JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Facile Synthetic Method for Diverse Polyfunctionalized Imidazoles by Means of Pd-Catalyzed C−H Bond Arylation of *N*-Methyl-4,5-dibromoimidazole

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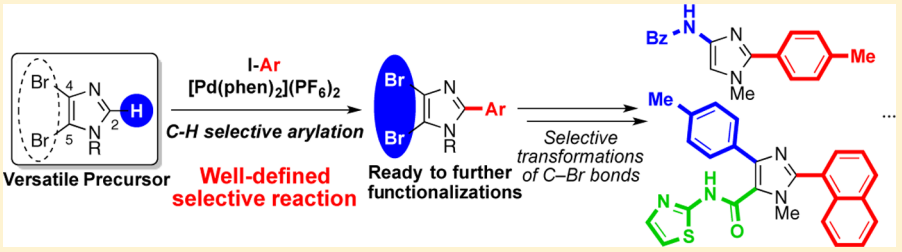
Supporting Information



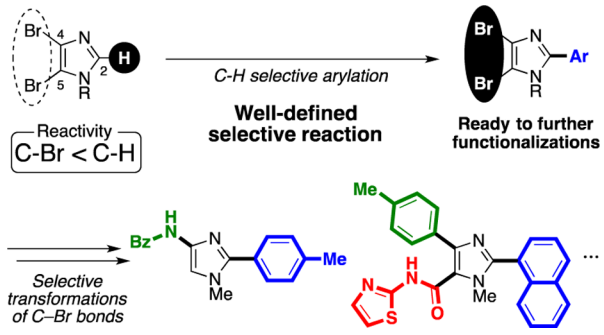
ABSTRACT: C−H bond-selective arylation reaction of 4,5-dibromoimidazole with aryl iodides, catalyzed by the palladium-1,10-phenanthroline complex $[Pd(phen)_2](PF_6)_2$, has been developed. The process tolerates the presence of a variety of functional groups on the aryl halide substrates. The products formed in these reactions were transformed to a variety of polyfunctionalized imidazoles by taking advantage of selective reactions of remaining C−Br bonds.

INTRODUCTION

Polyfunctionalized azoles, particularly imidazoles, are an important class of compounds owing to their unique bioactivities[1] and physical properties.[2] Therefore, the development of concise methods for the synthesis of members of this family is highly important.[3] Previously, such imidazoles were usually synthesized by condensation and/or substitution cyclization of functionalized carbonyl compounds and/or halides, and those alternative methods.[3,4] In these cases, functional groups have to be introduced at early stage of synthesis. However, such early stage functionalization strategies have a disadvantage for synthesis of diverse derivatives since these often translate into elaborate multistep syntheses. Thus, late-stage functionalization methods are highly desired. Recently, transition-metal-catalyzed direct C−H bond functionalization reactions of azoles have received significant attention because they enable the preparation of polyfunctionalized azoles from readily available unsubstituted azoles in a straightforward and late-stage functionalization manner.[5,6] Generally, transition-metal-catalyzed direct C−H functionalization reactions of imidazoles display a position-dependent reactivity order of C2 ≈ C5 ≫ C4[5g,7] and a C2 versus C5 reactivity order that depends on the catalytic system used.[8] In addition, only few direct C4−H functionalization reactions of azoles, and in particular imidazoles, have been described due to the low reactivity at this site.[5,6] Thus, 5-unsubstituted 2,4-substituted imidazoles and 2-unsubstituted 4,5-substituted imidazoles as well as 2,4,5-trisubstituted imidazoles are not readily prepared using direct C−H functionalization reactions of unsubstituted imidazoles.

Some conventional cross-coupling reactions of multihalogenated imidazoles have been employed to prepare polyfunctionalized derivatives, but site selectivities associated with these processes are low, particularly C2- versus C5-positions.[9] We envisioned that if conditions could be devised to enable selective C−H bond arylation reactions of readily available azoles, which possess both C−H and C−Br bonds, a novel and concise method for preparation of polyfunctionalized imidazoles would become available (Scheme 1). Unfortunately, conventional catalytic systems used for direct C−H bond arylation reactions typically display low activities for C−H bond

Scheme 1. New Synthetic Approach to Polyfunctionalized Imidazoles



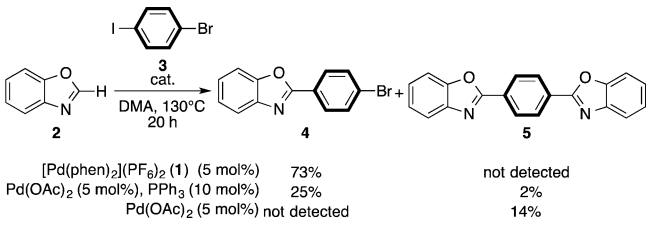
Received: June 17, 2014
Published: July 9, 2014

dx.doi.org/10.1021/jo5013493 | J. Org. Chem. 2014, 79, 7185−7192

cleavage but high activities for oxidative addition of aryl halides,[10] and those catalytic systems often need some additives such as silver salts and carboxylic acids or their salts to achieve efficient C−H bond cleavage.[5] As a result, these catalysts cannot be utilized to promote C−H-selective reactions. In a recent effort, we have shown that palladium complexes with nitrogen-based ligands, and in particular $[Pd(phen)_2](PF_6)_2$ (**1**) (phen: 1,10-phenanthroline), show excellent catalytic activities in direct C−H arylation reactions of azoles even in the absence of additives except base.[11] Following this report, direct C−H bond functionalizations of aromatic compounds promoted by Pd−nitrogen-based ligand systems have been extensively investigated and applied to the syntheses of polyfunctionalized azoles.[6] Most recently, Itami, Yamaguchi, and co-workers developed rare C4-selective oxidative direct arylation of thiazoles with boronic acids catalyzed by a Pd-1,10-phenanthroline system, and they have realized synthesis of all patterns of mono-, di-, triarylated thiazoles by combination of their methods and previously reported direct C−H arylation reactions.[12] However, the C4-selective arylation reaction did not take place with other azoles, in particular imidazoles, thus further investigations for developing methods to construct highly substituted imidazoles are still needed.

An important characteristic of Pd−nitrogen-based ligand containing catalysts is that they display relatively low activity in promoting reactions of aryl halides in contrast to C−H bond cleavage reactions.[11] By considering this feature, we envisaged that C−H bond-selective arylation reactions of halogenated imidazoles might be possible if highly reactive aryl iodides are used as coupling partners. Importantly, in this case, halogen atoms in the azoles would serve as protecting groups for otherwise reactive C−H bonds. In fact, the results of a preliminary investigation showed that C−I bond-selective reaction takes place between benzoxazole **2** and bromoiodobenzene **3** when **1** is utilized as the catalyst (Scheme 2). This

Scheme 2. Preliminary Result of C−I Bond-Selective, Direct C−H Bond Arylation Reaction

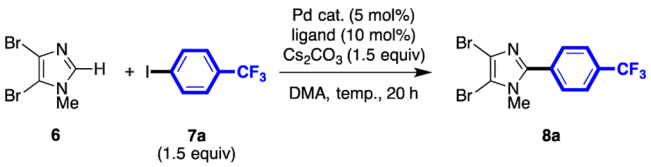


result prompted a general investigation of C−H bond-selective arylation reactions of brominated imidazoles. Below, we describe the results of this study, which have led to the development of a novel and concise synthetic method for the preparation of polyfunctional imidazoles, which employs C−H bond-selective arylation reactions of 1-methyl-4,5-dibromoimidazole promoted by Pd−1,10-phenanthroline complexes as a key step.

RESULTS AND DISCUSSION

Investigations of C−H-Selective Direct Arylation of a 4,5-Dibromoimidazole. In the initial phase of the studies, reaction of 1-methyl-4,5-dibromoimidazole (**6**) and 1-iodo-4-α,α,α-trifluoromethyltoluene (**7a**) was explored using several different palladium complexes as catalysts (Table 1).[11,13] Reaction promoted using $Pd(OAc)_2$ was found to give a

Table 1. Optimization of Conditions for Reaction of 6 with 7a



entry	Pd catalyst	ligand	temp (°C)	yield (%)[a]
1	$Pd(OAc)_2$		150	37
2	$Pd(OAc)_2$	PPh_3	150	38
3	$Pd(OAc)_2$	$P(4\text{-}CF_3C_6H_4)_3$	150	18
4	$Pd(OAc)_2$	$P(4\text{-}MeOC_6H_4)_3$	150	14
5	$Pd(OAc)_2$	dppb[b]	150	ND[c]
6	$Pd(OAc)_2$	$t\text{-}Bu_3P\cdot HBPh_4$	150	36
7	$Pd(OAc)_2$	PPh_3	130	17
8	$Pd(OAc)_2$	2,2′-bipyridyl	150	36[e]
9	$Pd(OAc)_2$	phen	150	45[e]
10	$Pd(OAc)_2$	phen[d]	150	67[e]
11	**1**		150	73
12	**1**		**130**	**85**
13	**1**		110	37
14	**1**		90	20

[a]Isolated yields. [b]Diphenylphosphinobutane. [c]Not detected. [d]$NaPF_6$ (10 mol %) was added. [e]The yield was determined by using ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

complex product mixture from which the coupling product **8a** is isolated in only 37% yield and a significant amount of unidentified side products is generated (entry 1). The addition of PPh_3 or its para-electron-withdrawing and -donating-group-substituted analogues as ligands to the $Pd(OAc)_2$ containing reaction mixture does not improve the yield of the process (entries 2−4). Moreover, **8a** was not generated when the bidentate phosphine ligand dppb was employed (entry 5), and the addition of $t\text{-}Bu_3P$ does not cause an enhancement in the efficiency of the reaction (entry 6). An attempt to suppress side processes by carrying out reaction of **6** with **7a** in the presence of $Pd(OAc)_2$ and PPh_3 at lower temperature (130 °C) was not successful (entry 7).

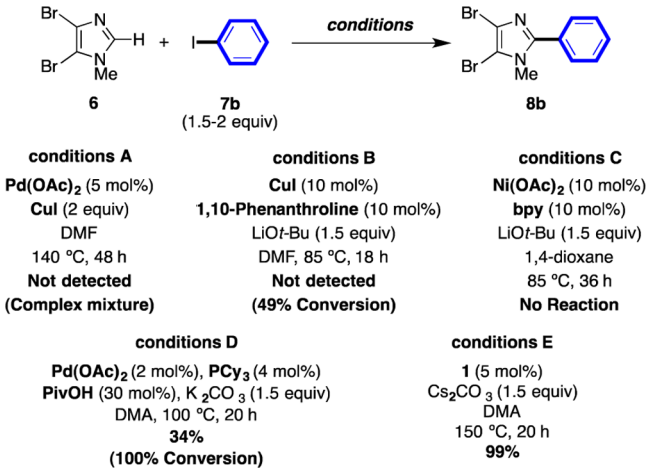
In contrast, addition of 2,2′-bipyridyl or 1,10-phenanthroline as a ligand dramatically suppressed the side processes, and only **8a** and substrates **6** and **7a** were recovered with high mass balance after the reaction, particularly with 1,10-phenanthroline as a ligand, though the product yield did not improve (entries 8 and 9). These results obviously indicated that the use of nitrogen-based ligands is critical for selective reaction with brominated substrates. Catalytic activity increased by adding $NaPF_6$ as an additive (entry 10). In addition, as anticipated, coupling reaction of **6** and **7a** takes place with high efficiency to form the C2-arylated product **8a** when preformed $[Pd(phen)_2](PF_6)_2$ (**1**) is utilized as the catalyst (entry 11). Studies of the effect of temperature (entries 11−14) showed that the use of 130 °C leads to an optimal yield of **8a** (85%, entry 12). Further lowering of the reaction temperature greatly affects the conversion of **6**, and the yields of **8a** drop at 110 and 90 °C (entries 13 and 14).

In previous investigations, several C2-selective arylations of N-protected imidazoles were observed to occur when additives CuI[8d] and $Ni(OAc)_2$[8b] were employed. In a study exploring the potential utility of these catalysts, we observed that C2-selective reaction of **6** with phenyl iodide (**7b**) to form **8b** does not take

dx.doi.org/10.1021/jo5013493 | J. Org. Chem. 2014, 79, 7185−7192

place, and in each case, a complex product mixture is produced (Scheme 3, conditions A–C). Also, the yield of the desired

Scheme 3. Reactions under Conventional C2-Selective Arylation Conditions

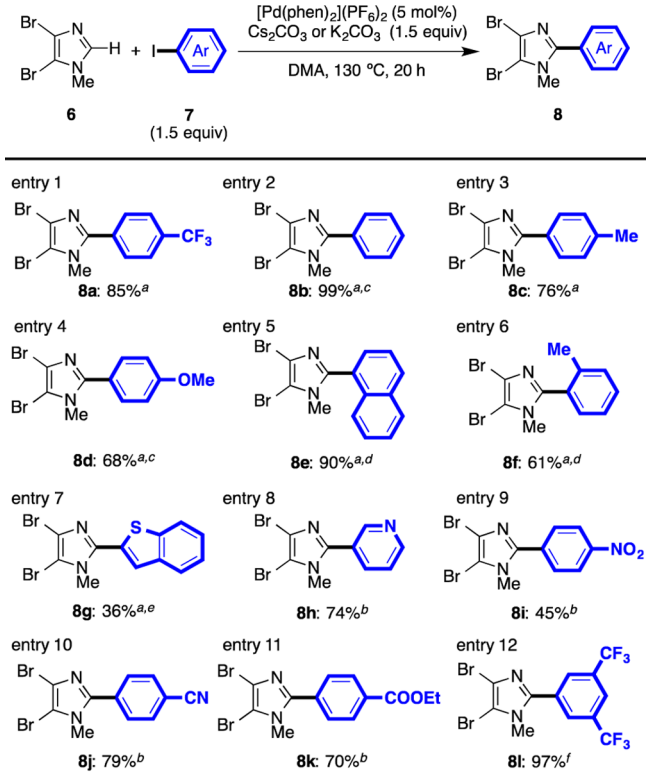


product was low when the previously reported catalytic system for 1-methyl-4,5-dichloroimidazole is employed to promote C–H-selective reaction (conditions D).[14] Again, the reaction proceeds smoothly with catalyst **1** to give **8b** in almost quantitative yield (conditions E).

Scope of Substrates. Based on the findings described above, the aryl iodide scope of the coupling reaction was investigated next. As the results tabulated in Table 1 and represented in Scheme 3 show, reaction of **6** with aryl iodides **7a** and **7b**, promoted by **1**, give the corresponding arylated imidazoles **8a** and **8b** in high yields (Table 2, entries 1 and 2). Relatively electron-rich aryl iodides, which are generally less reactive in oxidative addition processes, also react with **6** under these conditions to form the corresponding products **8c** and **8d** in high yields (entries 3 and 4). Steric hindrance in the aryl halides has little effect on the efficiencies of this process as exemplified by reactions with 1-naphthyl iodide **7e** and *o*-tolyl iodide **7f**, which generate the corresponding coupling products **8e** and **8f** in respective yields of 90 and 61% (entries 5 and 6). It should be noted that the use of Pd(phen)$(OAc)_2$ instead of **1** as a catalyst gives higher yields for coupling reactions of these substrates. Reaction of imidazole **6** with five-membered heteroaromatic iodide **7g** takes place to form arylation product **8g** in low yield (entry 7), but in contrast, the six-membered heteroaromatic iodide **7h** couples with **6** with high efficiency (entry 8). In addition, reactions of **6** with aryl iodides **7i–k**, containing strongly electron-withdrawing groups such as nitro, cyano, and ethoxycarbonyl, form the corresponding adducts **8i–k** in moderate to good yields (entries 9–11). Notably, selective cleavage of the C–Br bond in the highly electron-deficient 3,5-bis(trifluoromethylphenyl)bromide **9l** takes place in reaction with **6** while the C–Br bonds in the imidazole remain undisturbed (entry 12).

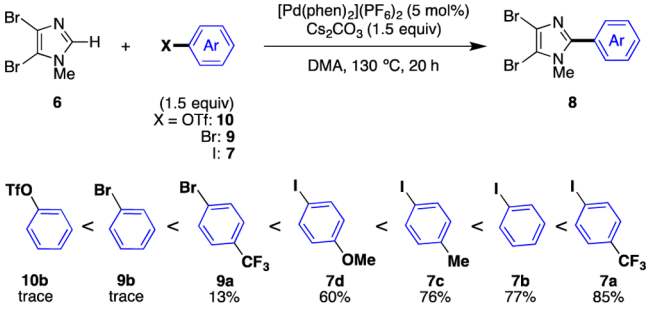
The efficiencies and selectivities of the C–H arylation reactions of **6** are governed by the high reactivity of aryl halides in transition-metal-catalyzed oxidative addition processes (Scheme 4).[15] In fact, reactions using less reactive aryl halides such as phenyl triflate (**10b**) and phenyl bromide (**9b**) are observed to result in formation of complex mixtures that contain only trace amounts of coupling products **8**. In these

Table 2. Scope of Reaction of 6 with Aryl Iodides



[a] Cs_2CO_3 was used. [b] K_2CO_3 was used. [c] Reaction was performed at 150 °C. [d] Pd(phen)$(OAc)_2$ was used as a catalyst. [e] The yield was determined by using ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [f] Aryl bromide was used instead of iodide.

Scheme 4. Reactivity Order of Aryl Halides and an Aryl Triflate

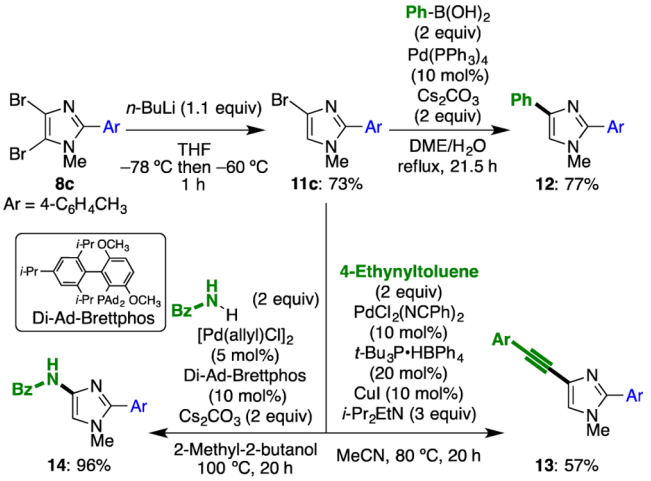


cases, unidentified insoluble materials, which probably contain oligomerized imidazole, are formed in significant amounts. Although arylated imidazole products are generated in reactions using the more reactive aryl bromides such as bromo-α,α,α-trifluorotoluene (**9a**), the yields are low. In contrast, highly selective incorporation of aryl groups is achieved using aryl iodides as substrates.

Synthetic Applications of the Selective Arylation Reaction. In this effort, we also investigated synthetic applications of the C2-arylated imidazoles **8** that are generated in selective Pd-catalyzed C–H bond arylation reactions of 1-methyl-4,5-dibromoimidazole. For example, 2,4-disubstituted imidazoles **12–14**, which are difficult to prepare from unsubstituted imidazoles using conventional methods, are produced by utilizing straightforward pathways (Scheme 5).

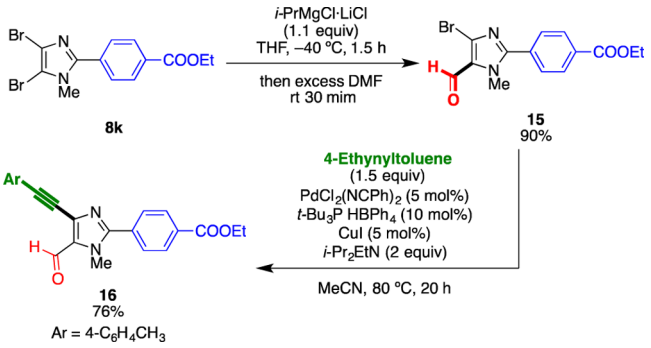
dx.doi.org/10.1021/jo5013493 | J. Org. Chem. 2014, 79, 7185–7192

Scheme 5. Synthesis of 2,4-Substituted Imidazoles



Treatment of dibromoimidazole **8b** with an equivalent of *n*-butyllithium at −78 °C followed by aqueous quenching gave rise selectively to the debrominated imidazole **11c** in high yield.[16] The remaining C4-bromo group in **11c** can be used to introduce aryl or acetylenic groups by employing conventional cross-coupling reactions. For example, Suzuki−Miyaura coupling of **11c** with phenylboronic acid efficiently generates the 2,4-diarylated *N*-methylimidazole **12**.[17] Application of a Sonogashira coupling enabled generation of 4-alkynyl-2-arylimidazole **13** in good yield.[18] Furthermore, cross-coupling reaction of **11c** with benzamide under conditions recently described by Buchwald produces the C4-amidated imidazole **14** in 96% yield.[19] The C5-selective debromination protocol can be applied to other 2-aryl-3,4-dibromoimidazoles, as exemplified by the debromination of the alkoxycarbonylated derivative **8k** under Knochel's conditions with *i*-PrMgCl·LiCl,[20] which is more tolerant of ester moieties than is butyllithium. Addition of DMF to the crude reduction mixture formed in this manner gives rise to formylimidazole **15** in excellent yield (Scheme 6).

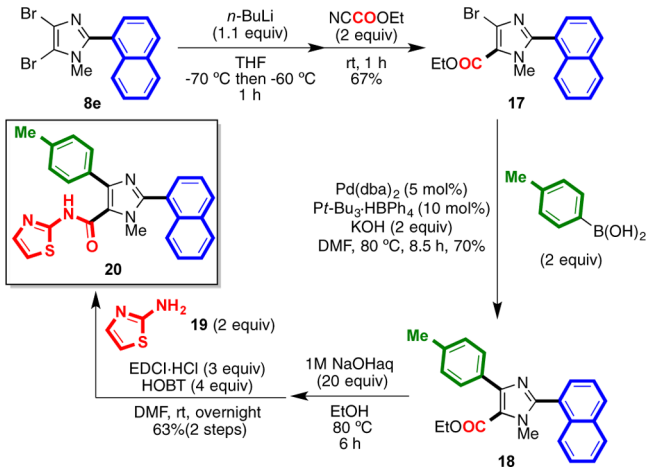
Scheme 6. Functionalization of Dibromoimidazole Bearing an Alkoxycarbonyl Group



These observations show that alkynyl and carbonyl groups, particularly a formyl group, which are typically sensitive to a variety of reagents, can be introduced at late stages of synthetic pathways using the new protocol. In fact, the formylimidazole derivative **15** can be coupled with a terminal alkyne by using Sonogashira conditions in the last step to produce the highly substituted imidazole **16** (Scheme 6).

To demonstrate the power of the new method developed in the studies described above, we employed it in the synthesis of the highly substituted imidazole **20**, which has been shown to possess antiallergic properties (Scheme 7).[1f] In previous efforts,

Scheme 7. Synthesis of 20



20 was synthesized using conventional condensation strategies that are difficult to apply for the preparation of derivatives. In the strategy we devised, the naphthyl group in the target is introduced in the first step through C−H arylation of 1-methyl-4,5-dibromoimidazole that provides **8e** (Table 2, entry 5). Selective C5 lithiation of **8e** followed by ethoxycarbonylation with ethyl cyanoformate efficiently generates ester **17**. The remaining bromo group in **17** is then used to direct Suzuki−Miyaura coupling with *p*-tolylboronic acid to give **18**, which is then transformed to **20** by hydrolysis followed by condensation with 2-aminothiazole (**19**).

CONCLUSIONS

In conclusion, a method for direct C−H-selective arylation of a dibromoimidazole with aryl iodides, using a Pd−1,10-phenanthroline catalyst, was developed in the investigation described above. The catalyst used for this process finely discriminates C−Br bonds of the imidazole from bonds of the arylating agents and consequently promotes reactions that chemo- and regioselectively form 2-aryl-4,5-dibromoimadazole products in high efficiencies. By employing this process, diversely functionalized azoles can be readily produced, making 4,5-dibromoimidazoles versatile precursors in the preparation of highly functionalized imidazoles. Selective C−H arylation reactions of other brominated azoles and applications of the generated functionalized imidazoles[1,21] and respective reaction mechanisms on each C−H bond as well as C−H bond-selective reactions are the focus of our continuing investigations in this area.

EXPERIMENTAL SECTION

General. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C are reported in δ values with reference to tetramethylsilane and $CDCl_3$ as internal standards, respectively. The ^{19}F chemical shifts are expressed in δ values deshielded with respect to CF_3COOH as an external standard. The mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained by ionizing samples via electron ionization (EI) in positive mode with a magnetic sector analyzer. All reactions were carried out in an argon atmosphere. Preparative recycling gel permeation chromatography (GPC) was performed on Japan Analytical Industry LC-908 or LC9201R/U recycling prepara-

dx.doi.org/10.1021/jo5013493 | J. Org. Chem. 2014, 79, 7185−7192

tive HPLC equipped with JAIGEL-1H and -2H columns (chloroform as eluent).

Reaction of Benzoxazole (2) and 4-Bromoiodobenzene (3). $[Pd(phen)_2](PF_6)_2$ (**1**) (5 mol %, 19 mg), Cs_2CO_3 (1.5 equiv, 245 mg), benzoxazole (**2**) (0.5 mmol, 60 mg), 4-bromoiodobenzene (**3**) (1.5 equiv, 212 mg), and DMA (1 mL) were added to a screw-capped test tube. The reaction mixture was stirred for 20 h at 130 °C under argon atmosphere. After the reaction completed, the mixture was cooled to room temperature. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 10:1, R_f = 0.63) to give 2-(4-bromophenyl)benzoxazole (**4**)[22] in 56% yield (38 mg) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.34−7.38 (m, 2H), 7.55−7.60 (m, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.74−7.79 (m, 1H), 8.12 (d, J = 8.8 Hz, 2H).

General Procedure for the C−H-Selective Arylation of 4,5-Dibromoimidazole. $[Pd(phen)_2](PF_6)_2$ (**1**) (5 mol %, 10 mg), Cs_2CO_3 (1.5 equiv, 122 mg) or K_2CO_3 (1.5 equiv, 52 mg), 4,5-dibromo-1-methylimdazole (**6**) (0.25 mmol, 60 mg), aryl iodides **7** (1.5 equiv), and DMA (0.5 mL) were added to a screw-capped test tube. The reaction mixture was stirred for 20 h at 130−150 °C under an argon atmosphere. After the reaction completed, the mixture was cooled to room temperature. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give 2-arylated 4,5-dibromoimidazole **8**.

4,5-Dibromo-1-methyl-2-(4-(trifluoromethyl)phenyl)-imidazole (8a): 85% yield (82 mg), colorless solid, mp 97.0−97.6 °C; R_f = 0.33 (*n*-hexane/EtOAc = 10:1); IR (KBr) 1619, 1494, 1449, 1409, 1330, 1167, 1124, 1092, 1014, 971, 848 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 7.73 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 34.8, 106.9, 117.4, 123.8 (q, J_{C-F} = 272.5 Hz), 125.8 (q, J_{C-F} = 3.8 Hz), 128.0, 131.5 (q, J_{C-F} = 32.9 Hz), 132.9, 147.0 (Ar); ^{19}F NMR ($CDCl_3$) δ −50.5; MS (EI) m/z (relative intensity %) 386 (45, M$^+$ + 4), 384 (100, M$^+$ + 2), 382 (49, M$^+$); HRMS (EI) exact mass calcd for $C_{11}H_7{}^{79}Br_2F_3N_2$ (M$^+$) 381.8928; found 381.8932.

4,5-Dibromo-1-methyl-2-phenylimdazole (8b):[23] 99% yield (78 mg), colorless solid; R_f = 0.29 (*n*-hexane/EtOAc = 10:1); ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 7.43−7.48 (m, 3H), 7.54−7.57 (m, 2H).

4,5-Dibromo-1-methyl-2-(4-methylphenyl)imidazole (8c): 76% yield (63 mg), colorless solid, mp 99.5−100.0 °C; R_f = 0.28 (*n*-hexane/EtOAc = 10:1); IR (KBr) 1496, 1455, 1377, 1236, 1096, 968, 822, 721, 496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.67 (s, 3H), 7.26 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) 21.5, 34.7, 105.3, 116.7, 126.8, 128.7, 129.5, 139.8, 148.8; MS (EI) m/z 332 (59, M$^+$ + 4), 330 (100, M$^+$ + 2), 328 (69, M$^+$); HRMS (EI) exact mass calcd for $C_{11}H_{10}{}^{79}Br_2N_2$ 327.9211; found 327.9217.

4,5-Dibromo-1-methyl-2-(4-methoxyphenyl)imidazole (8d): 66% yield (57 mg), colorless solid, mp 126.4−129.6 °C; R_f = 0.15 (*n*-hexane/EtOAc = 10:1); IR (KBr) 1608, 1495, 1464, 1437, 1372, 1252, 1175, 1020, 968, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 3.83 (s, 3H), 6.95 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 34.7, 55.5, 105.1, 114.2, 116.4, 122.0, 130.2, 148.6, 160.6; MS (EI) m/z (relative intensity %) 348 (27, M$^+$ + 4), 346 (55, M$^+$ + 2), 344 (27, M$^+$); HRMS (EI) exact mass calcd for $C_{11}H_{10}{}^{79}Br_2N_2O$ (M$^+$) 343.9160; found 343.9161.

4,5-Dibromo-1-methyl-2-(1-naphthyl)imidazole (8e): 90% yield (82 mg), colorless solid, mp 119.3−120.6 °C; R_f = 0.25 (*n*-hexane/EtOAc = 10:1); IR (KBr) 1502, 1453, 1369, 1235, 1095, 987, 956, 797, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 3H), 7.50−7.55 (m, 4H), 7.64−7.67 (m, 1H), 7.89−7.93 (m, 1H), 7.95−7.99 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 34.2, 105.0, 116.7, 125.1 (2C), 126.6, 127.1, 127.4, 128.6, 129.1, 130.6, 132.1, 133.6, 147.5; MS (EI) m/z (relative intensity %) 368 (54, M$^+$ + 4), 336 (100, M$^+$ + 2), 364 (49, M$^+$); HRMS (EI) exact mass calcd for $C_{14}H_{10}{}^{79}Br_2N_2$ (M$^+$) 363.9211; found 363.9216.

4,5-Dibromo-1-methyl-2-(2-methylphenyl)imidazole (8f): 61% yield (50 mg), yellow solid, mp 82.9−86.2 °C; R_f = 0.23 (*n*-hexane/EtOAc = 10:1); IR (KBr) 2923, 1493, 1442, 1378, 1221, 1086, 969, 775, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 3.43 (s, 3H), 7.25−7.30 (m, 3H), 7.34−7.38 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.8, 33.7, 104.3, 116.3, 125.9, 129.3, 130.1, 130.5, 130.6, 138.3, 148.2; MS (EI) m/z (relative intensity %) 332 (36, M$^+$ + 4), 330 (72, M$^+$ + 2), 328 (40, M$^+$); HRMS (EI) exact mass calcd for $C_{11}H_{10}{}^{79}Br_2N_2$ (M$^+$) 327.9211; found 327.9215.

2-(2-Benzothienyl)-4,5-dibromo-1-methylimidazole (8g): 36% yield (33 mg), yellow solid, mp 158.7−163.5 °C; R_f = 0.50 (*n*-hexane/EtOAc = 4:1); IR (KBr) 1486, 1443, 938, 741, 723 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.37−7.40 (m, 2H), 7.56 (s, 1H), 7.80−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.9, 106.9, 117.5, 122.3, 123.4, 124.3, 125.0, 125.6, 131.6, 139.5, 140.0, 142.8; MS (EI) m/z (relative intensity %) 374 (42, M$^+$ + 4), 372 (88, M$^+$ + 2), 370 (42, M$^+$); HRMS (EI) exact mass calcd for $C_{12}H_8{}^{79}Br_2N_2S$ 369.8775; found 369.8773.

4,5-Dibromo-1-methyl-2-(3-pyridyl)imidazole (8h): 74% yield (59 mg), brown oil; R_f = 0.04 (*n*-hexane/EtOAc = 1:1); IR (KBr) 1570, 1487, 1413, 1374, 1228, 1092, 1020, 971, 813, 711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 7.41−7.44 (m, 1H), 7.96 (d, J = 7.6 Hz, 1H), 8.68 (brd, J = 3.1 Hz, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.8, 106.9, 117.6, 123.8, 126.1, 136.4, 145.5, 148.9, 150.3; MS (EI) m/z (relative intensity %) 319 (57, M$^+$ + 4), 317 (100, M$^+$ + 2), 315 (50, M$^+$); HRMS (EI) NMR exact mass calcd for $C_9H_7{}^{79}Br_2N_3$ 314.9007; found 314.9005.

4,5-Dibromo-1-methyl-2-(4-nitrophenyl)imidazole (8i): 45% yield (41 mg), yellow solid, mp 177.2−178.4 °C; R_f = 0.43 (*n*-hexane/EtOAc = 4:1); IR (KBr) 1594, 1521, 1483, 1347, 970, 856, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 7.81 (d, J = 8.8 Hz, 2H). 8.33 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 35.1, 107.9, 118.0, 124.1, 129.3, 135.4, 146.1, 148.1; MS (EI) m/z (relative intensity %) 363 (53, M$^+$ + 4), 361 (100, M$^+$ + 2), 359 (46, M$^+$); HRMS (EI) exact mass calcd for $C_{10}H_7{}^{79}Br_2N_3O_2$ (M$^+$) 358.8905; found 358.8900.

4,5-Dibromo-2-(4-cyanophenyl)-1-methylimidazole (8j): 79% yield (67 mg), colorless solid, mp 190.3−192.6 °C; R_f = 0.10 (*n*-hexane/EtOAc = 4:1); IR (KBr) 2224, 1604, 1487, 1448, 969, 843 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 7.72 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 35.0, 107.6, 113.2, 117.7, 118.3, 129.1, 132.6, 133.6, 146.4; MS (EI) m/z (relative intensity %) 343 (44, M$^+$ + 4), 341 (86, M$^+$ + 2), 339 (50, M$^+$); HRMS (EI) exact mass calcd for $C_{11}H_7{}^{79}Br_2N_3$ (M$^+$) 338.9007; found 338.9010.

4,5-Dibromo-2-(4-ethoxycarbonylphenyl)-1-methyl-imidazole (8k): 70% yield (68 mg), colorless solid, mp 128.2−129.6 °C; R_f = 0.15 (*n*-hexane/EtOAc = 10:1); IR (KBr) 2923, 1713, 1281, 1110, 775, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 3.73 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 8.12 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 34.9, 61.4, 106.8, 117.4, 128.5, 130.0, 131.3, 133.5, 147.5, 166.0; MS (EI) m/z (relative intensity %) 390 (57, M$^+$ + 4), 388 (100, M$^+$ + 2), 386 (47, M$^+$); HRMS (EI) exact mass calcd for $C_{13}H_{12}{}^{79}Br_2N_2O_2$ (M$^+$) 385.9266; found 385.9268.

2-(3,5-Bis(trifluoromethyl)phenyl)-4,5-dibromo-1-methyl-imidazole (8l): 97% yield (109 mg), colorless solid, mp 96.9−97.1 °C; R_f = 0.25 (*n*-hexane/EtOAc = 10:1); IR (KBr) 1482, 1354, 1277, 1183, 1134, 902 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 7.97 (s, 1H), 8.10 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 34.9, 107.8, 117.9, 123.0 (q, J_{C-F} = 273.4 Hz), 123.1 (q, J_{C-F} = 3.8 Hz), 128.6, 131.6, 132.5 (q, J_{C-F} = 33.8 Hz), 145.4; ^{19}F NMR ($CDCl_3$) −62.9; MS (EI) m/z (relative intensity %) 454 (45, M$^+$ + 4), 452 (100, M$^+$ + 2), 450 (49, M$^+$); HRMS (EI) exact mass calcd for $C_{12}H_6{}^{79}Br_2F_6N_2$ 449.8802; found 449.8801.

4-Bromo-1-methyl-2-(4-methylphenyl)imidazole (11c). A solution of *n*-BuLi in *n*-hexane (1.5 M, 1.1 equiv) was added dropwise to a solution of 4,5-dibromo-1-methyl-2-(4-methylphenyl)imidazole (**8c**) (0.25 mmol, 83 mg) in anhydrous THF (1 mL) under an argon atmosphere at −78 °C. The mixture was stirred at −60 °C for 1 h. The reaction solution was quenched with cold H_2O then was warmed to room temperature and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 4:1; R_f = 0.54) to give 4-bromo-1-methyl-2-(4-methylphenyl)imidazole (**11c**) in 73% yield (46 mg) as a colorless solid: mp

dx.doi.org/10.1021/jo5013493 | J. Org. Chem. 2014, 79, 7185−7192

96.3−98.0 °C; IR (KBr) 3110, 1505, 1461, 1447, 1390, 1250, 951, 770, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 3.69 (s, 3H), 6.90 (s, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 34.7, 114.8, 121.0, 126.6, 128.7, 129.3, 139.3, 148.1; MS (EI) m/z (relative intensity %) 252 (95, M^+ + 2), 250 (100, M^+); HRMS (EI) exact mass calcd for $C_{11}H_{11}{}^{79}BrN_2$ 250.0106; found 250.0103.

1-Methyl-2-(4-methylphenyl)-4-phenylimidazole (12). A solution of 4-bromo-1-methyl-2-(4-methylphenyl) imidazole (**11c**) (0.25 mmol, 63 mg), $PhB(OH)_2$ (2 equiv, 61 mg), Cs_2CO_3 (2 equiv, 163 mg), and $Pd(PPh)_4$ (10 mol %, 29 mg) in 1,2-dimethoxyethane (1 mL) and water (1 mL) was stirred at reflux under an argon atmosphere for 21.5 h. The mixture was diluted with citric acid (1 M) and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 4:1, R_f = 0.59) to give 1-methyl-2-(4-methylphenyl)-4-phenylimidazole (**12**) in 77% yield (48 mg) as a brown solid: mp 99.3−101.4 °C; IR (KBr) 1464, 1383, 827, 753, 729, 695 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 2.37 (s, 3H), 3.81 (s, 3H), 7.14−7.18 (m, 1H), 7.28−7.33 (m, 4H), 7.54 (s, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) 21.5, 34.7, 117.9, 125.0, 126.9, 127.1, 128.6, 128.9, 129.4, 133.8, 139.0, 140.6, 148.3; MS (EI) m/z 248 (M^+); HRMS (EI) exact mass calcd for $C_{17}H_{16}N_2$ 248.1313; found 248.1313.

1-Methyl-2-(4-methylphenyl)-4-(4-tolylethynyl)imidazole (13). To a solution of 4-bromo-1-methyl-2-(4-methylphenyl)imidazole (**11c**) (0.25 mmol, 63 mg) in MeCN (1.2 mL) were added $PdCl_2(NCPh)_2$ (10 mol %, 10 mg), Pt-Bu_3·$HBPh_4$ (20 mol %, 26 mg), CuI (10 mol %, 5 mg), 4-ethynyltoluene (2 equiv, 70 μL), and i-Pr_2NEt (3 equiv, 130 μL) under an argon atmosphere. The resulting mixture was stirred at 80 °C for 20 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 10:1, R_f = 0.09) to give 1-methyl-2-(4-methylphenyl)-4-(4-tolylethynyl)imidazole (**13**) in 57% yield (41 mg) as a brown solid: mp 142.6−144.3 °C; IR (KBr) 2212, 1503, 1470, 1449, 1390, 822, 768, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.39 (s, 3H), 3.71 (s, 3H), 7.11 (d, J = 7.6 Hz, 2H), 7.17 (s, 1H), 7.25 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.6, 34.9, 82.1, 89.9, 120.3, 123.4, 125.8, 126.6, 128.8, 129.1, 129.4, 131.5, 138.2, 139.4, 148.3; MS (EI) m/z 286 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{18}N_2$ 286.1470; found 286.1469.

4-Benzamido-1-methyl-2-(4-methylphenyl)imidazole (14). A solution of 4-bromo-1-methyl-2-(4-methylphenyl)imidazole (**11c**) (0.25 mmol, 63 mg), benzamide (2 equiv, 61 mg), Cs_2CO_3 (2 equiv, 163 mg), $[Pd(allyl)Cl]_2$ (2.5 mol %, 2 mg), and Di-Ad-BrettPhos (10 mol %, 16 mg) in 2-methyl-2-butanol (0.5 M, 0.5 mL) was stirred under an argon atmosphere for 20 h at 100 °C. The mixture was diluted with CH_2Cl_2, filtered through Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1:1, R_f = 0.50) to give 4-benzamido-1-methyl-2-(4-methylphenyl)imidazole (**14**) in 96% yield (70 mg) as a brown solid: mp 85.4−93.1 °C; IR (KBr) 1657, 1546, 1462, 826, 731, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 3.73 (s, 3H), 7.25 (d, J = 7.6 Hz, 2H), 7.41−7.52 (m, 5H), 7.55 (s, 1H), 7.92 (d, J = 7.6 Hz, 2H), 9.35 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 34.9, 110.3, 125.8, 127.3, 128.5, 128.8, 129.6, 131.9, 133.5, 136.2, 139.6, 143.1, 164.3; MS (EI) m/z 291 (M^+); HRMS (EI) exact mass calcd for $C_{18}H_{17}N_3O$ 291.1372; found 291.1378.

4-Bromo-2-(4-ethoxycarbonylphenyl)-5-formyl-1-methylimidazole (15). A solution of i-PrMgCl·LiCl in THF (1.2 M, 1.1 equiv, 0.50 mL) was added dropwise to a solution of 4,5-dibromo-2-(4-ethoxycarbonylphenyl)-1-methylimidazole (**8k**) (0.55 mmol, 215 mg) in anhydrous THF (2.2 mL) under an argon atmosphere at −40 °C. The mixture was stirred for 1.5 h, and DMF (8 mL) was then added. The reaction mixture was stirred at room temperature for 30 min and quenched with H_2O. The crude mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 4:1, R_f = 0.54) to give 4-bromo-2-(4-ethoxycarbonylphenyl)-5-formyl-1-methylimidazole (**15**) in 90% yield (167 mg) as a colorless solid: mp 95.6−98.2 °C, IR (KBr) 1720, 1664, 1181, 1108, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 4.00 (s, 3H), 4.41 (d, J = 7.2 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 8.17 (d, J = 8.3 Hz, 2H), 9.83 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 34.8, 61.6, 128.1, 129.4, 130.0, 130.9, 131.7, 132.4, 152.2, 165.8, 179.8; MS (EI) m/z (relative intensity %) 338 (91, M^+ + 2), 336 (100, M^+); HRMS (EI) exact mass calcd for $C_{14}H_{13}{}^{79}BrN_2O_3$ (M^+) 336.0110; found 336.0109.

2-(4-Ethoxycarbonylphenyl)-5-formyl-4-(4-methylphenylethynyl)-1-methylimidazole (16). To a solution of 4-bromo-2-(4-ethoxycarbonylphenyl)-5-formyl-1-methylimidazole (**15**) (0.1 mmol, 34 mg) in MeCN (0.5 mL) were added $PdCl_2(NCPh)_2$ (5 mol %, 2 mg), t-Bu_3P·$HBPh_4$ (10 mol %, 5 mg), CuI (5 mol %, 1 mg), 4-ethynyltoluene (1.5 equiv, 24 μL), and i-Pr_2NEt (2 equiv, 33 μL) under an argon atmosphere. The resulting mixture was stirred at 80 °C for 9.5 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 4:1, R_f = 0.38) to give 2-(4-ethoxycarbonylphenyl)-5-formyl-4-(4-methylphenylethynyl)-1-methylimidazole (**16**) in 76% yield (28 mg) as a brown solid: mp 165.1−168.5 °C; IR (KBr) 1718, 1660, 1279, 1108, 722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (t, J = 7.2 Hz, 3H), 2.37 (s, 3H), 4.02 (s, 3H), 4.41 (q, J = 7.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 8.18 (d, J = 8.5 Hz, 2H), 10.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.7, 34.7, 61.5, 79.6, 95.4, 118.8, 129.3, 129.4, 130.0, 131.9, 132.2, 132.3, 133.2, 137.7, 139.7, 152.5, 165.8, 179.8; MS (EI) m/z (relative intensity %) 372 (M^+); HRMS (EI) exact mass calcd for $C_{23}H_{20}N_2O_3$ 372.1474; found 372.1475.

4-Bromo-5-ethoxycarbonyl-1-methyl-2-(1-naphthyl)-imidazole (17). A solution of n-BuLi in n-hexane (1.5 M, 1.1 equiv, 0.18 mL) was added dropwise to a solution of 4,5-dibromo-1-methyl-2-(1-naphthyl)imidazole (**8e**) (0.25 mmol, 92 mg) in anhydrous THF (0.5 M, 0.50 mL) under an argon atmosphere at −78 °C. The mixture was stirred at −60 °C for 1 h, and ethyl cyanoformate (2 equiv, 49 μL) was then added. The reaction mixture was warmed to room temperature. After 2 h, the reaction was quenched with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc = 1:4, R_f = 0.43) to give 4-bromo-5-ethoxycarbonyl-1-methyl-2-(1-naphthyl)-imidazole (**17**) in 76% yield (68 mg) as a colorless oil: IR (KBr) 1707, 1244, 1125, 1108, 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 3.67 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 7.51−7.57 (m, 5H), 7.91−7.93 (m, 1H), 7.99−8.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 35.2, 61.1, 121.5, 124.0, 125.0, 125.1, 126.3, 126.6, 127.5, 128.6, 129.2, 130.8, 132.0, 133.6, 150.7, 160.1; MS (EI) m/z (relative intensity %) 360 (100, M^+ + 2), 358 (91, M^+); HRMS (EI) exact mass calcd for $C_{17}H_{15}{}^{79}BrN_2O_2$ (M^+) 358.0317; found 358.0318.

5-Ethoxycarbonyl-1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)imidazole (18).[1f] To a solution of 4-bromo-5-ethoxycarbonyl-1-methyl-2-(1-naphthyl)imidazole (**17**) (1.1 mmol, 382 mg) in DMF were added 4-methylphenylboronic acid (1.5 equiv, 216 mg), KOH (2 equiv, 118 mg), $Pd(dba)_2$ (10 mol %, 61 mg), and Pt-Bu_3·$HBPh_4$ (20 mol %, 111 mg) under an argon atmosphere, and the mixture was stirred at 80 °C for 8.5 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by GPC to give 5-ethoxycarbonyl-1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)imidazole (**18**) in 70% yield (285 mg) as a colorless oil: n-hexane/EtOAc = 4:1, R_f = 0.44; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 3.69 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.49−7.66 (m, 5H), 7.69 (d, J = 8.1 Hz, 2H), 7.91−7.93 (m, 1H), 8.00 (d, J = 8.1 Hz, 1H).

1-Methyl-4-(4-methylphenyl)-2-(1-naphthyl)-5-((2-thiazolyl)-aminocarbonyl)imidazole (20).[1f] To a solution of 5-ethoxycarbonyl-1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)imidazole (**18**) (0.17 mmol, 63 mg) in EtOH (10 mL) was added 1 M NaOHaq (20 equiv, 3.4 mL), and the mixture was stirred at 80 °C for 4 h. The reaction mixture was neutralized by addition of 5% HCl(aq) and

dx.doi.org/10.1021/jo5013493 | J. Org. Chem. 2014, 79, 7185−7192

extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. To a solution of the crude product in DMF (3.4 mL) were added 2-aminothiazole (**19**) (2 equiv, 34 mg), 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (3 equiv, 98 mg), and 1-hydroxybenzotriazole (4 equiv, 92 mg) and stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with H_2O twice. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 4:1, R_f = 0.33) to give 1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)-5-((2-thiazolyl)-aminocarbonyl)imidazole (**20**) in 63% yield (45 mg) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.77 (s, 3H), 7.26 (d, J = 8.1 Hz, 2H), 7.40−7.45 (m, 2H), 7.52−7.64 (m, 3H), 7.69−7.74 (m, 2H), 7.87 (d, J = 8.1 Hz, 2H), 7.94−7.97 (m, 1H), 8.03−8.08 (m, 2H).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR for all new compounds and ^{1}H NMR for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to have been supported by a Grant-in-Aid for Scientific Research on InnovativeAreas “Molecular Activation Directed toward Straightforward Synthesis”.

■ REFERENCES

(1) (a) Shiro, T.; Kakiguchi, K.; Takahashi, H.; Nagata, H.; Tobe, M. *Bioorg. Med. Chem.* **2013**, *21*, 2068. (b) Xian, M.; Ahn, S.; Wang, J.; Chen, J.; Miller, D. D.; Dalton, T. J.; Li, W. *J. Med. Chem.* **2013**, *56*, 3318. (c) Biersack, B.; Muthukumar, Y.; Schoberrt, R.; Sasse, F. *Bioorg. Med. Lett.* **2011**, *21*, 6270. (d) Cho, H. J.; Gee, H. Y.; Beak, K.-H.; Ko, S.-K.; Park, J.-M.; Lee, H.; Kim, N.-D.; Lee, M. G.; Shin, I. *J. Am. Chem. Soc.* **2011**, *133*, 20267. (e) Wigienda, T.; Gust, R. *J. Med. Chem.* **2007**, *50*, 1475. (f) Sueoka, H.; Yasuoka, J.; Nishiyama, A.; Kiuchi, M.; Yamamoto, K.; Sugahara, K.; Ehara, S.; Sakata, K. Patent US 6288061(B1); Welfide Corp., Japan, 2001.

(2) (a) Yamaguchi, T.; Hatano, S.; Abe, J. *J. Phys. Chem. A* **2013**, *118*, 134. (b) Iida, H.; Umebayashi, N.; Yashima, E. *Tetrahedron* **2013**, *69*, 11064. (c) Murai, T.; Hori, F.; Maruyama, T. *Org. Lett.* **2011**, *13*, 1718. (d) Al-Hashimi, M.; Labram, J. G.; Watkins, S.; Motevalli, M.; Athopoulos, T. D.; Heeney, M. *Org. Lett.* **2010**, *12*, 5478. (e) Shibahara, F.; Yamaguchi, E.; Kitagawa, A.; Imai, A.; Murai, T. *Tetrahedron* **2009**, *65*, 5062.

(3) For classical synthetic routes to functional imidazoles, see: Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000; pp 418−423.

(4) For selected very recent advances on synthesis of imidazole derivatives based on multicomponent couplings, see: (a) Rajaguru, K.; Suresh, R.; Mariappan, A.; Muthusubramanian, S.; Bhuvanesh, N. *Org. Lett.* **2014**, *16*, 744. (b) Chen, C.-Y.; Hu, W.-P.; Yan, P.-C.; Sendi, G. C.; Wang, J.-J. *Org. Lett.* **2013**, *15*, 6116.

(5) For recent reviews of C−H bond functionalization, see: (a) Wencel-Delord, J.; Glorious, F. *Nat. Chem.* **2013**, *5*, 369. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *31*, 8960. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (e) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (g) Roger, J.; Gottumukkaia, A. L. *ChemCatChem* **2010**, *2*, 20. (h) Colby, D. A.; Bergman, R.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (i) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (j) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (k) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (l) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

(6) For a review of C−H bond functionalization with Pd−nitrogen-based ligand systems, see: Shibahara, F.; Murai, T. *Asian J. Org. Chem.* **2013**, *2*, 624.

(7) Joo, J. M.; Toure, B. B.; Sames, D. *J. Org. Chem.* **2010**, *75*, 4911.

(8) For C−H bond arylation at C2, see: (a) Liu, B.; Li, J.; Song, F.; You, J. *Chem.—Eur. J.* **2012**, *18*, 10830. (b) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.—Eur. J.* **2011**, *17*, 10113. (c) Han, W.; Mayer, P.; Ofial, A. R. *Chem.—Eur. J.* **2011**, *17*, 6904. (d) Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (e) Bellina, F.; Calandri, C.; Cauterccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. For direct arylation at C5, see: (f) Liu, X.-W.; Shi, J.-L.; Yan, J.-X.; Wei, J.-B.; Peng, K.; Dai, L.; Li, C.-G.; Wang, B.-Q.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 5774. (g) Kumar, P. V.; Lin, W.-S.; Shen, J. S.; Nandi, D.; Lee, H. W. *Organometallics* **2011**, *30*, 5160. (h) Bellina, F.; Cauteruccio, S.; Fiore, A. D.; Rossi, R. *Eur. J. Org. Chem.* **2008**, 5436. (i) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578. For switchable direct arylation at C2 and C5, see: (j) Tamba, S.; Okuba, Y.; Tanaka, S.; Moriguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998. (k) Strotman, N. A.; Chobanian, H. R.; Guo, Y.; He, J.; Willson, J. E. *Org. Lett.* **2010**, *12*, 3578.

(9) (a) Recnick, L.-M.; Hameid, M. A. E.; Haider, M.; Schnürch, M.; Mihovilovic, M. D. *Synthesis* **2013**, *45*, 1387. (b) Strotman, N. A.; Chobanian, H. R.; He, J.; Guo, Y.; Dormer, P. G.; Jones, C. M.; Steves, J. *J. Org. Chem.* **2010**, *75*, 1733.

(10) (a) Liu, B.; Wu, N.; Li, M.; You, J.; Lan, J. *Chem.—Eur. J.* **2012**, *18*, 1599. (b) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674. (c) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguch, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998. (d) Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169. (e) Chiong, H. A.; Dagulis, O. *Org. Lett.* **2007**, *9*, 1449.

(11) (a) Shibahara, F.; Yamauchi, T.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2012**, *77*, 8815. (b) Shibahara, F.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2011**, *76*, 2680. (c) Yamaguchi, E.; Shibahara, F.; Murai, T. *Chem. Lett.* **2011**, *40*, 939. (d) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471.

(12) Tani, S.; Uehara, T. N.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2014**, *5*, 123.

(13) (a) Blanchot, M.; Candito, D. A.; Larnaud, F.; Lautens, M. *Org. Lett.* **2011**, *13*, 1486. (b) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (c) Verrier, C.; Martin, T.; Hoarau, C.; Marsals, F. *J. Org. Chem.* **2008**, *73*, 7383. (d) Harayama, T.; Hori, A.; Serban, G.; Morikami, Y.; Matsumoto, T.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 1064. (e) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

(14) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

(15) Foà, M.; Cassar, L. *J. Chem. Soc., Dalton Trans.* **1975**, 2572.

(16) (a) Iddon, B.; Khan, N.; Lim, B. L. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1445. (b) Gribble, G. W. *Metalation of Azoles and Related Five-Membered Ring Heterocycles*; Springer: Berlin, 2012; Vol. *29*, pp 92−102.

(17) Kenow, L. E.; Collins, I.; Cooper, L. C.; Harrison, T.; Madin, A.; Mistry, J.; Reilly, M.; Shaimi, M.; Weich, C. J.; Clarke, E. E.; Lewis, H. D.; Wrigley, J. D.; Best, J. D.; Murray, F.; Shearman, M. S. *J. Med. Chem.* **2009**, *52*, 3441.

(18) Shibahara, F.; Dohke, Y.; Murai, T. *J. Org. Chem.* **2012**, *77*, 5381.

(19) Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710.

(20) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(21) Related applications on functionalized thiazoles and selenazoles: (a) Murai, T.; Yamaguchi, K.; Hori, F.; Maruyama, T. *J. Org. Chem.* **2014**, *79*, 4930. (b) Murai, T.; Hori, F.; Maruyama, T. *Org. Lett.* **2011**, *13*, 1718.

(22) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411.
(23) Lyaskovskyy, V.; Fröhlich, R.; Würthwein, E. *Synthesis* **2007**, *14*, 2144.