Functionalized Cycloolefin Ligand as a New Solution to *Ortho*-Constraint in the Catellani-Type Reaction

Feng-Yuan Wang, Yu-Xiu Li, and Lei Jiao*

AFFILIATION:

Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing 100084, China.

*Corresponding author. Email: leijiao@mail.tsinghua.edu.cn

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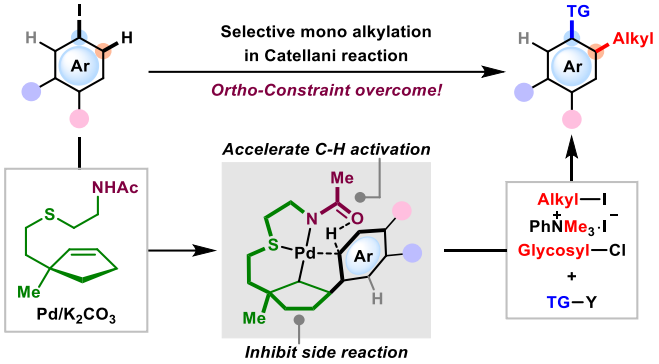


ABSTRACT:

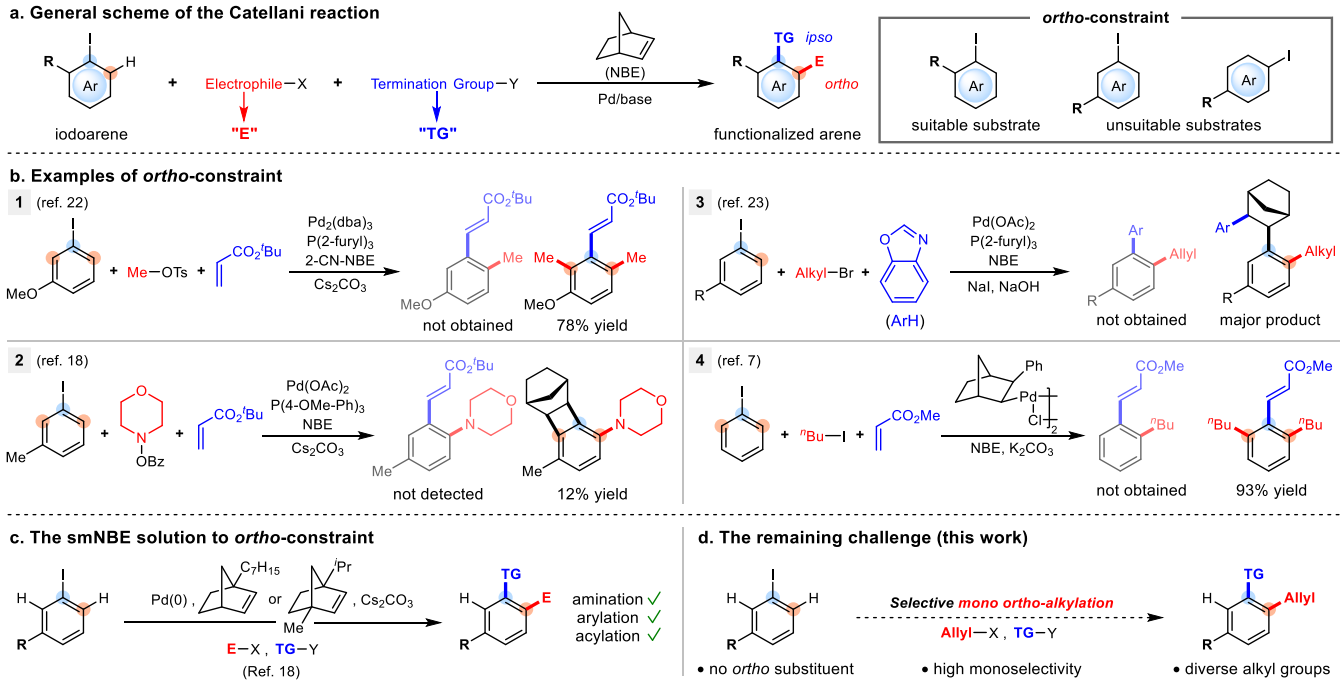
The Catellani reaction, i.e., the Pd/NBE catalysis, has been evolved into a versatile approach to multisubstituted arenes via the *ortho*-functionalization/*ipso*-termination process of a haloarene. Despite significant advances over the past 25 years, this reaction still suffered from an intrinsic limitation in the substitution pattern of the aryl halide, referred to as "*ortho*-constraint". When an *ortho* substituent is absent, the haloarene substrate often fails to undergo effective mono *ortho*-functionalization process, and either *ortho*-difunctionalization products or NBE-embedded byproducts predominate. To tackle this challenge, structurally-modified NBEs (smNBEs) have been developed, which were proved effective for the mono *ortho*-aminative, -acylative, and -arylative Catellani reactions of *ortho*-unsubstituted haloarenes. However, the smNBE strategy is incompetent for solving the *ortho*-constraint in Catellani reactions with *ortho*-alkylation, and to date there lacks a general solution to this challenging but synthetically useful transformation. Recently, our group developed the Pd/olefin catalysis, in which an unstrained hybrid cycloolefin ligand served as a covalent catalytic module to enable the *ortho*-alkylative Catellani reaction without an NBE mediator. In this work, we show that this chemistry could afford a new solution to *ortho*-constraint in the Catellani reaction. A functionalized hybrid cycloolefin ligand bearing an amide group as the internal base was designed, which allowed for mono *ortho*-alkylative Catellani reaction of iodoarenes suffering from *ortho*-constraint before. Mechanistic study revealed that the newly designed ligand is capable of both accelerating the C−H activation and inhibiting side reactions, which accounts for its superior performance. The present work showcased the uniqueness of the Pd/olefin catalysis as well as the power of rational ligand design in metal catalysis.

INTRODUCTION

Selectivity is one of the crucial pursuits in direct C−H functionalization. To distinguish different C−H bonds in organic molecules and achieve site-selective functionalization, directing group[1] and directing template[2] strategies have been proved powerful in transition-metal catalysis. To further improve efficiency, reactions guided by inherent directing groups,[3] transient directing groups,[4] and transient mediators[5] thrived later, enriching the chemical toolbox and facilitating organic synthesis. Among them, the Catellani reaction serves as a representative,[6] which originally achieved intermolecular *ortho*-alkylation/*ipso* termination of iodoarenes by utilizing the Pd/norbornene (NBE) catalysis (Scheme

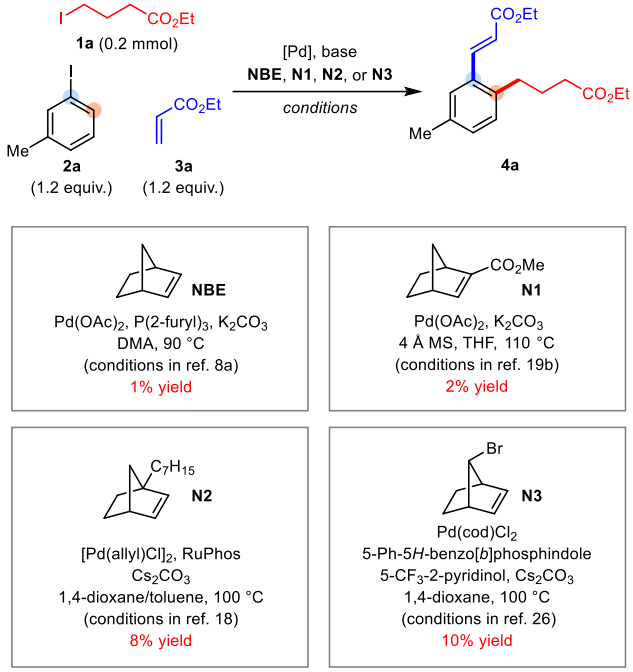
1a). The reaction was first disclosed by Catellani and co-workers in 1997,[7] and later became a reliable synthetic methodology owing to the efforts of the Lautens group.[8] More types of electrophiles, including acyl and heteroatom-containing ones, have been introduced into this reaction by the groups of Dong,[9] Gu,[10] Luan,[11] Liang,[12] and others, which further improved the generality of this chemistry. Moreover, Pd(II)-initiated Catellani-type reactions were developed as a new advance by the groups of Bach,[13] Yu,[5a] Dong,[14] Zhou,[15] Zhang,[16] and Fernández-Ibáñez.[17] In addition, a series of structurally-modified NBEs (smNBEs) have been designed to finely tune the Catellani reaction in terms of chemo-, regio-, and enantioselectivities, as witnessed by the works of the Yu,[5b] Dong,[18] and Zhou[19] groups. More recently, our group reported that the Catellani-type reaction can proceed without the participation of NBE by the development of an unstrained hybrid cycloolefin ligand, which extended the concept of Pd/NBE catalysis to more general Pd/olefin catalysis.[20]

Scheme 1. "*Ortho*-Constraint" in the Catellani Reaction



Despite great progresses of this elegant three-component reaction,[21] its scope has long been limited to *ortho*-substituted iodoarenes. For iodoarenes without an *ortho*-substituent (e.g., *meta*- and *para*-substituted ones), the Pd/NBE system usually faces a so-called "*ortho*-constraint" and fails to produce mono *ortho*-functionalization/*ipso*-termination products.[6g] Instead, either undesired *ortho*-difunctionalization/*ipso*-termination products or various NBE-embedded byproducts were produced predominately, which seriously limited the synthetic versatility of this chemistry (Scheme 1b).[7,18,22,23] One way to tackling this problem is to perform structural modifications of NBE in the Pd/NBE catalysis.[24] The Dong group demonstrated that, bridgehead-modified smNBEs were able to promote Catellani reactions of *ortho*-unsubstituted iodoarenes, in which mono *ortho*-amination, -acylation, and -arylation have been achieved (Scheme 1c).[18] Similar strategy was recently applied to Pd(II)-initiated mono *meta*-arylation of anisole derivatives by the Fernández-Ibáñez group.[17] Despite these advances, the smNBE strategy for overcoming the *ortho*-constraint still suffered from some limitations, such as diminished catalytic activity and limited scope of electrophile.[25] We noticed that, for another synthetically useful reaction category, the *ortho*-alkylative Catellani-type reaction, a general solution to *ortho*-constraint remained elusive (Scheme 1d).

Scheme 2. Performance of NBE/smNBEs in the Mono *Ortho*-Alkylative Catellani Reaction



Unfortunately, attempts to solve this problem by employing smNBEs were unsuccessful (Scheme 2). Our experimental results showed that, in a model reaction between *meta*-iodotoluene (**2a**), alkyl iodide **1a**, and ethyl acrylate (**3a**), neither NBE[8a] nor representative smNBEs **N1**,[19b] **N2**,[18] and **N3**[26] led to satisfactory yield of the desired product **4a**, and in most cases a messy mixture of unidentified byproducts was simultaneously produced (see Table S1 in the Supporting Information for details). It is noteworthy that, in sporadic examples NBE and smNBEs were found effective for Catellani-type annulations of *ortho*-unsubstituted aryl iodides with bifunctional alkylation/termination reagents,[26,27] while they were ineffective for the generic model reaction here. Therefore, a new solution to the *ortho*-constraint in the *ortho*-alkylative Catellani reaction is highly desirable. Herein, we describe our effort in the development of selective mono *ortho*-alkylative Catellani reaction of *meta*-substituted iodoarenes, in which the design of a functionalized cycloolefin ligand plays a crucial role.

RESULTS AND DISCUSSION

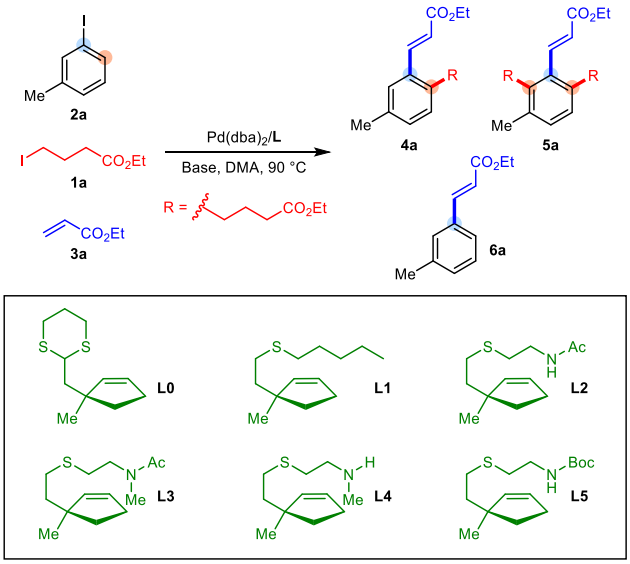
Reaction Development

Encountered with this challenge, we envisioned that the unique feature of the Pd/olefin catalysis developed by our group might provide an opportunity for overcoming the *ortho*-constraint in the *ortho*-alkylative Catellani reaction. Our preliminary study showed that, the Pd/olefin catalytic system with the standard sulfur-cycloolefin ligand **L0** exhibited a promising result in promoting the selective mono *ortho*-alkylation of **2a** with unfunctionalized *n*-butyl iodide, but was found unsuitable for either methylation or alkylation with functionalized alkyl iodides.[20] Therefore, we set out to search for reaction conditions and ligands with enhanced performance based on this starting point.

(1) Reaction Optimization. The same model reaction between **2a**, **1a**, and **3a** was employed in the assessment (Table 1). Under the previously established reaction conditions of the Pd/**L0** catalytic system, only 7% yield of the desired product **4a** was observed (entry 1). Given the lability of alkyl iodide in the presence of Cs_2CO_3,[28] the loading of **1a** was increased but resulted in limited enhancement (entry 2). Interestingly, when K_2CO_3 was used as the base in place of Cs_2CO_3, improved result was obtained (entry 3), which is different from the Pd/smNBE catalytic system.[18,26] The effect of olefin ligand structure was then explored. Switching from **L0** to thioether-olefin ligand **L1** resulted in a minor improvement in yield, albeit more Heck byproduct (**6a**) was generated (entry 4). In order to favor the desired Catellani pathway, we envisioned to introduce a basic functional group to the side arm of the olefin ligand to assist *ortho*-C−H

activation, as inspired by base-assisted concerted metalation-deprotonation (CMD) process in Pd-catalyzed C−H activation.[29] An *N*-acetylcysteamine-derived olefin ligand **L2** was designed, which was expected to facilitate *ortho*-C−H activation via a six-membered transition state (TS). Excitingly, **L2** was found to perform much better than **L1**, as the yield of **4a** increased to 70% with a high mono-/di- alkylation selectivity, and the Heck byproduct (**6a**) was suppressed to some extent (entry 5). Variations of component stoichiometry and catalyst loading did not further improve the performance of the reaction (entries 6-8, see Table S2 in the Supporting Information for detailed optimization). In order to verify the role of amide structure, we tested the activity of the *N*-methylated **L3**, which produced inferior results similar to simple thioether-olefin ligand **L1** (entry 9), indicating that an internal basic functionality in the olefin ligand was beneficial for efficient mono *ortho*-alkylation reaction. Interestingly, ligand **L4** bearing a methyl group instead of the Ac group blocked the reactivity thoroughly (entry 10), probably due to the strong coordination ability of the secondary amine moiety. Additionally, ligand **L5** bearing an *N*-Boc-cysteamine moiety was found less efficient than **L2** in this model reaction (entry 11).

Table 1. Reaction Optimization



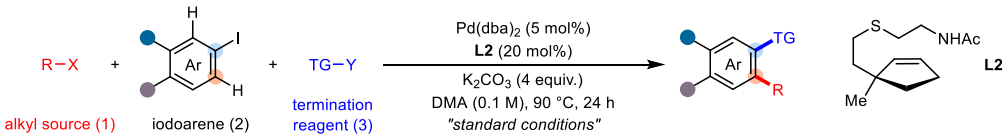
Entry	Ligand	**1a / 2a / 3a**	Base	Yield of **4a** (%)[a]	**4a / 5a / 6a**[a]
1	**L0**	1 / 1.2 / 1.2	Cs_2CO_3	7	1 / 1 / 1
2	**L0**	2 / 1 / 1.2	Cs_2CO_3	22	1 / 0.6 / 0.4
3	**L0**	1 / 1.2 / 1.2	K_2CO_3	43	1 / 0.1 / 0.3
4	**L1**	1 / 1.2 / 1.2	K_2CO_3	52	1 / trace / 1
5	**L2**	1 / 1.2 / 1.2	K_2CO_3	70 (66)	1 / trace / 0.6
6[b]	**L2**	2 / 1 / 1.2	K_2CO_3	54	1 / trace / 0.6
7[bc]	**L2**	2 / 1 / 1.2	K_2CO_3	52	1 / trace / 0.4
8[bc]	**L2**	3 / 1 / 1.2	K_2CO_3	48	1 / trace / 0.4
9	**L3**	1 / 1.2 / 1.2	K_2CO_3	45	1 / trace / 1.3
10	**L4**	1 / 1.2 / 1.2	K_2CO_3	0	0 / 0 / 0
11	**L5**	1 / 1.2 / 1.2	K_2CO_3	52	1 / trace / 1

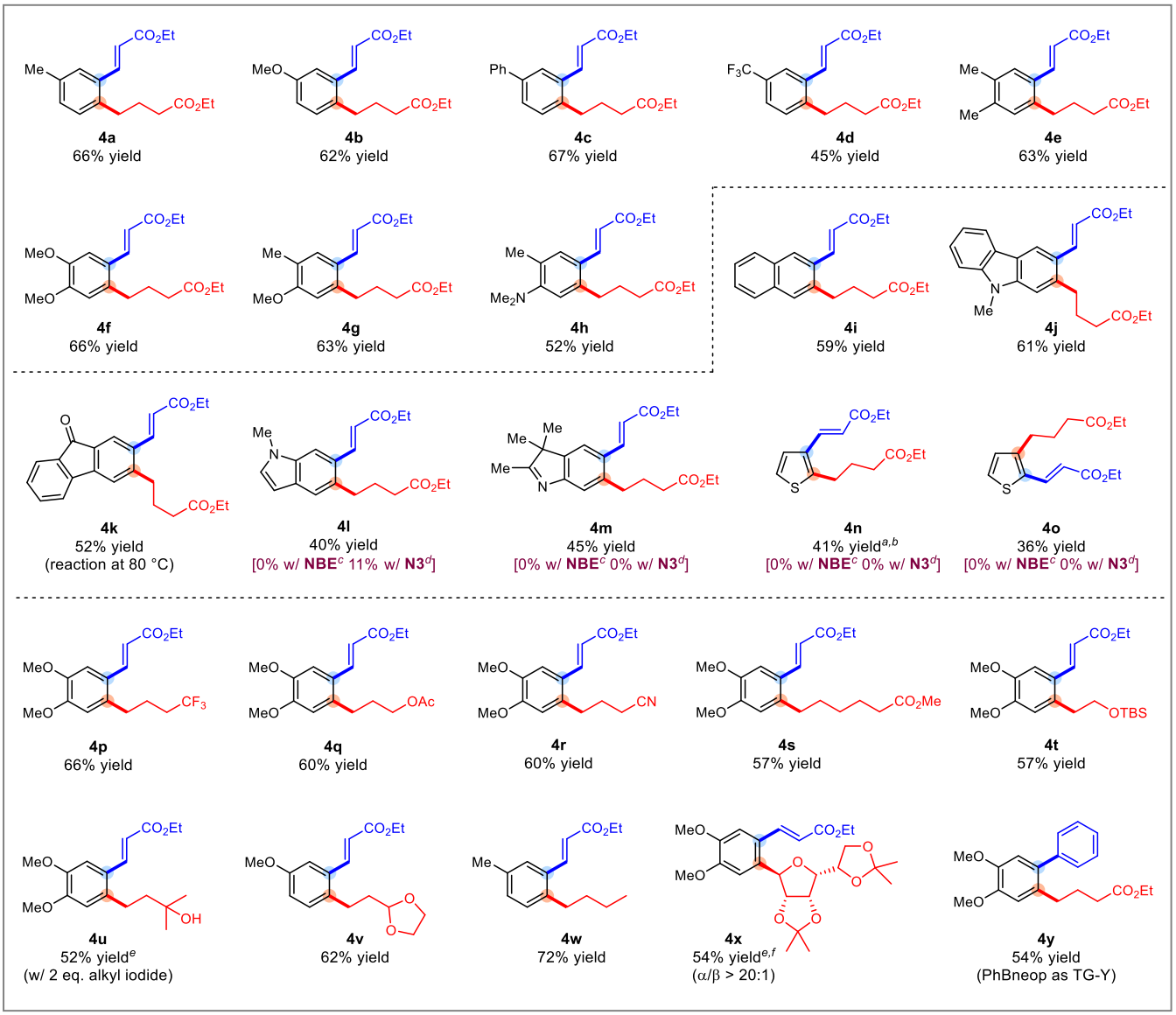
Reaction conditions: alkyl iodide **1** (0.20 mmol, 1.0 equiv.), iodoarene **2a**, termination reagent **3a**, $Pd(dba)_2$ (0.01 mmol, 5 mol%), **L** (0.04 mmol, 20 mol%), base (0.80 mmol, 4.0 equiv.), DMA (2 mL, 0.1 M) as the solvent, 90 °C, sealed tube, 24 h. [a] Yields and ratios were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. The yield of isolated **4a** was shown in parentheses. [b] Iodoarene **2a** (0.20 mmol) used as the limiting reagent. [c] 30 mol% **L2** used.

(2) *Ortho*-Alkylation. With the optimized conditions, we explored the selective mono *ortho*-alkylative Catellani-type

reactions of various iodoarene substrates suffering from *ortho*-constraint, which were found problematic in the Pd/NBE or Pd/smNBE catalysis (Table 2). First, keeping alkyl iodide **1a** and ethyl acrylate (**3a**) unchanged, phenyl iodides bearing electron-donating or electron-withdrawing substituents were all suitable for the syntheses of tri- or tetrasubstituted benzenes (**4a-4h**). Delightedly, we found that this method was competent for facile modification of various poly- and heterocycles, producing multisubstituted naphthalene (**4i**), carbazole (**4j**), fluorenone (**4k**), indole (**4l**), indolenine (**4m**), and thiophene (**4n-o**) derivatives. In general, the Pd/**L2** catalytic system favors the selective C−H alkylation of the less hindered *ortho* position (**4a-4m**), while for 3-iodothiophene substrate the reaction tends to occur at the C2 position favoring CMD process (**4n**).[29a]

Table 2. Substrate Scope for the Mono *Ortho*-Alkylation Reaction





Reaction conditions: alkyl iodide **1** (0.20 mmol), iodoarene **2** (0.24 mmol, 1.2 equiv.), termination reagent **3** (0.24 mmol, 1.2 equiv. for Heck-termination; 0.40 mmol, 2.0 equiv. for Suzuki-termination), $Pd(dba)_2$ (0.01 mmol, 5 mol%), **L2** (0.04 mmol, 20 mol%), K_2CO_3 (0.80 mmol, 4.0 equiv.), DMA (2 mL, 0.1 M), 90 °C, sealed tube, 24 h. Yields of isolated products were reported. [a] **L5** (0.04 mmol) used instead of **L2**, 100 °C. [b] $^nBu_4P^+I^-$ (0.20 mmol) added. [c] ^1H NMR yield under

the conditions in ref. 8a. [d] ^{1}H NMR yield under the conditions in ref. 26. [e] Iodoarene (0.20 mmol) used as the limiting reagent. [f] Glycosyl chloride (0.40 mmol) used as the electrophile, DMA/THF 1:1 (V/V).

For comparison, the performance of Pd/NBE catalysis with both NBE and **N3** in selected reactions was assessed. It was found that, both were much inferior to ligand **L2** in promoting the formation of products **4l**, **4m**, **4n**, and **4o**. In most cases either a messy mixture of unidentified byproducts or a low yield of dialkylation product was produced, and only product **4l** was detected in 11% yield with **N3** (see the Supporting Information for details). This showcased the advantage of the Pd/**L2** catalytic system in overcoming the *ortho*-constraint in the alkylative Catallani reactions.

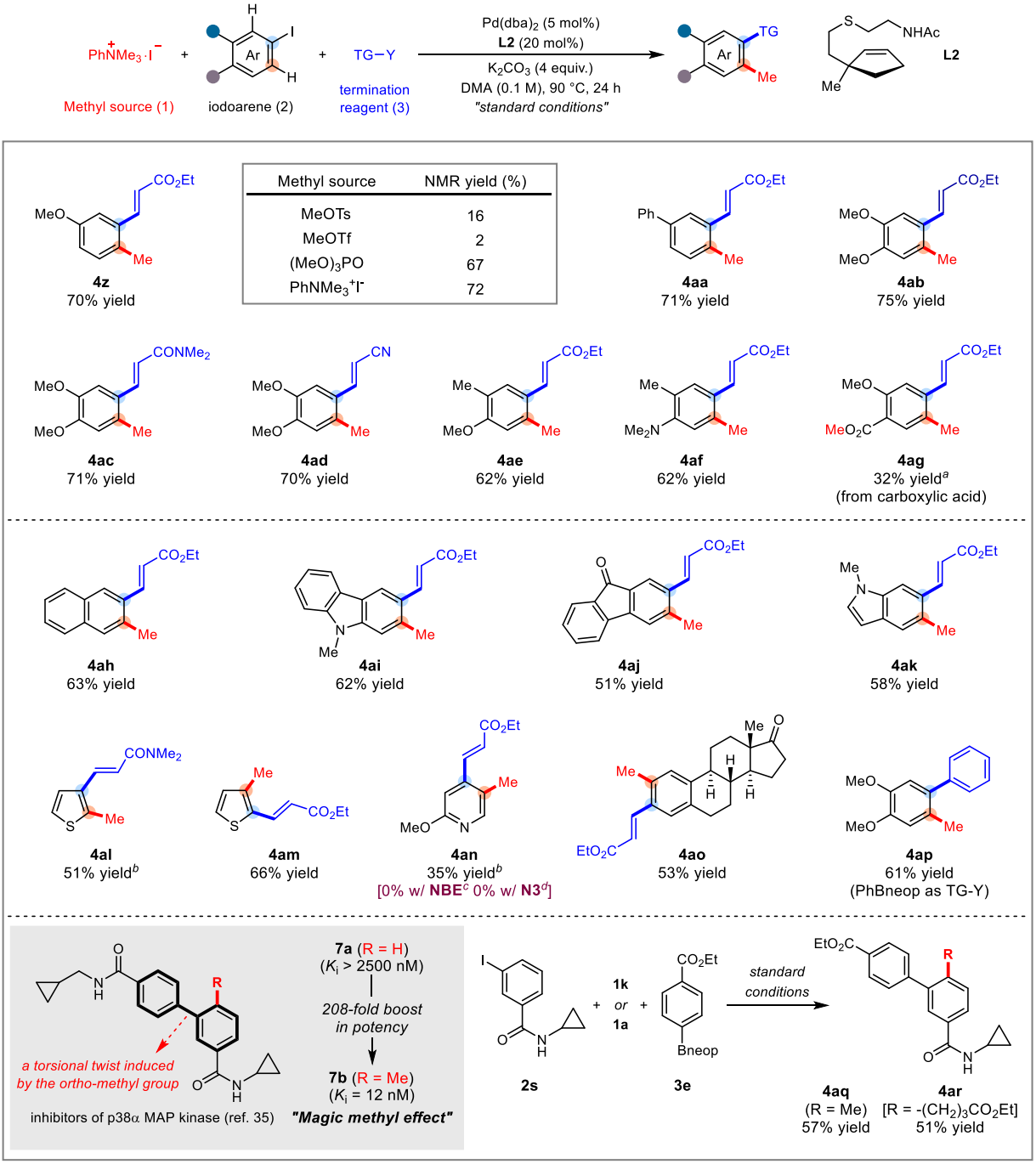
Next, we studied the substrate spectrum with respect to alkyl electrophiles. Different functional groups on the alkyl moiety were well-tolerated, affording monoalkylation products bearing trifluoromethyl (**4p**), acetoxyl (**4q**), cyano (**4r**), methyl ester (**4s**), protected alcohol (**4t**), free alcohol (**4u**), and acetal (**4v**) groups. Interestingly, glycosyl chloride[30] could be used as an applicable electrophile in the selective monoalkylation reaction to prepare α-C-aryl glycoside **4x**. To our disappointment, secondary alkyl halide, a more challenging electrophile for the Catellani-type reaction,[31] could only afford the desired product in a low yield (see the Supporting Information for details). Apart from the variation of iodoarene and alkyl electrophile substrates, we found that the Suzuki coupling could be used in place of Heck coupling in the termination stage by employing phenylboronic acid neopentyl ester (PhBneop) as the termination reagent (**4y**).

(3) *Ortho*-Methylation. In addition to alkylation with functionalized alkyl groups, methylation on the arene ring is also of significance, especially in medicinal chemistry.[32] Therefore, we pursued to achieve mono *ortho*-methylation of iodoarenes utilizing the present protocol. However, achieving selective monomethylation on *ortho*-unsubstituted iodoarenes seemed more challenging, since both Pd/NBE[22] and Pd/**L0**[20] catalytic systems exhibited preferences for dimethylation in previous reports. Encouraged by the success of selective monoalkylation with the present catalytic system, we envisioned that the combination of ligand **L2** and a suitable methyl source might enable selective monomethylation.

Inspired by the work of Chatani[33] and Dong,[34] we found that phenyltrimethylammonium iodide ($PhNMe_3^+ \bullet I^-$) served as the most suitable methyl source for our reaction system, while other methyl sources such as MeOTs or MeOTf led to both low yields and poor selectivities (Table 3 and Table S3). This method enabled monomethylation of various iodoarenes in decent yields and high monoselectivities. A variety of iodobenzene substrates with substitutions at the C3 and C4 positions underwent the methylation process smoothly to afford the mono *ortho*-methylation/*ipso*-Heck products in good yields (**4z**-**4af**). When 4-iodo-2-methoxybenzoic acid (**2p**) was used as the iodoarene substrate, the free carboxylate acid group was also methylated under the reaction conditions to afford methyl ester **4ag**. The present monomethylation protocol was competent for various poly- and heterocycles (**4ah**-**4ao**), including an estrone derivative (**4ao**). Notably, *ortho*-methylation reaction of 4-iodo-2-methoxypyridine (**2q**) afforded multi-substituted pyridine derivative **4an** with a good mono-/di- methylation selectivity, while neither NBE nor **N3** was competent for this transformation (only the dimethylation product was observed). Suzuki coupling as the termination method was also found compatible (**4ap**).

The present protocol could find its application in drug discovery. Reported by a GlaxoSmithKline's discovery team, the introduction of a methyl group adjacent to the biaryl axis of p38α MAP kinase inhibitor **7a** boosted its potency remarkably, which served as a profound case of the "magic methyl effect".[35] Previous synthesis of methylated inhibitor **7b** based on Suzuki coupling required the preparation of *ortho*-methylated iodoarene coupling partner. The current mono *ortho*-alkylation/*ipso*-termination strategy allowed for combinatorial introduction of alkyl groups from a common iodoarene **2s** without the need for pre-functionalization. Both a methyl group and a functionalized alkyl group could be smoothly introduced to the inhibitor precursors **4aq** and **4ar** in satisfactory yields.

Table 3. Substrate Scope for the Mono *Ortho*-Methylation Reaction and Synthetic Application



Reaction conditions: $PhNMe_3^+I^-$ (**1k**, 0.20 mmol), iodoarene **2** (0.24 mmol, 1.2 equiv.), termination reagent **3** (0.24 mmol, 1.2 equiv. for Heck-termination; 0.40 mmol, 2.0 equiv. for Suzuki-termination), $Pd(dba)_2$ (0.01 mmol, 5 mol%), **L2** (0.04 mmol, 20 mol%), K_2CO_3 (0.80 mmol, 4.0 equiv.), DMA (2 mL, 0.1 M), 90 °C, sealed tube, 24 h. Yields of isolated products were reported. [a] Iodoarene (0.20 mmol) used as the limiting reagent. [b] **L5** (0.04 mmol) used instead of **L2**, 100 °C. [c] ^{1}H NMR yield under the conditions in ref. 8a. [d] ^{1}H NMR yield under the conditions in ref. 26.

Mechanistic Studies

After revealing the unique catalytic activity of the Pd/**L2** system, we were curious about the inherent principles behind. We hope to figure out the answers to two crucial questions regarding the reaction mechanism: (1) What is the function of ligand **L2** in the *ortho*-alkylative Catellani reaction, especially the internal base moiety; and (2) How important is this function for overcoming the *ortho*-constraint.

(1) Ligand Comparisons. Although the superior performance of **L2** has been noted during the optimization study

(Table 1), it is essential to figure out the difference in ligand reactivity by more extensive comparisons. To this end, ligand **L1**, which has the same thioether coordination unit as **L2** but lacks an intramolecular base unit, was taken out and its performance in the reactions of three iodoarenes (**2k**, **2l**, and **2s**) has been evaluated for comparison (Figure 1a). It was found that, in all cases **L2** exhibited better performance than **L1**, and in the reactions with *ortho*-methylation more significant yield boost was observed than in the reactions with *ortho*-alkylation. More detailed analysis revealed that, the advantage of **L2** over **L1** was attributed to more prominent inhibition of Heck (for **2k** and **2l**) or Suzuki (for **2s**) byproducts (see Tables S4 and S5 in the Supporting Information for details).

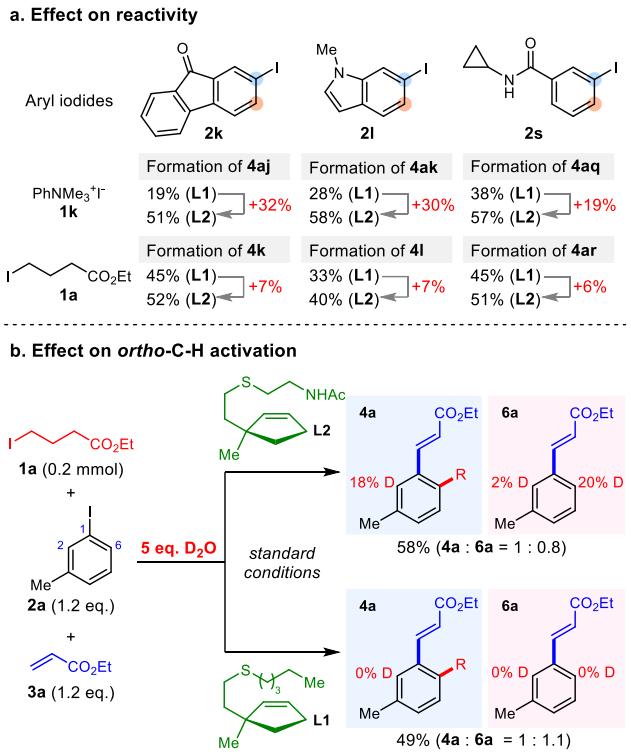


Figure 1. Ligand comparisons.

Although **L2** showed less profound ligand effect on Catellani reactions with *ortho*-alkylation, deuteration experiments revealed that it had a significant impact on *ortho*-C-H activation (Figure 1b). When the model reaction with *ortho*-alkylation was performed in the presence of 5 equivalents of D_2O, remarkable deuterium incorporation at the *ortho*-position was observed in both product **4a** (18% 2-D) and the Heck byproduct **6a** (20% 6-D and 2% 2-D) when **L2** was employed, while **L1** did not result in any detectable deuterium incorporation. Control experiments confirmed that deuterium incorporation occurred within the Catellani reaction sequence, rather than in any off-cycle process (see the Supporting Information for details). This indicated that **L2** rendered the *ortho*-C-H activation steps in the model reaction reversible but **L1** could not, in consistent with the expectation that ligand with an internal base unit could facilitate C-H activation through a CMD process. However, to figure out the detailed function of the NHAc group in ligand **L2**, a more detailed mechanistic analysis is required.

(2) General Mechanistic Considerations. To understand the activity and selectivity of the Catellani reaction, the catalytic cycle and key side pathways should be taken into consideration. Since the Catellani reactions with Pd/NBE and Pd/olefin catalytic systems proceed through similar reaction pathways, a general mechanistic scheme for the Catellani reaction with a *meta*-substituted iodoarene is depicted in Figure 2, which includes both the main catalytic cycle and the competitive side pathways.

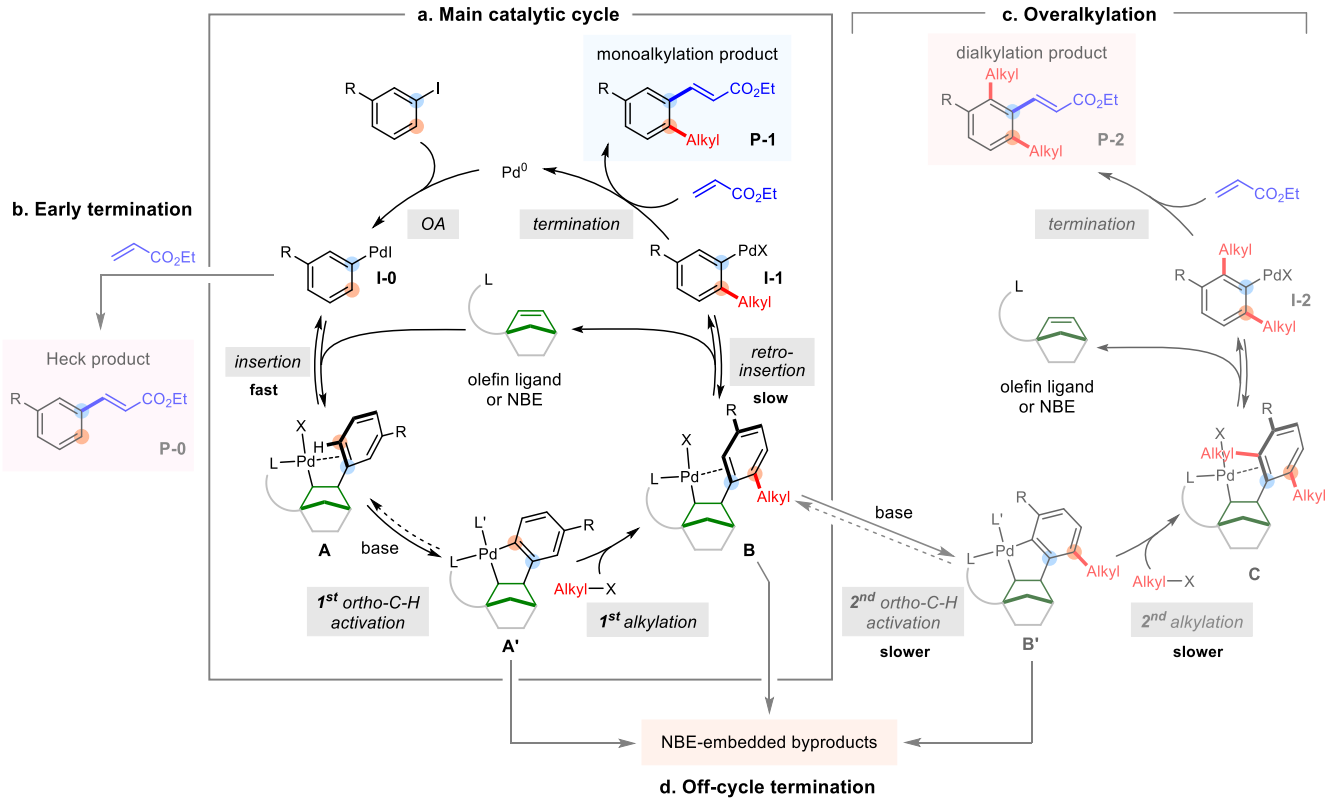


Figure 2. General mechanistic scheme of the Pd(0)-initiated Catellani-type reaction under the *ortho*-constraint regime.

The main catalytic cycle (Figure 2a) starts from oxidative addition (OA) of the substrate to Pd(0) to form arylpalladium species **I-0**. Insertion of the olefin ligand or the NBE mediator with **I-0** gives insertion intermediate **A**, which undergoes the first C-H activation at the less hindered *ortho*-position to form palladacycle **A'** in the presence of base. This intermediate reacts with an alkyl halide to finish the first alkylation step, affording *ortho*-alkylated intermediate **B**. Expectedly, retro-insertion (namely, a *β*-carbon elimination) on **B** forms alkylated arylpalladium species **I-1** together with release of the olefin ligand or NBE. Termination process then takes place on **I-1** to give the desired monoalkylation product **P-1**.

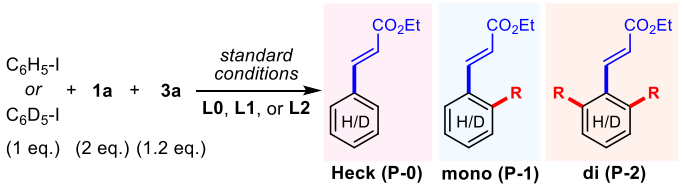
A series of side pathways compete with the main catalytic cycle. Early termination leads to Heck product **P-0** without *ortho*-alkylation (Figure 2b). Notably, since **I-0** usually reacts more rapidly with the olefin ligand or NBE than with the termination reagent, the byproduct **P-0** generated in the reaction system mainly comes from the insertion complex **A** (**A** →**I-0**→**P-0**), rather than direct termination of **I-0** upon its formation.[6g] Another pathway, denoted as overalkylation (Figure 2c), starts from the second C-H activation of alkylated intermediate **B** at the remaining *ortho*-position to form palladacycle **B'**. It then follows an alkylation/retro-insertion/termination sequence like the main catalytic cycle to produce dialkylated Catellani product **P-2**. Due to the steric bulkiness of the R group, the second *ortho*-C-H activation and alkylation is kinetically less favorable compared with the first one. In addition, several key intermediates in this complex network, including **A'**, **B**, and **B'**, may undergo off-cycle termination (Figure 2d) to form NBE-embedded byproducts (e.g., the ones depicted in Scheme 1b).

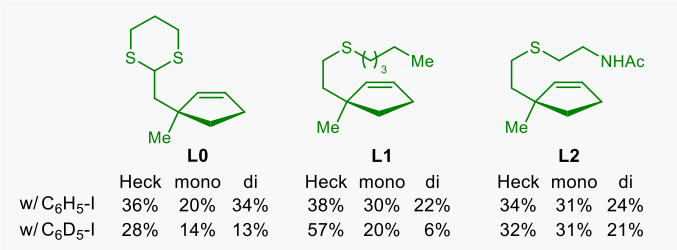
Therefore, for *meta*-substituted iodoarene substrates, although the first and second overall C-H alkylation processes exhibit different reactivities, realizing selective mono *ortho*-alkylation remains challenging because it requires subtle tuning of the kinetics of all potential pathways.

(3) Function of the Amide Group in L2. Based on the above mechanistic analysis and the results of the deuterium labeling experiment (Figure 1b), the effect of the NHAc group could be rationalized. With ligand **L1**, byproduct **6a** (**P-0** type) was formed without detectable deuterium incorporation at the C6-position, indicating that the first *ortho*-C-H activation to form palladacycle **A'** is irreversible, and this process is likely rate-determining in the overall alkylation

process **A**→**B**. Similarly, the lack of deuterium incorporation at the C2-position in product **4a** (**P-1** type) implied that second *ortho*-C-H activation is kinetically unfavorable. In contrary, with ligand **L2**, byproduct **6a** was formed with deuterium incorporation at both C2- and C6-positions, and product **4a** also had significant deuteration at the C2-position. This indicated that both the first and the second C-H activation step are reversible, and C-H activation is no longer rate-determining in the overall alkylation process. Thus, we drew a tentative conclusion that **L2** could remarkably accelerate the *ortho*-C-H activation process in the catalytic cycle, assuming that the activation barrier for the alkylation step does not change dramatically with respect to the ligand.

To unambiguously verify the role of the NHAc group in accelerating the C-H activation process, we studied the H/D isotope effect of the aryl ring on product distribution. According to the mechanistic picture shown in Figure 2, the Catellani/Heck product ratio [(**P-1** + **P-2**)/**P-0**, defined as α] reflects the competition between the first *ortho*-C−H activation/alkylation sequence (**A**→**A'**→**B**) and the early termination pathway (**A**→**I-0**→**P-0**), which equals to the ratio of the apparent rate constants of the two pathways ($\alpha = k_{\mathbf{A}\rightarrow\mathbf{B}}/k_{\mathbf{A}\rightarrow\mathbf{P\text{-}0}}$); the di-/monoalkylation ratio [**P-2**/**P-1**, defined as β] indicates the competition between the second *ortho*-C−H activation/alkylation sequence (**B**→**B'**→**C**) and the first termination pathway (**B**→**I-1**→**P-1**), which follows a similar relationship ($\beta = k_{\mathbf{B}\rightarrow\mathbf{C}}/k_{\mathbf{B}\rightarrow\mathbf{P\text{-}1}}$). We defined α_H/α_D and β_H/β_D as indicators of the isotope effect. Since deuterium substitution on the iodoarene substrate merely alters the kinetics of the first and the second C-H activation steps without affecting other steps, α_H/α_D could indicate the kinetic isotope effect (KIE) of the first overall alkylation process **A**→**B**, and β_H/β_D could reflect the KIE of the second overall alkylation process **B**→**C**. If the C−H activation step is rate-limiting in the process of **A**→**B** or **B**→**C**, remarkable isotope effect could be observed (i.e., α_H/α_D and $\beta_H/\beta_D > 1$); otherwise, no remarkable isotope effect will be observed (i.e., α_H/α_D and $\beta_H/\beta_D \approx 1$).





	L0			L1			L2		
	Heck	mono	di	Heck	mono	di	Heck	mono	di
w/ C_6H_5-I	36%	20%	34%	38%	30%	22%	34%	31%	24%
w/ C_6D_5-I	28%	14%	13%	57%	20%	6%	32%	31%	21%

Product distribution index
α = (mono + di) / Heck, β = di / mono

ligand	α_H	α_D	α_H / α_D	β_H	β_D	β_H / β_D
L0	1.5	0.96	**1.6**	1.7	0.93	**1.8**
L1	1.4	0.46	**3.0**	0.73	0.30	**2.4**
L2	1.6	1.6	**1.0**	0.77	0.68	**1.1**

Figure 3. H/D isotope effect experiments. Yields were determined by ^{1}H NMR analysis using CH_2Br_2 as the internal standard.

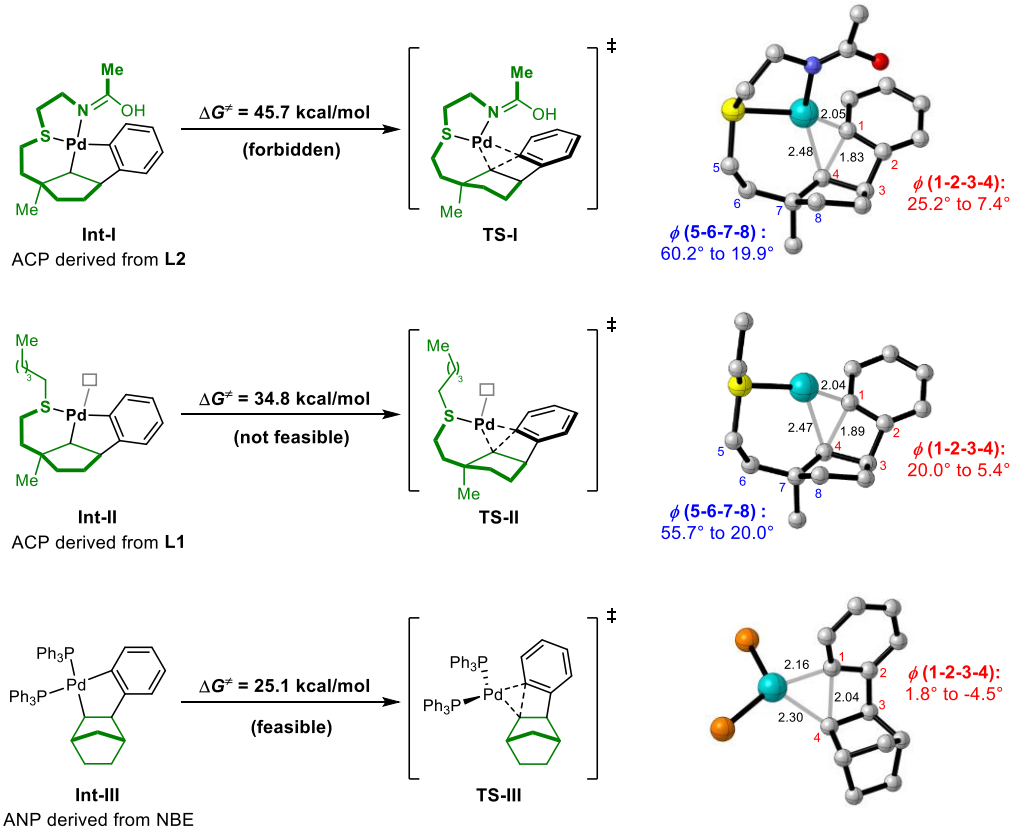
To assess the H/D isotope effect, a model Catellani reaction was performed in the presence of ligands **L0**, **L1**, and **L2**, respectively (Figure 3). Considering the ease of access to deuterated material, we chose iodobenzene as the substrate in this study, which also has the merit of affording a reasonable distribution of **P-0**, **P-1**, and **P-2** type products that facilitates the determination of both product distribution indexes α and β in a single experiment. It was found that, ligand **L0** and **L1** without the NHAc functionality showed profound isotope effects ($\alpha_H/\alpha_D = 1.6$ and 3.0, $\beta_H/\beta_D = 1.8$ and 2.4 for **L0** and **L1**, respectively), while **L2** resulted in negligible isotope effect ($\alpha_H/\alpha_D = 1.0$, $\beta_H/\beta_D = 1.1$). This is clear evidence that with

L0 and **L1** the *ortho*-C-H activation is rate-determining in the overall alkylation process, and with **L2** the *ortho*-C-H activation is no longer rate-determining. The acceleration effect is attributed to the NHAc functionality that can facilitate the CMD process, which corroborates the design concept of ligand **L2**.[36]

This feature allows the Pd/**L2** catalytic system to use relatively weak base (K_2CO_3) while maintaining a low activation barrier for C-H activation, which is beneficial for accommodation of base-labile alkyl electrophiles and suppression of the early termination byproduct. It is reasonable to deduce that, in the reactions where C-H activation dictates the kinetics of the overall alkylation process (i.e., the alkylation of **A'** is facile), the promotive effect of **L2** would be more profound. This accounts for the observation that **L2** exhibited more positive effect on reactions with *ortho*-methylation than on those with *ortho*-alkylation.

(4) Byproduct Inhibition Effect of the Cycloolefin Ligand. NBE-embedded byproduct formation in the Catellani reaction is another reason for the *ortho*-constraint problem. Generation of norbornyl-fused benzocyclobutane byproducts via direct reductive elimination (RE) from the palladacycle intermediate was reported as a major side pathway in Pd/NBE catalysis.[6] As depicted in Figure 2, under the *ortho*-constraint regime, the retro-insertion from intermediate **B** is more difficult when an *ortho*-substituent is absent.[6g] Under this circumstance, second *ortho*-C-H activation occurs to form palladacycle **B'**, which tends to undergo direct RE to form the benzocyclobutane-type byproduct because the second alkylation of **B'** is also difficult due to a bulky R group. In some cases, direct RE from palladacycle **A'** could also be observed.[26] On contrary, in Pd/olefin catalysis, similar byproducts were never detected. We reasoned that, the ability to avoid such side pathways is an important reason for the success of cycloolefin ligand in overcoming the *ortho*-constraint, and we sought to understand this by DFT computational study.

Scheme 3. DFT Calculation on the Direct RE Pathway[a]



[a] DFT calculations were performed at the SMD(DMA)-M06/SDD/6-311+G(d,p)//B3LYP/LANL2DZ/6-31G(d) level of theory. Key distances (in unit of Å) were marked in the transition structures. Hydrogen atoms and irrelevant groups were omitted for clarity in the 3D structures.

Direct RE from the palladacycle intermediates in the Pd/olefin and Pd/NBE catalytic systems were studied by DFT calculation (Scheme 3). It was found that, direct RE from the arylcyclopentylpalladacycle (ACP) intermediate **Int-I** via **TS-I** is not possible under the reaction conditions ($\Delta G^{\neq}$ = 45.7 kcal/mol), while direct RE from ACP intermediate **Int-II** exhibits a decreased activation barrier ($\Delta G^{\neq}$ = 34.8 kcal/mol) but is still kinetically difficult. This is in good agreement with the absence of benzocyclobutane-type byproducts in the Pd/olefin catalytic system. In contrast, direct RE from the arylnorbornylpalladacycle (ANP) intermediate **Int-III** via **TS-III** exhibits a much lower energy barrier ($\Delta G^{\neq}$ = 25.1 kcal/mol),[37] which accounts for the frequent observations of benzocyclobutane-type byproducts in the Pd/NBE system.

By comparing these transition states, we reasoned that different torsional strains associated with the formation of benzocyclobutane product are the key factor dictating the direct RE pathway. Since the RE transition structure requires a nearly coplanar conformation of the forming cyclobutane ring, the change of dihedral angle φ(C1-C2-C3-C4) during the RE process reflects the energy required for conformational change. For RE from the ANP intermediate **Int-III**, the dihedral angle changes from 1.8° to -4.5°, implying an insignificant raise of strain during RE. In contrary, RE from the ACP intermediate **Int-I** and **Int-II** results in a more significant change in dihedral angle, indicating more profound raise in strain energy. We attribute another factor inhibiting the RE pathway of the ACP intermediate to the additional torsional strain associated with the cyclic structure formed by the coordination side arm. During RE via **TS-I** and **TS-II**, there is also a dramatic change in dihedral angle C5-C6-C7-C8 to create remarkable torsional strain in the ring, which does not exist in **TS-III**. It is also interesting to note that, RE from palladacycles with more ring structures is generally more difficult (**TS-I** *vs* **TS-II**). Therefore, the unique structural feature of cycloolefin ligands renders it less prone to form benzocyclobutane-type byproducts, which represents an advantage of the Pd/olefin catalytic system. Interestingly, DFT study by the Dong group disclosed that smNBE **N3** was also found to disfavor the direct RE pathway, which accounted for its superior performance in the annulative *ortho*-amination of *meta*-substituted iodoarenes.[26]

Overall, based on the mechanistic studies described above, the uniqueness of ligand **L2** in selective mono *ortho*-alkylative Catellani-type reaction lies in two aspects: (1) The NHAc group remarkably accelerates the C−H activation step, which ensures a good reactivity and suppresses early termination byproduct; (2) The cycloolefin scaffold tethered with a coordination side arm efficiently inhibits the undesired direct RE pathway. These features nicely meet the kinetic requirements discussed above, rendering the Pd/**L2** catalytic system competent for promoting the selective mono-alkylative Catellani reaction of *meta*-substituted iodoarenes.

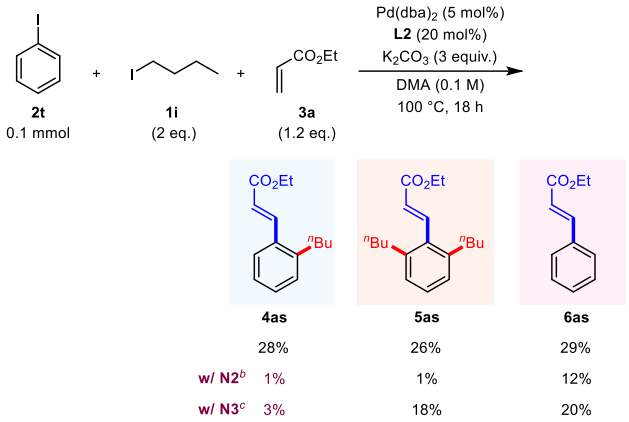
CONCLUSION

Summary. Utilizing the Pd/olefin catalysis, we offered an efficient solution to the *ortho*-constraint in the mono *ortho*-alkylative Catellani-type reaction. A newly designed functional cycloolefin ligand comprised of a cyclopentene backbone, a thioether coordination unit, and an NHAc internal base played an important role in this chemistry. The catalytic system exhibited good functional group tolerance and broad substrate scope, in particular, the mono *ortho*-methylation/*ipso*-termination reaction with *ortho*-unsubstituted iodoarene substrates was accomplished for the first time. The present work nicely showcases the extensibility of the Pd/olefin catalysis for different synthetic tasks by ligand design. The mechanistic studies provided insights into the reactivity paradigm of this ligand, which may shed light on future development of the Pd/olefin catalysis.

Future Challenge. One of the more challenging tasks in Catellani reaction is to achieve selective mono *ortho*-alkylation on *ortho*- and *meta*-unsubstituted iodoarene substrates. Because the two *ortho*-C−H positions exhibit similar activities in the alkylation process (**A→A'→B** *vs* **B→B'→C**, when R = H in Figure 2), to efficiently distinguish them is rather difficult. In previous studies, the Pd/NBE system could only afford dialkylation products with this type of substrate,[6,7] and smNBEs were also found incompetent. For the Catellani reaction between simple iodobenzene (**2t**), *n*-butyl iodide (**1i**) and acrylate **3a**, the Catellani product with mono *ortho*-C−H alkylation (**4as**) was produced in only 1-3% yields with the representative smNBEs **N2** and **N3** (Scheme 4). We were delighted to find that, the Pd/**L2** system was able to afford a fraction of the desired product **4as**, albeit dialkylation product (**5as**) and Heck product (**6as**) accompanied in similar yields. This represents the first example for obtaining the mono *ortho*-alkylative Catellani product with an

ortho- and *meta*-unsubstituted iodoarene in a synthetically meaningful yield. Currently we are not able to achieve a high chemoselectivity for monoalkylation based on the present ligand design, and we regard this as a key challenge for future development of the Catellani-type reaction. We expect that, more powerful ligand design in Pd/olefin catalysis could provide an opportunity for addressing this challenge.

Scheme 4. Future Challenge[a]



[a] Yields were determined by ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [b] Conditions in ref. 18 were used. [c] Conditions in ref. 26 were used.

ASSOCIATED CONTENT

Detailed experimental procedure, NMR spectra, and DFT studies are available.

AUTHOR INFORMATION

Corresponding Author

Lei Jiao − Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing, 100084, China; Email: leijiao@mail.tsinghua.edu.cn

Authors

Feng-Yuan Wang − Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing, 100084, China.

Yu-Xiu Li − Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing, 100084, China.

Author Contributions

All authors have given approval to the final version of the manuscript.

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Notes

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