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Direct (Hetero)arylation of Heteroarenes Catalyzed by Unsymmetrical Pd-PEPPSI-NHC Complexes under Mild Conditions

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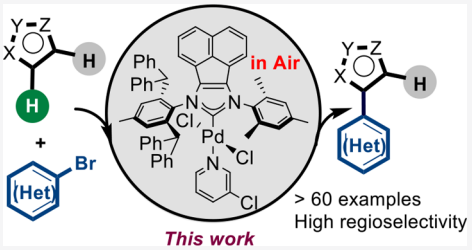
ABSTRACT: With the aim of developing a facile and efficient method to access structurally intriguing and valuable functionalized (hetero)aryls, two unsymmetrical Pd-PEPPSI-type NHC complexes (PEPPSI, pyridine-enhanced precatalyst preparation, stabilization, and initiation; NHC, N-heterocyclic carbene) were designed and synthesized to catalyze the direct arylation of heteroarenes with (hetero)aryl bromides. The results demonstrated that the utilization of this "unsymmetrical" strategy led to much higher efficiency in comparison to the commonly used C_2-symmetric Pd-PEPPSI-type NHC complexes. Furthermore, a broad range of heteroaromatics and (hetero)aryl bromide partners with a wide variety of functional groups were all amenable to the developed protocol even at as low as 0.05 mol % catalyst loading and under aerobic conditions. More importantly, along with our study, we also found that the present protocol could provide expedient access to the gram-scale synthesis of the muscle relaxant drug dantrolene and conjugated mesopolymers.



INTRODUCTION

Arylated heteroarenes are ubiquitous structural units widely found in a variety of pharmaceuticals, natural products, and functional materials.[1] Consequently, over the past decades, a tremendous effort has been devoted to the synthesis of such pivotal patterns.[2] Among all of the reported methods, the palladium-catalyzed direct arylation of heteroarenes has been recognized as an atom-economical and environmentally benign method, since it avoids the prefunctionalization of organometallic reagents and the generation of stoichiometric metal wastes.[3] However, some longstanding challenges remain in this field. First, issues regarding the use of relatively high loadings of costly palladium catalysts associated with toxic phosphine-based ligands have to be solved to provide more economically and environmentally attractive procedures.[4] Second, because of the diverse C−H bonds with comparable dissociation energies in the heteroarene molecules, the regioselective arylation of a single C−H bond has proven challenging.[5] Third, reactions that can be performed under aerobic conditions are still rare and limit their applications in large-scale production.[6] Therefore, to find a way to address the aforementioned issues, further optimization of the catalytic system in terms of the design of the phosphine-free ligand and/or the structure of the Pd precatalysts may be a fundamental strategy to develop a more facile, economical, and versatile direct arylation methodology.

Since the elegant work of Organ in 2006,[7] Pd-PEPPSI-type NHC complexes (PEPPSI, pyridine-enhanced precatalyst preparation, stabilization, and initiation; NHC, N-heterocyclic carbene) have been proven to be highly active precatalysts for a variety of cross-coupling reactions, such as Suzuki−Miyaura reactions, Negishi reactions, and direct arylation reactions.[8] For example, in 2017, the facile direct C5 arylation of a few heteroaromatics, such as imidazoles and imidazo[1,2-*a*]-pyridine, utilizing the Pd-PEPPSI-type NHC complexes as efficient catalysts, were reported by Lee and coauthors.[8m] So far, it has been revealed that increasing the steric hindrance at the *ortho* and *para* positions of *N*-aryl moieties on the NHC and modification of the NHC backbone can effectively elevate the catalytic abilities of Pd-PEPPSI-type NHC complexes and help to achieve direct arylation reactions under aerobic conditions.[9] Furthermore, the "bulky yet flexible" strategy proposed by Glorius[10] demonstrates that the steric bulk benefits the reductive elimination step of the catalytic cycle of cross-coupling reactions, while it is unfavorable for the oxidative addition and transmetalation steps, especially for sterically hindered substrates.[9,10] In the meantime, considering that the concerted metalation−deprotonation (CMD) pathway has been generally accepted for palladium-catalyzed direct C−H arylation reactions, we envisioned that the systematic fine-tuning of the catalyst structures, especially the electronic and steric effects of the substituents around the palladium center, is essential to promote the catalytic abilities of Pd-PEPPSI-NHC complexes in direct arylation reactions. Recently, our group has succeeded in developing a series of bulky C_2-symmetrical NHC ligand supported Pd-PEPPSI complexes, which demonstrated

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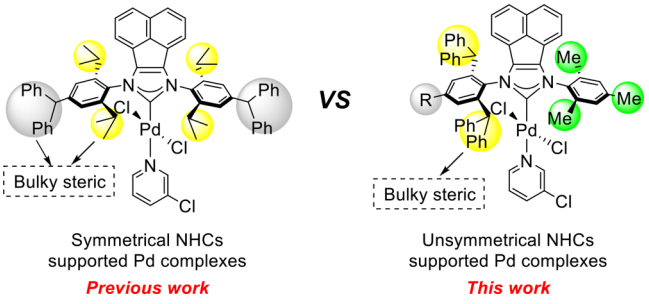
excellent catalytic capabilities for the direct arylation of azoles with as low as 0.05 mol % catalyst loading under aerobic conditions (Scheme 1, left).[9b] Therefore, we wondered

Scheme 1. Strategy of the Pd-NHCs for Direct Arylation Cross-Coupling Reactions



whether unsymmetrical Pd-PEPPSI-NHC complexes, which combine bulky groups onto the one flanking *N*-aryl moiety to facilitate the reductive elimination and one small enough yet sufficiently bulky substituent onto the other flanking *N*-aryl moiety to benefit the oxidative addition and transmetalation, would help to further enhance the efficacy of Pd-PEPPSI-NHC complexes on the direct arylation of heteroaromatics (Scheme 1, right).

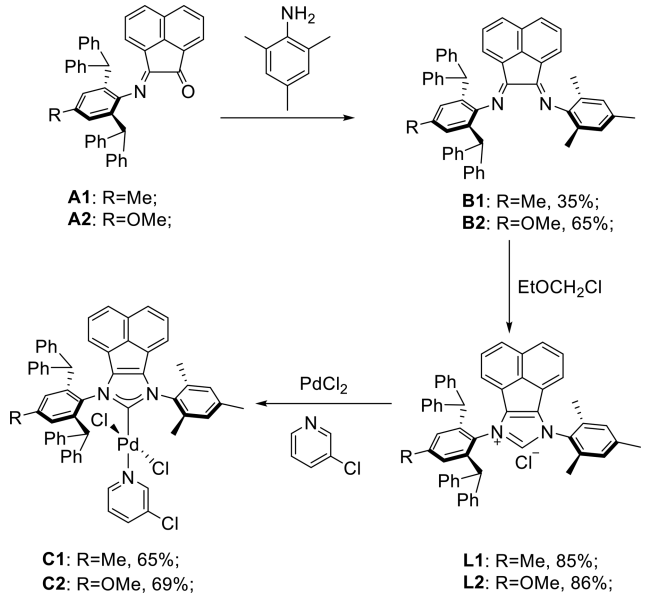
Herein, we describe our efforts in direct C−H arylation reactions of heteroarenes by taking advantage of unsymmetrical Pd-PEPPSI-NHC complexes, which turned out to exhibit a significant improvement in catalytic activities over the sterically bulky C_2-symmetrical NHC ligand supported Pd complexes. Furthermore, during the investigation, we found that the developed catalytic protocol not only has a considerably wide functional group tolerance but also demonstrates a general versatility toward a variety of (hetero)arylation reactions of heteroarene derivatives. More importantly, the powerful synthetic utility of the present protocol can be easily extended to the synthesis of the valuable drug dantrolene and π-conjugated mesopolymers.

RESULTS AND DISCUSSION

Synthesis and Characterization of the Pd-PEPPSI-NHC Complexes C1 and C2. The synthetic route of these unsymmetrical complexes **C1** and **C2**, as shown in Scheme 2, was modified from our previous methods.[11] These complexes were obtained in moderate to excellent yields and isolated as air-stable, yellowish solids. Their chemical structures were characterized by ^{1}H and ^{13}C NMR spectroscopy and HR-MS. The complex **C1** was further crystallographically characterized, and its solid-state structure is illustrated in Figure 1.

As depicted in Figure 1, the palladium atom has a slightly distorted square-planar coordination geometry with the carbene and "throw away" pyridine ligand *trans* to each other. Although the complex bears bulky substituents on the *N*-aryl moieties, the Pd−$C_{carbene}$ bond length of this structure turned out to be 1.965(4) Å, which is quite similar to those observed for the reported Pd-PEPPSI analogues with IPr* and IPr^{An} (1.974(6) and 1.960(6) Å, respectively).[12] It is worth pointing out that the bulky 2,6-dibenzhydryl groups on one of the two *N*-aryl moieties occupy the spaces above and below the palladium coordination plane, oriented over the axial sites of the palladium atom. Thus, it is expected that the combination of the bulky sterics of 2,6-dibenzhydryl groups and the

Scheme 2. Synthetic Route for Pd-PEPPSI-NHC Complexes C1 and C2



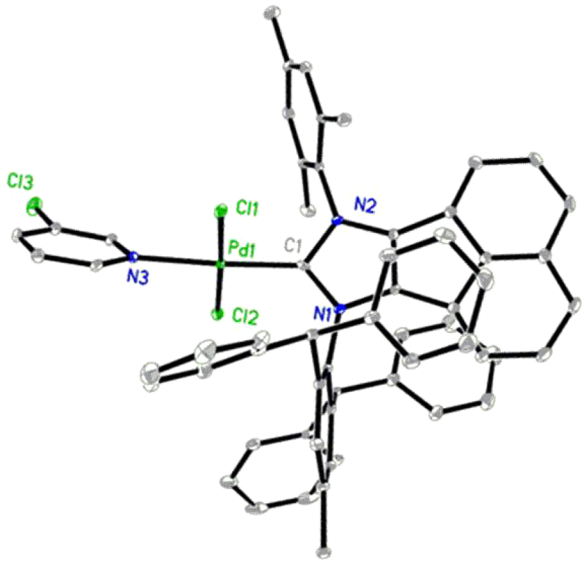


Figure 1. Molecular structure of complex **C1**. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Pd(1)−C(1) 1.965(4), Pd(1)−N(3) 2.095(3), Pd(1)−Cl(1) 2.2982(9), Pd(1)−Cl(2) 2.3052(9), N(3)−Pd(1)−C(1) 176.82(13), N(3)−Pd(1)−Cl(1) 88.93(8), N(3)−Pd(1)−Cl(2) 89.08(8), C(1)−Pd(1)−Cl(1) 92.68(10), C(1)−Pd(1)−Cl(2) 89.39(10), Cl(1)−Pd(1)−Cl(2) 177.49(3).

ancenaphthyl framework may effectively shield the axial positions of the palladium center, which may provide sufficient protection for the metal center. On the other hand, the 2,6-dimethyl groups on the other N-aryl moiety is small enough, providing a certain degree of ligand flexibility as needed for oxidative addition and transmetalation in the catalytic cycle. Thus, it can be anticipated that this unsymmetric structural design may enhance the catalytic activities of palladium complexes on direct arylation reactions.

Pd-PEPPSI-NHC Complex Catalyzed Direct C−H (Hetero)arylation Reactions under Aerobic Conditions. (Hetero)arylated furans are prevalent structural motifs, which

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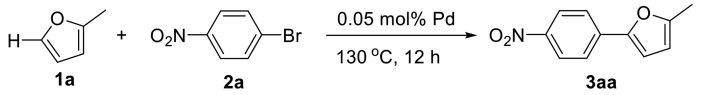
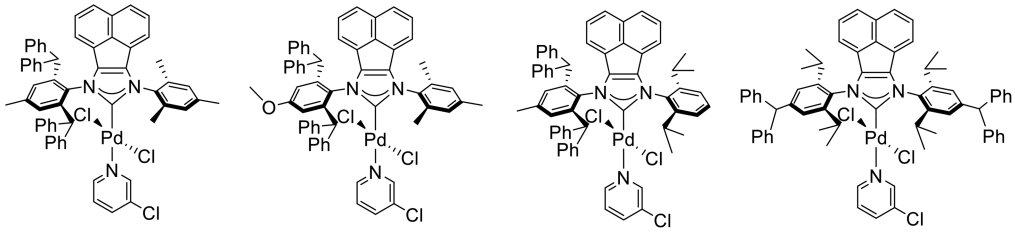
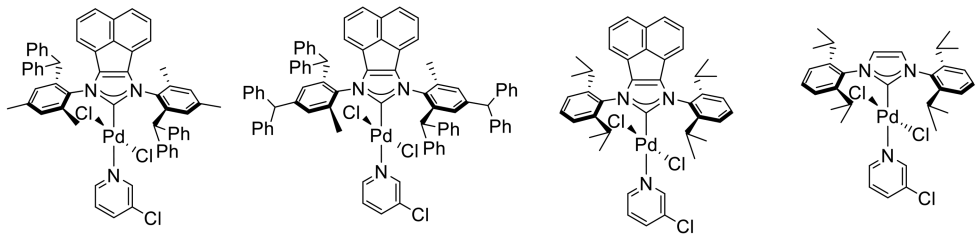
Table 1. Screening of Palladium Complexes for the Direct Arylation Reaction of 2-Methylfuran with 1-Bromo-4-nitrobenzene[a,b]





C1: 90% C2: 81% C3: 80% C4: 84%



C5: 60% C6: 84% PEPPSI-IPr^{An}: 52% PEPPSI-IPr: 42%

[a]Reagents and conditions: 1-bromo-4-nitrobenzene (1 mmol), 2-methylfuran (3 equiv), palladium source (0.05 mol %), base K_2CO_3 (2 equiv), solvent DMAc (3 mL), additive PivOH (30 mol %), 130 °C, 12 h, under aerobic conditions. [b]Isolated yields.

are frequently found in many biologically active agents and pharmaceuticals and also play an essential role in optical materials.[13] Due to their wide range of applications, the development of highly efficient methodologies for the synthesis of (hetero)arylated furan derivatives is of great importance. To test the feasibilities of these unsymmetrical Pd-PEPPSI-NHC complexes on the direct (hetero)arylation of furans, 2-methylfuran and 1-bromo-4-nitrobenzene were selected as the model substrates to initiate our catalytic investigation. The arylation reaction was conducted in the open air by employing 0.05 mol % of palladium loading, K_2CO_3 as the base, PivOH as the additive, and DMAc as the solvent with heating at 130 °C for 12 h, under conditions that have been established from our previous studies.[9b]

To our delight, as shown in Table 1, complexes **C1** and **C2** are highly effective for this coupling reaction. The C5-arylated product 2-methyl-5-(4-nitrophenyl)furan (**3aa**) was obtained in satisfactory yields of 90% and 81%, respectively. Increasing the steric resistance by changing two methyl groups in **C1** to two isopropyl groups afforded relatively lower catalytic efficiencies (80% yield for **C3**). This is presumably due to the small and flexible methyl groups allowing the ligands to better adapt to the needs of the catalytic cycle. In an attempt to verify our hypothesis, various available Pd complexes bearing bulky C_2-symmetrical NHC ligand skeletons were subsequently screened. Complexes **C4**−**C6**, bearing bulky substituents at the *ortho* and/or *para* positions of the *N*-aryl moieties on the NHC, which were previously reported to be excellent precatalysts for the direct arylation reactions and Suzuki−Miyaura cross-coupling reactions, resulted in lower conversions in comparison to those of **C1**. This result may be attributed to the bulky steric hindrance possibly facilitating the reductive elimination step in the course of the direct arylation reaction but being detrimental for the oxidative addition and transmetalation steps. The classical precatalyst PEPPSI-IPr^{An} with an acenaphthyl skeleton afforded the coupled product in a yield of 52%, which was higher than that of PEPPSI-IPr (42%). A control experiment was also conducted using palladium acetate as the precatalyst under exactly the same conditions. The results revealed that palladium acetate also could catalyze the direct arylation reaction; however, it yielded the desired product in a moderate yield of 47% (see in Table S1 in the Supporting Information). All these data demonstrate that the introduction of unsymmetrical ligands greatly enhances the catalytic abilities of the Pd-PEPPSI complexes. Therefore, **C1** was identified as the most effective precatalyst to carry out the catalytic investigation.

With all these promising results in hand, the effects of base, solvent, temperature, and additive were subsequently tested to further optimize the reaction conditions (Table 2). As depicted in Table 2, after the examination of bases, K_2CO_3 was found to be more compatible with this catalytic system and afforded the C5-arylated product in excellent yield (97%, Table 2, entry 3). In contrast, other bases, either inorganic or organic bases, provided the product in extremely low to moderate yields (Table 2, entries 1, 2, and 4−11). Furthermore, raising or lowering the amount of K_2CO_3 decreased the catalytic efficiency (Table 2, entries 3, 12, and 13). Subsequently, the solvent effect was determined. Among all of the solvents examined, DMAc afforded the highest conversion. Other solvents such as DMF, NMP, toluene, 1,4-dioxane, DMSO, EtOH, and xylene provided inferior values or even shut down the reaction (Table 2, entries 3 and 14−20). The influence of temperature was also investigated, and the analysis revealed a general trend: a lower reaction temperature resulted in a decrease in catalytic efficiency (Table 2, entries 3, 21, and 22). A survey of additive effect was then conducted. The reaction did not occur at all in the absence of the PivOH additive

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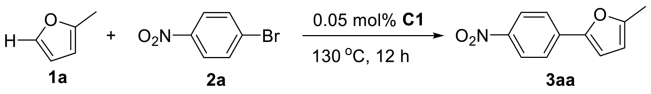
Table 2. Optimization of the Pd-Catalyzed Cross-Coupling of Aryl Bromides and Furans via C−H Direct (Hetero)arylation[a]



run	base	solvent	additive	conversn (%)[b]
1	K_3PO_4	DMAc	PivOH	44
2	CsF	DMAc	PivOH	42
3	K_2CO_3	DMAc	PivOH	97
4	Cs_2CO_3	DMA_C	PivOH	7
5	$NaHCO_3$	DMA_C	PivOH	60
6	NaO^tBu	DMA_C	PivOH	12
7	KOH	DMA_C	PivOH	44
8	KO^tBu	DMA_C	PivOH	0
9	triethylamine	DMA_C	PivOH	5
10	CH_3COONa	DMA_C	PivOH	50
11	DBU	DMA_C	PivOH	55
12[c]	K_2CO_3	DMA_C	PivOH	94
13[d]	K_2CO_3	DMA_C	PivOH	93
14	K_2CO_3	DMF	PivOH	11
15	K_2CO_3	NMP	PivOH	0
16	K_2CO_3	toluene	PivOH	53
17	K_2CO_3	1,4-dioxane	PivOH	2
18	K_2CO_3	DMSO	PivOH	7
19	K_2CO_3	EtOH	PivOH	3
20	K_2CO_3	xylene	PivOH	1
21[e]	K_2CO_3	DMA_C	PivOH	85
22[f]	K_2CO_3	DMA_C	PivOH	28
23[g]	K_2CO_3	DMA_C	PivOH	0
24[h]	K_2CO_3	DMA_C	HCOOH	3
25[i]	K_2CO_3	DMA_C	HCOOH	66
26[j]	K_2CO_3	DMA_C	CH_3COOH	61
27[k]	K_2CO_3	DMA_C	CH_3COOH	82
28[l]	K_2CO_3	DMA_C	CH_3COOH	100
29	K_2CO_3	DMA_C	H_3PO_4	19
30	K_2CO_3	DMA_C	succinic acid	0
31	K_2CO_3	DMA_C	lactic acid	10
32	K_2CO_3	DMA_C	acrylic acid	22
33	K_2CO_3	DMA_C	propanedioic acid	0

[a]Reagents and conditions: 1-bromo-4-nitrobenzene (1 mmol), 2-methylfuran (3 equiv), Pd source (0.05 mol %), base (2 equiv), solvent (3 mL), additive, 130 °C, 12 h, under aerobic conditions. [b]Cross-coupling product determined by GC. The cross-coupling yield is given as an average of two experiments. [c]K_2CO_3 (1.5 mmol). [d]K_2CO_3 (3 mmol). [e]120 °C. [f]100 °C. [g]In the absence of PivOH. [h]HCOOH (0.3 equiv). [i]HCOOH (0.8 equiv). [j]CH_3COOH (0.6 equiv). [k]CH_3COOH (2 equiv). [l]CH_3COOH (4 equiv).

(Table 2, entry 23). Additionally, a comparison of the PivOH with other acid additives under the standard conditions revealed that other acid additives were all inferior to PivOH (Table 2, entries 3, 24, and 29−33). It is worth pointing out that increasing the amount of additives resulted in significantly increased product formation (Table 2, entries 24−28). To our surprise, when 4 equiv of CH_3COOH was used, a quantitative yield was obtained (Table 2, entry 28). Given the abundance and economic costs, CH_3COOH can be regarded as the right choice of additive in the C−H direct (hetero)arylation, even though 4 equiv needs to be used. Eventually, the optimized reaction conditions were established as furans (3.0 equiv), aryl bromides (1.0 equiv), **C1** (0.05 mol %) as the precatalyst, K_2CO_3 (2.0 equiv) as the base, and CH_3COOH (4.0 equiv) as the acid additive in 3 mL of DMAc at 130 °C in an aerobic environment.

To demonstrate the efficacy and generality of this catalytic system, the scope of this transformation was then explored. Gratifyingly, as shown in Table 3, a variety of 2-substituted furans and a range of (hetero)aryl bromides with different substituents were amenable to this strategy. With regard to (hetero)aryl bromides, a broad range of functional groups on the aryl bromides, such as nitro, cyano, aldehyde, acetyl, chloro, and bromo, were well tolerated, allowing the transformation of substrates to the corresponding products **3aa−ae** and **3ag−ai** in moderate to excellent yields. Moreover, it was found that substrates bearing electron-withdrawing substituents were generally more reactive than those bearing electron-donating substituents (e.g., **3ah** vs. **3ai**). Meanwhile, it has to be mentioned that, for the sterically hindered 1-bromo-2-methylnaphthalene, the corresponding products **3an** and **3dn** were afforded in low yields. This result shows that the reaction is sensitive to steric hindrance in the *ortho* position of the substrates. Fortunately, with this kind of substrate, moderate yields (65% and 63%) could be obtained when PivOH (0.3 equiv) was employed as the additive instead of CH_3COOH or the amount of the palladium loading was increased (0.2 mol %). In comparison with aryl bromides, substituted heteroaryl bromides, especially π-electron-deficient nitrogen-containing heteroaryl bromides, such as pyridine, quinoline, isoquinoline, and pyrimidine, generally led to lower yields. This may be due to the low reactivity of heterocyclic substrates. To our delight, increasing the amount of the palladium loading (0.05−0.2 mol %) could result in significantly increased product formation and afford the desired products **3ai,aj,bq,cl,cs,dh,dk,ds** in moderate to excellent yields (35−97%). With regard to the furan counterparts, alkyl-, aldehyde-, and ester-substituted furans reacted with (hetero)aryl bromides smoothly, thereby furnishing the corresponding products in good yields. It is worth pointing out that, under our protocol, 2-furfuraldehyde, for which there have been very few reports due to the presence of a chemically reactive formyl group, underwent efficient coupling, affording the products **3ca,cl,cs** in moderate to excellent yields (35−99%). Benzofuran was also compatible under the developed reaction conditions, although it required higher Pd loadings (**3ea,ed**).

The preparation of heteroaromatic biaryls is well-known to be complicated. To further define the scope and limitations of the reaction, we were interested in examining the reactions of heterocycles other than substituted furans with (hetero)aryl bromides. After a preliminary test, it was found that for heterocyclic substrates other than substituted furans, acetic acid was demonstrated to be inferior (see Table S2 in the Supporting Information). Thus, we switched back to using PivOH instead of acetic acid as the acid additive to continue to explore the substrate scope. As shown in Table 4, a wide variety of heteroarenes, such as thiophene, thiazole, oxazole, isoxazole, imidazole, pyrazole, pyrrole, and imidazo[1,2-*a*]pyridine, were compatible under our protocol, affording the corresponding coupled products in synthetically useful yields.[14] However, these yields, except in the case of (hetero)arylated thiazole products **5bd,bt**, are remarkably lower than those of furan substrates. To our delight, increasing the palladium loading (0.1−2 mol %) resulted in significantly increased product formation and provided the desired

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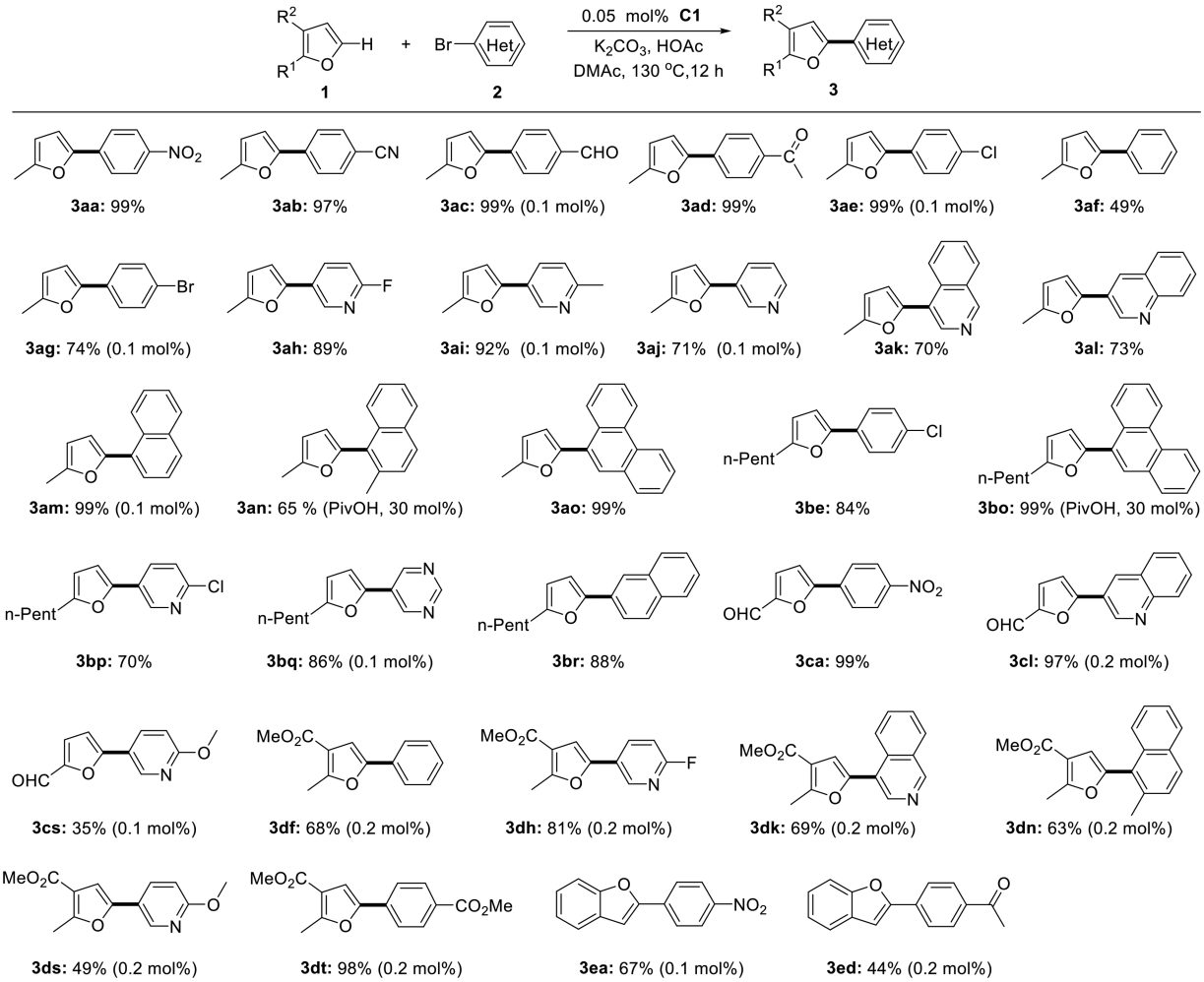
Table 3. Direct (Hetero)arylation of Furans with (Hetero)aryl Bromides Catalyzed by C1[a,b]



[a]Unless otherwise stated, reagents and conditions: (hetero)aryl bromides (1 mmol), furans (3 equiv), **C1** (0.05 mol %), K_2CO_3 (2 equiv), DMAc (3 mL), CH_3COOH (4 equiv), 130 °C, 12 h, in air. [b]Isolated yields.

products in moderate to excellent yields. The electronic effect of the substituents, with substrates bearing electron-withdrawing substituents being generally more reactive (e.g., **5bd** vs **5bf**), was observed once again. It is worth noting that, when 4-bromo-1-methylpyrazole (**4f**) was used as a coupling partner, no cleavage of the C−Br bond was observed during the catalytic process, which allowed for further useful transformations. For example, as shown in Scheme 3, 4-bromo-1-methylpyrazole smoothly reacted with 5-bromo-2-methylpyridine in the presence of **C1**, producing the C5-arylated product **5fi** in 71% yield. After sequential Suzuki coupling reactions, the intermediate **5fi** could be feasibly transformed into the diarylated product **7** in an excellent yield of 88%. It has to be mentioned that, under our developed protocol, the coupling reactions are highly regioselective for five-membered heteroaryl substrates which contain several C−H bonds with different reactivities, exclusively producing C5-arylated products. By the same process, the reaction of 1-methylindole with 5-bromo-2-methylpyridine (**4h**) was found to afford the C-2 arylated indole **5hi** as the major product in 66% yield with 2 mol % Pd loading. Furthermore, 2-substituted imidazo[1,2-*a*]pyridines were also tolerated in our catalytic process with 0.1 mol % Pd loading, giving the C-3 heteroarylated products **5ii**,**iv**,**jp**,**kq**,**lh**,**lq** in 41−99% yields, and this may be very favorable for the synthesis of the related functional motifs containing bioactive molecules. Thus, it can be seen that our protocol is highly regioselective for the most acidic C−H bond of the (hetero)arene substrates.[15]

To further access the potential utility of our catalytic protocol, we carried out the synthesis of dantrolene (as shown in Scheme 4), which is a specific and effective muscle relaxant drug for the treatment of malignant hyperthermia.[16] As illustrated in Scheme 4, using readily available 2-furfuraldehyde and 1-bromo-4-nitrobenzene as the starting materials, the key intermediate 5-(4-nitrophenyl)furan-2-carbaldehyde (**3ca**) was obtained in almost quantitative yield under the standard conditions in a scale-up protocol of 20 mmol. Followed by condensation of the resulting **3ca** with 1-aminoimidazolidine-2,4-dione, the final product dantrolene was furnished in an overall yield of 51%. This proves that our catalytic protocol can be successfully extended for the gram-scale synthesis of dantrolene.

So far, polycondensation via direct C−H arylation has been recognized as a promising strategy for the construction of mesopolymers, which are privileged structures with many fascinating functions.[17] For example, it has been disclosed that sterically encumbered adamantyl phosphine ligand coordinated palladium catalysts successfully converted heteroaryl mono-

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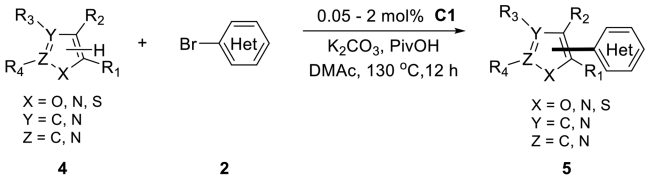
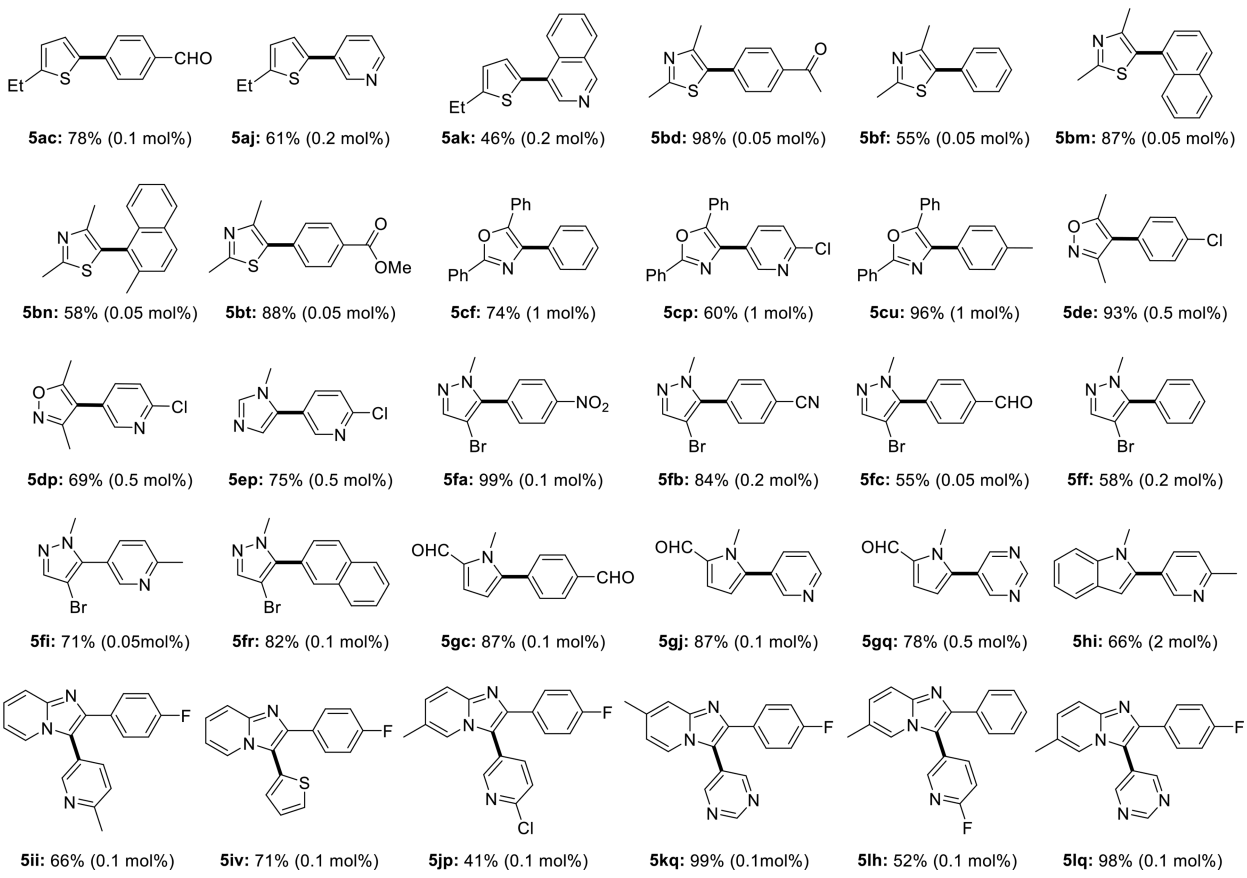
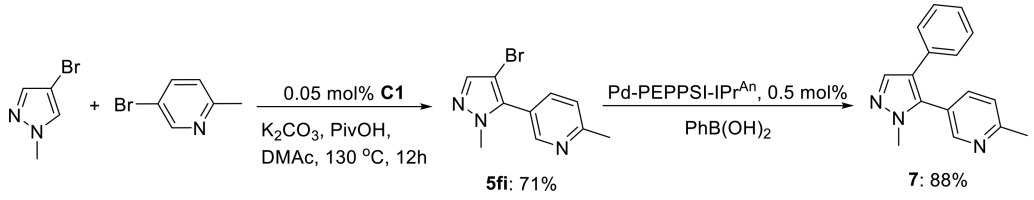
Table 4. Direct (Hetero)arylation of (Hetero)arenes with (Hetero)aryl Bromides Catalyzed by C1[a,b]





[a]Unless otherwise stated, reagents and conditions: (hetero)aryl bromides (1 mmol), heteroaryl (3 equiv), **C1** (0.05 mol %), K_2CO_3 (2 equiv), DMAc (3 mL), PivOH (30 mol %), 130 °C, 12 h, in air. [b]Isolated yields.

Scheme 3. Synthetic Route for Complex 7



mers into mesopolymers.[17b] However, reactions that can be conducted under aerobic conditions are still rare.[17a] Intrigued by the unusual activities of **C1** under aerobic conditions, 3,4-ethylenedioxythiophene (EDOT) and 2,7-dibromo-9,9-dioctylfluorene were selected to perform a direct arylation polycondensation to further explore the versatility of our catalytic system. To our delight, as shown in Scheme 5, the reaction carried out under aerobic conditions using **C1** (1 mol %) and pivalic acid (30 mol %) in a mixed solvent (DMAc/THF 5/1) at 80 °C for 12 h furnished the desired mesoEDOT in 56% yield, which has an M_n value of 6.2 kDa and a dispersity of 1.64. These results revealed that the unsymmetrical Pd-PEPPSI-NHC complex **C1** is also a promising precatalyst to promote the direct arylation polycondensation for the synthesis of mesopolymers.

CONCLUSION

In summary, we have developed a versatile catalytic system which is based on unsymmetrical Pd-PEPPSI-NHC complexes for the effective direct (hetero)arylation of furans and other (hetero)arenes with (hetero)aryl bromides. The results demonstrate that applying the concept of an unsymmetrical NHC ligand is the key to the success of the reactions. In all cases for the five-membered heteroaryl substrates which

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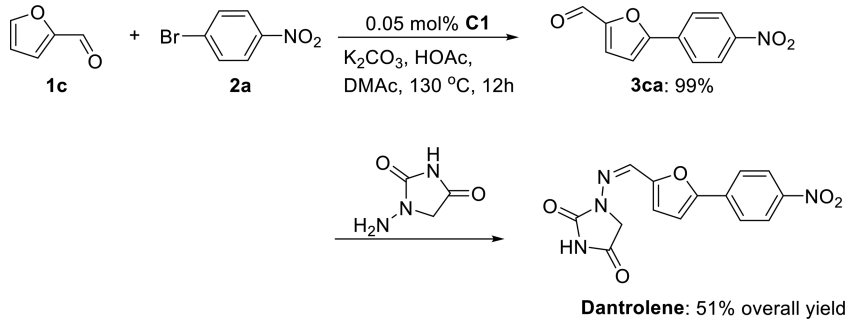
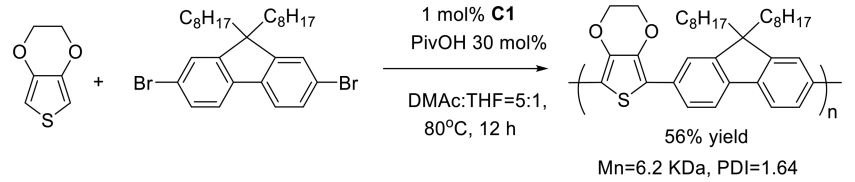
Scheme 4. Gram-Scale Synthesis of the Muscle Relaxant Drug Dantrolene



Scheme 5. Polycondensation of 3,4-Ethylenedioxythiophene (EDOT) with 2,7-Dibromo-9,9-dioctylfluorene



contain chemically distinct C(sp^2)−H bonds, the regioselective C5-(hetero)arylated products were efficiently obtained in moderate to excellent yields in the presence of 0.05−2 mol % catalyst loadings and under aerobic conditions. Furthermore, the readily accessible catalytic system exhibits a high functional group tolerance and a broad substrate scope. More importantly, the developed protocol can be readily scalable to the gram-level synthesis of the prescription drug dantrolene and can be applied to mesopolymer synthesis. Attempts at further applications of this catalytic system on other reactions are currently ongoing in our laboratory.

EXPERIMENTAL SECTION

Physical Measurements and Materials. All arenes and aryl bromides were purchased from Aldrich Chemical. 2,4,6-Trimethylaniline, chloromethyl ethyl ether, palladium chloride, 1-aminoimidazolidine-2,4-dione, 3,4-ethylenedioxythiophene (EDOT), acid additives, and inorganic bases were also purchased from Aldrich Chemical. Pyridine, 3-chloropyridine, dimethylacetamide, and other solvents were purchased from Guangzhou Chemical Reagent Factory and used as received. The α-ketoimines **A1** and **A2**),[18] PEPPSI-IPr,[7] PEPPSI-IPr^{An},[12a] and complexes **C3**−**C6** were prepared according to the previously reported procedures.[9b,10d,11]

The NMR data of the compounds were obtained on a Varian Mercury-Plus 400 MHz or a Bruker AV 500 MHz spectrometer at ambient temperature with the decoupled nucleus, using $CDCl_3$ as the solvent and referenced versus TMS as the standard. The X-ray diffraction data of single crystals were obtained with the $\omega-2\theta$ scan mode on a Bruker SMART 1000 CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) for **C1**. The structure was solved by direct methods using the Olex2 software, and further refinement with full-matrix least squares on F^2 was obtained with the SHELXTL program package.[19] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced in calculated positions with the displacement factors of the host carbon atoms. CCDC 2010557 (**C1**) contains the supplementary crystallographic data for this paper. High-resolution mass spectroscopy (HRMS) analyses were performed with a Bruker Daltonics mass instrument (ESI). GPC analyses were performed with a Waters Breeze2 GPC system.

General Procedure for the Synthesis of α-Diimine Compounds B1 and B2. Under a nitrogen atmosphere, a catalytic amount of *p*-toluenesulfonic acid (0.08 g, 0.50 mmol) was added to a solution of the α-ketoimine (5.00 mmol) and 2,4,6-trimethylaniline (0.68 g, 5.00 mmol) in toluene (20 mL), and the resulting mixture was heated at 110 °C for 10 h. After the reaction was completed, the reddish brown crude reaction mixture was cooled to room temperature and evaporated to dryness. The resulting brownish black residue was redissolved and purified by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent.

*[2,6-(CHPh$_2$)$_2$-4-(CH$_3$)C$_6$H$_2$N═C(An)(An)C═N(2,4,6-(CH$_3$)$_3$C$_6$H$_2$)] (**B1**).* **B1** was obtained as a yellow solid (1.36 g) in 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.2 Hz, Ar-H, 1H), 7.60 (d, J = 8.2 Hz, Ar-H, 1H), 7.33−7.11 (m, Ar-H, 12H), 6.99 (dd, J = 23.5, 9.8 Hz, Ar-H, 7H), 6.81 (s, Ar-H, 2H), 6.63 (t, J = 6.7 Hz, Ar-H, 4H), 6.44 (t, J = 7.3 Hz, Ar-H, 2H), 6.12 (d, J = 7.1 Hz, Ar-H, 1H), 5.64 (s, Ar-H, Ph_2CH, 2H), 2.41 (s, CH_3, 3H), 2.30 (s, CH_3, 3H), 2.21 (s, CH_3, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.4, 161.4, 146.7, 143.1, 141.8, 139.8, 132.8, 132.4, 132.1, 129.7, 129.5, 128.9, 128.8, 128.6, 128.6, 128.4, 128.0, 127.9, 127.6, 127.3, 126.7, 126.0, 125.3, 124.5, 124.0, 121.6, 52.1, 21.5, 20.9, 18.0. HRMS (ESI$^+$): 721.3565 (calcd for $C_{54}H_{45}N_2$ [M + H]$^+$ 721.3583).

*[2,6-(CHPh$_2$)$_2$-4-(CH$_3$O)C$_6$H$_2$N═C(An)(An)C═N(2,4,6-(CH$_3$)$_3$C$_6$H$_2$)] (**B2**).* **B2** was obtained as a red solid (2.39 g) in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.1 Hz, Ar-H, 1H), 7.60 (d, J = 8.2 Hz, Ar-H, 1H), 7.29−7.27 (m, Ar-H, 1H), 7.24 (dd, J = 7.0, 5.7 Hz, Ar-H, 4H), 7.18 (d, J = 7.2 Hz, Ar-H, 2H), 7.11 (d, J = 7.3 Hz, Ar-H, 4H), 7.02 (dd, J = 8.2, 7.3 Hz, Ar-H, 1H), 6.98−6.92 (m, Ar-H, 6H), 6.59 (dd, J = 15.8, 7.9 Hz, Ar-H, 7H), 6.42 (t, J = 7.4 Hz, Ar-H, 2H), 6.17 (d, J = 7.1 Hz, Ar-H, 1H), 5.61 (s, CH, 2H), 3.63 (s, OCH_3, 3H), 2.38 (s, CH_3, 3H), 2.16 (s, CH_3, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.1, 161.5, 155.7, 146.7, 142.8, 141.5, 139.9, 133.7, 132.8, 129.8, 129.5, 129.0, 128.5, 128.2, 127.7, 127.4, 126.8, 126.2, 125.5, 124.5, 124.0, 121.7, 113.7, 55.2, 52.3, 20.9, 18.0. HRMS (ESI$^+$): 737.3520 (calcd for $C_{54}H_{45}N_2O$ [M + H]$^+$ 737.3532).

General Procedure for the Synthesis of Imidazolium Salts L1 and L2. Under a nitrogen atmosphere, a mixture of the α-diimine compound (1.00 mmol) and chloromethyl ethyl ether (4 mL) was stirred at 100 °C overnight. Then the resulting solution was cooled to room temperature, treated with 25 mL of anhydrous Et_2O, and stirred for another 1 h, resulting in the formation of a great deal of yellowish white precipitate. The solid was isolated by filtration and washed three times with anhydrous Et_2O. The title compounds were obtained in excellent purity, and no further purification was needed.

*[2,6-(CHPh$_2$)$_2$-4-(CH$_3$)C$_6$H$_2$]{[N═C(An)(An)C═N]CH$^+$Cl$^-$}[(2,4,6-(CH$_3$)$_3$C$_6$H$_2$)] (**L1**).* **L1** was obtained as a yellow solid (0.65 g) in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.75 (s, Ar-H, 1H), 7.86 (d, J = 8.3 Hz, Ar-H, 1H), 7.77 (d, J = 8.3 Hz, Ar-H, 1H), 7.51−7.43 (m, Ar-H, 1H), 7.30 (t, J = 7.4 Hz, Ar-H, 4H), 7.27−7.22 (m, Ar-H, 4H), 7.18 (t, J = 7.0 Hz, Ar-H, 2H), 7.14 (d, J = 7.0 Hz, Ar-H, 1H), 7.07 (s,

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Ar-H, 2H), 6.88 (s, Ar-H, 2H), 6.83−6.77 (m, Ar-H, 8H), 6.70 (dd, J = 9.3, 4.3 Hz, Ar-H, 2H), 6.60 (d, J = 7.0 Hz, Ar-H, 1H), 5.59 (s, Ph_2CH, 2H), 2.38 (s, CH_3, 3H), 2.28 (s, CH_3, 3H), 2.14 (s, CH_3, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.1, 141.5, 141.4, 141.3, 141.2, 141.2, 137.7, 135.5, 133.9, 130.7, 130.1, 130.0, 129.7, 129.6, 129.4, 129.2, 129.0, 128.7, 128.2, 127.5, 127.1, 126.9, 126.5, 123.5, 122.9, 122.6, 122.1, 51.8, 21.9, 21.2, 18.1. HRMS (ESI^+): 733.3564 (calcd for $C_{55}H_{45}N_2$ $[M - Cl]^+$ 733.3583).

*[2,6-(CHPh$_2$)$_2$-4-(OCH$_3$)C$_6$H$_2$]{[N═C(An)(An)C═N]CH$^+$Cl$^-$}[(2,4,6-(CH$_3$)$_3$C$_6$H$_3$)] (**L2**).* **L2** was obtained as an orange solid (0.67 g) in 86% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 11.76 (d, J = 16.5 Hz, 1H), 7.86 (d, J = 8.3 Hz, Ar-H, 1H), 7.79 (d, J = 8.3 Hz, Ar-H, 1H), 7.49−7.44 (m, Ar-H, 1H), 7.29 (t, J = 6.5 Hz, Ar-H, 9H), 7.19 (d, J = 6.5 Hz, Ar-H, 2H), 7.13 (d, J = 6.9 Hz, Ar-H, 1H), 7.06 (s, Ar-H, 2H), 6.82 (dd, J = 12.8, 7.1 Hz, Ar-H, 8H), 6.70 (d, J = 6.4 Hz, Ar-H, 3H), 6.57 (s, Ar-H, 2H), 5.63 (s, CH, 2H), 3.59 (s, OCH_3, 3H), 2.38 (s, CH_3, 3H), 2.12 (s, CH_3, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.0, 143.4, 141.2, 141.1, 141.0, 137.8, 135.4, 133.9, 130.1, 129.6, 129.3, 129.2, 129.0, 128.8, 128.3, 127.5, 127.1, 127.0, 126.6, 124.8, 123.5, 123.0, 122.1, 115.5, 55.2, 51.9, 21.2, 18.1. HRMS (ESI^+): 749.3510 (calcd for $C_{55}H_{45}N_2O$ $[M - Cl]^+$ 749.3532).

General Procedure for the Synthesis of PEPPSI-Pd Compounds C1 and C2. A mixture of $PdCl_2$ (0.19 g, 1.10 mmol), the imidazolium salt (1.00 mmol), K_2CO_3 (1.38 g, 10.00 mmol), and 3-chloropyridine (5 mL) was stirred at 80 °C for 24 h under a nitrogen atmosphere. After the mixture was cooled to room temperature, 10 mL of dichloromethane was added to the resultant solution. Then the solution was filtered through a pad of silica covered with Celite and the solvents were removed under reduced pressure. The resulting residue was redissolved and recrystallized from dichloromethane/pentane to afford the corresponding products. A single crystal of **C1** suitable for X-ray diffraction studies was obtained by layering its dichloromethane solution with pentane at ambient temperature. Two solvent molecules (dichloromethane) were found in the lattice.

*[Pd(IPr*IMe)^{An}(3-Cl-pyridinyl)Cl$_2$] (**C1**).* **C1** was obtained as a yellow solid (0.68 g) in 65% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 8.91 (d, J = 2.3 Hz, Ar-H, 1H), 8.80 (dd, J = 5.5, 1.0 Hz, Ar-H, 1H), 7.77−7.63 (m, Ar-H, 1H), 7.51 (d, J = 8.2 Hz, Ar-H, 1H), 7.34 (d, J = 7.7 Hz, Ar-H, 4H), 7.23−7.18 (m, Ar-H, 6H), 7.18−7.14 (m, Ar-H, 4H), 7.11 (s, Ar-H, 2H), 6.83 (t, J = 7.5 Hz, Ar-H, 5H), 6.62−6.54 (m, Ar-H, 1H), 6.45 (s, Ar-H, 2H), 6.39 (t, J = 7.6 Hz, Ar-H, 4H), 6.25 (t, J = 7.4 Hz, Ar-H, 2H), 5.22 (d, J = 6.9 Hz, Ph_2CH, 2H), 2.61 (s, CH_3, 6H), 2.44 (s, CH_3, 3H), 2.37 (s, CH_3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.2, 150.8, 149.8, 144.2, 143.7, 141.6, 140.5, 139.2, 139.0, 137.6, 137.3, 135.9, 134.8, 134.1, 132.1, 130.4, 130.2, 129.8, 129.7, 128.2, 127.9, 127.5, 127.3, 127.2, 126.2, 126.0, 125.8, 125.7, 125.6, 124.7, 124.4, 124.2, 122.1, 119.5, 51.2, 21.9, 21.3, 20.0. HRMS (ESI^+): 873.2230, 733.3565 (calcd for $C_{55}H_{44}N_2ClPd$ $[M - C_5H_4NCl - Cl - H]^+$ 873.2228, $C_{55}H_{45}N_2$ $[M - C_5H_4NCl - Cl_2 - Pd]^+$ 733.3583).

*[Pd(IPr^{OMe}*IMe)^{An}(3-Cl-pyridinyl)Cl$_2$] (**C2**).* **C2** was obtained as a yellow solid (0.72 g) in 69% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, J = 2.1 Hz, Ar-H, 1H), 8.81 (dd, J = 5.5, 1.3 Hz, Ar-H, 1H), 7.69 (ddd, J = 8.2, 2.3, 1.3 Hz, Ar-H, 1H), 7.51 (d, J = 7.9 Hz, Ar-H, 1H), 7.37−7.34 (m, Ar-H, 4H), 7.24−7.19 (m, Ar-H, 6H), 7.17 (d, J = 6.6 Hz, Ar-H, 4H), 6.87 (d, J = 1.1 Hz, Ar-H, 2H), 6.85 (s, Ar-H, 2H), 6.82 (s, Ar-H, 2H), 6.59 (dd, J = 8.3, 7.0 Hz, Ar-H, 1H), 6.48 (s, Ar-H, 2H), 6.39 (t, J = 7.6 Hz, Ar-H, 4H), 6.25 (dd, J = 10.5, 4.2 Hz, Ar-H, 2H), 5.28 (d, J = 6.8 Hz, Ar-H, 1H), 3.69 (s, OCH_3, 3H), 2.61 (s, CH_3, 6H), 2.44 (s, CH, 2H), 1.60 (s, CH_3, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 155.5, 150.8, 149.8, 145.6, 143.8, 141.8, 140.2, 139.3, 137.6, 137.3, 136.0, 134.1, 132.1, 130.3, 130.3, 129.9, 129.7, 128.2, 127.8, 127.5, 127.4, 127.3, 126.2, 126.0, 126.0, 125.8, 125.7, 124.7, 124.5, 124.2, 122.2, 119.5, 115.2, 55.2, 51.4, 21.3, 20.0. HRMS (ESI^+): 889.2175, 749.3513 (calcd for $C_{55}H_{44}N_2ClOPd$ $[M - C_5H_4NCl - Cl - H]^+$ 889.2177, $C_{55}H_{45}N_2O$ $[M - C_5H_4NCl - Cl_2 - Pd]^+$ 749.3532).

General Procedure for Direct Arylation Reactions Promoted by PEPPSI-Pd Complexes. Unless otherwise noted, the direct arylation reactions were conducted under aerobic conditions. All solvents were used as received. the Pd-PEPPSI complex (0.05−2.00 mol %), aryl bromide (1.00 mmol), heteroarene (3.00 mmol), base (2.00 mmol), acid additive (0.30−4.00 mmol), and 3 mL of solvent were placed in a parallel reactor. The reaction mixture was heated with vigorous stirring at 130 °C for 12 h. After the mixture was cooled to ambient temperature, 20 mL of water and 20 mL of dichloromethane were placed in the reactor, and the mixture was stirred for another few minutes, followed by extraction three times with dichloromethane (3 × 5 mL). The organic layers were then combined, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give the crude products. The crude products were then purified by silica gel column chromatography using petroleum ether/dichloromethane (15/1) as the eluent. The pure products obtained were characterized by ^1H NMR and ^{13}C NMR spectroscopy, and the spectra can be found in the Supporting Information. The isolated yields of products were obtained on the basis of the amounts of (hetero)aryl bromides.

Procedure for the Synthesis of Compound 7. As described in the general procedure for the direct arylation reactions, intermediate **5fi** was obtained in 71% yield. Then **5fi** (0.25 g, 1.00 mmol), phenylboronic acid (1.46 g, 1.20 mmol), 0.5 mol % of Pd-PEPPSI-IPr^{An} (0.004 g, 0.005 mmol) and K_2CO_3 (0.28 g, 2.00 mmol) were dissolved in 3 mL of ethanol under an aerobic atmosphere. The reaction mixture was stirred at 80 °C for 4 h. After completion of the reaction, the resulting mixture was cooled to ambient temperature and 20 mL of water was added to it. Then the mixture was diluted with dichloromethane (5 mL) and extracted three times with dichloromethane (3 × 5 mL). The organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title product **7** in 88% yield as a white solid.

*2-Methyl-5-(1-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine (**7**).* ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 1.9 Hz, Ar-H, 1H), 7.73 (s, Ar-H, 1H), 7.49 (dd, J = 8.0, 2.3 Hz, Ar-H, 1H), 7.24−7.20 (m, Ar-H, 3H), 7.20−7.17 (m, Ar-H, 1H), 7.15 (dd, J = 6.8, 1.6 Hz, Ar-H, 2H), 3.80 (s, CH_3, 3H), 2.63 (s, CH_3, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0, 149.9, 137.9, 137.9, 136.6, 132.6, 128.6, 127.6, 126.4, 123.6, 123.3, 122.1, 37.4, 24.4.

Procedure for the Synthesis of Dantrolene. As described in the general procedure for the direct arylation reactions, intermediate **3ca** was obtained in almost quantitative yield. Then 1-amino-imidazolidine-2,4-dione (2.53 g, 22 mmol) in 30 mL of 0.67 M HCl was added to a solution of **3ca** (4.04 g, 20 mmol) in 100 mL of DMF at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, 500 mL of water was added to the reaction mixture, which furnished a great amount of a reddish yellow precipitate. Then the pure dantrolene was obtained by filtration, washed with water, and dried under vacuum (3.17 g, 10.10 mmol, overall yield 51%). Its characterization data were fully consistent with the reported data.[20] ^1H NMR (400 MHz, DMSO): δ 11.36 (s, NH, 1H), 8.32−8.28 (m, Ar-H, 2H), 8.01−7.97 (m, Ar-H, 2H), 7.76 (s, N═CH, 1H), 7.44 (d, J = 3.6 Hz, Ar-H, 1H), 7.03 (d, J = 3.7 Hz, Ar-H, 1H), 4.36 (s, CH_2, 2H).^{13}C NMR (101 MHz, DMSO): δ 168.9, 153.4, 152.2, 151.1, 146.3, 135.2, 132.7, 124.6, 124.6, 115.7, 112.5, 49.0.

Procedure for the Synthesis of Mesopolymers. Under an aerobic atmosphere, 3,4-ethylenedioxythiophene (0.142 g, 1 mmol), 2,7-dibromo-9,9-dioctylfluorene (0.548 g, 1 mmol), **C1** (0.010 g, 1 mol %), and pivalic acid (1 mL, 30 mol %) were added to 3 mL of mixed solvent (DMAc/THF 5/1). Then the reaction mixture was stirred at 80 °C for 12 h. After it was cooled to room temperature, the resulting mixture was poured into chilled acidic methanol (0.1 M HCl), which furnished a great amount of precipitate. The crude product was then obtained by filtration and washed with distilled water, methanol, and hexane in sequence. The washed precipitate was then recrystallized from MeOH. The desired mesopolymers were obtained as brownish yellow solids in 56% yield (0.312 g), which has an M_n value of 6.2 kDa and a dispersity of 1.64. ^1H NMR (400 MHz,

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$CDCl_3$): δ 7.85−7.83 (2H), 7.72−7.67 (4H), 4.44 (4H), 2.06 (4H), 1.20−1.12 (24H), 0.83−0.80 (6H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00494.

NMR spectra and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2010557 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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