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Modular and regioselective synthesis of all-carbon tetrasubstituted olefins enabled by an alkenyl Catellani reaction

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Abstract

All-carbon tetrasubstituted olefins have been found in numerous biologically important compounds and organic materials. However, regio- and stereocontrolled construction of this structural motif still constitutes a significant synthetic challenge. Here, we show that a modular and regioselective synthesis of all-carbon tetrasubstituted olefins can be realized via alkenyl halide- or triflate-mediated palladium/norbornene (Pd/NBE) catalysis, which is enabled by a modified NBE containing a C2 amide moiety. This new NBE co-catalyst effectively suppressed undesired cyclopropanation pathways, which have previously been a main obstacle for developing such reactions. Diverse cyclic and acyclic alkenyl bromides or triflates with a wide range of functional groups can be employed as substrates. Various substituents can be introduced at the alkene C1 and C2 positions regioselectively simply by changing the coupling partners. Initial mechanistic studies provide insights on the rate-limiting step as well as the structure of the actual active ligand in this system.

Graphical Abstract

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Author contributions

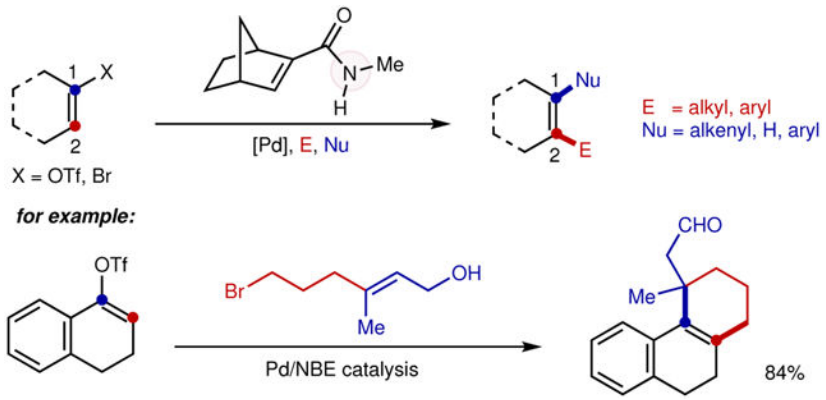
J.W., Z.D. and G.D. conceived and designed the experiments. J.W. performed experiments. C.Y. prepared a few substrates. J.W. and G.D. co-wrote the manuscript.

Data availability. The data supporting the findings of this study are available within the paper and its Supplementary Information. Crystallographic data for compound **4e** have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition no. CCDC 1908383. These data can be obtained free of charge from the CCDC (http://www.ccdc.cam.ac.uk/data_request/cif).

Competing interests

The authors declare no competing interests.

Supplementary information and chemical compound information are available in the online version of the paper.



All-carbon tetrasubstituted olefins are commonly found in natural products (Fig. 1), pharmaceuticals and organic materials, and often serve as the precursors for preparing highly substituted epoxides, aziridines and cyclopropanes[1]. However, synthesis of all-carbon tetrasubstituted olefins has constituted significant challenges, particularly in a regio- and stereocontrolled fashion[1]. Among various approaches, the one involving carbometallation of alkynes appears to be most efficient and modular, resulting from a rapid assembly of three common components[2-11]. However, controlling regioselectivity with electronically or sterically unbiased alkynes is nontrivial. In addition, the product scope is somewhat limited due to the accessibility of cyclic alkynes[12]. Hence, alternative, regioselective and general methods for preparing unsymmetrical all-carbon tetrasubstituted olefins remain highly sought after.

The palladium/norbornene (Pd/NBE) cooperative catalysis, originally discovered by Catellani[13], offers streamlined synthesis of poly-substituted arenes[14-19]. Taking advantage of a unique aryl-norbornyl-palladacycle (ANP) intermediate, an electrophile could be introduced at the *ortho* position, while a nucleophile could be coupled at the *ipso* position, thus allowing vicinal difunctionalization of aryl halides (Fig. 2a)[13,20-22]. One would imagine that, the corresponding reaction with alkenyl halides as substrates would afford distinct access to all-carbon tetrasubstituted olefins in a regioselective manner. However, such an alkenyl Catellani reaction remains underexplored, and the corresponding alkenyl ANP intermediate has been elusive primarily owing to the high reactivity of the olefin π bond compared to a more stable aryl structure.

In the 1980s, Catellani and co-workers found that reactions of alkenyl bromides with NBE gave rise to two types of cyclopropanation products, through a 3-*exo*-trig reaction pathway (Fig. 2b)[23]. Recently, Van Vranken and co-workers further extended the reaction scope for such cyclopropanation reactions[24]. The 3-*exo*-trig reaction is likely to be kinetically facile, partially due to a favored geometry of the olefin complex towards migratory insertion. On the other hand, Lautens[25] and later Yamamoto[26] demonstrated that uracil and 2-quinolone-derived iodides successfully delivered the Catellani products, likely benefited by the partial aromaticity of these substrates (Fig. 2c). To the best of our knowledge, the Pd/NBE catalysis with non-aromatic, regular alkenyl halides has not been reported to date. Here, we describe our initial development of an alkenyl Catellani reaction that employs regular alkenyl

bromides and triflates as substrates as a unique strategy for preparing unsymmetrical all-carbon tetrasubstituted olefins (Fig. 2d).

Compared to the aryl Catellani reactions, several new challenges can be envisaged for using alkenyl substrates (Fig. 2c): (1) the complete loss of aromaticity would greatly enhance the reactivity of the olefin π bond towards the undesired cyclopropanation reaction; (2) the presence of allylic β-Hs would make the cyclopropanation reaction irreversible through following β-H elimination; (3) the absence of *ortho* substituent may hinder the NBE de-insertion step[27]; (4) while alkenyl bromides or triflates[28] are more available than the corresponding iodides, they are clearly more challenging substrates[29].

The anticipated catalytic cycle indicates that two steps can potentially lead to cyclopropanation side-products (Fig. 2d). First, after NBE migratory insertion into the vinyl Pd species, if the C−H metalation to give the alkenyl-ANP (**II**) is slower than the alkyl migratory insertion into the olefin, a 3-*exo*-trig cyclopropanation would dominate (*vide infra*, Table 1). Second, after the C2 (*ortho*) functionalization with the electrophile (E−X), if the NBE extrusion via β-carbon elimination is slow, 3-*exo*-trig insertion could again take place to give the undesired side-products. Therefore, the key for the success of the reaction would be suppress the 3-*exo*-trig pathway and/or promote the C−H metalation and β-carbon elimination processes.

Results and discussion

We hypothesized that use of substituted NBEs may hamper the cyclopropane formation due to the increased bulkiness of the migrating alkyl group, and could simultaneously promote the β-carbon elimination[27]. To test this hypothesis, *ortho* alkylation/*ipso* Heck reaction[13,20,30,31] of alkenyl bromide **1a** was chosen as the model reaction and a range of substituted NBEs were employed as the cofactor (Table 1). Not surprisingly, simple NBE (**N1**) or remotely substituted NBE (**N2**)[32] only gave cyclopropanation product **4a'**. C1 and C7-substituted NBEs (**N3** and **N4**) inhibited cyclopropanation to some extent, but still provided no desired product. It is likely that these substituents also hampered forming the alkenyl-ANP intermediate. The C2-substiutted NBEs (**N5-N18**) were found more effective on suppressing cyclopropane side products. While NBEs having cyano (**N5**), trifluoromethyl (**N6**), and methyl ketone (**N7**) groups at 2-positions were not reactive, majorly affording direct Heck product **4a''**, methyl ester-substituted NBE (**N8**), pioneered by the Yu group[33], gave the desired product **4a** in 23% yield along with 16% cyclopropane product **4a'**. In addition, the free carboxylic acid-derived NBE (**N9**) shows similar reactivity as **N8**. It was surprising that primary amide-substituted NBE (**N10**) exhibited remarkable selectivity and reactivity to provide the desired tetrasubstituted olefin in 54% yield with almost no cyclopropane formation. Further modification on **N10** showed that *N*-methyl amide-substituted NBE (**N11**) was most efficient with 74% yield. Further increasing the sterics on the amide moiety (**N12**) reduced the reactivity, therefore giving more direct Heck product **4a''**. The trend was clearly observed for the *N*,*N*-dialkylamide-substituted NBEs (**N13**−**N16**): the less sterically hindered azetidine-derived NBE showed better reactivity. *N*-Methoxy amide-substituted NBE (**N17**) gave a low conversion, though the reason is unclear.

Unsurprisingly, an additional methyl substituent at the bridgehead position (**N18**) reduced the reactivity.

The reaction was further investigated with alkenyl triflate **5a** as the substrate, given the ease of preparing vinyl triflates from simple ketones. Under the "standard" conditions (entry 1, Table 2), 74% yield of the desired product (**4a**) was obtained using 50 mol% of **N11**, 10 mol % of Pd(cod)Cl_2 and 10 mol% of Buchwald's Ph-DavePhos (**L1**)[34]. A relatively high loading of **N11** was used to suppress direct *ipso* functionalization[19]. A series of control experiments were subsequently conducted to understand the role of each reactant. In the absence of the palladium, phosphine ligand or **N11**, no desired product was formed (entries 2-4). Pd(cod)Cl_2 was found to be slightly more efficient than Pd$(OAc)_2$ (entry 5). A survey of ligands showed that Ph-DavePhos (**L1**) and Ph-JohnPhos (**L2**) were the best choices (entry 6), while the use of more electron-rich DavePhos (**L3**) or ^{t}Bu-DavePhos (**L4**) shut down the reaction (for mechanistic studies, *vide infra*). The 2,6-dimethoxy analogue of **L1** and PPh_3 (**L5** and **L6**) were much less effective. The use of potassium carbonate as the base dramatically decreased the yield compared to cesium carbonate (entry 7). In addition, 5-trifluoromethyl-2-pyridinol (20 mol%) was previously discovered by Yu[35,36] to be an excellent co-catalyst to promote concerted metalation deprotonation (CMD); use of pivalic acid instead gave a low yield (entry 8). Besides 1,4-dioxane, toluene is also a suitable solvent (entry 9). Finally, a lower reaction temperature slightly decreased the yield (entry 10).

With the optimized conditions in hand, the substrate scope was studied (Table 3). Besides methyl acrylate, other Michael acceptors, such as *tert*-butyl acrylate, *N*,*N*-dimethylacrylamide, ethylvinyl ketone, and *N*-*tert*-butylacrylamide, can all be smoothly coupled at the *ipso*-position (**4b**−**4e**). Less electron-deficient olefins, such as 2-vinylpyridine (**4f**) and regular styrene (**4g**), can also be employed. Regarding the scope of the alkyl electrophiles, alkyl iodides with various functional groups, such as silyl protected alcohol (**4i**), alkyl nitrile (**4j**), alkyl chloride (**4k**), and methyl ester (**4m**), were suitable. The bulkier isobutyl iodide gave a lowered yield (**4n**), while secondary alkyl iodides were unreactive, likely due to the steric congestion of the alkenyl-ANP species. Gratifyingly, the use of phenyltrimethylammonium salt (**2o'**) was found to serve as a mild electrophile for delivering the methylation product (**4o**)[37]. To the best of our knowledge, ammonium salts have not been used as electrophiles in Catellani-type reactions before.

The scope with respect to different alkenyl triflates or bromides was examined next. Good functional group compatibility was observed with tolerance of ester (**4q**), trifluoromethyl (**4r**), benzoyl-protected alcohol (**4s**), *N*-methyl pyrrole (**4t**), thiophene (**4u**), Boc-protected amine (**4w**), ketal (**4ac**) and regular olefin (**4ad**). The benzofused vinyl triflates gave higher efficiencies (**4x**−**4z**), probably due to an easier NBE extrusion in the presence of *ortho* substituents. Vinyl triflates directly derived from a lactone (**4aa**) or an enone (**4ab**) could also be employed. In addition, vinyl triflates derived from ketone-containing natural products, such as nootkatone and dihydrocholestrone, delivered the desired products (**4ad** and **4ae**) in good to moderate yields. Besides six-membered ring substrates, preliminary successes have been obtained with other types of alkenyl substrates. Seven-membered (**4af**)

and five-membered alkenyl triflates (**4ag** and **4ah**) proved to be competent for this transformation. With slightly modified reaction conditions, acyclic alkenyl bromides also successfully delivered the desired products (**4ai**−**4ao**).

To demonstrate the generality of this reaction, different couplings at the C1 (*ipso*) position were then investigated. In addition to the Heck termination, Suzuki coupling[38] (**7a** and **7b**) and hydrogenation[39-42] (**7c**) can also be used to install an aryl group, a methyl group, or hydrogen at the C1 position. Besides intermolecular couplings, an intramolecular *ortho* alkylation/redox-Heck annulation was achieved[43,44], which provides a rapid synthesis of tricycles containing an all-carbon tetrasubstituted olefin and an adjacent quaternary stereocenter (**7d** and **7e**). Furthermore, beyond alkylation at the vicinal C2 position, this catalytic system was also effective for C2-arylation using aryl bromides[21,22] as the external electrophile (**9a**-**9c**).

The preliminary mechanistic study started with measuring the kinetic profiles of the reaction with substrate **5a**. The initial-rate method was employed to determine the reaction order of each component (Fig. 3a). Not surprisingly, the dependence of the initial rate on the concentration of [Pd/**L1**] was found to be first-order. Moreover, the rate of reaction shows zero-order dependences on [**5a**], [**2a**], [**3a**] and [**N11**], indicating that oxidative addition of aryl triflate **5a**, migratory insertion into **N11**, the reaction between alkenyl-ANP and electrophile **2a**, and migratory insertion into acrylate **3a** are not the turnover-limiting step. Interestingly, the turnover rate for the formation of side-product **4a''** increases with lower loadings of **N11**, indicating that migratory insertion into **N11** is a pre-equilibrium before the turnover-limiting step (see Supplementary Fig. 13 for a detailed discussion). In addition, the kinetic isotopic effect (KIE) was found to be 1.5 using two parallel reactions (Fig. 3b); while a competition KIE study employing a mixture of **5a** and **5a**-d_3 revealed a KIE of 1.6. Taken together, these values suggest that the C–H cleavage step is partially turnover-limiting and that another elementary step either before or after the C–H cleavage (e.g., subsequent ligand exchange step) also contributes to the catalytic turnover rate.

As an interesting observation during our investigation, cyclized phosphafluorene oxides (**10**) were isolated from the reaction mixture when using Ph-DavePhos (**L1**) and Ph-JohnPhos (**L2**) (Fig. 3c). Presumably, a sequential C−H and C−P bond activation would transform, i.e., **L2** into phosphafluorene **L7**, along with the formation of by-product **11** (see Supplementary Fig. 16 for the proposed mechanism)[45]. To examine whether phosphafluorene **L7** was the "real" ligand (instead of **L2**) in the alkenyl Catellani reaction, a parallel kinetic study was conducted. First, the reaction with **L2** exhibited a notable induction period, while the one with cyclic phosphine **L7** did not. Second, the reaction with **L7** had an almost identical initial reaction rate to that with **L2**. Altogether, these results indicated that **L7** was likely the actual ligand in this system and, during the induction period, **L1** or **L2** was transformed into cyclized phosphafluorenes. These phosphafluorene ligands are less bulky, less σ-donating and more π-accepting than PPh_3[46], which could be beneficial to generate a more π-acidic Pd species thereby promoting the alkenyl-ANP formation (see Supplementary Table 10 for a survey of ligand effect). This finding may also explain why the structurally similar ligand **L5** was significantly less effective due to the inability of forming cyclic phosphines. Finally, to

show utility of this method, a tricyclic compound **14**, previously synthesized in 7 steps[47], can now be accessed in a concise manner from the known vinyl triflate **6y** (prepared in one step from commercially available chemicals) (Fig. 3d).

In summary, a new approach for regioselective preparation of all-carbon tetrasubstituted olefins from readily available alkenyl bromides/triflates is realized, which is enabled by Pd-catalyzed alkenyl Catellani reactions. A class of amide-substituted NBEs has been identified and plays a pivotal role in preventing undesired cyclopropanation pathways. The first use of tetraalkylammonium salts as electrophiles and phosphafluorenes as ligands in Pd/NBE catalysis may have further implications. The broad functional group tolerance could make the reaction attractive for complex molecule synthesis. Future efforts will focus on understanding the unique function of the amine moiety in **N11** and expanding the reaction scope to more acyclic alkenyl halides and other types of C1 and C2 functionalizations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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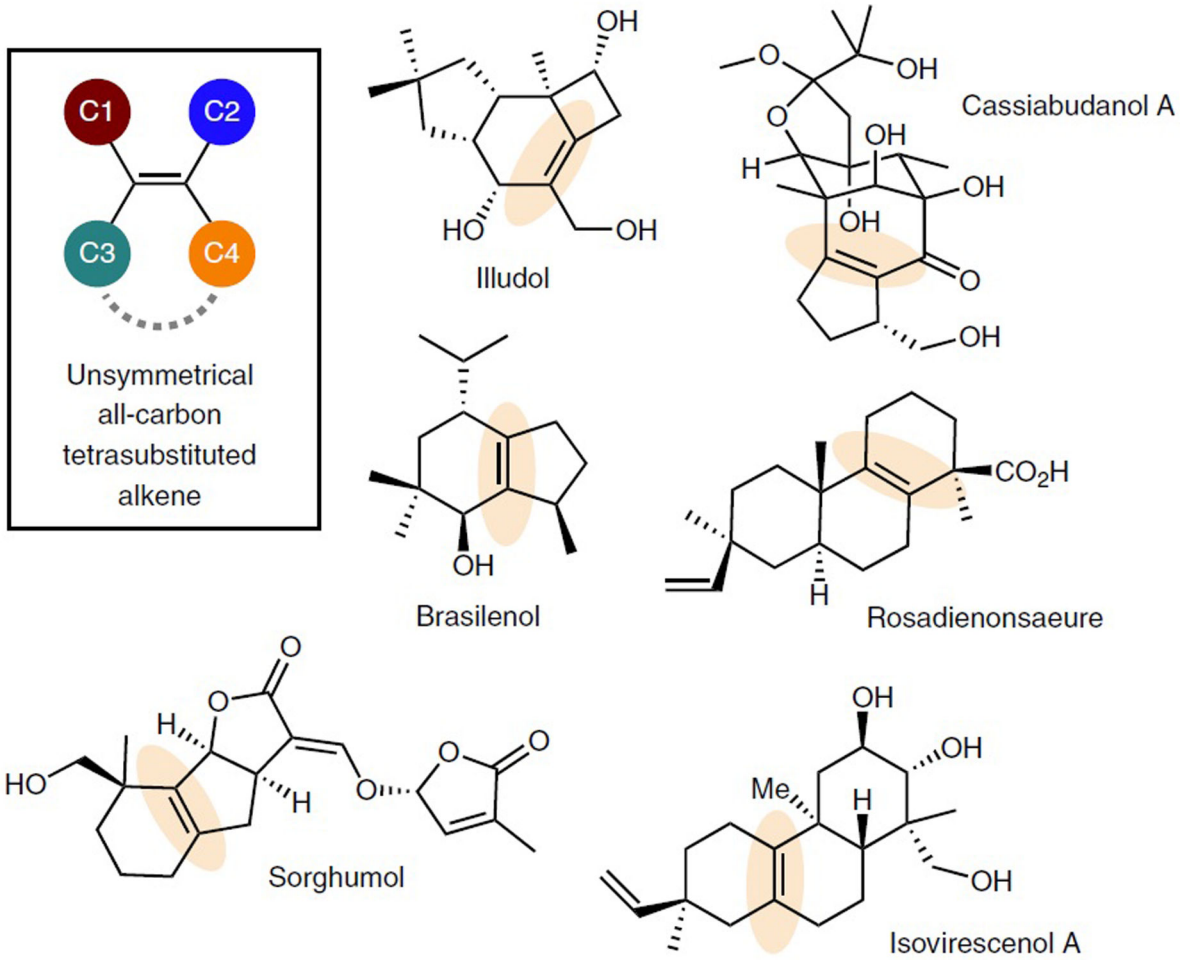


Figure 1l. Representative Natural Products Containing All-carbon Tetrasubstituted Olefins.
All-carbon tetrasubstituted olefins are often found in natural products and other bioactive compounds. Regio- and stereoselective synthesis of this structural motif still poses a significant challenge.

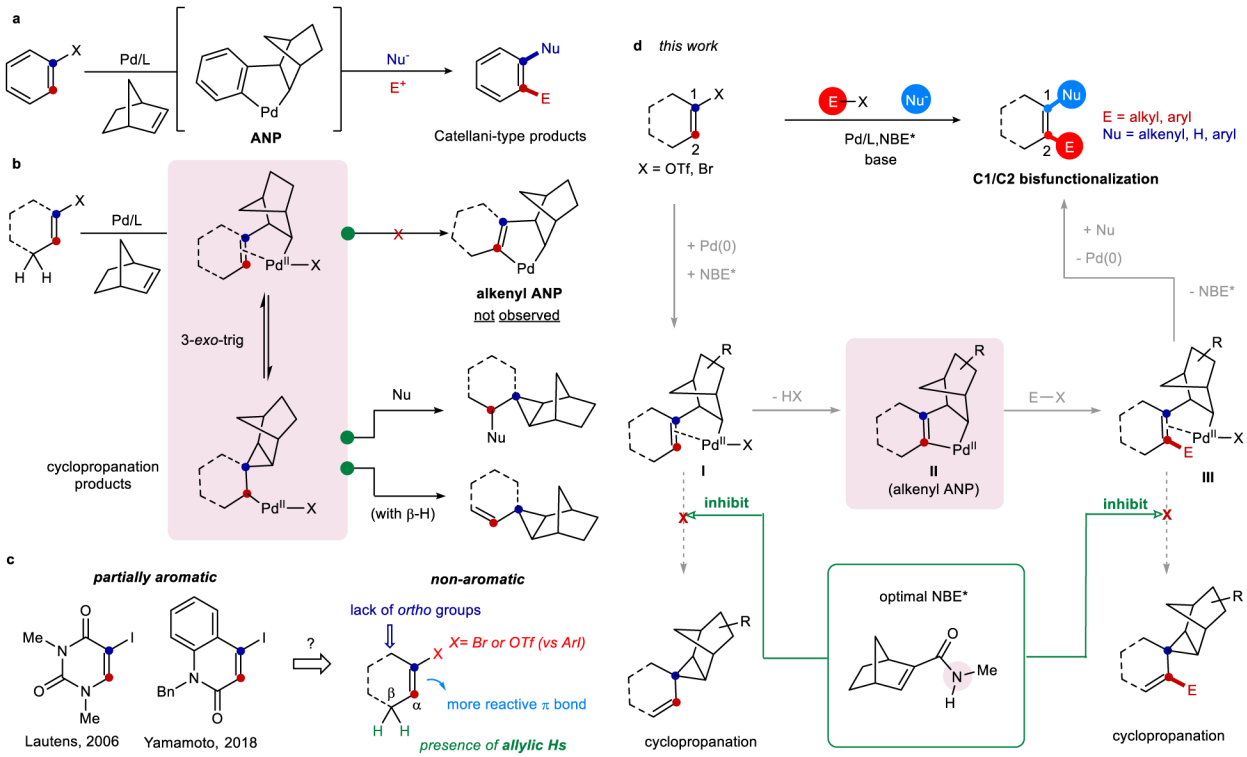


Figure 2|. Alkenyl Catellani-type Reactions.

a, Classical Pd/NBE catalysis employs aryl halides as substrates through the aryl-norbornyl-palladacycle (ANP) intermediate. **b**, Prior works showed that reaction of alkenyl halides with NBE majorly led to cyclopropanation side-products without forming the analogous alkenyl ANP intermediate. **c**, Related examples with partially aromatic alkenyl halides could gave Catellani-type products; however, non-aromatic alkenyl halides are more challenging substrates. **d**, This work realizes the alkenyl Catellani reaction enabled by an amide-substituted NBE, which in turn leads to regioselective synthesis of all-carbon tetrasubstituted alkenes.

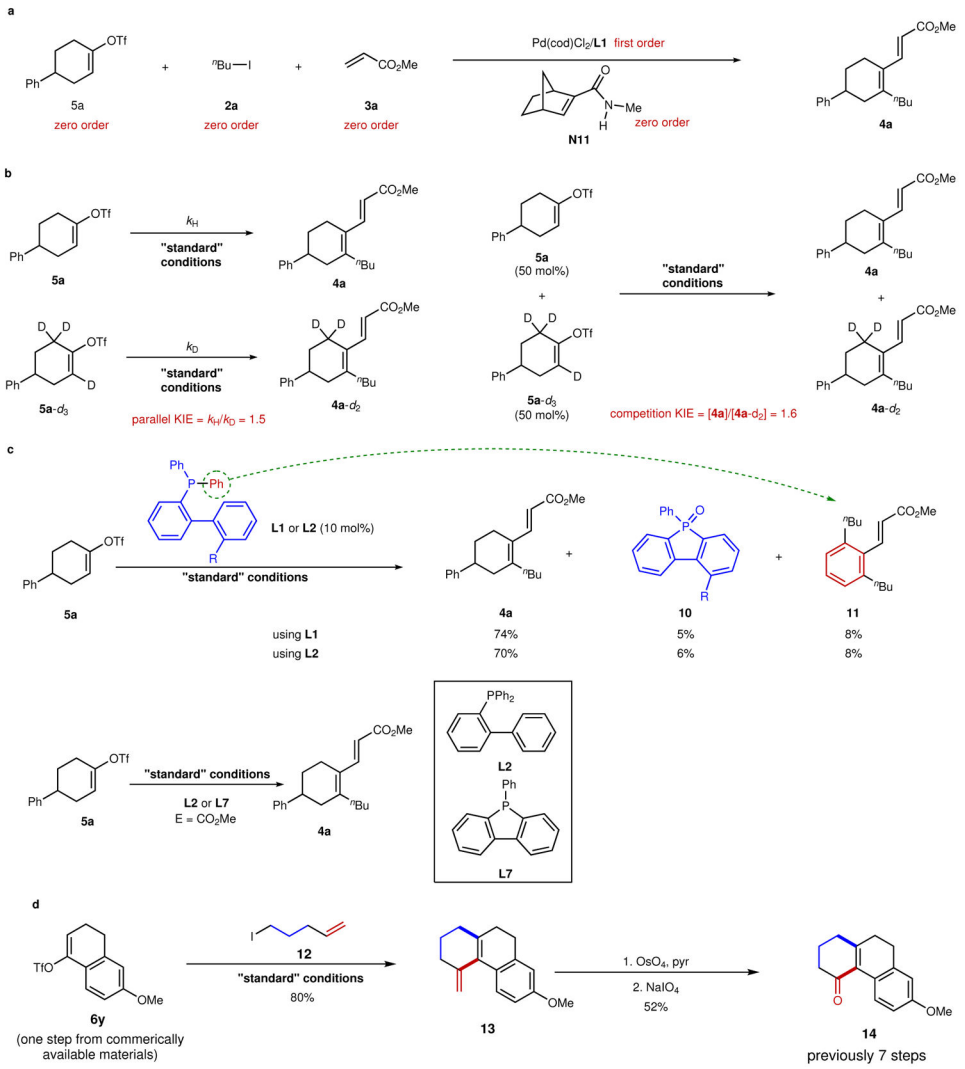
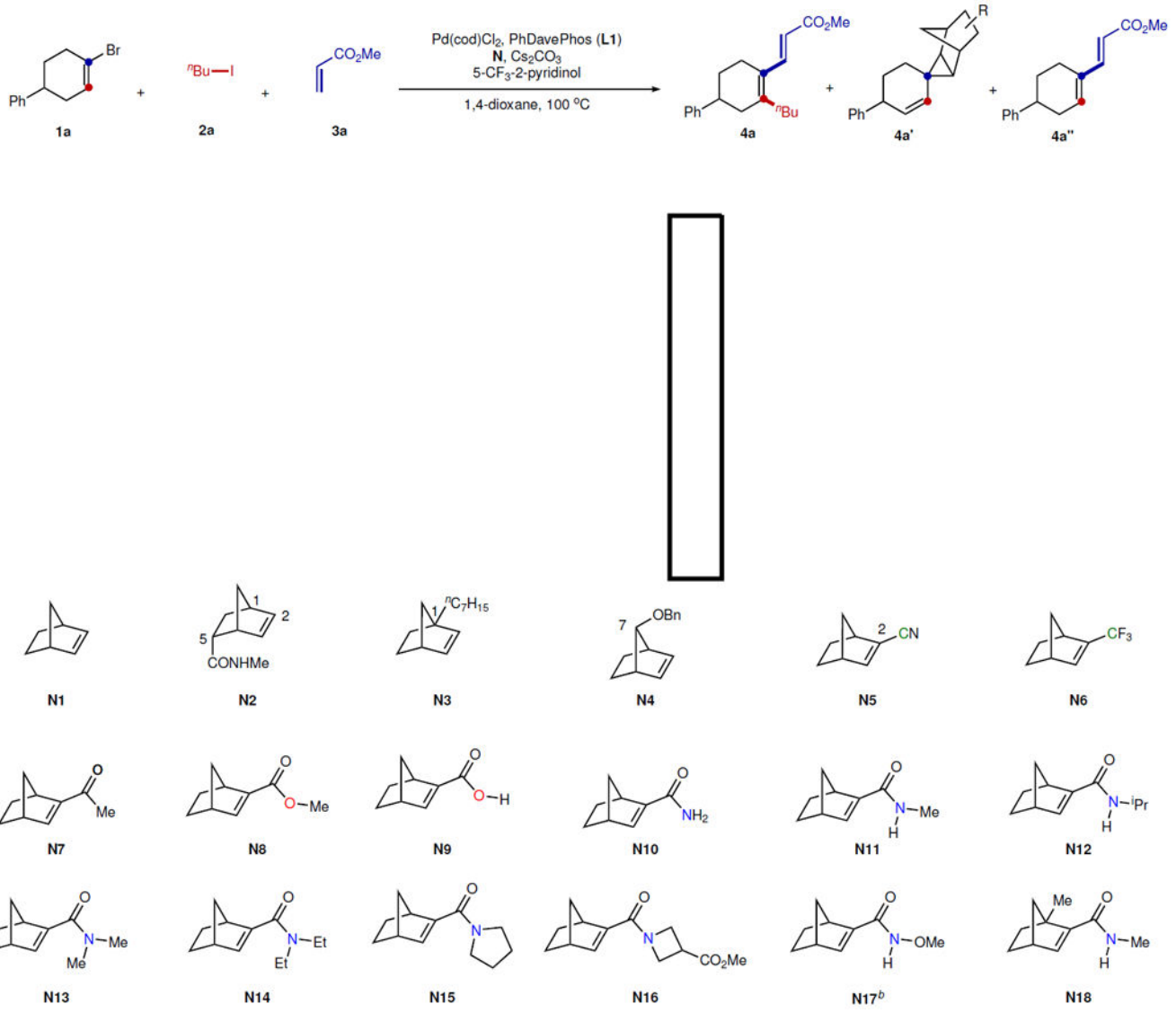


Figure 3|. Mechanistic studies and synthetic utility.

a, Determination of the reaction order: zero-order kinetics for **5a**, **2a**, **3a** and **N11**, and first-order kinetics for [Pd/**L1**] were observed, indicating that oxidative addition of **5a**, migratory insertion into **N11**, the reaction with **2a**, and migratory insertion into **3a** are not the turnover-limiting step. **b**, The parallel and competition kinetic isotopic effects (KIE) were measured, indicating that the C–H cleavage step is only partially turnover-limiting. **c**, The observation of cyclized phosphafluorene oxide 10 and by-product 11, together with the parallel kinetic study between L2 and L7, indicate that the actual ligand in this system is likely the corresponding phosphafluorene. **d**. Synthesis of tricyclic compound **14** is illustrated using this method, which uses fewer steps than the prior route.

Table 1.

NBE Effect for the Alkenyl Catellani Reaction[a]

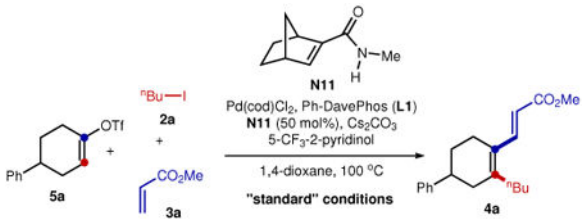


*Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), **3a** (0.15 mmol), $Pd(cod)Cl_2$ (0.01 mmol), **L1** (0.01 mmol), **N** (0.15 mmol), 5-trifluomethyl-2-pyridinol (0.02 mmol), Cs_2CO_3 (0.30 mmol), 100 °C, 16 h. Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

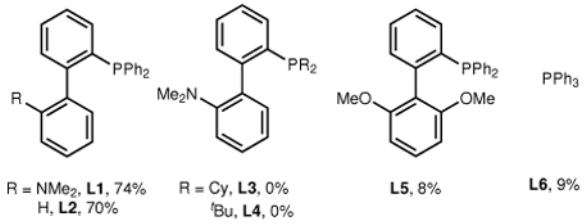
[a]The conversion was 19%.

Table 2.

Control Experiments



Entry	Variations from the "standard" conditions	Yield of 4a (%)[a]
1	None	74
2	No $Pd(cod)Cl_2$	0
3	No Ph-DavePhos	0
4	No **N11**	0
5	$Pd(OAc)_2$ instead of $Pd(cod)Cl_2$	70
6	**L2-L6** instead of **L1**	Listed below
7	K_2CO_3 instead of Cs_2CO_3	12
8	PivOH instead of 5-CF_3-2-pyridinol	12
9	Toluene instead of 1,4-dioxane	74
10	85 °C instead of 100 °C	62

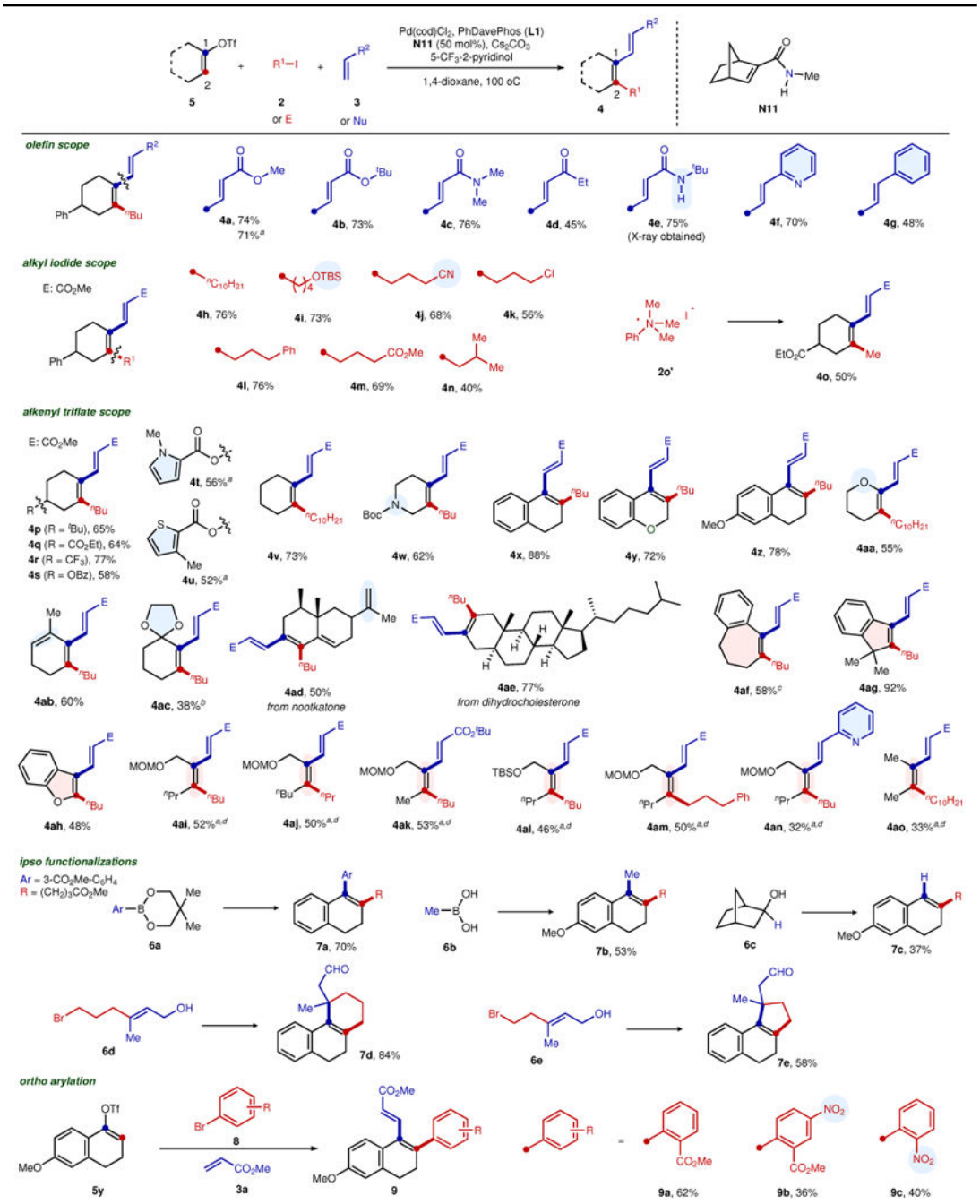


*Reaction conditions: **5a** (0.10 mmol), **2a** (0.30 mmol), **3a** (0.15 mmol), $Pd(cod)Cl_2$ (0.01 mmol), **L1** (0.01 mmol), **N11** (0.05 mmol), 5-trifluomethyl-2-pyridinol (0.02 mmol), Cs_2CO_3 (0.30 mmol), 100 °C, 16 h.

[a]Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

Table 3.

Reaction scope



*Reaction conditions: **5** (0.30 mmol), **2** (0.90 mmol), **3** (0.45 mmol), $Pd(cod)Cl_2$ (0.03 mmol), **L1** (0.03 mmol), **N11** (0.15 mmol), 5-trifluomethyl-2-pyridinol (0.06 mmol), Cs_2CO_3 (0.90 mmol), 1,4-dioxane (6 mL), 100 °C, 16 h.

[a]The corresponding alkenyl bromides were used instead of **5**.

[b] The corresponding alkenyl iodide was used instead of **5**.

[c] **L2** (0.03 mmol) was used instead of **L1**.

[d] **N11** (0.30 mmol) was used, K_3PO_4 (0.90 mmol) was used instead of Cs_2CO_3, and a mixed solvent of 1,4-dioxane (3 mL) and toluene (3 mL) was used instead of 1,4-dioxane alone.