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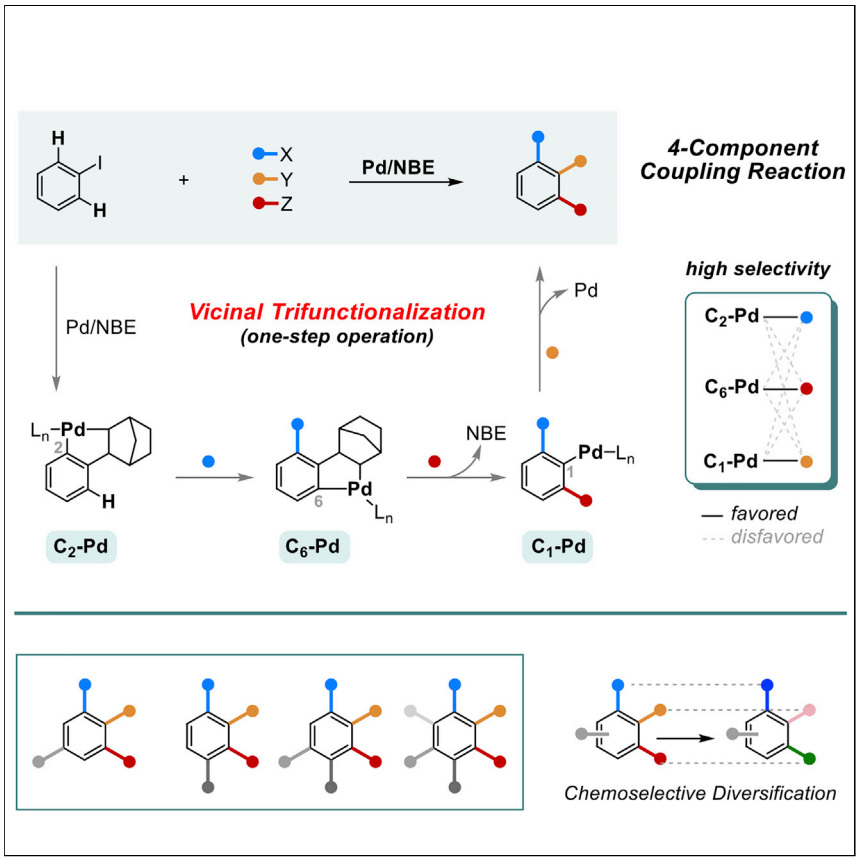
Regioselective Synthesis of Polyfunctional Arenes by a 4-Component Catellani Reaction



Polyfunctional arenes are essential chemicals with wide-ranging applications. Herein, we describe their preparation by a 4-component Catellani reaction. Multicomponent reactions assemble simple and inexpensive building blocks into functional molecules of much higher value. To do this effectively, bond formation between components must be orchestrated with high precision and must discriminate subtle differences between reactive centers. We accomplish these tasks by overcoming the long-standing "*ortho* effect" and show that it can become a predictable and constructive element of reaction design.

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HIGHLIGHTS

A 4-component Catellani reaction affords an efficient synthesis of substituted arenes

The well-known *ortho* effect is used as a constructive element of reaction design

Predictable chemo- and regioselectivity result from subtle substituent effects

Atom and step economic synthesis of polyfunctional arenes

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Regioselective Synthesis of Polyfunctional Arenes by a 4-Component Catellani Reaction

Jing Wang,[1,3] Cheng Qin,[1,3] Jean-Philip Lumb,[2,*] and Xinjun Luan[1,4,*]

SUMMARY

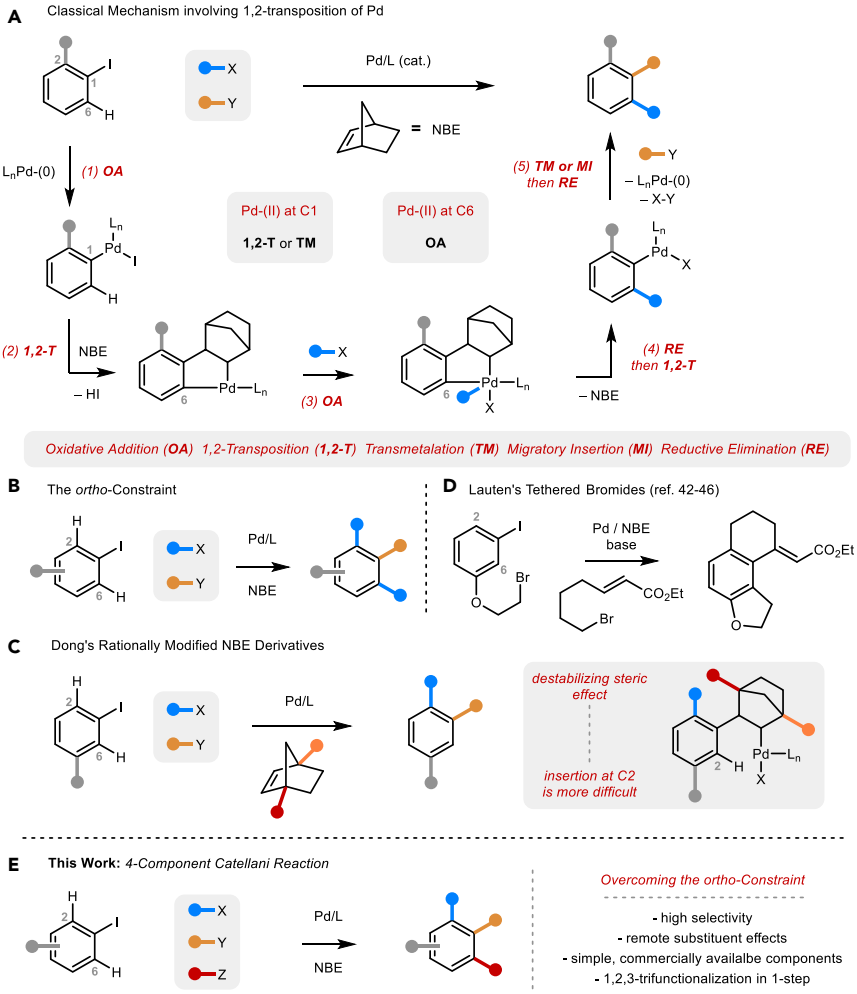
Polyfunctional arenes are an important part of the chemical value chain. To improve the efficiency of their synthesis, we have investigated a multicomponent approach built upon the Catellani platform. Here, we describe a 4-component coupling of aryl iodides lacking an *ortho* substituent that installs 3 discrete functional groups on the arene in a single step. The process is regio- and chemoselective and uncovers remote substituent effects that have a pronounced influence over intermediate Pd-(II) complexes. These intermediates have been a long-standing focus of the Catellani-reaction development, but persistent challenges have given rise to the well-known "*ortho* effect." We now show that the *ortho* effect can be a positive element of reaction design, and that previously problematic iodides can now be used in complexity-generating transformations. In expanding the scope of the Catellani platform, we hope to provide mechanistic considerations to guide future reaction design, while also improving the environmental footprint of synthesizing polyfunctional arenes.

INTRODUCTION

By introducing more than one functional group in a single transformation, multicomponent coupling reactions can provide an efficient synthesis of polyfunctional molecules.[1–4] In the particular case of substituted aromatic rings, Catellani's conditions, combining palladium (Pd) and norbornene (NBE) provide a versatile platform for a number of 3-component coupling reactions (Scheme 1A).[5–9] The inclusion of NBE promotes a characteristic 1,2-transposition (**1,2-T**) of Pd following oxidative addition (**OA**), that allows functionalization of both *ortho*- and *ipso*-carbons of the starting halide (C6 and C1, respectively, see Scheme 1A for numbering).[9] High chemo- and regioselectivity result from the distinct coordination environments of Pd, which change over the course of the catalytic cycle. The Pd-(II) center at C1 is relatively electropositive and coordinatively unsaturated, making it well suited for migratory insertion (**MI**) or transmetalation (**TM**), whereas the Pd-(II) center at C6 is relatively electron rich, making it better suited for **OA**.[10] While the complementarity of these environments has led to the successful combination of many pairs of coupling partners, a persistent limitation requires an *ortho* substituent on the starting aromatic halide to ensure high degrees of selectivity.[11–31] In its absence, the Pd-(II) centers at C1 and C6 behave quite differently, and a number of competitive pathways erode selectivity in what is commonly referred to as the *ortho* effect or constraint (Scheme 1B).[32–34] This includes products of over functionalization at both C2 and C6,[10,14–17,21] as well as additional NBE-containing by-products (not shown, see Maestri et al.,[33] Wang et al.,[34] and Lei et al.[35]). A series of elegant studies addressing aspects of this limitation were recently described by Dong and co-workers, whose carefully engineered NBE derivatives restore steric effects in classical 3-component reactions (Scheme 1C).[34,36–38] These examples illustrate the influence of remote-

The Bigger Picture

Polyfunctional arenes touch the lives of nearly every human on earth. They are integral components of the chemical value chain with wide-ranging applications in the pharmaceutical and agrochemical sectors. In this work, we describe a new way of synthesizing polyfunctional arenes by multicomponent coupling. Multicomponent reactions are attractive, because they assemble simple and inexpensive building blocks into functional molecules of much higher value. If each component can be varied, the resulting transformation can rapidly search chemical space around a given scaffold at low cost with minimal waste. To do this effectively, bond formation between components must be orchestrated with high precision and must often discriminate subtle differences between reactive centers. Our work accomplishes this task by advancing the Catellani platform to a 4-component coupling that can provide polyfunctional arene products containing up to 6 unique substituents in a single transformation.



Scheme 1. Pd/NBE Catalysis

steric effects in selective aromatic C–H functionalization, which continue to motivate new designs for catalysis.[39–41]

Our own interest in remote substituent effects surfaced recently, while attempting to design a 4-component Catellani reaction (Scheme 1E). We were interested in functionalizing two aromatic C–H bonds in a single transformation with distinct coupling partners, recognizing its potential value for the synthesis of 1, 2, 3-tri-substituted arenes. We were also interested in a more fundamental question of chemoselectivity and whether the *ortho* effect could be leveraged in order to differentiate the 2 and 6 positions of an *ortho*-unsubstituted aromatic iodide. The only examples where distinct groups have been introduced to the *ortho* positions of an iodide come from Lautens, who used a tethered electrophile at the *meta* position of the iodide (Scheme 1D).[42–46] To our knowledge, the introduction of distinct substituents on simple, *ortho*-unsubstituted iodides has not been previously reported, so far preventing a 4-component coupling, as we describe here (Scheme 1E).

At the center of this challenge are the subtle differences between the Pd-(II) complexes that would occupy C2 and C6 over the evolution of a 4-component coupling (Scheme 2A). The Pd-(II) complex at C2 [C_2-Pd-(A)] lacks a substituent at C6, whereas the

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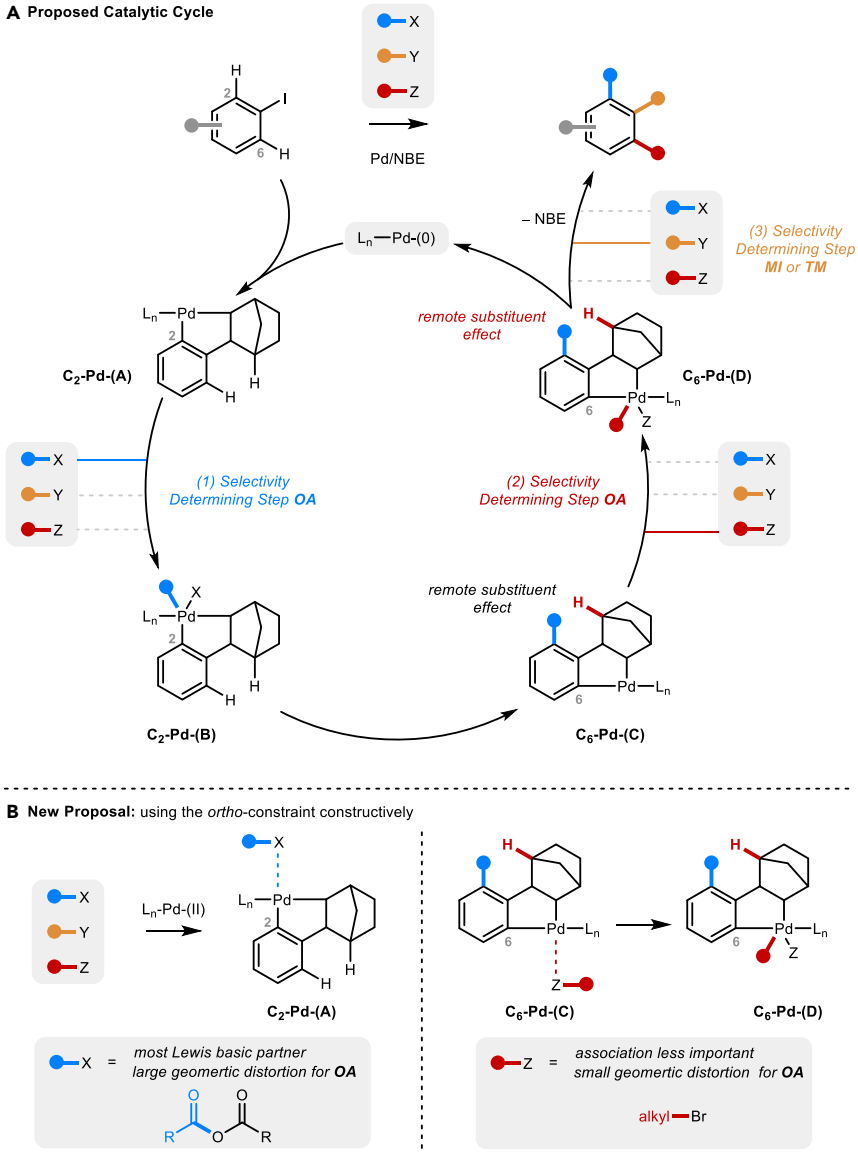

Scheme 2. Mechanistic Framework for Reaction Design

downstream complex at C6 [C_6-Pd-(C)] possesses the substituent previously introduced at C2. Since C2 and C6 are not in direct electronic communication, we speculated that the principal difference between these complexes would derive from a remote-steric interaction between the C2 substituent and the hydrogen atom on the NBE bridge. We questioned whether this remote-steric effect could be used constructively in order to functionalize C_2-Pd-(A) and C_6-Pd-(C) with distinct coupling partners (Scheme 2B). We reasoned that complex **A** would not be constrained by steric effects and might, therefore, favor the coupling partner that could best coordinate to the Pd-(II) center. By contrast, complex **C** would have a substituent at C2 and would, therefore, progress to Pd-(IV) intermediate C_6-Pd-(D) by the least sterically demanding pathway possible.[33]

RESULTS AND DISCUSSION

As a point of departure, we considered the 4-component coupling between iodobenzene (**1a**), benzoic anhydride (**2a**), benzyl bromide (**3a**), and ^{t}Bu-acrylate (**4a**), with the

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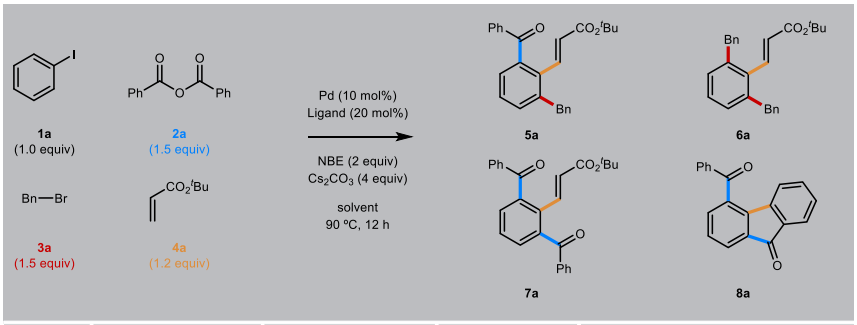
Table 1. Optimization of the Reaction Conditions



Entry	Catalyst	Ligand	Solvent	Yield(%)[a]			
				5a	6a	7a	8a
1	$Pd(OAc)_2$	PPh_3	THF	15	10	0	<5
2	$Pd(OAc)_2$	P(o-tol)$_3$	THF	11	20	0	7
3	$Pd(OAc)_2$	P(*p*-OMeC$_6$H$_4$)$_3$	THF	<5	<5	0	0
4	$Pd(OAc)_2$	P(*p*-FC$_6$H$_4$)$_3$	THF	31	11	0	9
5	$Pd(OAc)_2$	P(*p*-ClC$_6$H$_4$)$_3$	THF	26	13	0	11
6	$Pd(OAc)_2$	P(2-furyl)$_3$	THF	44	9	<5	7
7	$Pd(TFA)_2$	P(2-furyl)$_3$	THF	12	61	0	0
8	$PdCl_2$	P(2-furyl)$_3$	THF	62	10	5	16
9	$[Pd(allyl)Cl]_2$	P(2-furyl)$_3$	THF	56	5	13	19
10	$Pd(CH_3CN)_2Cl_2$	P(2-furyl)$_3$	THF	53	5	7	25
11	$PdCl_2$	P(2-furyl)$_3$	DME	37	13	0	7
12	$PdCl_2$	P(2-furyl)$_3$	1,4-dioxane	26	<5	19	32

Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), **3a** (0.45 mmol), **4a** (0.36 mmol), Pd (10 mol%), ligand (20 mol%), NBE (0.6 mmol), and base (1.2 mmol) in the indicated solvent (3 mL) at 90 °C for 12 h under a nitrogen atmosphere.

[a]All yields were determined by ^{1}H-NMR using dibromomethane as the internal standard.

goal of preparing 1, 2, 3-tri-substituted benzene (**5a**) (Table 1). While in principle, there could be two complementary pathways to achieve selective product formation (see Scheme S1 for a complete comparison), our initial design was to functionalize C2 by acylation before benzylation at C6, following the mechanistic rationale presented in Scheme 2B.[17,19,47–52] Among the many competitive pathways that could erode selectivity for **5a**, di-benzylation to provide **6a** and di-acylation to provide **7a** or **8a** were anticipated, and would reflect poor selectivity in either of the two **OA** steps (See Table 1). These pathways have been observed in previous Catellani reactions when using *ortho*-unsubstituted aromatic iodides,[17,52,53] and indeed, exposure of our coupling partners to standard Catellani conditions consisting of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %) and NBE (2 equiv) in THF at 90°C led to the formation of **5a** and **6a** in 15% and 10% yields, respectively (Table 1, entry 1). We also observed appreciable quantities of benzyl benzoate (**9**) from a competitive background reaction between the carbonate base, the anhydride, and the bromide (See Table S1). While selectivity for the desired pathway could be improved to some extent by using a less electron-donating phosphine ligand (Table 1, compare entries 1–3 with 4–5), it was not until we evaluated tris-2-furyl-phosphine that we observed a significant improvement for the formation of **5a** (Table 1, entry 6). Initially, we attributed this effect to the decreased steric demands of P(2-furyl)$_3$ relative to PPh_3, as well as its reduced donating ability to Pd, and thought that it would create a more electropositive and less sterically encumbered Pd-(II) center (C_2-**Pd-(A)** in Scheme 3B). In turn, we thought that this would favor coupling with the more Lewis basic and

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sterically demanding anhydride partner. In addition to this ligand effect, we also observed a noticeable counterion effect and obtained our highest yield of 62% for **5a** by using $PdCl_2$ as the pre-catalyst (Table 1, entry 8). The beneficial effects of $PdCl_2$ in previous Cattelani reactions have been noted, but the reasons behind the effect remain unclear.[18,19,21] Results with additional pre-catalysts, including the allyl-Cl Pd-(II) dimer (Table 1, entry 9) and the bis-acetonitrile $PdCl_2$ complex (Table 1, entry 10), were also superior to most other Pd-pre-catalysts, but did not offer an improvement to the results obtained with $PdCl_2$. Therefore, we selected the conditions of entry 9 for additional development. Before advancing, we note an important solvent effect, as selectivity decreased dramatically for **5a** when we used solvents other than THF, including DME or 1,4-dioxane (Table 1, entries 11 and 12). We will return to this solvent effect below. Finally, we wish to mention that additional NBE derivatives did not improve upon the results of entry 8. Therefore, we did not pursue this line of reaction optimization, and instead, focused on the use of NBE itself and the scope of the reaction.

While we had initially considered steric effects as the principle determinant of selectivity, our investigation of substituents in the *para* position of the starting iodide revealed an unexpected electronic effect that appears to correlate with the substituent's σ_{meta} value. When using THF as solvent, we observed our highest selectivity for the 4-component coupling when the *para* substituent was moderately electron releasing and not inductively withdrawing (Figure 1, entries 1–3). However, as this substituent became more strongly withdrawing, selectivity changed to favor dibenzylation (Figure 1, entries 4–7). In the most extreme cases where the *para* substituent was either a nitrile or a nitro group (Figure 1, entries 8–9), we only observed small amounts of acylation, and dibenzylation dominated. If, however, THF was replaced with 1,4-dioxane, selectivity for the 4-component coupling could be regained. The effect was most pronounced for moderately withdrawing substituents (Figure 1, entries 13–16), for which the yields of 4-component coupling improved consistently by ~20%. While the root cause of this solvent effect remains unclear, it appears to have on overall effect of favoring acylation over benzylation. For relatively electron-rich iodides (**1a–1c**), this has a detrimental effect and leads to over acylation and the increased formation of **6** and **7** (Figure 1, entries 10–12). But for moderately deactivated substrates (**1d–1g**), this effect is quite positive and improves the yield of the 4-component coupling to the point of becoming synthetically useful (Figure 1, entries 13–16). We do note that previous mechanistic studies have invoked CsI as a labile ligand to Pd-(II) in other Catellani reactions[47] and speculate that the solvent's polarity and chelating abilities might affect these interactions.

Equipped with the combination of our optimized conditions in THF and 1,4-dioxane, we proceeded to explore the reaction's scope (Figure 2A). In addition to the substituents discussed in Figure 1, our conditions tolerate electron withdrawing aldehyde (**5i**), ketone (**5j**), and ester substituents (**5k**), as well as a trifluoromethyl ether (**5l**). Likewise, a Boc-protected phenol (**5m**) and a 3° amide (**5n**) are similarly tolerated. Notably, these substrates perform best when 1,4-dioxane is used as the solvent, consistent with our observations in Figure 1. As the *para* substituent becomes increasingly donating, the use of THF is imperative. Under these conditions, a methyl group (**5o**), as well as oxygen or nitrogen heteroatoms (**5o–5r**), could be tolerated. Certain common functional groups, including phenols or anilines, as well as a benzylic alcohol, undergo *in situ* acylation, returning the corresponding products as their benzoate protected derivatives (**5s–5u**).

Next, we evaluated the scope of the anhydride, benzyl bromide, and olefin components (Figures 2B–2D). We selected 4-fluoro-iodo-benzene (**1d**) as our iodide component, and

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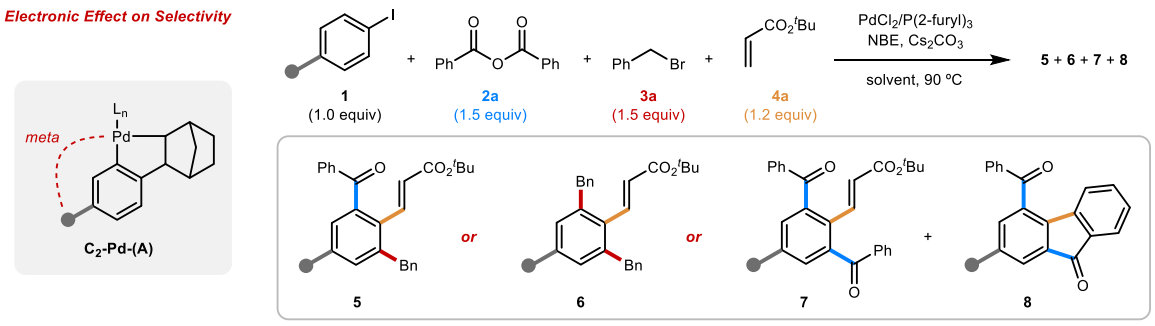
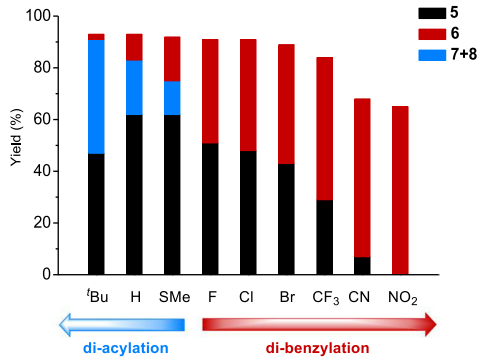


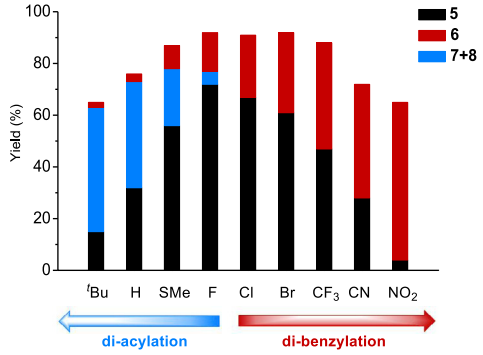
Solvent = THF

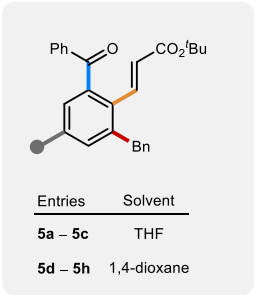
Entry		σ_{meta}	Yield (%)[a]		
		σ_{meta} | -0.1 - 0.3	5	6	7 / 8
1	^{t}Bu	-0.10	47	<5	44
2	H	0.00	62	10	21
3	SMe	0.15	62	17	13
		σ_{meta} | 0.3 - 0.5			
4	F	0.34	51	40	0
5	Cl	0.37	48	43	0
6	Br	0.39	43	46	0
7	CF_3	0.43	29	55	0
		σ_{meta} | 0.5 - 0.8			
8	CN	0.56	7	61	0
9	NO_2	0.71	0	65	0



Solvent = 1,4-dioxane

Entry		σ_{meta}	Yield (%)[a]		
		σ_{meta} | -0.1 - 0.3	5	6	7 / 8
10	^{t}Bu	-0.10	15	<5	48
11	H	0.00	32	<5	41
12	SMe	0.15	56	9	22
		σ_{meta} | 0.3 - 0.5			
13	F	0.34	72	15	5
14	Cl	0.37	67	24	0
15	Br	0.39	61	31	0
16	CF_3	0.43	47	41	0
		σ_{meta} | 0.5 - 0.8			
17	CN	0.56	28	44	0
18	NO_2	0.71	<5	61	0





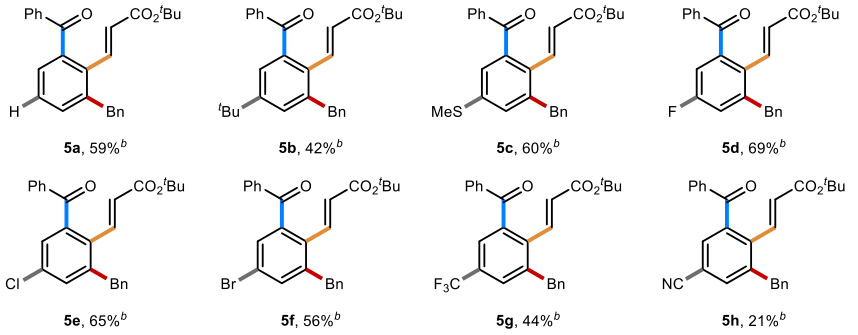


Figure 1. Electronic Effect for the Reaction

[a]All yields were determined by ^{1}H-NMR using dibromomethane as the internal standard.[b]Isolated yields.

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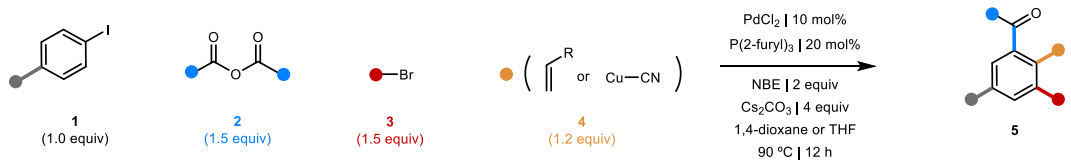
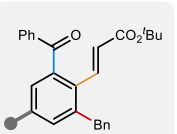
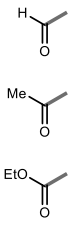


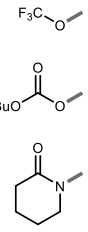
A *Aryl Iodides*



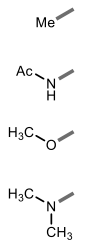
Entries	Solvent
5i – 5n	1,4-dioxane
5o – 5u	THF



Entry		Yield (%)
5i		41
5j		54
5k		45

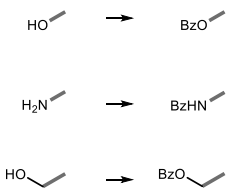


Entry		Yield (%)
5l		58
5m		62
5n		61



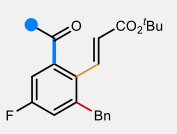
Entry		Yield (%)
5o		60
5p		45
5q		57
5r		49

in situ acylation

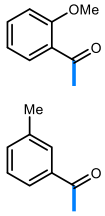


Entry		Yield (%)[a]
5s		54
5t		57
5u		59

B *Acylation*

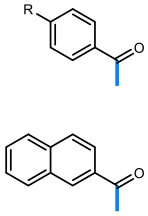


Entries	Solvent
5v – 5ac	1,4-dioxane



Entry		Yield (%)
5v		64

Entry		Yield (%)
5w		65



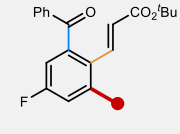
R	Entry		Yield (%)
Cl	**5x**		68
F	**5y**		63

Entry		Yield (%)
5z		58

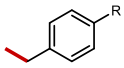
X	Entry		Yield (%)
S	**5aa**		53
O	**5ab**		52

Entry		Yield (%)[b]
5ac		35

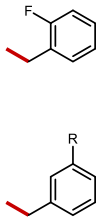
C *Alkylation*



Entries	Solvent
5ad – 5as	1,4-dioxane

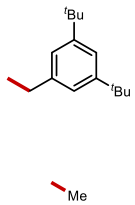


R	Entry		Yield (%)
Me	**5ad**		70
F	**5ae**		63
Cl	**5af**		65
Br	**5ag**		62
CF_3	**5ah**		63
NO_2	**5ai**		42
OCF_3	**5aj**		67
CN	**5ak**		45
SO_2Me	**5al**		36



Entry		Yield (%)
5am		64

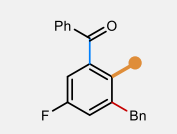
R	Entry		Yield (%)
Me	**5an**		71
OMe	**5ao**		68
F	**5ap**		67
Cl	**5aq**		70



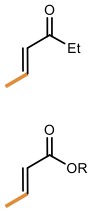
Entry		Yield (%)
5ar		66

Entry		Yield (%)[c]
5as		74

D *ipso Substitution*

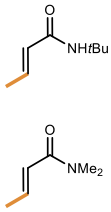


Entries	Solvent
5at – 5bb	1,4-dioxane



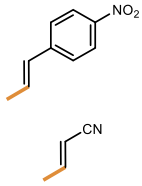
Entry		Yield (%)
5at		72

R	Entry		Yield (%)
Me	**5au**		71
Bn	**5av**		70



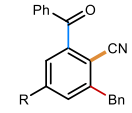
Entry		Yield (%)
5aw		73

Entry		Yield (%)
5ax		57



Entry		Yield (%)
5ay		58

Entry		Yield (%)
5az		67



R	Entry		Yield (%)
H	**5ba**		65
F	**5bb**		56

Figure 2. Substrate Scope with *para*-Substituted Aryl Iodides

1 (0.3 mmol), **2** (0.45 mmol), **3** (0.45 mmol), **4** (0.36 mmol), $PdCl_2$ (0.03 mmol), P(2-furyl)$_3$ (0.06 mmol), NBE (0.6 mmol), Cs_2CO_3 (1.2 mmol) in 1,4-dioxane at 90°C. All yields are isolated yields.

[a]**3s**, **3t**, and **3u** were run with 2.5 equiv of **2a** (0.75 mmol) and 5 equiv of Cs_2CO_3 (1.5 mmol).[b]Dong's carbonate anhydride was used (Catellani et al.[11]), and **1o** was used instead of **1d**.

[c]Methyl iodide was used instead of benzyl bromide.

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therefore, employed 1,4-dioxane as the solvent. By comparison to the pronounced electronic effects that we had observed on the aryl iodide, substituent effects on these reaction components seems to be attenuated. For the anhydride, this included the more sterically demanding and electron-rich *ortho*-methoxy benzoate (**5v**), as well as benzoates with a Cl– or F substituent in the *para* position (**5x** and **5y**). Substituents other than benzene rings were also tolerated, including 2-napthyl, 2-furan, and 2-thiopene rings (**5z–5ab**). Finally, a preliminary step toward the incorporation of esters was investigated using Dong's carbonate anhydride, which provided ethyl ester **5ac** in an unoptimized but encouraging yield of 35%.[21]

The scope of the benzyl bromide revealed a relatively high tolerance for a range of common functional groups (Figure 2C). These included electron withdrawing substituents in the *para* position, such as trifluoromethyl- (**5ah**), nitro- (**5ai**), trifluoromethyl ether- (**5aj**), cyano- (**5ak**), and methanesulfonyl- (**5al**) groups. Fluorine substitution was also tolerated in both the *ortho*- (**5am**) and *meta*-positions (**5ap**). Likewise, halogen substituents, suitable for product diversification, were tolerated in *meta*- (**5aq**) and *para*-positions (**5ae–5ag**). An important extension of scope was to methyl iodide,[29] which allows us to incorporate a methyl group at C6 while retaining high levels of selectivity (**5as**). Finally, we investigated variations to the acrylate and found that a range of electron-deficient olefins could be used, including those in conjugation with an ester, amide, or ketone (**5at–5ax**), along with an electron-deficient styrene (**5ay**) or acrylonitrile (**5az**). A notable extension is to the incorporation of a cyano group—from Cu–CN. This is a well-known component of the Catellani toolbox that interfaces nicely with our multicomponent process to rapidly prepare valuable aromatic nitriles (**5ba** and **5bb**).[15,54,55]

Because *para*-substituted iodides and iodobenzene are symmetrical, the first C–H insertion is not regiodetermining, and product selectivity is governed at the stage of **OA**. If, however, symmetry around the iodide is broken, the first C–H insertion must become regioselective for C2 in order for the same sequence of acylation followed by alkylation to proceed with high positional control (Figure 3). Based upon literature precedent,[31,41,42,44] we anticipated that **OA/1,2-T** would be selective for the less sterically encumbered C–H at C2. However, the effects of multiple substituents on the reactivity of **C_2-Pd-(A)** and **C_6-Pd-(C)** were less clear. Therefore, we were pleased to retain high selectivity across a relatively broad range of these more challenging substrates. This included simple, *meta*-substituted iodides (Figure 3A) that afforded *tetra*-substituted products with the acyl group at C2, a nitrile or an olefin at C1, a benzyl or a methyl at C6, and a range of substituents at C5 (**11a–11l**). Likewise, if the iodide is 4,5-disubstituted (Figure 3B), penta-substituted arenes are produced with the predicted regioselectivity (**11m–11w**). The successful use of 3-iodothiophene in THF to provide **11x** also provides a proof of concept for the application of our strategy on heterocyclic scaffolds. Finally, when the iodide is tri-substituted (Figure 3C), arenes with up to 6 different substituents can be prepared in a single step, creating a streamlined approach to fully substituted aromatic rings (**11y** and **11z**). To our knowledge, this is the first multicomponent synthesis of such highly substituted arenes, which should create interesting opportunities for future diversification.

Because the 4-component coupling installs functional handles with complementary reactivity, a range of chemoselective transformations can diversify the polysubstituted aromatic core (Scheme 3). For example, **5d** and **5bb** are prepared on gram scale in isolated yields of 62% and 50%, respectively, and then transformed into a range of downstream products with different functional properties. This spans the

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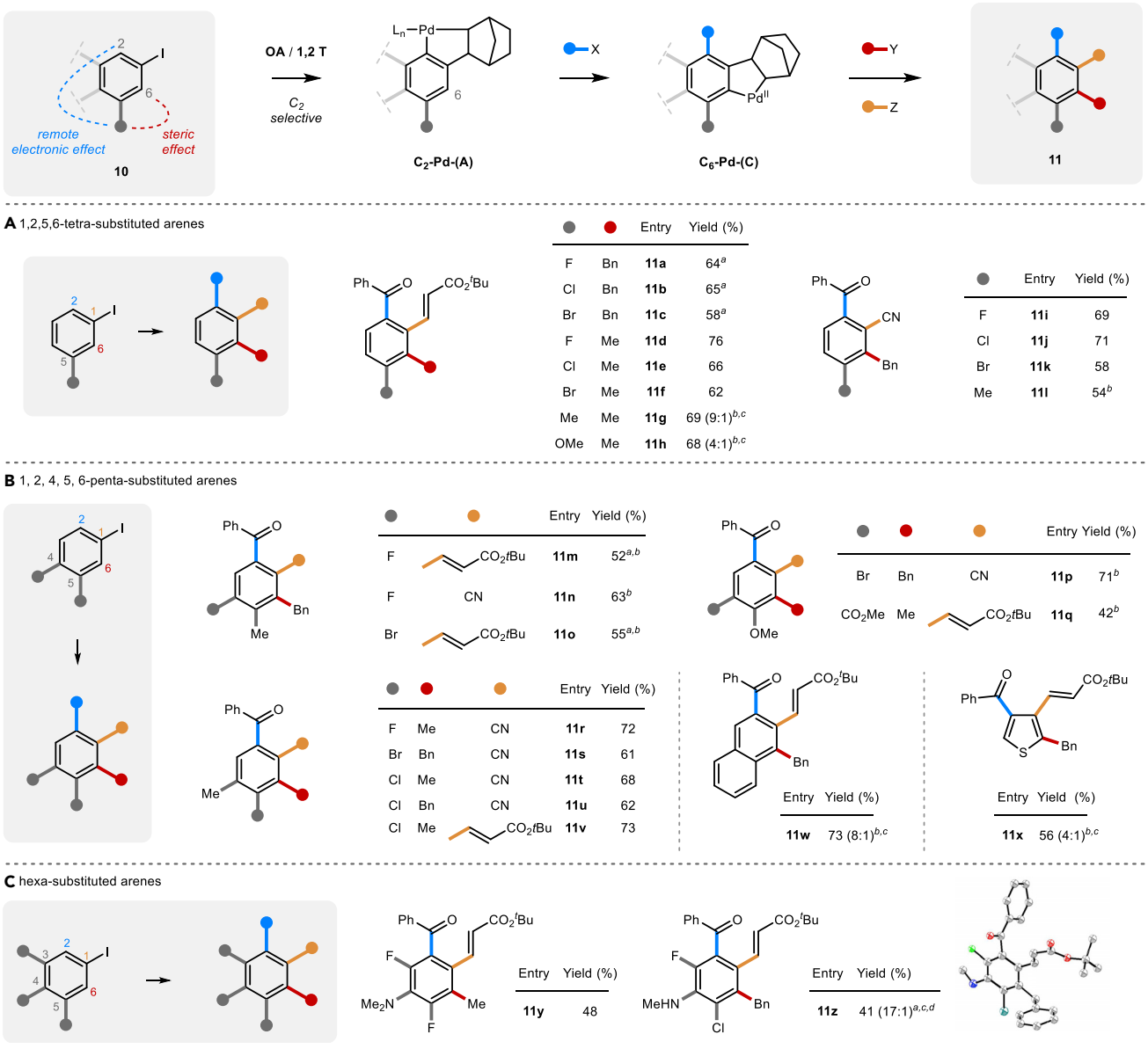


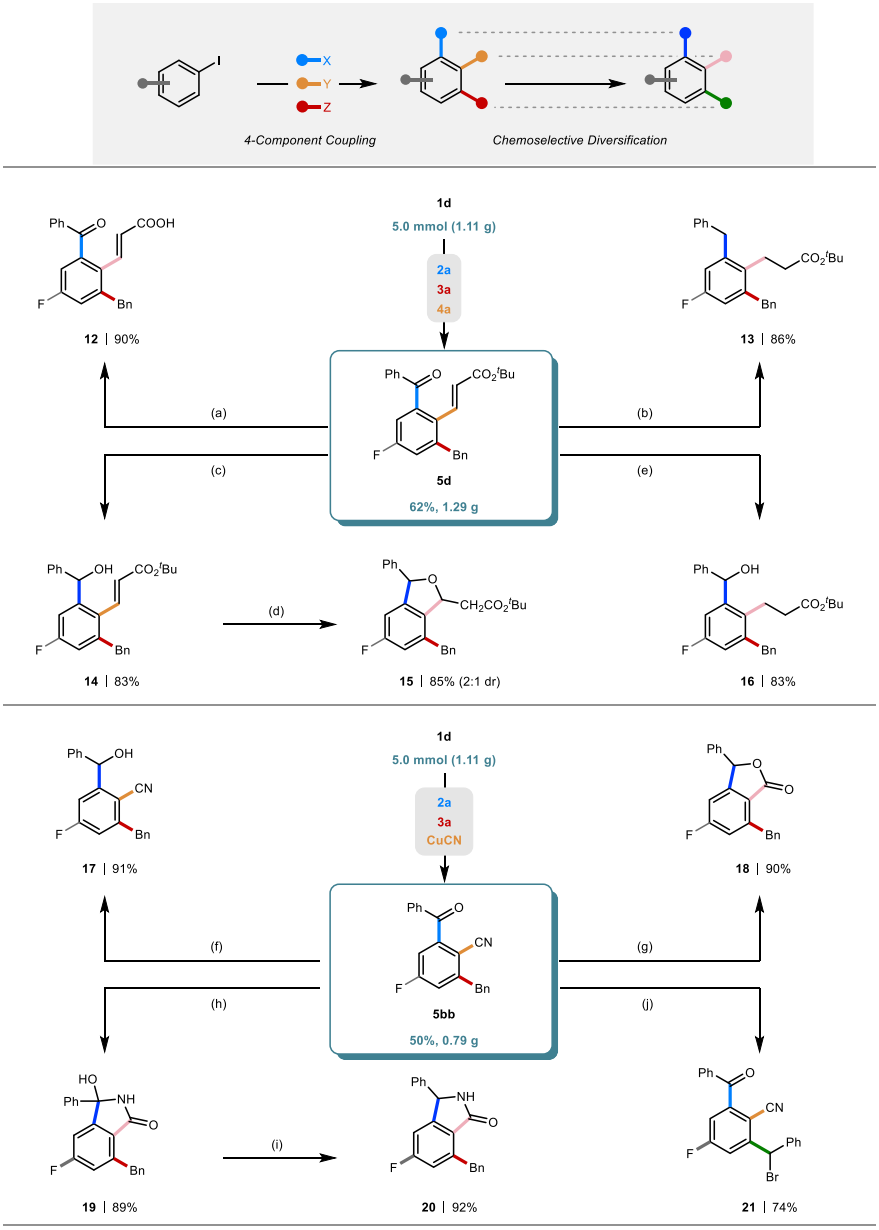
Figure 3. Substrate Scope with *meta*-Substituted Aryl Iodides

9 (0.3 mmol), **2a** (0.45 mmol), **3a** or **MeI** (0.45 mmol), **4a** or **CuCN** (0.36 mmol), $PdCl_2$ (0.03 mmol), P(2-furyl)$_3$ (0.06 mmol), NBE (0.6 mmol), Cs_2CO_3 (1.2 mmol) in 1,4-dioxane at 90°C. All yields are isolated yields.[a]2.0 equiv **4a** was used.[b]THF was used instead of dioxane.[c]Mixture of regioisomers: see Supplemental Information for details.[d]2.0 equiv **2a** and **3a** were used.

relatively simple vinyl acid (**12**) to the increasingly functionalized dihydroisofuran. (**15**) The value of incorporating a nitrile at C1 becomes apparent upon chemoselective hydration or reduction of **5bb**, which leads to complementary lactone (**18**) or isoindolinones (**19** and **20**). Finally, chemoselective oxidation of the benzylic group affords benzylic bromide (**21**) and completes a selection of transformations that selectively manipulates each of the three newly introduced groups.

Conclusion

In this work, we have demonstrated that simple *meta*- and *para*-substituted iodides are effective coupling partners in 4-component Catellani reactions. These



Scheme 3. Synthetic Utility

Reaction conditions:

(A) **5d** (0.3 mmol), TFA (1.8 mmol), in DCM (2.0 mL) at room temperature (RT) for 15 h.

(B) **5d** (0.2 mmol), Pd/C (0.4 mmol) in EtOH (2.0 mL) at 80°C for 48 h under 15 atm of hydrogen.

(C) **5d** (0.5 mmol), $CeCl_3 \cdot 7H_2O$ (0.52 mmol) in MeOH (4.0 mL) at −20°C for 10 min; then $NaBH_4$ (1.0 mmol) was added, warm to RT for 12 h.

(D) **14** (0.3mmol), NaH (0.9 mmol) in THF at RT for 12 h.

(E) **5d** (0.2 mmol), Pd/C (0.2 mmol) in MeOH (4.0 mL) at 80°C for 48 h under 15 atm of hydrogen.

(F) **5bb** (0.2 mmol), Pd/C (0.05 mmol) in MeOH (4.0 mL) at 50°C for 15 h under 10 atm of hydrogen.

(G) **5bb** (0.6 mmol), $NaBH_4$ (0.6 mmol) in EtOH (3.0 mL) at 50°C for 1 h, then cooled to 20 °C for 24 h; 2N HCl until weakly acidic reaction, H_2O (90.0 mL) at 100°C for 0.5 h.

(H) **5bb** (0.6 mmol), KOH (0.02 mmol) in MeCN (6.0 mL) and H_2O (0.6 mL) at RT for 3 h.

(I) **19** (0.3 mmol), triethylsilane (3.0 mmol), trifluoroboron etherate (1.0 mmol) in DCM (3.0 mL) at −15°C for 2 h.

(J) **5bb** (0.2 mmol), NaOH (0.2 mmol) in DCM (2.0 mL); then Br_2 (0.2 mmol) in DCM (3.0 mL) was added, refluxed at 40°C for 6 h.

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conditions provide many opportunities for the efficient and diversifiable synthesis of aromatic rings with up to 6 distinct substituents. They also set the stage for complementary diversification reactions, providing an efficient means of diversifying chemical space around a common aromatic core. Historically, simple aromatic iodides lacking an *ortho* substituent have been incompatible with standard Catellani protocols, giving rise to the well-known "*ortho* effect." By careful analysis of the remote-steric interactions that give rise to this effect, we have discovered that these substrates are in fact compatible with selective Catellani protocols and that they can be used in a higher-order, multicomponent coupling with good levels of control. Over the course of exploring the reaction's scope, we observed a correlation between the selectivity in the Pd-(II)/(IV) **OA** and the nature of a *meta*-substituent on the aromatic ring. This correlation serves as a reminder that the aryl iodide is both a substrate and a ligand in the Catellani process and that its steric and electronic properties change over the course of the reaction. Given the multitude of effects that exist for increasingly sophisticated substrates, we see many future opportunities to investigate and expand the currently accessible substitution patterns. We hope that the observation of these effects will help others interested in expanding the Catellani toolbox and also those more generally interested in the remote and often subtle effects that control aromatic C–H functionalization.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xinjun Luan (xluan@nwu.edu.cn).

Materials Availability

All unique reagents generated in this study are available from the lead contact without restriction.

Data and Code Availability

Crystallographic data have been deposited in the Cambridge Crystallographic Data Center under accession number CCDC: 1989038, 1989075, 1989077, 1989081, 1989082, 1989090, 1989092, 1989098, 1989103, 1989104, 1989105, 1989106, 1989108, 1989109, 1989110, and 1989112.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.06.021.

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AUTHOR CONTRIBUTIONS

J.W. carried out the reaction exploration. J.W. and C.Q. investigated the substrate scope and application. X.L. and J.L. directed the project and wrote the manuscript with input from all of the authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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