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Entry to 1,2,3,4-Tetrasubstituted Arenes through Addressing the "*Meta* Constraint" in the Palladium/Norbornene Catalysis

Jianchun Wang[†‡], Yun Zhou[†‖‡], Xiaolong Xu[†#], Peng Liu[§], and Guangbin Dong*[†]

[†] Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States

[‖] Department of Applied Chemistry, China Agricultural University, Beijing 100193, China

[#] School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China

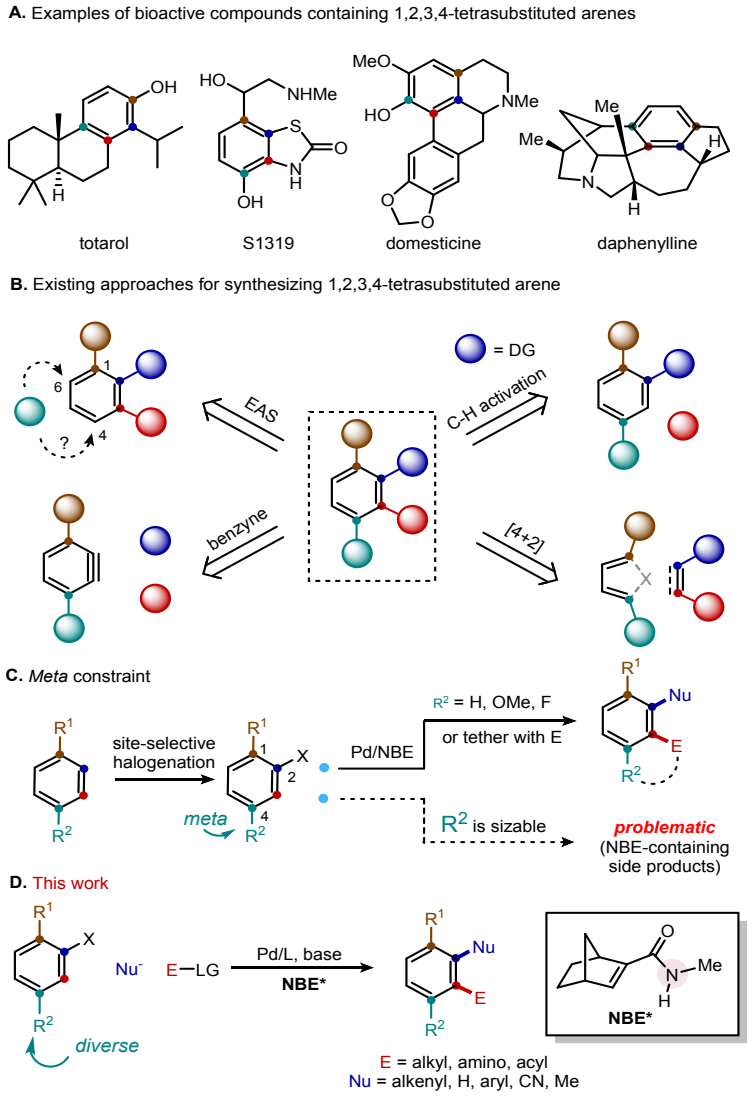
[§] Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

ABSTRACT: Arenes with four different contiguous substituents, i.e. 1,2,3,4-tetrasubstituted arenes, are commonly found in bioactive compounds, but they are non-trivial to access via conventional methods. Through addressing the "*meta* constraint" in the palladium/norbornene (Pd/NBE) cooperative catalysis, which is the difficulty of tolerating a sizable *meta* substituent in aryl halide substrates, here a modular and regioselective approach is realized for preparing 1,2,3,4-tetrasubstituted arenes. One key is the use of a C2-amide-substituted NBE, and a combined experimental and computational study reveals its role in promoting the NBE insertion and the *ortho* C−H metalation steps. The scope is broad: a variety of electrophiles and nucleophiles could be introduced to the *ortho* and *ipso* positions, respectively, with 1,4-disubstituted aryl halides, leading to diverse unsymmetrical contiguous tetrasubstituted arenes. Application of this approach has been demonstrated in streamlined syntheses of several bioactive compounds.

INTRODUCTION

Polysubstituted arenes commonly exist in natural products, pharmaceuticals and agrochemicals (Scheme 1A).[1] While numerous effective arene functionalization approaches have been developed to date, it is non-trivial to regioselectively construct unsymmetrical contiguous tetrasubstituted arenes, i.e. 1,2,3,4-tetrasubstituted benzenes, with each substituent being different (Scheme 1B).[2] For example, electrophilic aromatic substitution (EAS) of a 1,2,3-trisubstituted arene could encounter a site-selectivity issue (C4 vs C6 positions). In addition, directed C−H activation strategies[3] could provide the desired site-selectivity yet the use of a directing group (DG) is required. The aryne chemistry offers a unique opportunity for vicinal difunctionalization, but, to generate benzynes from aromatic substrates, it typically requires either strong bases or pre-difunctionalized arenes.[4] Apart from arene functionalization methods, the 1,2,3,4-tetrasubstituted arenes could also be prepared via the Diels−Alder reaction, though it has been challenging to control regioselectivity for unsymmetrical substrates.[5] Hence, a modular and general approach to access aromatic compounds that contain four contiguous different substituents remains highly sought after.

Scheme 1. Synthesis of 1,2,3,4-tetrasubstituted arenes

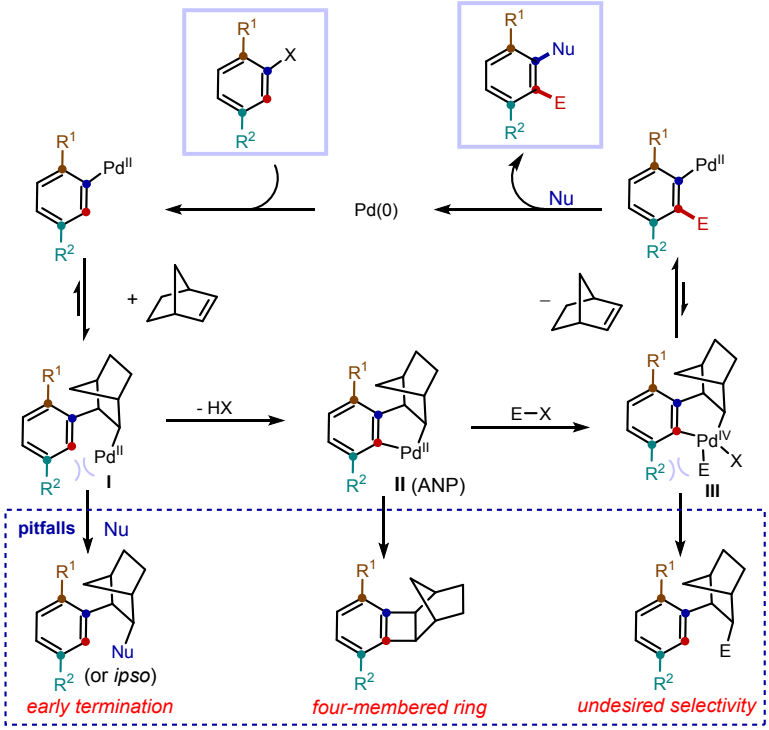


The palladium/norbornene (Pd/NBE) cooperative catalysis, originally discovered by Catellani,[6] has emerged as a useful approach for site-selective arene functionalization.[7] In principle, electrophilic halogenation of common 1,4-disubsitituted arenes followed by the Catellani-type reaction could afford the desired 1,2,3,4-tetrasubstituted arenes in a regioselective manner. However, such an approach has been held back largely due to an intrinsic limitation of the Pd/NBE catalysis, namely the "*meta* constraint" (Scheme 1C).[8] That is, substitution at the C4 *meta* position (R^2) can greatly hamper the efficiency of the *ortho* functionalization and often lead to NBE-attached side products or direct *ipso* substitution, with a few exceptions such as using tethered electrophiles (pioneered by Lautens[9]) or very small *meta* substituents[10] (e.g. F and OMe). The "*meta* constraint" can be quite significant: even a methyl group[11] or a moderately strong electron-withdrawing group, such as an ester moiety, at the C4 position could greatly inhibit the Catellani pathway.[8] Therefore, to enable the Pd/NBE catalysis to be a general and useful method for constructing 1,2,3,4-tetrasubstituted arenes from readily available 1,4-disubsitituted arenes, the *meta* constraint ought to be addressed. Herein, we describe the initial development of a unique catalytic system that can tolerate *meta* substituents with various steric and electronic properties in the

Pd/NBE catalysis. This approach provides a convenient entry to diverse 1,2,3,4-tetrasubstituted arenes in a modular fashion.

Compared with regular haloarene substrates without a *meta* substituent (R^2 = H), the challenge of using the C4 *meta*-substituted ones is three-fold (Scheme 2). First, formation of the key aryl-norbornyl-palladacycle (ANP) intermediate (**II**) would be more difficult due to the increased steric hindrance to access the *ortho* C−H bond via concerted metallation deprotonation (CMD),[8] which could lead to an early *ipso* termination with the nucleophile. Second, even though the *ortho* metallation could be successful, the bulkiness around ANP would hinder its reaction with the electrophile (E-X), which would promote direct reductive elimination to form the norbornyl-benzocyclobutene side products.[12] Third, the reductive elimination from the proposed Pd(IV) intermediate **III** could have a selectivity issue due to the eclipsing interaction between the *meta* substituent and the E moiety, which could introduce the E group to the norbornyl part.[13]

Scheme 2. Challenges for overcoming the "*meta* constraint"

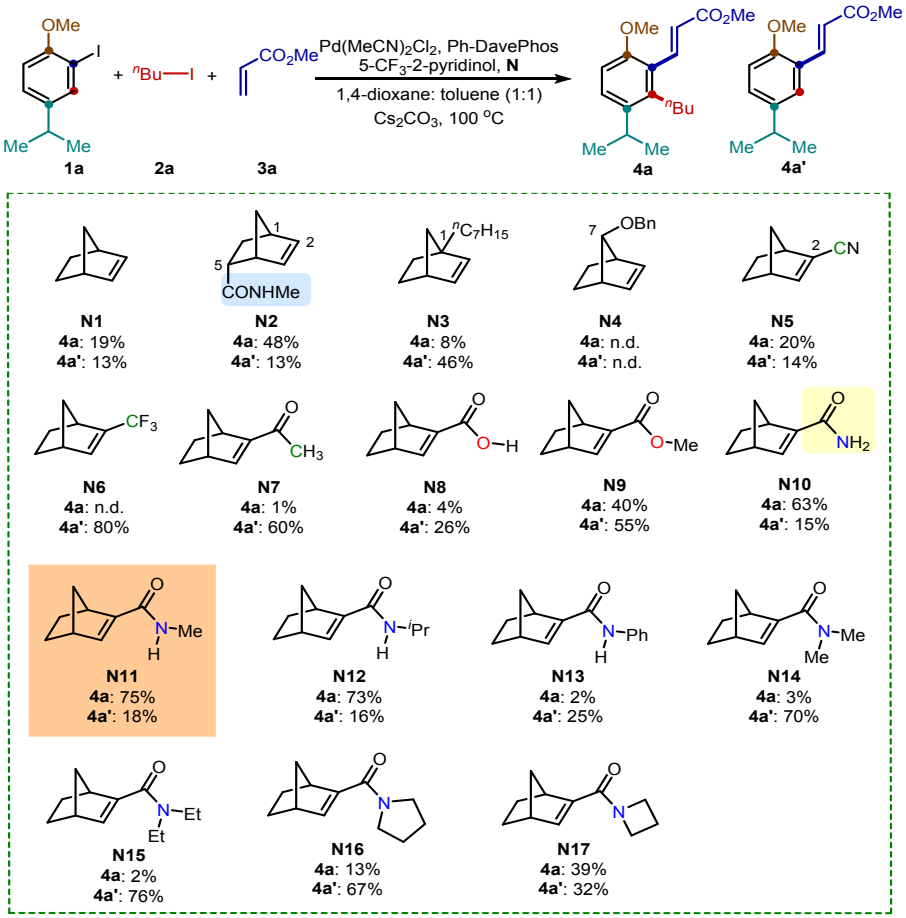


RESULTS AND DISCUSSION

To seek solutions to the *meta* constraint, it was clear that the steric and electronic properties of the X-type and L-type ligands on the Pd, as well as the structure of the NBE cocatalyst, would play critical roles. To explore the feasibility, substrate **1a** bearing a bulky isopropyl group at the C4 position *meta* to the iodide was chosen as the standard substrate, and *ortho* alkylation/*ipso* Heck reaction was chosen as the model reaction.[6,14] Not

surprisingly, under the previously reported conditions, only a trace amount of the desired product **4a** was observed. After carefully examining various phosphine ligands and additives, 19% yield of **4a** was afforded with simple NBE (**N1**) and the direct Heck product **4a'** and the corresponding norbornyl benzocyclobutene was found as the major side product. The structurally modified NBEs were then investigated. Interestingly, the C5-amide-substituted NBE (**N2**) gave a notably better performance,[15] though the exact reason is unclear. In contrast, C1- or 7-subsituted NBEs (**N3** and **N4**) were ineffective.[16] For C2-substituted NBEs, we anticipated that electronic effect could have a pronounced impact on their reactivity (*vide infra*, Table 4). While NBEs with cyano (**N5**), trifluoromethyl (**N6**), methyl ketone (**N7**), and carboxylic acid (**N8**) groups at 2-positions were not effective, the methyl ester substituted NBE (**N9**), pioneered by the Yu group,[17] gave the desired product in 40% yield, albeit still favoring the direct Heck product **4a'** in 55% yield. Gratifyingly, amide-substituted NBEs (**N10-N12**)[18] were found more reactive and selective for the desired product. While the *N*-methyl amide-substituted NBE (**N11**) proved to be optimal, the free NH_2 and *N*-^{i}Pr amide-derived NBEs (**N10** and **N12**) were also effective. The *N*-phenyl amide-substituted NBE (**N13**) would lead to undesired C−H activation on the phenyl ring, while bulky tertiary amides (**N14**−**N17**) were less reactive.

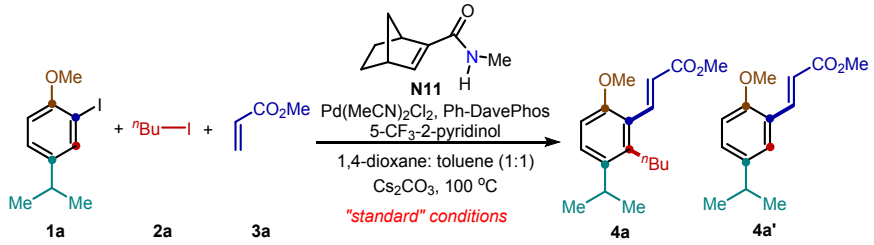
Table 1. NBE Effect for the *meta*-Substituted Aryl Iodide[a,b]



[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), **3a** (0.15 mmol), $Pd(MeCN)_2Cl_2$ (0.01 mmol), Ph-DavePhos (0.01 mmol), **N** (0.10 mmol), 5-CF_3-2-pyridinol (0.02 mmol), Cs_2CO_3 (0.30 mmol), 100 °C, 16 h. [b] Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. Ph-DavePhos: 2-Diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl.

A series of control experiments were subsequently conducted to understand the role of each reactant (Table 2). In the absence of the Pd or **N11**, no desired product was formed (entries 2 and 3). The "ligandless" conditions gave a much lower yield (entry 4). $Pd(MeCN)_2Cl_2$ was slightly more active than $Pd(OAc)_2$ (entry 5), while Ph-DavePhos was more effective than the commonly used P(2-furyl)$_3$ (entry 6). Consistent with the previous studies,[14,18] the use of a weaker base decreased the yield (entry 7). 5-Trifluoromethyl-2-pyridinol, previously employed by Yu to promote CMD processes,[19] is more efficient than pivalic acid (entries 8 and 9). Moreover, instead of using a mixed solvent, 1,4-dioxane or toluene alone were not as efficient (entries 10 and 11). While stoichiometric NBE was used to suppress the competing direct Heck reaction, 80 mol% of **N11** can be recovered. Reduction of the **N11** loading to 50 mol% still afforded a 59% yield of the desired product (entry 12).

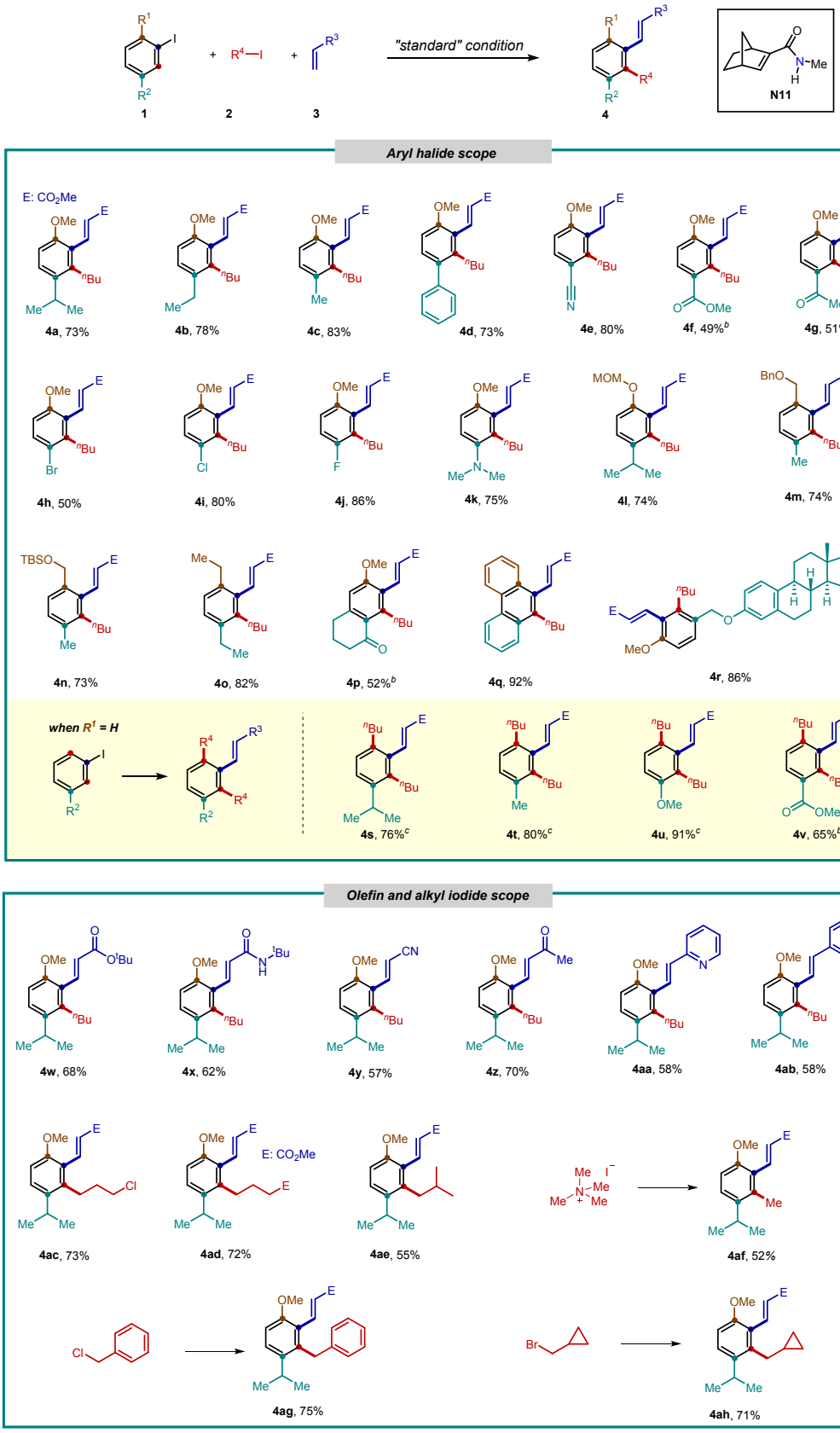
Table 2. Control Experiment[a,b]



Entry	Variations from the "standard" conditions	Yield of **4a** (%)	Yield of **4a'** (%)
1	none	75[c]	18
2	no $Pd(MeCN)Cl_2$	n.d.	n.d.
3	no **N11**	n.d.	80
4	no Ph-DavePhos	30	33
5	$Pd(OAc)_2$ instead of $Pd(MeCN)_2Cl_2$	69	15
6	P(2-furyl)$_3$ instead of Ph-DavePhos	26	26
7	K_2CO_3 instead of Cs_2CO_3	40	36
8	no 5-CF_3-2-pyridinol	n.d.	45
9	PivOH instead of 5-CF_3-2-pyridinol	24	18
10	1,4-dioxane alone	64	32
11	toluene alone	27	26
12	50 mol% of **N11**	59	29

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), **3a** (0.15 mmol), $Pd(MeCN)_2Cl_2$ (0.01 mmol), Ph-DavePhos (0.01 mmol), **N11** (0.10 mmol), 5-CF_3-2-pyridinol (0.02 mmol), Cs_2CO_3 (0.30 mmol), 100 °C, 16 h. [b] Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c] 80 mol% of **N11** was recovered after the reaction.

Table 3. Substrate Scope[a]

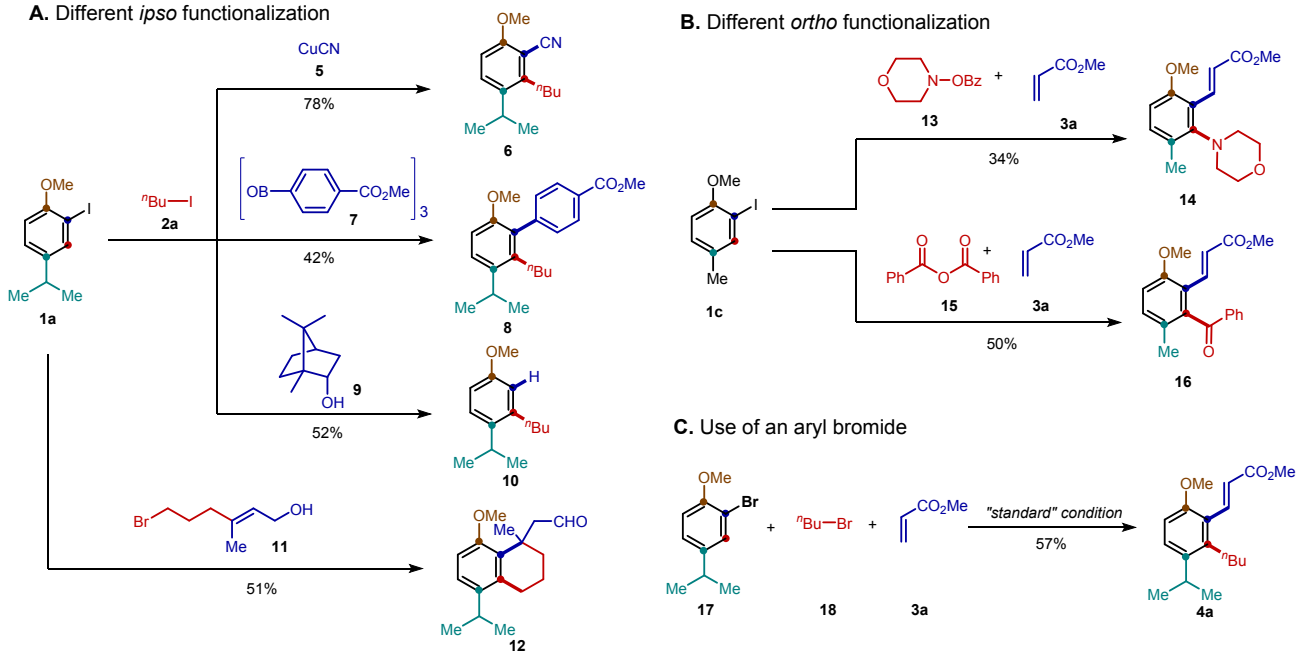


[a] Reaction conditions: **1** (0.30 mmol), **2** (0.90 mmol), **3** (0.45 mmol), $Pd(MeCN)_2Cl_2$ (0.03 mmol), Ph-DavePhos (0.03 mmol), **N11** (0.30 mmol), 5-CF_3-2-pyridinol (0.06 mmol), Cs_2CO_3 (0.90 mmol), 100 °C, 16 h. [b] K_2CO_3 was used instead of Cs_2CO_3. [c] Cs_2CO_3 (1.80 mmol) was used.

Substrate scope. With the optimized conditions in hand, the scope of iodoarenes was studied first (Table 3). First, various *meta* substituents with different steric and electronic properties could be tolerated. Not surprisingly, reduction of steric hindrance from an isopropyl to a methyl group increased the yield (**4a**−**4c**). Phenyl group (**4d**) and electron-withdrawing moieties, such as nitrile (**4e**), methyl ester (**4f**), methyl ketone (**4g**), aryl bromide (**4h**), aryl chloride (**4i**) and aryl fluoride (**4j**) were tolerated.[20] Strongly electron-donating and bulky dimethylamine substrate (**4k**) still afforded a good yield. Besides anisole derivatives, other types of substituents (**4l**−**4o**) at the *ortho* position (R^1) were also suitable. Functional groups, such as MOM, benzyl and TBS ethers, were compatible. In addition, aryl iodides derived from α-tetralone (**4p**), phenanthrene (**4q**), and estrone (**4r**) were all competent substrates. Notably, in the absence of *ortho* substituents, double *ortho* functionalizations could take place to afford 1,2,3,4-tetrasubstituted arenes from 3-substituted iodobezenes (**4s**−**4v**).

The scope of olefins and electrophiles was examined next. Various Michael acceptors including *tert*-butyl acrylate, *N*-*tert*-butylacrylamide, acrylonitrile and methylvinyl ketone, and 2-vinylpyridine were smoothly coupled at the *ipso*-position (**4w**−**4aa**). Less electron-deficient regular styrene (**4ab**), could also be employed. For the electrophiles, primary alkyl iodides with different functional groups, such as chloride (**4ac**), methyl ester (**4ad**) and cyclopropane (**4ah**), can be employed. The use of more sterically hindered alkyl halides led to a lowered yield (**4ae**), while secondary alkyl iodides were unreactive under the current condition. It is worthy to note that methylation (**4af**) and benzylation (**4ag**) products could also be obtained using the less reactive phenyltrimethylammonium salt[18] and benzyl chloride, respectively.

Scheme 3. Extension of the reaction scope[a]



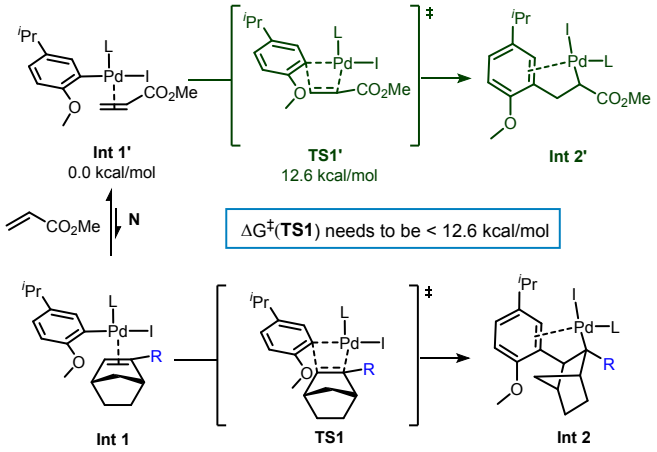
[a] For detailed reaction conditions, see Supporting Information.

To demonstrate the modularity and generality of the synthetic strategy for 1,2,3,4-tetrasubstituted arenes, different *ipso* couplings were then investigated (Scheme 3A). In addition to Heck coupling, preliminary success was obtained with cyanation (**6**),[9c] Suzuki quench (**8**),[21] and hydrogenation (**10**),[10c] allowing for installation of a cyanide group, an aryl group or hydrogen, respectively, at the *ipso* positions. Besides intermolecular reactions, an intramolecular redox-Heck coupling at the *ipso* position could also be achieved (**12**),[22] when an allylic alcohol moiety was tethered with the alkyl iodide. Apart from alkyl electrophiles, *ortho* amination (**14**)[23] and *ortho* acylation (**16**)[15,24] reactions could also be achieved at this stage using *O*-benzoyl hydroxylamine and benzoyl anhydride as the electrophiles, respectively (Scheme 3B), albeit with moderate yields. Further, besides using aryl iodides, a promising level of reactivity has also been observed with aryl bromide **17** as the substrate, in which alkyl bromide **18** was employed as the electrophile instead under otherwise the standard conditions (Scheme 3C).[25]

Study of the NBE effect. Elucidation of the effect of substituted NBEs that underlies different activities may serve as a foundation for discovery of more effective NBE co-catalysts, which in turn could enable new capability. Hence, a combined experimental and computational investigation was undertaken to understand the beneficial role of the amide-substituted NBE (**N11**) in the context of addressing the "*meta* constraint". It is worth mentioning that, similar to the previous finding,[18] Ph-DavePhos was first transformed into the corresponding cyclized phosphafluorene under the reaction conditions, which was the actual ligand and therefore used in our DFT study.

When using 2-substituted NBEs as co-catalysts, one major side-product was the direct Heck product (**4a'**), which potentially comes from the competitive migratory insertion of methyl acrylate **3a**. Thus, we first investigated the electronic and steric effects of the 2-substituent on the NBE binding and migratory insertion steps via DFT calculation (Table 4). Previously, when studying the migratory insertion of *para*-substituted vinylarenes into palladium-methyl bonds, Brookhart and coworkers found that electron-deficient styrenes bind weaker to Pd, but meanwhile could facilitate the migratory insertion step.[26] This observation parallels the trend found in the computational study of the NBE insertion step. Strongly electron-withdrawing substituents like CF_3 (σ_p = 0.54) and CN (σ_p = 0.66) greatly disfavor the NBE binding (ΔG(**Int 1**)). The higher energies required to bind these electron-deficient NBEs lead to higher overall migratory insertion activation barriers with respect to **Int 1'** ($\Delta G^{\ddagger}$(**TS1**)). As a result, these NBEs mainly afforded the direct Heck product (**4a'**) via **TS1'**. The same trend was observed among NBEs with moderately electron-withdrawing substituents, such as CONHMe (σ_p = 0.36), CO_2Me (σ_p = 0.45), and COMe (σ_p = 0.50): the overall insertion ($\Delta G^{\ddagger}$ (**TS1**)) is the fastest with the least electron-withdrawing substituent, i.e. CONHMe, due to the more favorable NBE binding. It should be noted that CONHMe-substituted NBE **N11** even gave a lower overall insertion barrier than unsubstituted NBE **N1**. This is because, although **N11** requires slightly more energy to coordinate with Pd, the rate of the subsequent migratory insertion step ($\Delta G^{\ddagger}$ (**TS1**) − ΔG (**Int 1**)) is significantly accelerated by the weakly electron-withdrawing substituent. Hence, the CONHMe substituent exhibits the most favorable overall NBE-insertion barrier through balancing the opposite electronic requirements in the NBE binding and migratory insertion steps.

Table 4. Computed NBE Binding Energies and Overall Olefin-Insertion Barriers[a]



NBE	R	ΔG (**Int 1**)	$\Delta G^{\ddagger}$ (**TS1**)
N11	CONHMe	1.0	**10.1**
N12	CONH^{i}Pr	1.0	10.4
N1	H	0.1	**11.8**

N17	$CON(CH_2)_3$	2.4	11.9
N9	CO_2Me	2.4	12.1
N7	COMe	3.6	12.3
N13	CONHPh	1.0	12.6
N5	CN	4.6	13.2
N16	$CON(CH_2)_4$	4.1	13.9
N6	CF_3	5.8	14.2
N14	$CONMe_2$	5.5	14.6

[a] All energies are with respect to **Int 1'** and in kcal/mol. Calculations were performed at the M06/SDD-6-311+G(d,p)-SMD(1,4-dioxane)//B3LYP/LANL2DZ-6-31G(d) level of theory. L is *N*,*N*-dimethyl-5-phenyl-5H-benzo[b]phosphindol-1-amine.

Besides electronic effects, steric effects of the 2-substituent are also expected to play an important role in dictating the NBE insertion activity. Experimentally, compared to secondary amides (**N11** and **N12**), tertiary amides (**N14**–**N17**) were generally less reactive and gave more direct Heck product **4a'**. The computational results are in agreement with the experimental observations (Table 4). In the migratory insertion transition states (**TS1**) with **N16** and **N14**, this steric effect is evidenced by the short distances between the alkyl group on the amide nitrogen and the norbornyl skeleton (2.01 Å and 2.19 Å, respectively). Such a destabilizing steric effect is absent in the transition state **TS1** for the secondary amide **N11** and **N12.**

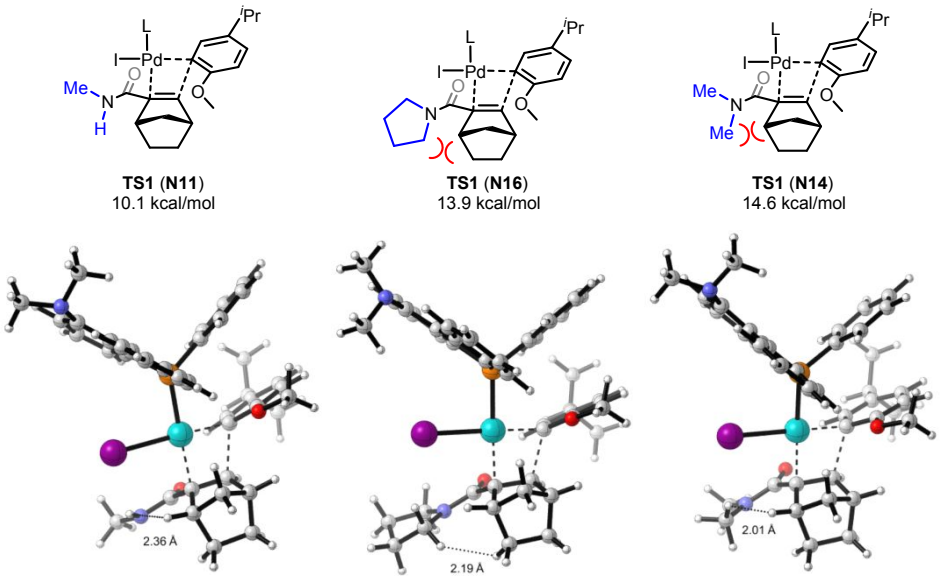


Figure 1. Migratory-insertion transitions states with **N11**, **N16**, and **N14**. L is *N*,*N*-dimethyl-5-phenyl-5H-benzo[b]phosphindol-1-amine.

To understand why amide-substituted **N11** is more effective than ester-substituted **N9** or simple NBE **N1**, the initial reaction rates with these NBEs were measured via kinetic analysis (Figure 2).[27] It is clear that ester-NBE **N9** and **N1** showed similar initial rates in forming the desired product **4a**; however, the one with **N11** is 5.7 times faster. On the other hand, these three NBEs showed comparable initial rates for forming the Heck side product (**4a'**). Note that besides **4a'**, the simple NBE (**N1**) also gave various other side products (*vide supra*, Scheme 2).

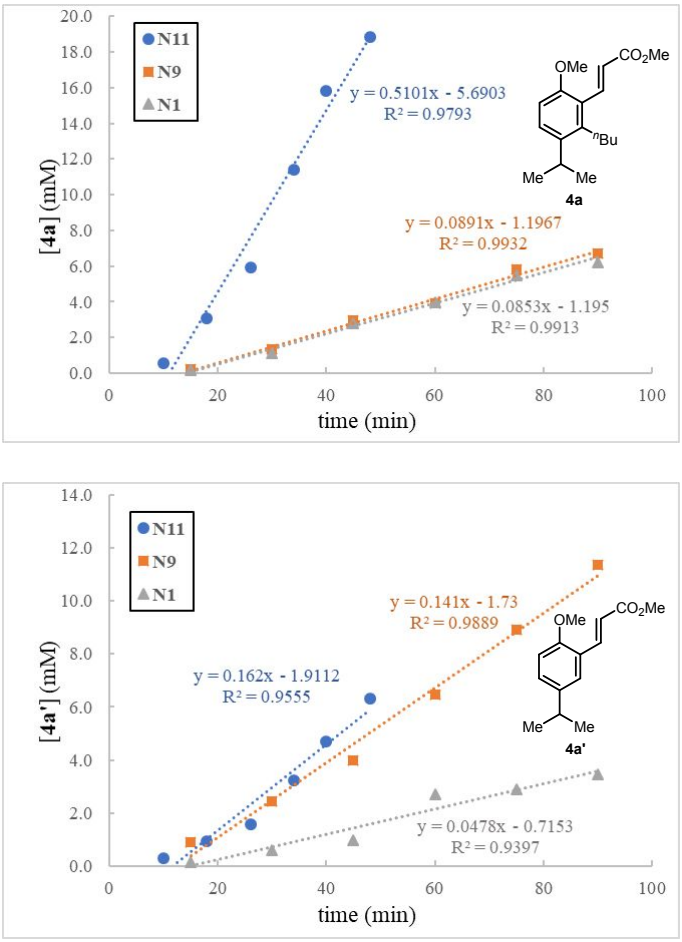


Figure 2. Formation of **4a** (top) and **4a'** (bottom) over time with different NBEs under the standard conditions.

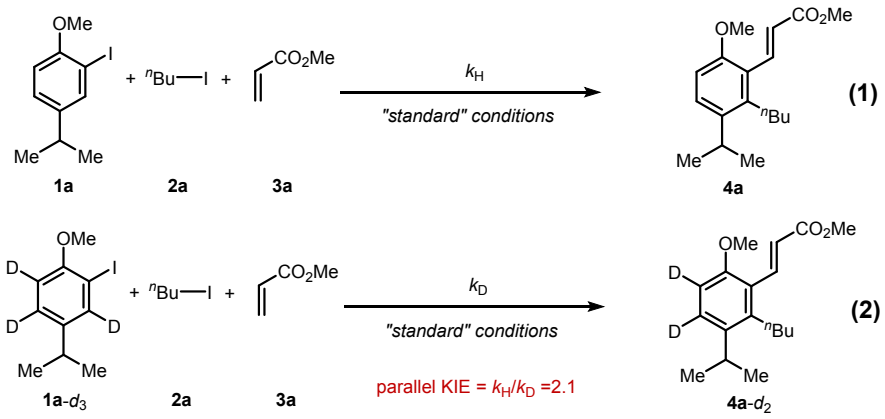
To understand the origin of such rate acceleration with amide-substituted **N11**, a series of kinetic studies were undertaken to probe the turnover-limiting step (TLS). First, the kinetic order of NBEs showed pseudo zero-order rate dependence of [**N11**] or [**N9**] for forming the desired product **4a**, but a negative rate dependence (inverse first order) for the direct Heck reaction (Table 5). These data suggest that migratory insertion into NBE **N11** or **N9** is *not* the TLS in this reaction, and a higher NBE concentration can suppress the undesired direct Heck pathway. Second, the rate of reaction shows pseudo zero-order dependencies on [**1a**] and [5-CF_3-2-pyridinol], but first-order dependence on the concentration of Pd and ligand, [Pd/Ph-DavePhos] (see Supporting Information for

details). These data indicate that the TLS does not involve oxidative addition of aryl iodide **1a** or ligand exchange with 5-CF_3-2-pyridinol. Third, a primary kinetic isotopic effect (KIE) of 2.1 was observed by conducting two parallel reactions with **1a** and **1a**-d_3 (eq 1 and 2). Such a KIE value is close to those found in other Pd-catalyzed sp^2 C−H activation reactions with CMD (*ortho* C−H palladation) being the TLS.[28]

Table 5. The rate dependence of the NBE concentration[a]

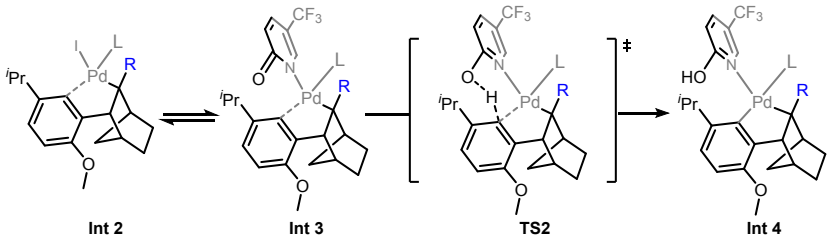
NBE loading	N11		N9	
	d[**4a**]/dt	d[**4a'**]/dt	d[**4a**]/dt	d[**4a'**]/dt
100 mol%	0.510	0.162	0.089	0.141
50 mol%	0.483	0.250	0.101	0.256
25 mol%	0.508	0.456	0.112	0.390

[a] Rates are in mM/min.



To understand why the amide-substituted **N11** is beneficial during the TLS of the Catellani reaction, the energy profile of the complete catalytic cycle was then computed by DFT (see Supporting Information for details). The computational study indicates that the TLS of this reaction is the CMD step (**TS2**), which is consistent with the above kinetic results. In line with the comparison experiments in Figure 2, the computed energy barrier of **TS2** is 1.1 kcal/mol lower for **N11** than that for **N9** (Figure 3). Unexpectedly, analysis of the transition state structure with **N11** revealed a hydrogen bonding interaction between the N−H bond of the amide moiety and the oxygen of 5-CF_3-2-pyridinol that approaches the C−H bond. Such a hydrogen bonding interaction is evidenced by the short H···O distance (2.24 A) and the bond angle (145.7˚), which fall in the range of favorable O···H···N hydrogen bonding interactions.[29] The NPA (natural population analysis) charge calculations indicated the oxygen has a negative charge of -0.730 and the hydrogen has a positive charge of +0.410, supporting the favorable electrostatic interactions in the hydrogen bonding.

Taken all these mechanistic studies together, the merits of the CONHMe substituent on **N11** could be three-fold: (1) the balanced electronic and steric effect on the NBE scaffold accelerates the 2π insertion step; (2) the ability to form hydrogen bonding further stabilizes the transition state of the CMD step, which is the TLS of the reaction; (3) the presence of the C2-substituent inhibits formation of the benzocyclobutene side-product, consistent with the previous experimental[17] and computational[30] studies.



	experimental	*computed*
NBE	d[**4a**]/dt	$\Delta G^{\ddagger}$(**TS2**)
N11	0.510	24.9
N9	0.089	26.0

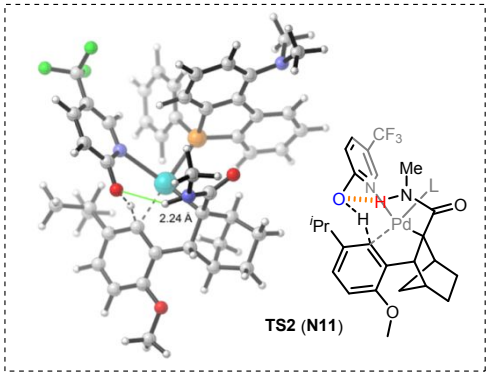
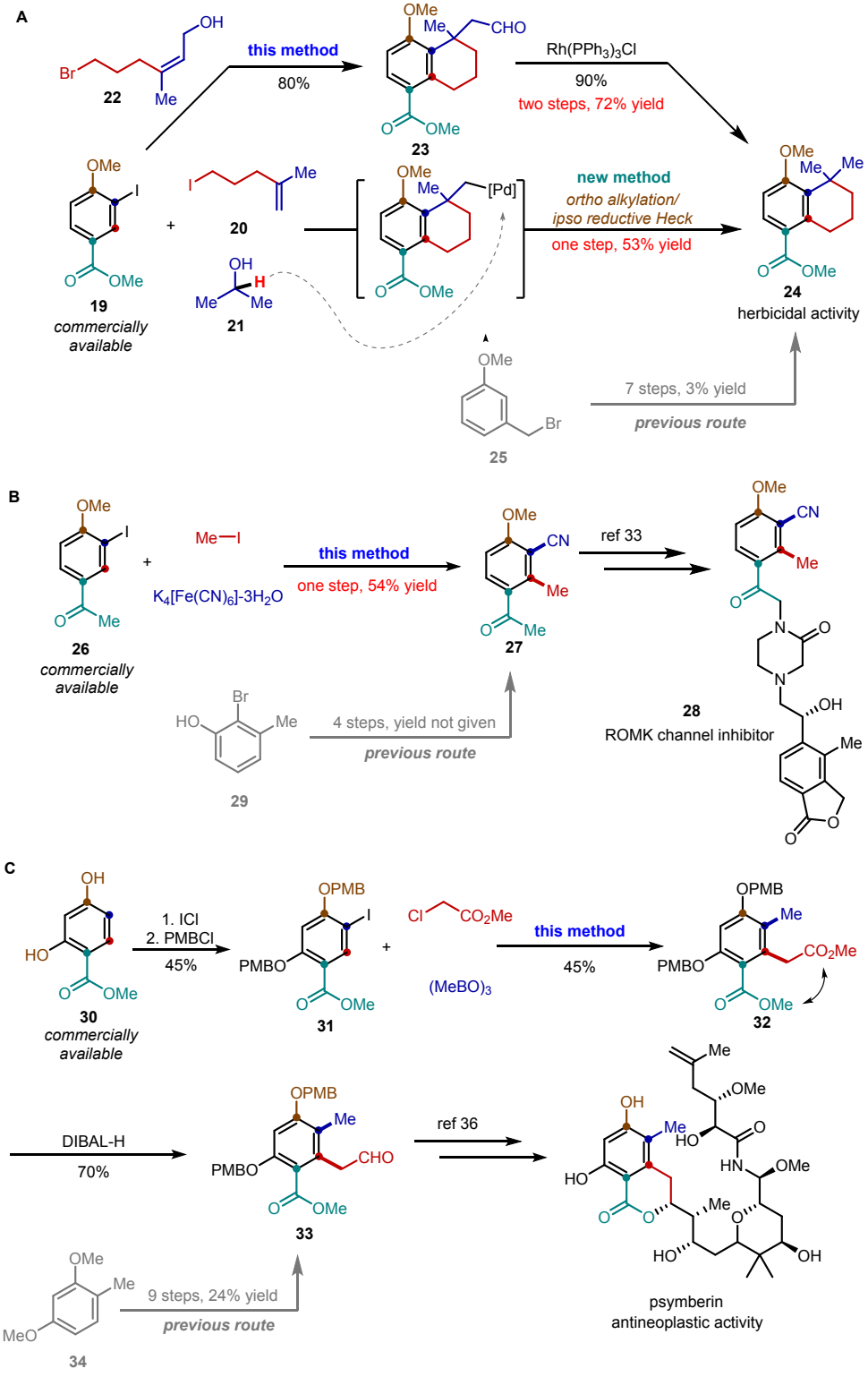


Figure 3. The computed transition states for the CMD step, which is the TLS. Experimentally determined rates are in mM/min, and computed activation free energies are in kcal/mol. L is *N*,*N*-dimethyl-5-phenyl-5H-benzo[b]phosphindol-1-amine.

Synthetic application. Finally, the synthetic utility of this strategy was evaluated. Given the wide presence of 1,2,3,4-tetrasubstituted aryl moieties in various bioactive compounds, we anticipated that this Catellani reaction-based approach could be useful to streamline syntheses of established target molecules. For example, tetrahydronaphthalene **24** is a known compound with promising herbicidal activity, which was originally prepared in 7 steps with a 3% overall yield from benzyl bromide **25**.[31] Now, compound **24** can be prepared in one or two steps from commercially available aryl iodide **19** (Scheme 4A). Through an *ortho* alkylation followed by intramolecular *ipso* redox-Heck-relay reaction,[22] the corresponding aldehyde (**23**) was obtained in 80% yield. The following Tsuji−Wilkinson decarbonylation[32] provided the target compound (**24**) in an excellent yield. Alternatively, a *previously unknown ipso reductive Heck reaction* was developed here to further streamline the synthesis. Using an alkene-tethered alkyl iodide (**20**) as the coupling partner, 2-propanol was found to be effective to terminate the final alkyl-Pd(II) intermediate, directly leading to the desired *tert*-alkyl-substituted arene product (**24**).

Scheme 4. Applications in the synthesis of bioactive compounds



In the second case, compound **28** is an effective inhibitor of the ROMK (renal outer medullary potassium) channel and a pharmaceutical candidate for treating cardiovascular diseases. This compound can be synthesized from a 1,2,3,4-tetrasubstituted aryl intermediate (**27**) that previously required four steps of

preparation from a trisubstituted phenol **29**.[33] Employing the *ortho* methylation/*ipso* cyanation chemistry, the same intermediate was conveniently accessed in a single step (Scheme 4B). In this case, $K_4[Fe(CN)_6]\cdot 3H_2O$[9c] was found to be a better cyanide source than CuCN, and simple methyl iodide was more effective for the *ortho* methylation[9c,34] than the phenyltrimethylammonium salt.

In the third example, psymberin, a cytotoxic natural product isolated from the marine sponge *Psammocinia* sp., displays strong antineoplastic activities (Scheme 4C).[35] In the existing route, the key penta-substituted aromatic intermediate (**33**) was synthesized in 9 steps involving a directed *ortho* allylation.[36] Using the Pd/NBE catalysis strategy, a four-step sequence was realized to access compound **33**. Aryl iodide **31**, prepared in two steps from commericaly available diphenol **30**, underwent the *ortho* alkylation/*ipso* Suzuki coupling, to install two alkyl groups at the *ortho* and *ipso* positions simultaneously. While product **32** contains two methyl ester moieties, it was found that the alkyl-derived one was more reactive and can be chemoselectively reduced to the corresponding aldehyde, which offers a simplified synthetic route to intermediate **33**.

CONCLUSION

In conclusion, a unique amide-substituted NBE has been identified as an effective promoter to overcome the long-standing "*meta* constraint" in the Pd/NBE catalysis. Consequently, the selective *ortho*/*ipso* difunctionalization of various aryl halides with sizable *meta* substituents provides a modular and efficient strategy for constructing unsymmetrical contiguous tetrasubstituted arenes, which are challenging to be prepared with conventional approaches. The broad reaction scope and excellent chemoselectivity could make this method attractive for preparing complex arene-containing compounds with high biological significance. Detailed experimental and computational studies revealed the roles of the amide substituent on the NBE in facilitating the migratory insertion and *ortho* palladation steps, which could have broader implications in the future design of more effective NBE co-catalysts. Further improvements of the reaction efficiency and selectivity, as well as expansion of the reaction scope, are ongoing.

ASSOCIATED CONTENT

Supporting Information

Supporting Information Experimental procedures, computational data, kinetic studies, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

Corresponding Author

gbdong@uchicago.edu

ORCID

Jianchun Wang: 0000-0002-3998-8699

Guangbin Dong: 0000-0003-1331-6015

Notes

The authors declare no competing financial interests.

‡These authors contribute equally to this work.

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SYNOPSIS TOC