the S_N2 displacement of Pd(IV) intermediate[34] was not operating under our conditions and that reductive C–F bond formation from pentacoordinated $Pd(IV)^+$ species **8a** and **9a** accounted for the formation of products **6l** and **2l**, respectively. Nevertheless, direct electrophilic fluorination of **7a** leading to **6l** without changing the oxidation state of Pd could not be eliminated at this stage of the mechanistic understanding.[23,29] The formation and accumulation of the (±)-**7a** are also observed by monitoring the reaction of **1a** with 4-acetylphenylboronic acid, and Selectfluor® in the presence of $Pd(OAc)_2$ and ligand **L1** indicating that oxidation of Pd(II) complex **7a** to Pd(IV) $^+$ species **8a** could be the turnover-limiting step. The slow oxidation of Pd(II) to Pd(IV) is important as it avoids the premature oxidation of Pd(II) intermediate **A** (*c.f.* Fig. 1d) that could lead to the formation of 1,2-arylfluorination product. Finally, heating a DCE solution of (±)-**7a** in the presence or absence of base led only to its partial decomposition. We therefore assume that Pd(IV), not the Pd(II), undergoes the facial dyotropic rearrangement under our reaction conditions. However, since the Pd(IV) intermediate **9a** has not been isolated and spectroscopically characterized, we cannot rule out other mechanistic possibilities at the present stage of the development.

To further probe the reaction mechanism,[35] the Pd complex **7a** was treated with $PhICl_2$,[36] $Ce(SO_4)_2$ [37] or $[Cp_2Fe]PF_6$,[38] which are known to be good single-electron-transfer (SET) oxidants. As it is shown in Fig. 3c, the reaction course was diverted under these conditions to afford alkene **5l** albeit in low to moderate yields. No product resulting from the dyotropic

rearrangement was observed under these SET conditions. These results provided indirect evidence that Pd(III) species might not be involved under our standard conditions.

Applications

As we noted in the scope exploration, the electron-rich indol-3-yl boronic acid is a poor substrate for the present reaction. To overcome this limitation and to examine the compatibility of the 1,2-aryl(alkyl)/Pd(IV) dyotropic rearrangement with other transition metal catalyzed elementary reactions, a cyclizative cross-coupling of 2-alkynylanilines **10** with cyclopentene **2a** in the presence of Selectfluor® (**4**) was investigated (Table 2).[39] Under our previously established conditions, the desired product **11** was indeed obtained but only in low yield. We quickly realized that the presence of sodium carbonate was harmful to the domino process due to the competitive base-promoted cyclization of **10**. After a brief survey of the reaction conditions and the stoichiometry of the reactants, following conditions [mol ratio **2a**/**10**/**4** = 1:1.3:1.5, $Pd(OAc)_2$ (10 mol%), **L2** (12 mol%), DCE, 50 °C, Ar] were found to be optimum affording compounds **11a**-**11d** in good yields with high enantiomeric excesses (Table 2). We note that under these operationally simple conditions, a highly ordered domino sequence involving aminopalladation/carbopalladation/β-hydride elimination/reinsertion/1,2-aryl(alkyl)/Pd(IV) dyotropic rearrangement/reductive C–F bond forming process occurred with concurrent generation of four chemical bonds (2 C–C, 1 C–N and 1 C–F).

Conclusion

In summary, we demonstrate the feasibility of the 1,2-aryl(alkyl)/Pd dyotropic rearrangement. By merging this elementary reaction with the enantioselective carbopalladation and palladium walking process, prochiral cyclopentenes are transformed into chiral cyclopentanes with concurrent creation of three stereocenters, including a C–F quaternary center, in a highly diastereo- and enantio-selective manner. We anticipate that the dyotropic rearrangement of a Pd complex could provide a new dimension in the realm of C–C bond activation hardly realizable by conventional methods.

Methods

All reactions were carried out under an argon atmosphere using dry solvents under anhydrous conditions. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography. For full experimental details, including procedures for all reactions and characterization of all new compounds, see the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Crystallographic data for the structure reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 1979593 (**2a**), CCDC 1978762 (**2d**), CCDC 1978761 (**6s**), CCDC 2024253 (**7b**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. The data supporting the findings of this study are available within the article and its Supplementary Information files.

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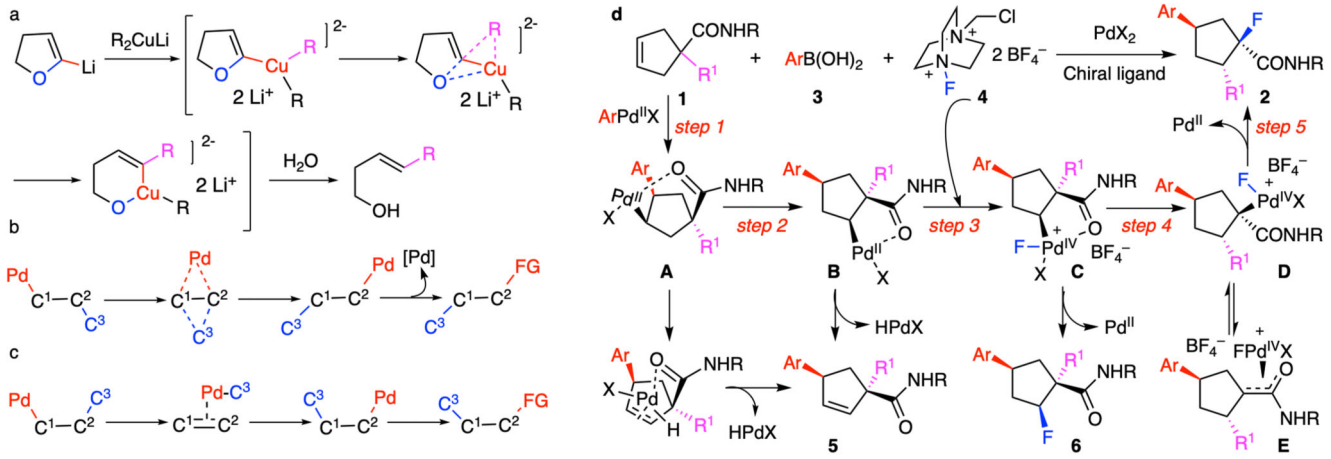

Figure 1. Dyotropic rearrangement involving metals.

a, Dyotropic rearrangement of 1-hetero-1-alkenyl higher order organocuprates. The reaction is stoichiometric in Cu using C–Cu bond as a stationary scaffold. **b**, Schematic presentation of proposed 1,2-aryl(alkyl)/Pd dyotropic rearrangement. The Pd species is one of the migrating group involving C–C bond as a stationary phase. The reaction could be catalytic in metal if catalytically active [Pd] species could be regenerated at the end of the catalytic cycle. **c**, β-Carbon elimination/*syn*-carbopalladation sequence. The β-carbon elimination happens nevertheless seldomly within a non-strained acyclic framework. **d**, Reaction design. The proposed reaction sequence involves an enantioselective carbopalladation (step 1), Pd-walking (step 2), oxidation of Pd(II) to Pd(IV) species (step 3), the 1,2-aryl(alkyl)/Pd(IV) positional interchange (step 4) and finally, the C–F bond forming reductive elimination process (step 5). Generation of α-carbonyl Pd(IV) species **D** is thought to be a driving force for the programmed dyotropic rearrangement. A quaternary C–Pd bond (**D**) is generated after the dyotropic rearrangement. Ligand was omitted for the sake of clarity.

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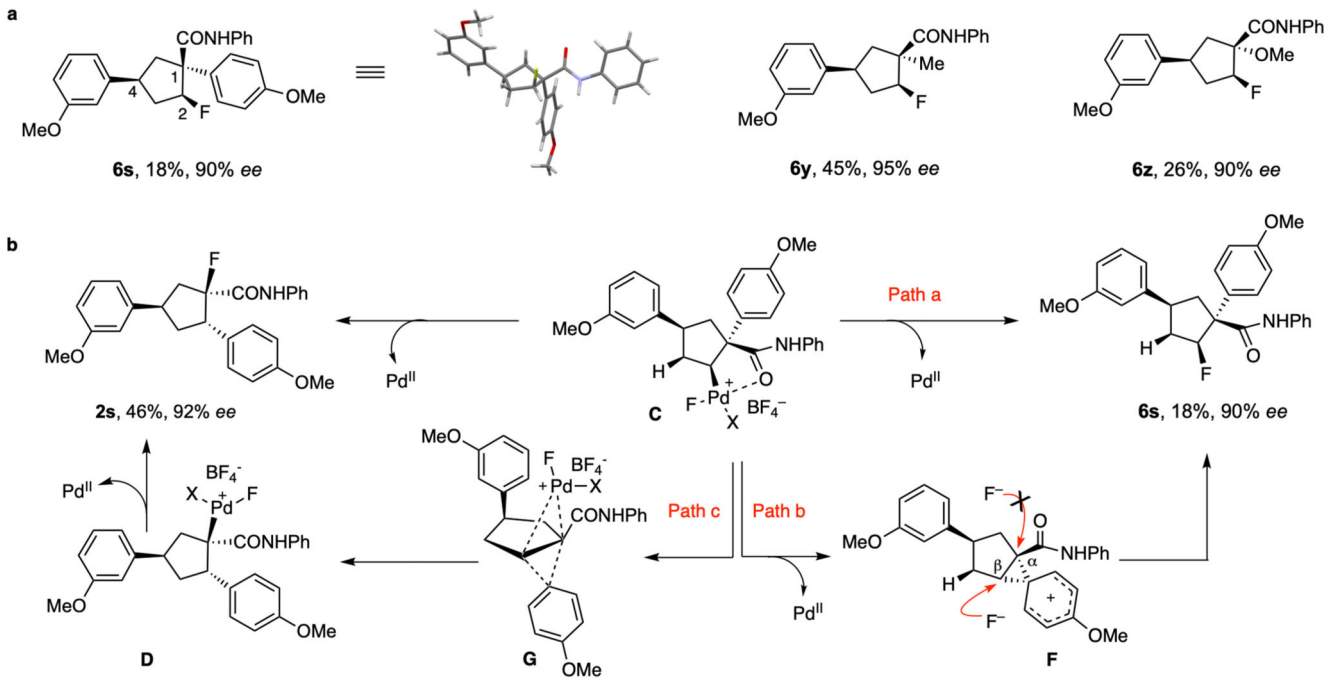

Figure 2. Side products and mechanistic implication.

a, The isolated 1,3-fluoroarylation products **6s**, **6y**, **6z**. The formation of these products not only materialize the presence of intermediate **C**, but also indicate that the C–F bond forming reductive elimination from **C** is a competitive process to the dyotropic rearrangement. **b**, Possible reaction pathways. Path a, reductive elimination of complex **C** leading to the side product **6s**; Path b, ring-opening of the phenonium ion **F** by fluoride could also produce the side product **6s**, but not the rearranged product **2s**. The phenonium ion **F** could potentially be generated *via* intramolecular nucleophilic displacement of the Pd(IV) species, which is a good nucleofuge, by the neighboring 4-methoxyphenyl group; Path c, dyotropic rearrangement pathway leading to the product **2s**. Release of steric interactions and the formation of a thermodynamically more stable α-carbonyl Pd(IV) species could be the driving force of the rearrangement. Ligand was omitted for the sake of clarity.

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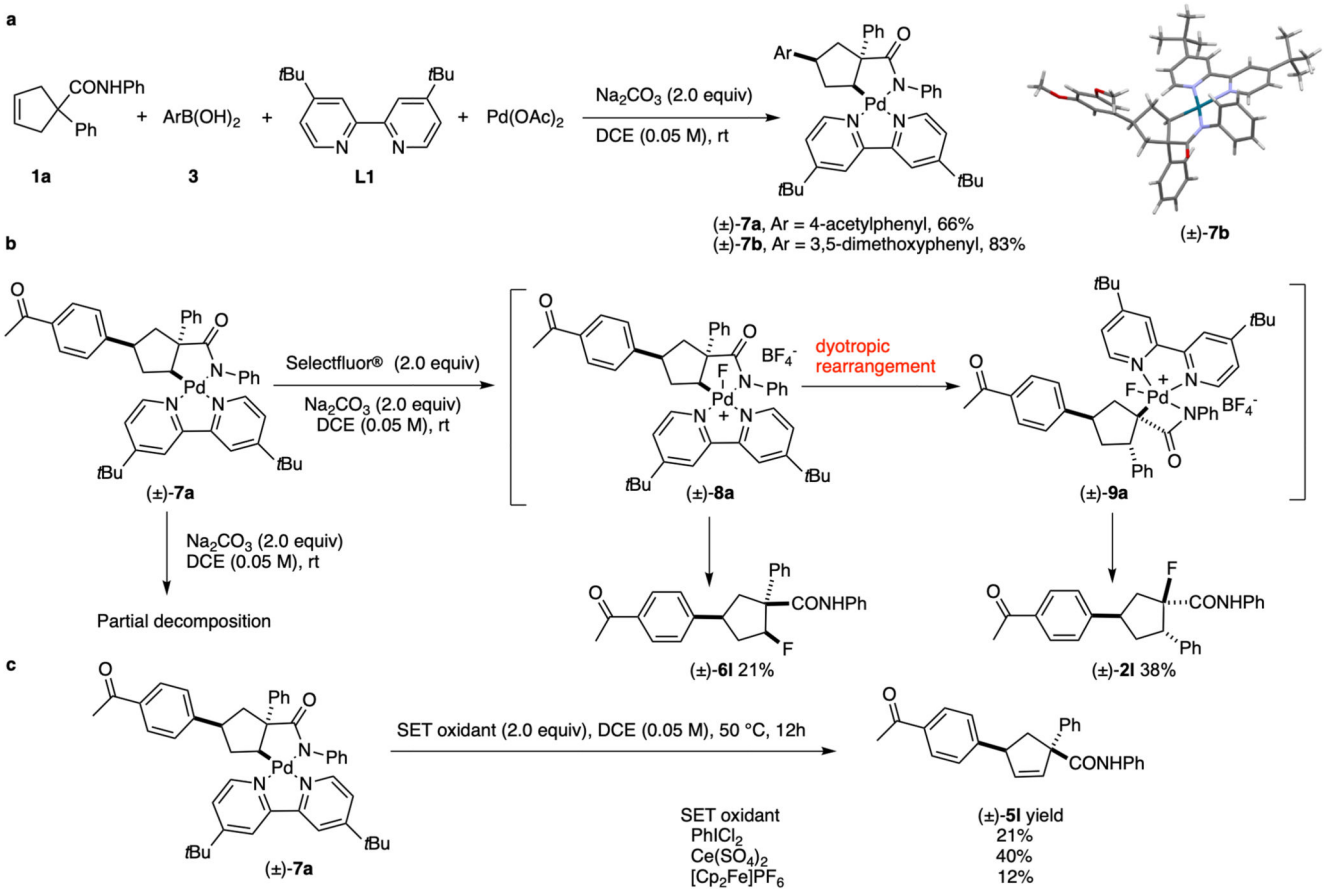

Figure 3. Structure characterization of key reaction intermediates.

a, Synthesis, isolation and structural characterization of the Pd(II) intermediates (±)-**7a** and (±)-**7b**, precursors of the dyotropic rearrangement. **b**, Detection of the Pd(IV) intermediates (±)-**8a** and/or (±)-**9a**. C–F bond forming reductive elimination of (±)-**8a** affords (±)-**6l**, while that of (±)-**9a** produce (±)-**2l**. **c**, Control experiments on the oxidation of Pd-complex **7a** with SET oxidants. Only β-hydride elimination product (±)-**5l** was isolated indicating that Pd(III) species might not be involved in the conversion of **7a** to **2l**. SET = Single electron transfer. Ligand was omitted for the sake of clarity.

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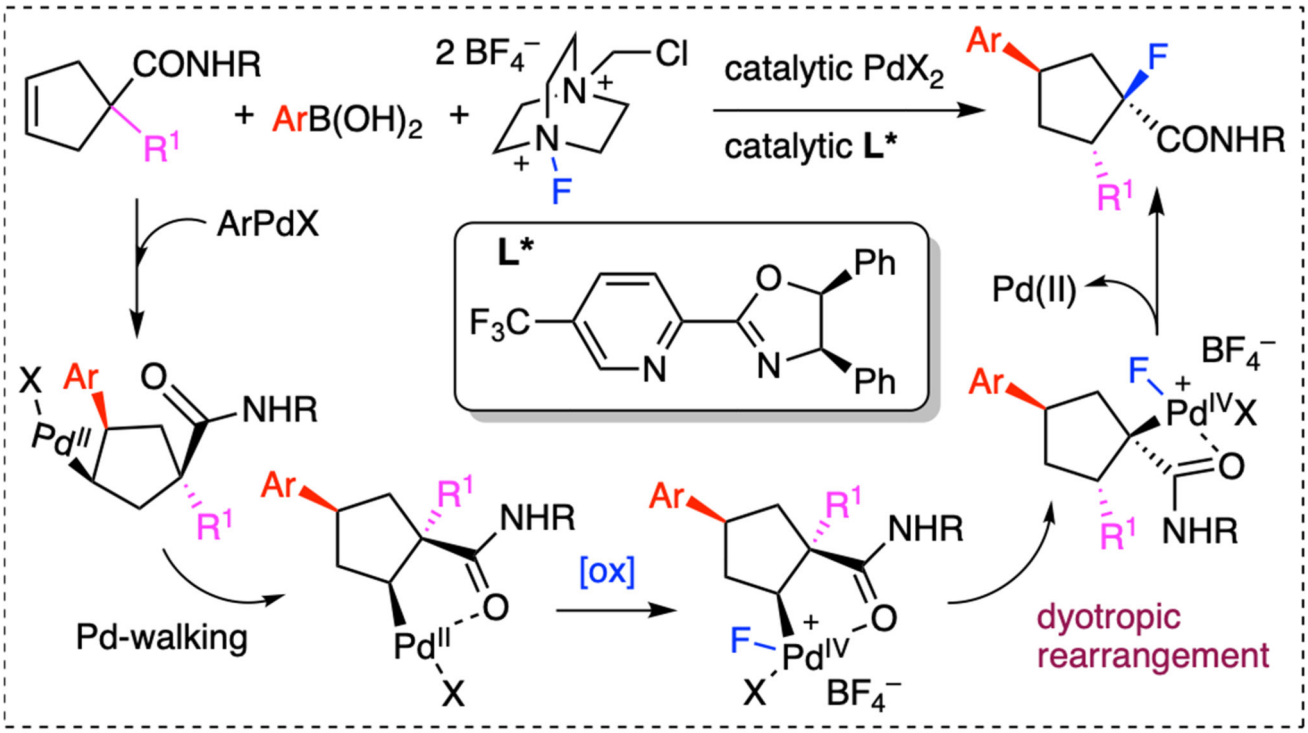

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Table 1

Scope of enantioselective remote arylative fluorination of cyclopentenes.

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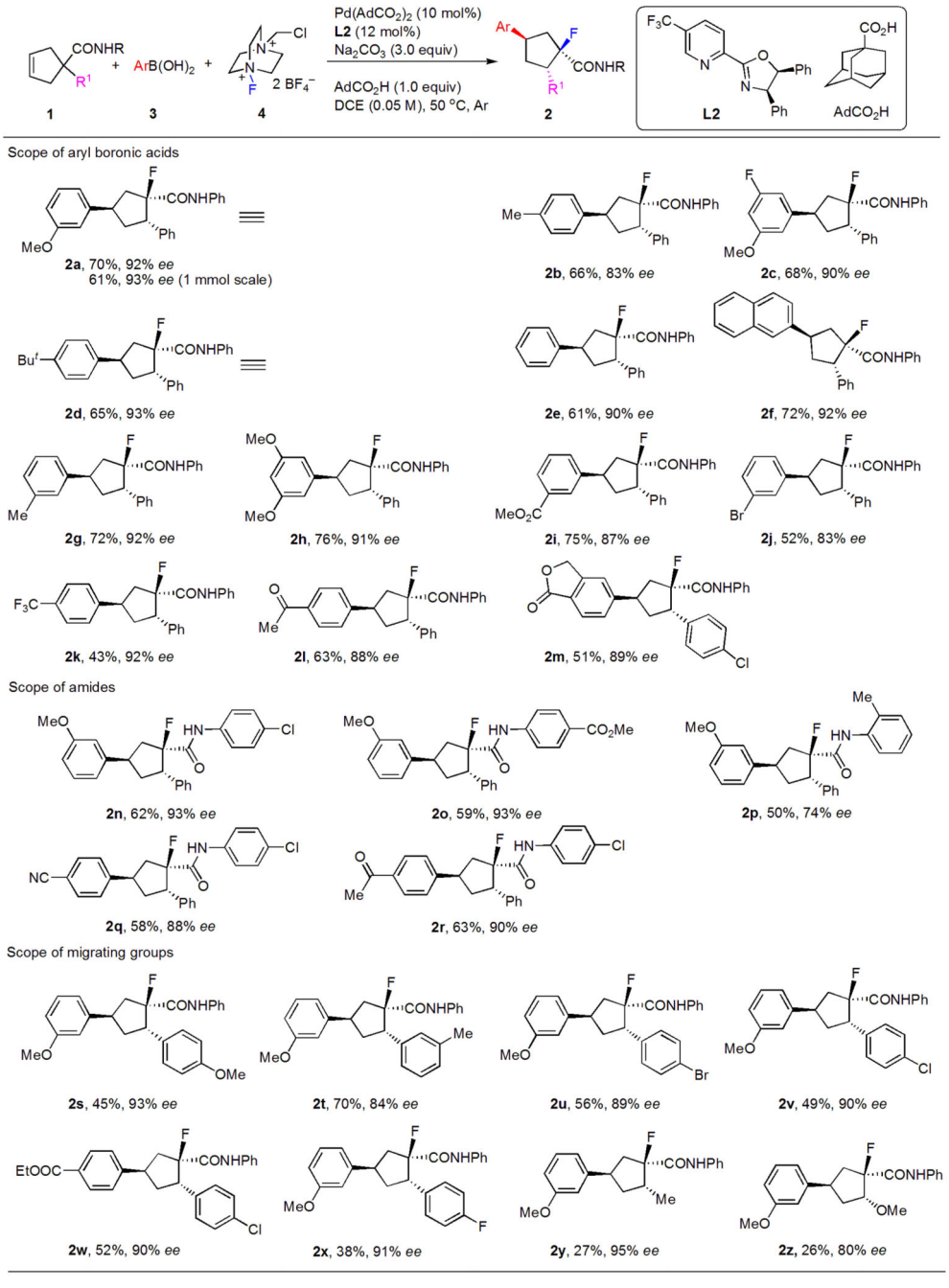

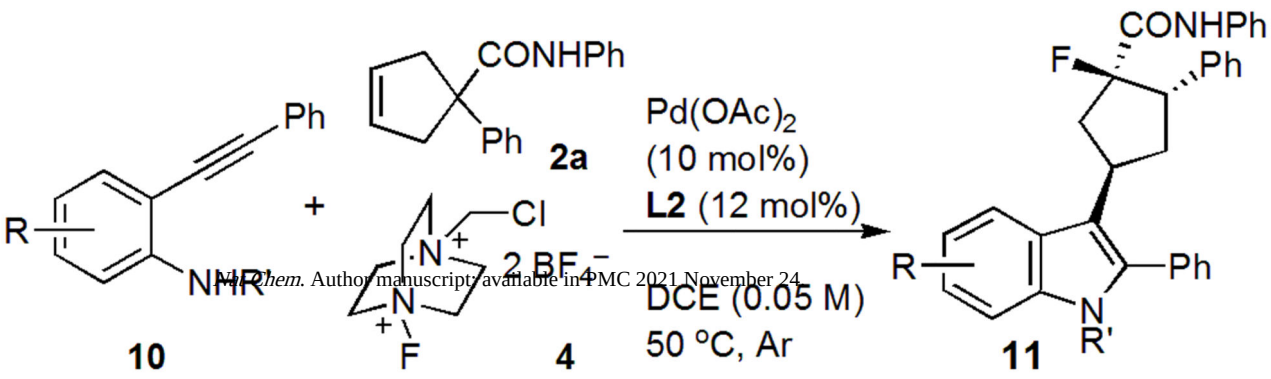

Standard reaction conditions: $Pd(AdCO_2)_2$ (10 mol%), **L2** (12 mol%), cyclopentene (**1**) (0.1 mmol), $ArB(OH)_2$ (**3**) (0.2 mmol), Selectfluor® (**4**) (0.2 mmol), Na_2CO_3 (0.3 mmol), $AdCO_2H$ (0.1 mmol) in DCE (2.0 mL) at 50 °C under argon. $AdCO_2H$, adamantane-1-carboxylic acid; ^{t}Bu, *t*-butyl group; Ar, aryl group.

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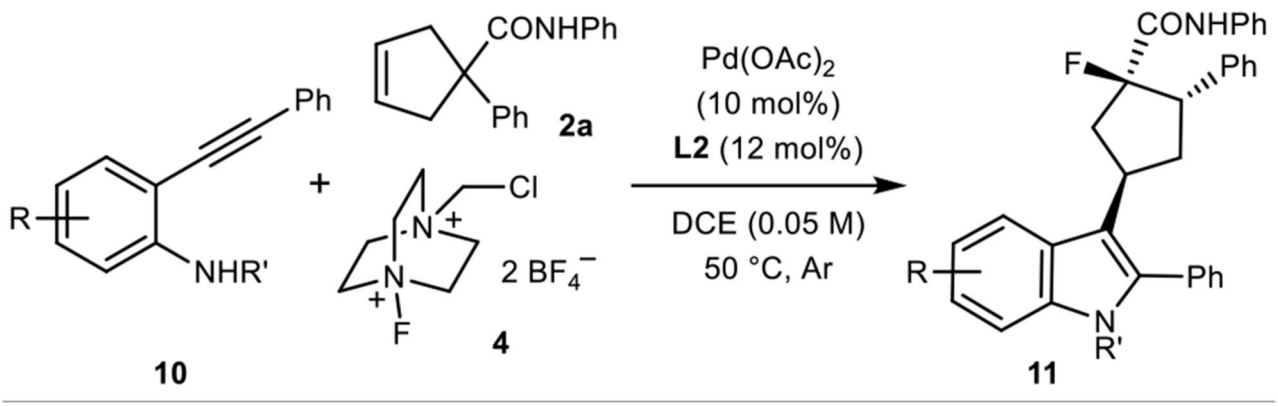
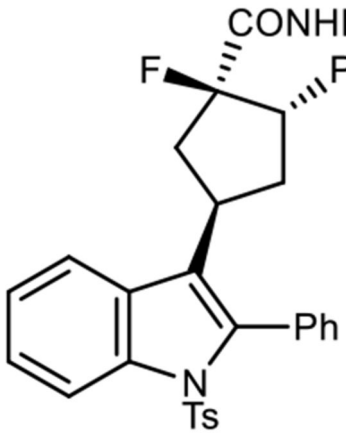
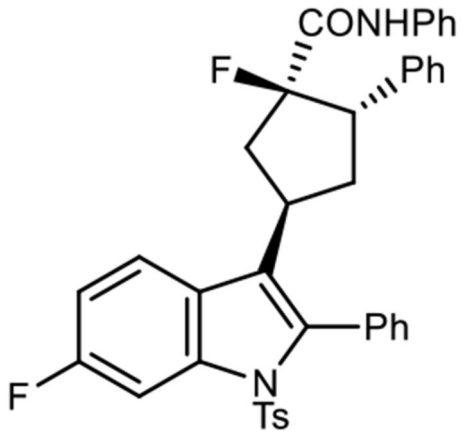
Table 2

Pd-catalyzed cyclizative cross-coupling of alkynes with alkenes in the presence of Selectfluor®

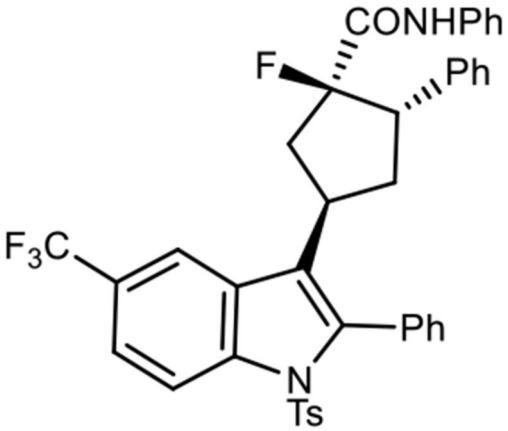




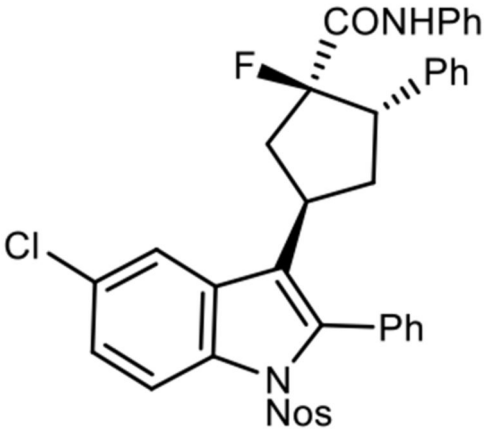
11a, 35% yield, 76% e.e.



11b, 40% yield, 83% e.e.



11c, 44% yield, 90% e.e.



11d, 46% yield, 86% e.e.

Standard reaction conditions: **2a** (0.1 mmol), **10** (1.3 equiv.), Selectfluor® (1.5 equiv.), $Pd(OAc)_2$ (10.0 mol%), **L2** (12.0 mol%) in DCE (2.0 mL) at 50 °C under argon atmosphere. Ts = 4-toluenesulfonyl; Nos = 2-nitrobenzenesulfonyl.

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