Dual Ligand Enabled Pd-Catalyzed *Ortho*-Alkylation of Iodoarenes

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Abstract:

The synthesis of complex polysubstituted aromatic molecules from simple precursors is a central goal in organic chemistry. In this study, we developed an approach for the *ortho*-alkylation of iodoarenes utilizing a dual ligand catalytic system. By combining Pd/olefin ligand cooperative catalysis with bulky trialkylphosphine ligand-promoted C(sp^2)-I reductive elimination, we have established an *ortho*-alkylative Catellani-type reaction with the aryl-iodine bond reconstruction as the final step, which opens new synthetic opportunities within the Catellani-type reactions. Through in-depth mechanistic investigations, we have isolated and characterized key organopalladium intermediates, revealing the synergistic interaction of the dual ligands in merging the Catellani-type process with C(sp^2)-I reductive elimination. The present study showcases the unique advantages of Pd/olefin ligand catalysis and emphasizes the effectiveness of the dual ligand system in expanding the chemical space of the Catellani chemistry.

Introduction

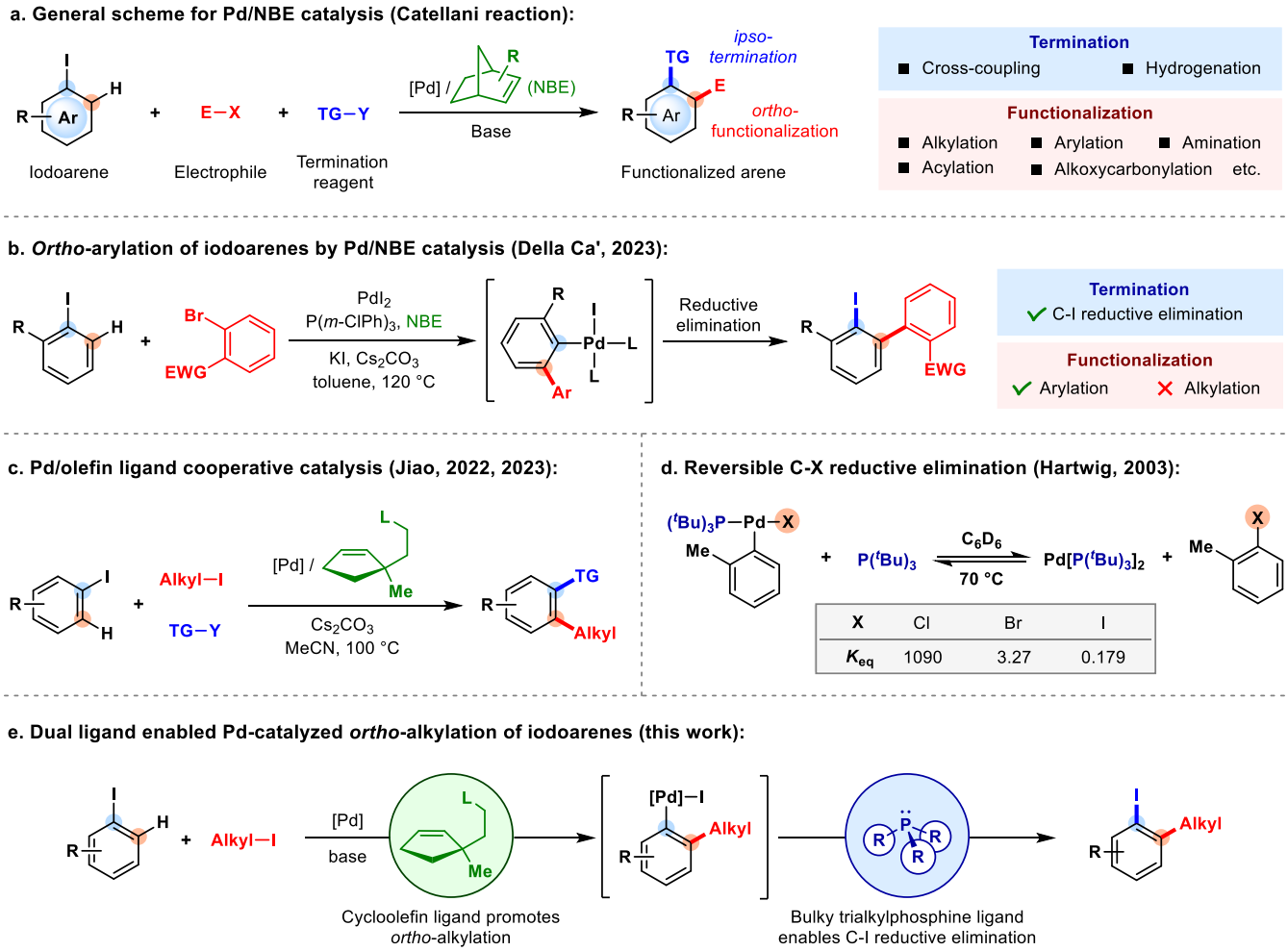
The synthesis of complex polysubstituted aromatic molecules through the modification of simple ones is a crucial aspect of organic synthesis.[1,2,3] Transition metal-catalyzed cross-coupling reactions have been developed to create structurally diverse aromatic compounds by connecting an aryl halide or pseudohalide with various coupling partners.[4] The palladium/norbornene (Pd/NBE) catalysis, also known as the Catellani reaction,[5] represents a significant advancement as it enables simultaneous *ortho*-functionalization and *ipso*-cross-coupling of aryl halides to produce polysubstituted arenes (Scheme 1a). The reaction is compatible with a wide range of electrophiles[6] for *ortho*-functionalization and termination reagents[7] for *ipso*-cross-coupling, thereby enhancing the versatility of this chemistry.

Despite the significant synthetic power of the Catellani reaction,[8,9] the reaction mode at the *ipso*-position is limited by palladium catalysis. Thus, an alternative approach that preserves the carbon-halogen bond of the substrate in Pd/NBE catalysis could enable the *ortho*-functionalization of iodoarenes, and the generated *ortho*-functionalized iodoarenes can serve as valuable substrates for transformations that are not accessible using palladium chemistry,[10-12] which will expand the potential of the Catellani reaction. It is notable that, although the C(sp^3)-I reductive elimination in Pd catalysis has been well established,[13] the C(sp^2)-I reductive elimination[14] is rarely employed in synthetic reactions. The Della Ca' group recently reported the first example of formal *ortho*-C-H arylation of *ortho*-substituted aryl iodides by Pd/NBE catalysis with tris(3-chlorophenyl)phosphine (*m*-TCPP) as the ligand (Scheme 1b).[15] In combination with the NBE-mediated *ortho*-arylation, the *ipso*-C-I bond is cleaved and reformed by reversible reductive elimination, leading to the formation of richly decorated *ortho*-iodobiaryls.

However, the *ortho*-alkylation of iodoarenes remained unsolved with this protocol. Given that the *ortho*-alkylation of iodoarenes is highly attracting, we envisioned to tackle this challenge through the utilization of Pd/olefin ligand cooperative catalysis developed in our group.[16] In previous studies, we have developed a thio-cycloolefin ligand for Pd catalysis to enable *ortho*-alkylative Catellani-type reactions without the need of NBE (Scheme 1c), which exhibited a distinct advantage in promoting the C-H alkylation process. On the other hand, the Hartwig group demonstrated that sterically hindered trialkylphosphines can promote the reductive elimination of monomeric arylpalladium(II) halide complexes, leading to the formation of haloarenes (Scheme 1d).[17] We expected that, the combination of these two ligands with Pd catalysis could create an efficient system for the *ortho*-alkylation of iodoarenes. Specifically, the thio-cycloolefin

ligand would enable the *ortho*-alkylation of the arylpalladium intermediate, while the bulky trialkylphosphine ligand would promote C-I reductive elimination (Scheme 1e). Herein, we report our progress in realizing this dual ligand catalytic system that integrates Pd/olefin ligand cooperative catalysis and reversible C(sp^2)-I reductive elimination, as well as elucidating the mechanism of synergistic interaction of the dual ligands.

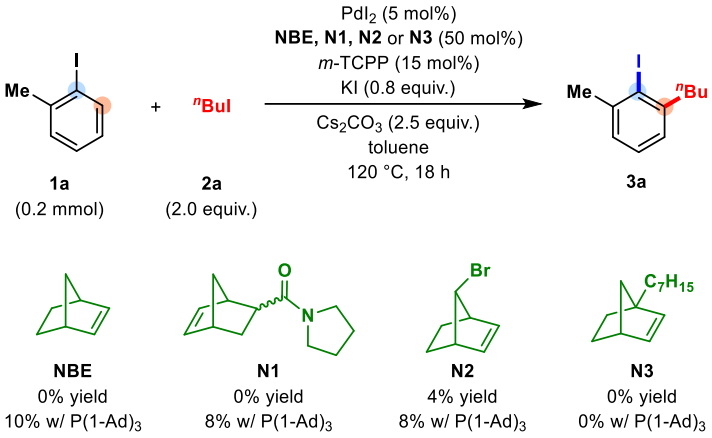
Scheme 1. *Ortho*-Functionalization of Iodoarenes Utilizing the Catellani Reaction



Results and Discussion

Performance of the established catalytic system. Our study commenced on investigating the performance of the Pd/NBE catalytic system in the presence of TCPP as established by the Della Ca' group for the *ortho*-alkylation of iodoarene (Scheme 2).[15] Despite our efforts, the use of 2-iodotoluene (**1a**) as the substrate and *n*-butyl iodide as the alkylation reagent did not lead to the formation of the desired product **3a** under the reported reaction conditions. Furthermore, several structurally-modified NBEs **N1**,[15] **N2**,[18] and **N3**,[19] which have shown optimal performance in other Catellani-type reactions, exhibited minimal reactivity, with only **N3** providing a 4% yield. Inspired by the findings of the Hartwig group that bulky trialkylphosphine is beneficial for C-I reductive elimination, we conducted the same reactions using tri(1-adamantyl)phosphine)[20] instead of *m*-TCPP. The reaction yields were increased to a maximum of 10% for NBE, **N1**, and **N2**, while still far from satisfactory. These results suggest that the combination of Pd/NBE catalysis and a phosphine ligand is not effective in promoting the *ortho*-alkylation of iodoarene.

Scheme 2. *Ortho*-Alkylation of Iodoarenes Using Established Protocols

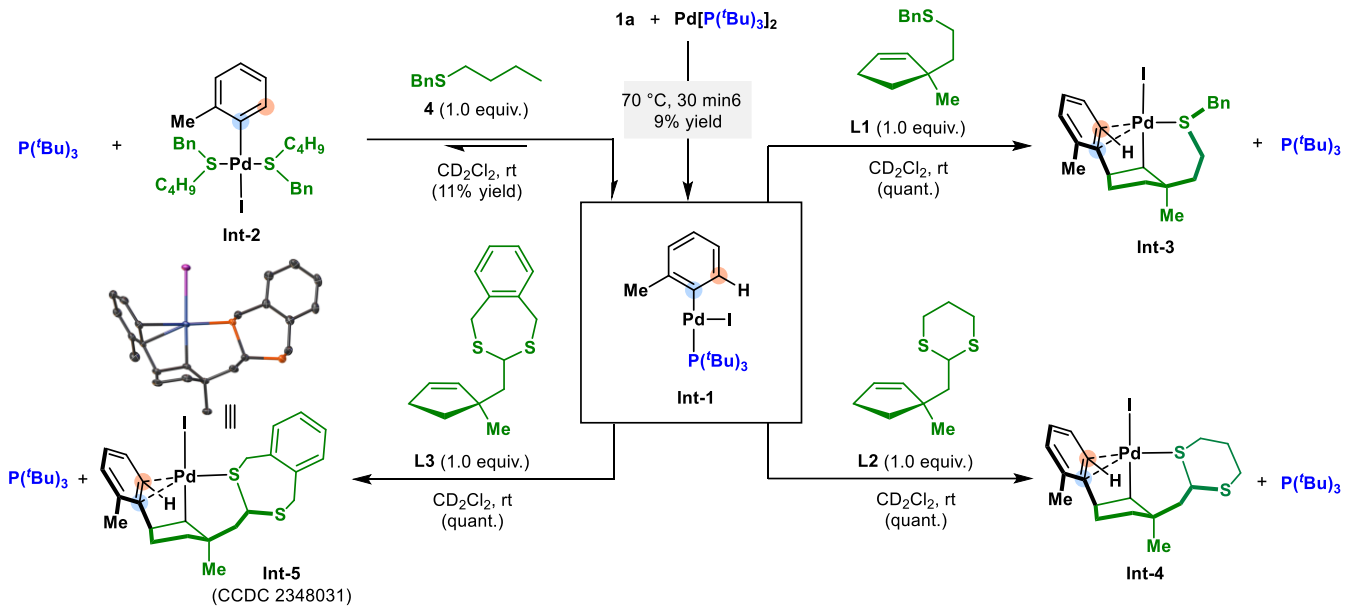


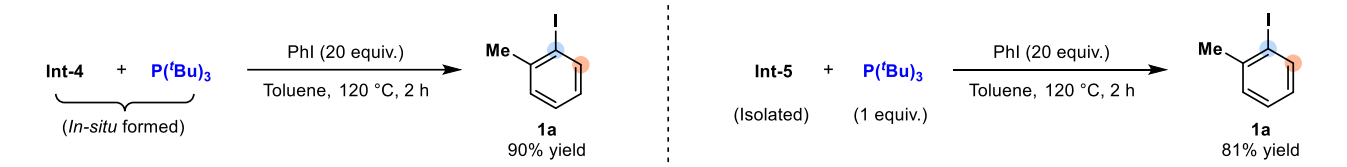
Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), **2a** (0.40 mmol, 2.0 equiv.), PdI_2 (0.01 mmol, 5 mol%), NBE/sm NBEs (0.10 mmol, 50 mol%), P(*m*-TCPP)$_3$ (0.03 mmol, 15 mol%), KI (0.16 mmol, 0.8 equiv.), Cs_2CO_3 (0.50 mmol, 2.5 equiv.), toluene (3 mL), 120 °C, sealed tube, 18 h. Yields were determined by GC analysis using *n*-dodecane as the internal standard. *m*-TCPP = tris(3-chlorophenyl)phosphine.

Potential of the cycloolefin/trialkylphosphine dual ligand system. We then examined the potential of the thio-cycloolefin ligand in the targeted reaction by integrating Pd/olefin ligand catalysis with phosphine-promoted C-I reductive elimination. This necessitated the independent operation of two distinct ligands to avoid mutual interference. An organometallic study was undertaken to explore this prospect (Scheme 3). Starting with the synthesis of the monomeric P(^{t}Bu)$_3$-ligated arylpalladium complex **Int-1** following Hartwig's reported procedure,[21] we examined its reactivity with various thioether ligands (Scheme 3a). Notably, dialkyl thioether ligand **4** showed low capacity to displace P(^{t}Bu)$_3$ in the complex, indicating its weaker coordination ability compared to P(^{t}Bu)$_3$. Conversely, thio-cycloolefin ligands **L1**, **L2**, and **L3** readily reacted with **Int-1** to form insertion intermediates **Int-3**, **-4**, and **-5** quantitatively, with the release of equimolar of P(^{t}Bu)$_3$. The structure of complex **Int-5** was confirmed through single-crystal X-ray diffraction (XRD) analysis. This observation highlights the thermodynamic driving force provided by C=C migratory insertion for the overall transformation, despite the initially unfavorable phosphine to thioether ligand exchange.

Interestingly, heating of the *in-situ* formed mixture of **Int-4** and P(^{t}Bu)$_3$ in the presence of excess iodobenzene resulted in a 90% yield of iodoarene **1a**. A similar outcome was acquired when the isolated **Int-5** was subjected to heating with P(^{t}Bu)$_3$ and excess iodobenzene (Scheme 3b). This validated the reversibility of migratory insertion involving the cycloolefin ligand, as well as the compatibility of the insertion/retro-insertion step and the P(^{t}Bu)$_3$-promoted C-I reductive elimination. Since the *ortho*-alkylation of the insertion intermediate in the presence of a base and an alkyl electrophile was demonstrated in our previous study,[16a] the present finding serves as a proof-of-concept of the dual ligand catalytic system. Building on this discovery, we proceeded to identify the optimal reaction conditions for the *ortho*-alkylation of iodoarenes utilizing the dual ligand system.

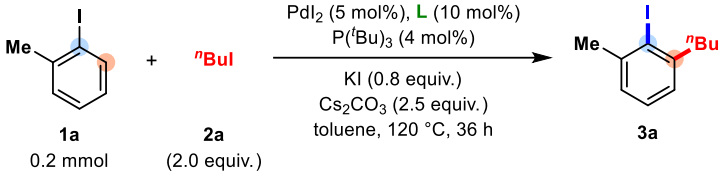
Scheme 3. Combined Use of Cycloolefin Ligands and tri(*tert*-butyl)phosphine in Palladium Catalysis



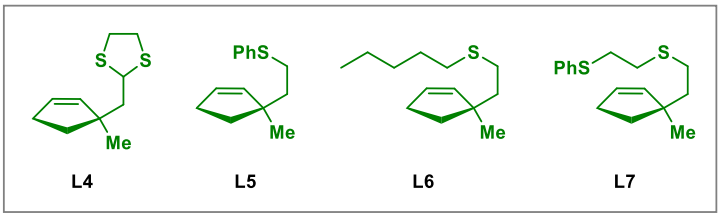


Optimization of reaction conditions. The *ortho*-butylation of aryl iodide **1a** was selected as the model reaction. Employing PdI_2 as the palladium source, Cs_2CO_3 as the base, KI as the additive, and P(^{t}Bu)$_3$ as the promoter for C-I reductive elimination, a series of thio-cycloolefin ligands were evaluated for their performance (Table 1). Encouragingly, ligands **L1**-**L3** demonstrated activity in producing the desired product **3a**, with **L2** exhibiting the highest efficiency (entries 1-3). Ligand **L4**, containing a five-membered dithiane moiety, showed comparable performance to its six-membered counterpart **L2** (entry 4). Conversely, the phenylthiol ligand **L5** proved to be ineffective (entry 5), while the the *n*-pentylthio ligand **L6** exhibited improved performance compared with **L5** (entry 6). Ligand **L7** with both phenylthiol and alkylthio coordination sites displayed no reactivity (entry 7). Lastly, in the absence of a thio-cycloolefin ligand, no product was formed (entry 8), emphasizing the significance of the dual ligand system.

Table 1. Optimization of Cycloolefin Ligands[a]



1a 0.2 mmol | 2a (2.0 equiv.) | 3a



L4 L5 L6 L7

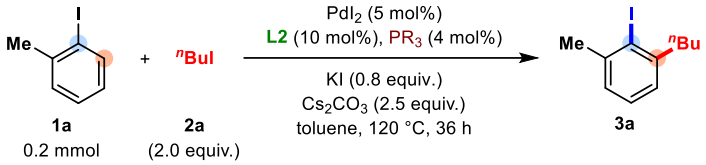
Entry	Ligand	Yield of **3a** (%)	Conversion (%)
1	**L1**	2	81
2	**L2**	29	86
3	**L3**	13	86
4	**L4**	25	77
5	**L5**	0	79
6	**L6**	16	75
7	**L7**	0	68
8	No ligand[b]	0	24

[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), **2a** (0.40 mmol, 2.0 equiv.), PdI_2 (0.01 mmol, 5 mol%), **L** (0.02 mmol, 10 mol%), $P(^tBu)_3$ (0.008 mmol, 4 mol%), KI (0.16 mmol, 0.8 equiv.), Cs_2CO_3 (0.50 mmol, 2.5 equiv.), toluene (3 mL), 120 °C, sealed tube, 36 h. [b] No ligand was used. Yields were determined by GC analysis using *n*-dodecane as the internal standard.

To enhance the effectiveness of the catalytic system, we investigated the structure-activity relationship of the phosphine ligand (Scheme 4a). Initially, triarylphosphines[22] with distinct steric and electronic properties, including P(*o*-tol)$_3$, P(2-furyl)$_3$, and P(C_6F_5)$_3$, were tested, yielding unsatisfactory yields of **3a**. Subsequently, trialkylphosphines[23] with varying steric hinderances were examined, revealing a significant enhancement in the yield of **3a** with increasing steric bulkiness. Notably, P(1-Ad)$_3$ showcased superior performance compared to other phosphine ligands, resulting in a remarkable increase in the yield of **3a**. Further optimization indicated that KI had negligible impact on the reaction and could be omitted. The loadings of the two ligands were found to be subtle. Through systematic optimization, we established an optimal procedure that involved incubating the catalytic system at 40 °C for 30 minutes (to reduce the Pd(II) to Pd(0) by excess phosphine ligand) followed by raising the reaction temperature to 120 °C, resulting in a satisfactory yield of **3a** up to 78% (Scheme 4b).

Scheme 4. Optimization of Reaction Conditions[a]

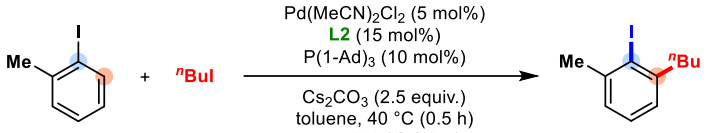
a. The effect of phosphine ligand:



1a, 0.2 mmol; 2a, (2.0 equiv.); 3a

PPh_3 No product 60% conv.	$P(o\text{-tol})_3$ 1% yield 41% conv.	$P(2\text{-furyl})_3$ 3% yield 51% conv.	$P(C_6F_5)_3$ 1% yield 30% conv.
$P(c\text{-Hex})_3$ No product 97% conv.	$P(^iPr)_3$ 1% yield 69% conv.	$P(^tBu)_3$ 29% yield 86% conv.	$P(1\text{-Ad})_3$ 50% yield 63% conv.

b. The optimal standard conditions[b]:



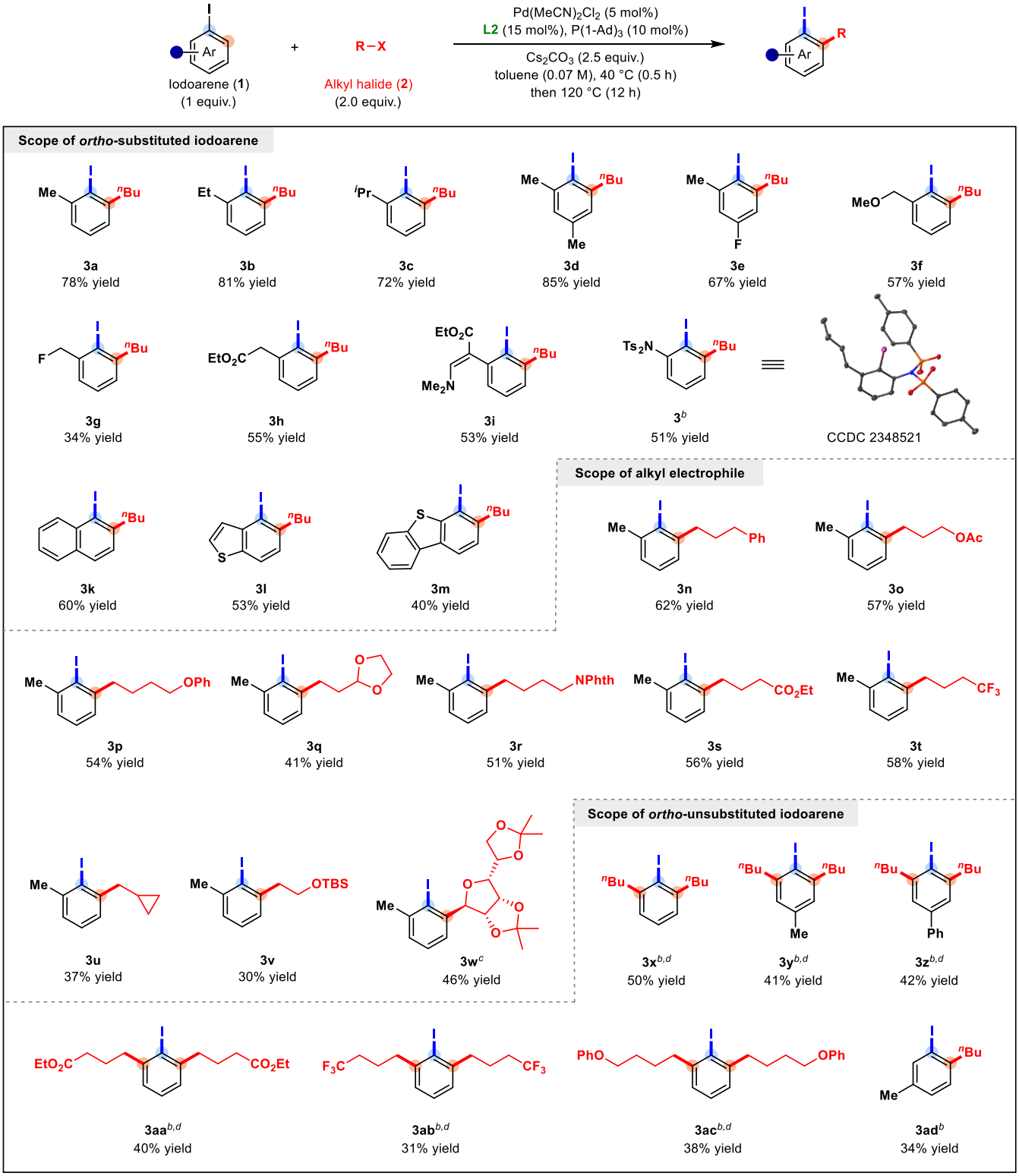
1a, 0.2 mmol; 2a, (2.0 equiv.); 3a, 78% yield, 94% conv.

[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), **2a** (0.40 mmol, 2.0 equiv.), PdI_2 (0.01 mmol, 5 mol%), **L2** (0.02 mmol, 10 mol%), PR_3 (0.008 mmol, 4 mol%), KI (0.16 mmol, 0.8 equiv.), Cs_2CO_3 (0.50 mmol, 2.5 equiv.), toluene (3 mL), 120 °C, sealed tube, 36 h. Yields were determined by GC analysis using *n*-dodecane as the internal standard. [b] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), **2a** (0.40 mmol, 2.0 equiv.), $Pd(MeCN)_2Cl_2$ (0.01 mmol, 5 mol%), **L2** (0.03 mmol, 15 mol%), $P(1\text{-Ad})_3$ (0.02 mmol, 10 mol%), Cs_2CO_3 (0.50 mmol, 2.5 equiv.), toluene (3 mL), sealed tube, 40 °C for 0.5 h, then 120 °C for 12 h. Isolated yield.

Substrate scope and synthetic utility. Under the optimal conditions, we investigated the *ortho*-alkylation reaction of various iodoarene substrates (Table 2). Initially, the scope of iodoarene was examined by using *n*-butyl iodide as the alkylation reagent. Iodoarenes bearing weak electron-donating or electron-withdrawing *ortho*-substituents were found to be suitable for the synthesis of di- or trisubstituted iodoarenes (**3a**-**3j**). The 2,6-substitution pattern of the alkylation product was confirmed through single-crystal XRD analysis of **3j**. However, iodoarenes bearing strongly electron-donating or electron-withdrawing substituents, such as methoxyl, trifluoromethyl, and ester groups, exhibited low yields of the desired products (Figure S4).

Furthermore, this approach proved effective in facilely modifying poly- and heterocycle iodides, yielding alkylated iodonaphthalene (**3k**), iodobenzothiophene (**3l**) and iododibenzothiophene (**3m**). Subsequent investigations encompassed a range of alkyl electrophiles containing functional groups such as phenyl (**3n**), acetoxyl (**3o**), ether (**3p**), acetal (**3q**), N-phthaloyl (**3r**), ethyl ester (**3s**), trifluoromethyl (**3t**), cyclopropyl (**3u**) and protected alcohol (**3v**) groups. It was found that, primary alkyl iodides bearing a variety of functional groups were identified as suitable electrophiles for this reaction (**3n**-**3t**), while an increase in steric hindrance of alkyl iodides resulted in decreased yields (**3u**-**3v**). Secondary alkyl iodide could not afford the desired product (Figure S5).[24] Additionally, glycosyl chloride could also be used as a viable electrophile for the synthesis of *α*-*C*-2-iodoaryl glycoside **3w**.[25]

Table 2. Substrate Scope for the *Ortho*-Alkylation of Iodoarenes[a]

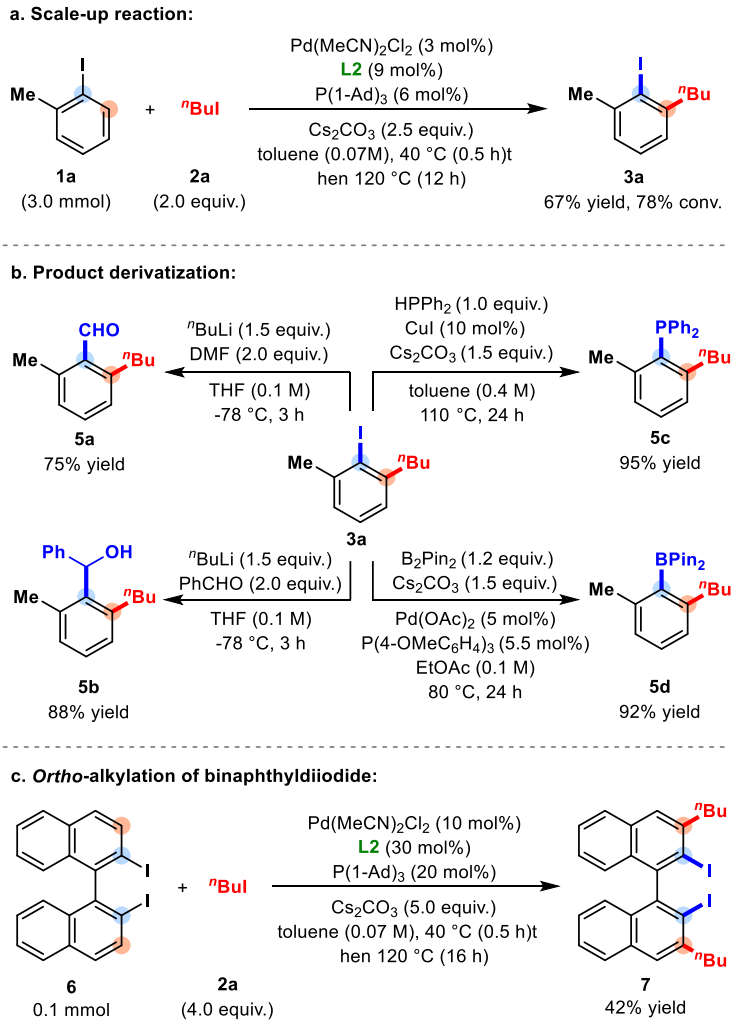


[a] Reaction conditions: iodoarene **1** (0.20 mmol, 1.0 equiv.), alkyl iodide **2** (0.40 mmol, 2.0 equiv.), $Pd(MeCN)_2Cl_2$ (0.01 mmol, 5 mol%), **L2** (0.02 mmol, 15 mol%), $P(1\text{-}Ad)_3$ (0.02 mmol, 10 mol%), Cs_2CO_3 (0.50 mmol, 2.5 equiv.), toluene (3 mL), sealed tube , 40 °C for 0.5 h, then 120 °C for 12 h. Isolated yield. [b] $Pd(MeCN)_2Cl_2$ (0.015 mmol, 7.5 mol%), **L2** (0.045 mmol, 22.5 mol%) and $P(1\text{-}Ad)_3$ (0.03 mmol, 15 mol%) were used. [c] Glycosyl chloride (0.4 mmol, 2.0 equiv.) was used as the electrophile. [d] Alkyl iodide was 1.0 mmol (5 equiv.). Yields of isolated products were reported.

When iodobenzene or 4-substituted iodobenzene[26] were used as the substrate, both *ortho* positions were alkylated to afford 2,6-dialkyliodobenzene **3x-3ac** in moderate yields. It is noteworthy that, when *meta*-iodotoluene was used as substrate, the mono *ortho*-alkylation product **3ad** was exclusively formed,[19,27] with no evidence of dialkylation product.

The *ortho*-alkylation of compound **1a** was successfully carried out on a 3 mmol scale using 3 mol% of $Pd(MeCN)_2Cl_2$, 6 mol% of $P(1\text{-}Ad)_3$, and 9 mol% of **L2**, resulting in a good yield of product **3a** (Scheme 5a). Subsequently, we demonstrated that the combination of our developed protocol with traditional iodoarene chemistry effectively addresses synthetic challenges typically encountered in Catellani reactions (Scheme 5b). Iodoarene derivative **3a** underwent halogen-lithium exchange with *n*-butyllithium, generating an aryllithium species which, upon reaction with DMF, yielded aldehyde **5a** and upon addition to benzaldehyde, afforded alcohol **5b**.[28] Furthermore, a copper-catalyzed cross-coupling of **3a** with $HPPh_2$ furnished the phosphine ligand **5c**,[29] a compound previously difficult to obtain using conventional methods. Additionally, the Pd-catalyzed cross-coupling of **3a** with B_2pin_2 proceeded smoothly, resulting in the formation of arylbronic ester **5d**.[30] Interestingly, this strategy could also be extended to binaphthyldiiodide, enabling the one-step synthesis of di-*ortho*-alkylated binaphthyldiiodide, thereby providing a step-economical approach to functionalized binaphthyl-type ligands[31] (Scheme 5c).

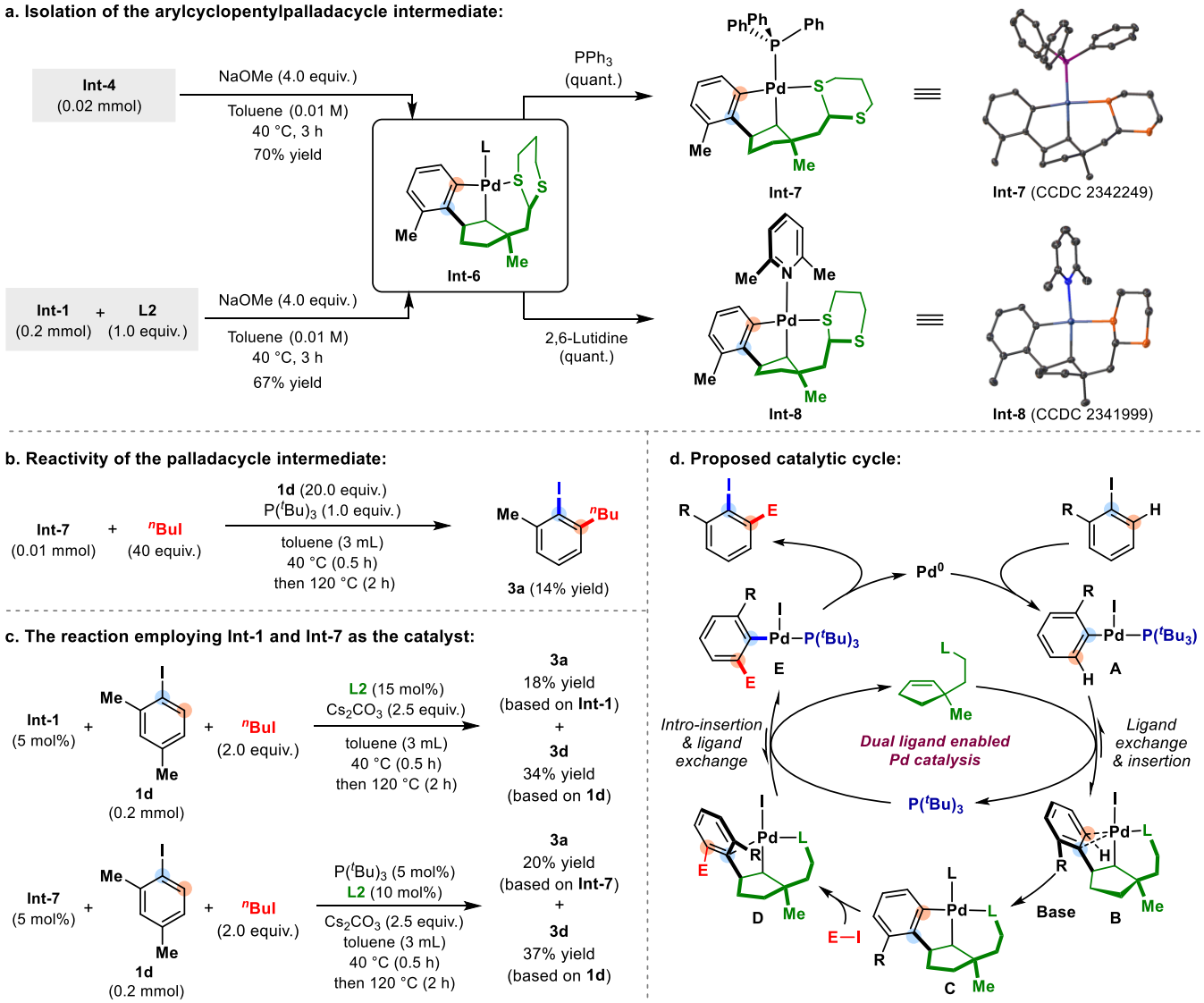
Scheme 5. Scale-Up Study and Synthetic Applications



Mechanistic study. As we have demonstrated the compatibility of the insertion/retro-insertion and C-I reductive elimination steps in prior proof-of-concept study, the remaining mechanistic puzzle of this dual ligand catalysis is the

verification of the palladacycle formation and *ortho*-alkylation steps. Although direct isolation of the palladacycle intermediate from the catalytic reaction system proved challenging, we achieved the transformation of the insertion complexes **Int-4** into the arylcycloalkylpalladacycle (ACP) intermediate **Int-6** through treatment with NaOMe (Scheme 6A). By reacting the arylpalladium complex **Int-1** and ligand **L2** in the presence of NaOMe, **Int-6** was obtained directly in a good yield. As **Int-6** presents as an insoluble yellow solid, further characterization was facilitated by treating this intermediate with triphenylphosphine or 2,6-lutidine. Two structurally well-defined ACP complexes **Int-7** and **Int-8** were successfully isolated, and their structures were confirmed through single-crystal XRD analysis. This represents the first example of isolating and explicitly characterizing such ACP intermediates, which was not achieved in our previous study.

Scheme 6. Mechanistic Study



Treatment of ACP complex **Int-7** with ^{n}BuI and P(^{t}Bu)$_3$ at 120 °C resulted in the formation of the *ortho*-alkylation/*ipso*-iodization product **3a**, albeit with a low yield (Scheme 6b). This observation provides crucial evidence supporting the *ortho*-alkylation/retro-insertion/C-I reductive elimination sequence of the ACP intermediate. Additionally, when **Int-1** was utilized as the catalyst in the presence of **L2** to facilitate the *ortho*-alkylation of **1d**, the desired product **3d** was obtained along with a minor amount of **3a**, representing the *ortho*-alkylation/*ipso*-iodization product of the aryl moiety in **Int-1**. Similarly, when **Int-7** was employed as the catalyst for the same transformation, product **3d** was also produced

with an accompanying 20% yield of **3a** (Scheme 6c). These experimental results affirm that both **Int-1** and **Int-7** function as reactive intermediates in the dual ligand enabled *ortho*-alkylation reaction.

Based on these experimental observations, we propose the mechanism of this dual ligand enabled Pd catalysis (Scheme 6d). The process begins with the oxidative addition of Pd(0) to the iodoarene substrate, forming complex **A**. Ligand exchange with the thio-cycloolefin ligand and subsequent C=C insertion lead to intermediate **B**, which undergoes base-assisted C-H activation to form the ACP intermediate **C**. In the presence of an alkyl iodide, complex **C** undergoes *ortho*-alkylation to afford alkylated intermediate **D**. Retro-insertion and ligand exchange then take place, releasing the cycloolefin ligand and re-coordinating the bulky phosphine ligand. The formed intermediate **E** then undergoes C-I reductive elimination to yield the desired product.

Conclusion

In conclusion, our study has successfully introduced a dual ligand catalytic system that combines Pd/olefin ligand cooperative catalysis with reversible C-I reductive elimination facilitated by a bulky phosphine ligand for the *ortho*-alkylation of iodoarenes. The mechanism of dual ligand cooperation has been elucidated through the isolation and stoichiometric reactions of the key organometallic intermediates. The present protocol offers valuable synthetic opportunities for the synthesis of complex polysubstituted aromatic molecules, thereby expanding the scope of applications for Catellani-type reactions. This research highlights the unique synthetic potential of the Pd/olefin ligand cooperative catalysis as a complementary system to Pd/NBE catalysis.

Acknowledgements

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