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Ether-Imidazolium Carbenes for Suzuki–Miyaura Cross-Coupling of Heteroaryl Chlorides with Aryl/Heteroarylboron Reagents

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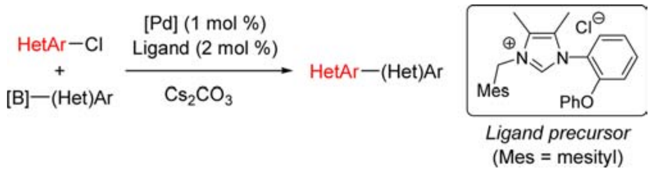
ABSTRACT



Easily accessible and handled ether-imidazolium chlorides were developed as ligand precursors. The coupling reactions of heteroaryl chlorides with aryl/heteroarylboronic acids and esters were catalyzed by the palladium/ether-imidazolium chloride system with high substrate tolerance to give various heterobiaryls in good to excellent yields.

Heterobiaryls are known as ubiquitous and significant structures in naturally occurring and biologically active compounds.[1] Suzuki–Miyaura coupling has been widely utilized to construct this class of compounds due to the advantageous features of organoboronic acids and their derivatives, such as low toxicity, easy manipulation, and ready availability.[2,3] In particular, the coupling of heteroaryl chlorides with heteroarylboron reagents remains a quite important but challenging task on the grounds of lower reactivity of chlorides and detrimental influences of heterocyclic motifs on catalytic activity,[4,5] though several efficient palladium–phosphine catalysts for this type of transformation have been reported.[6]

N-Heterocyclic carbenes (NHCs) have been focused on as useful ligands for transition metals because of their strong σ-electron-donating ability that allows formation of active and stable catalysts in addition to flexible access to their varying precursors.[7] These basic properties hold the promise of producing practically superior ligands bearing beneficial effects on catalytic performance. Although the development of Pd–NHC catalysts for challenging Suzuki–Miyaura reactions has been actively pursued,[8,9] examples of the heterobiaryl synthesis from heteroaryl chlorides and

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(1) Recent examples of biheteroaryl motifs: (a) Liu, Q.; Wang, J.; Kang, S. A.; Thoreen, C. C.; Hur, W.; Ahmed, T.; Sabatini, D. M.; Gray, N. S. *J. Med. Chem.* **2011**, *54*, 1473–1480. (b) Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Kenichiro Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660–19663. (c) Beaulieu, P. L.; Bös, M.; Cordingley, M. G.; Chabot, C.; Fazal, G.; Garneau, M.; Gillard, J. R.; Jolicoeur, E.; LaPlante, S.; McKercher, G.; Poirier, M.; Poupart, M.-A.; Tsantrizos, Y. S.; Duan, J.; Kukolj, G. *J. Med. Chem.* **2012**, *55*, 7650–7666. (d) Burckhardt, T.; Harms, K.; Koert, U. *Org. Lett.* **2012**, *14*, 4674–4677.

(2) For reviews of Suzuki–Miyaura cross-coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240–9261.

(3) Cyclic triolborate: (a) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928–931. MIDA ester: (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963. Triisopropyl borate: (c) Oberli, M. A.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 4606–4609.

(4) (a) Zhao, D.; You, J.; Hu, C. *Chem.—Eur. J.* **2011**, *17*, 5466–5492. (b) Ge, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12837–12841.

(5) Chlorides are known as ideal coupling partners in terms of cost and diversity: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.

(6) (a) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284. (b) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488. (c) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104–5112. (d) Fleckenstein, C. A.; Plenio, H. *Chem.—Eur. J.* **2008**, *14*, 4267–4279. (e) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973–980. (f) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.

(7) (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (b) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* **2011**, *111*, 2705–2733.

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heteroarylboron reagents are very few, and effective NHCs for this kind of cross-coupling are still desired.[10] Herein, we describe the coupling of heteroaryl chlorides with aryl/heteroarylboronic acids and esters catalyzed by the palladium/ether-imidazolium chloride system.

The ether-imidazolium chlorides (**2b** and **2d**–**e**) were simply prepared as ligand precursors in two steps from inexpensive reagents (Scheme 1). The one-pot synthesis of imidazoles (**1b** and **1d**–**e**) was carried out as the first step, leading to good yields.[11] The subsequent benzylation of imidazoles gave the desired products in high yields. Other ligand precursors were prepared in the same manner.[12] These ether-imidazolium chlorides were crystalline solids stable enough to handle and store exposed to air.

To evaluate the effects of ether-imidazolium chlorides, the coupling of 4-chloroanisole (**3a**) with phenylboronic acid (**4a**) using 1 mol % of catalysts (Pd/L = 1/2) formed in situ from carbene precursors **2a**–**i** and palladium(II) acetate was conducted at 80 °C (Table 1, entries 1–9).[13] The ether-imidazolium chloride with methyl groups at the 4- and 5-position led to high catalytic performance though the coupling with precursor **2a** gave 4-methoxybiphenyl (**5aa**) in moderate yield (entries 1 and 2). The extremely low result was obtained in the case of using the bulkier precursor bearing the 2,4,6-triisopropylbenzyl group (entry 3).

Scheme 1. Synthesis of Ether-Imidazolium Chlorides

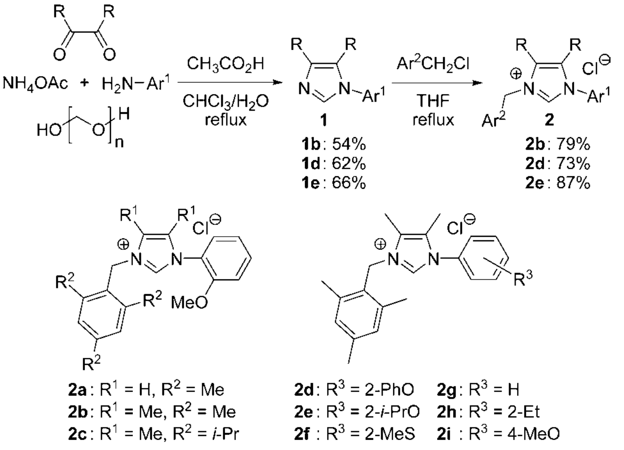
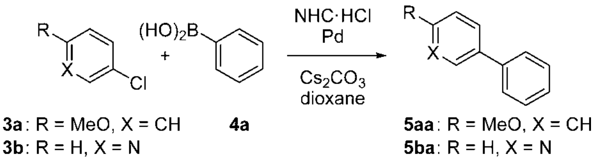


Table 1. Effects of Ether-Imidazolium Chlorides in Suzuki–Miyaura Coupling[a]



entry	substrate	NHC·HCl	Pd	yield (%)[b]
1	**3a**	**2a**	Pd(OAc)$_2$	49
2	**3a**	**2b**	Pd(OAc)$_2$	88
3	**3a**	**2c**	Pd(OAc)$_2$	2
4	**3a**	**2d**	Pd(OAc)$_2$	94
5	**3a**	**2e**	Pd(OAc)$_2$	94
6	**3a**	**2f**	Pd(OAc)$_2$	trace
7	**3a**	**2g**	Pd(OAc)$_2$	0
8	**3a**	**2h**	Pd(OAc)$_2$	4
9	**3a**	**2i**	Pd(OAc)$_2$	0
10	**3b**	**2b**	Pd(OAc)$_2$	3
11	**3b**	**2d**	Pd(OAc)$_2$	94(99)[d]
12	**3b**	**2e**	Pd(OAc)$_2$	91
13	**3b**	**2d**	[Pd(allyl)Cl]$_2$	90(98)[d]
14	**3b**	**2d**	PdCl$_2$	14
15	**3b**	**2d**	Pd$_2$(dba)$_3$	6
16	**3b**	**2d**	Pd(dba)$_2$	0
17[c]	**3b**	**2d**	Pd(OAc)$_2$	4

[a] Reaction conditions: **3** (1 mmol), **4a** (1.5 mmol), **2** (2 mol %), Pd (1 mol %), Cs$_2$CO$_3$ (2 mmol), dioxane (2 mL), 80 °C, 18 h. [b] Isolated yield. [c] Pd/**2d** = 1/1 (Pd: 1 mol %). [d] 90 °C.

Whereas the ether-imidazolium chlorides with the phenyl or isopropyl group on the oxygen afforded a 94% yield, the reaction with the precursor bearing the thioether group hardly proceeded (entries 4–6). The carbene precursors without an ether group and with a methoxy group at the *para*-position did not show beneficial effects (entries 7–9),

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(8) For examples of effective monodentate NHCs in the coupling with aryl/heteroaryl chlorides, see: (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805. (b) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363–1365. (c) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195. (d) Song, C.; Ma, Y.; Chai, Q.; Ma, C.; Jiangb, W.; Andrus, M. B. *Tetrahedron* **2005**, *61*, 7438–7446. (e) Özdemir, I.; Demir, S.; Çetinkaya, B. *Tetrahedron* **2005**, *61*, 9791–9798. (f) Luan, X.; Mariz, R.; Gatti, M.; Costabile, C.; Poater, A.; Cavallo, L.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 6848–6858. (g) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523–1533. (h) Jin, Z.; Guo, S.-X.; Gu, X.-P.; Qiu, L.-L.; Song, H.-B.; Jian-Xin Fang, J.-X. *Adv. Synth. Catal.* **2009**, *351*, 1575–1585. (i) Wu, L.; Drinkel, E.; Gaggia, F.; Capolicchio, S.; Linden, A.; Falivene, L.; Cavallo, L.; Dorta, R. *Chem.—Eur. J.* **2011**, *17*, 12886–12890. (j) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314–3332. (k) Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P. *Chem.—Eur. J.* **2012**, *18*, 4517–4521. (l) Tu, T.; Sun, Z.; Fang, W.; Xu, M.; Zhou, Y. *Org. Lett.* **2012**, *14*, 4250–4253.

(9) For examples of effective bidentate NHCs in the coupling with aryl/heteroaryl chlorides, see: (a) Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595–598. (b) Liao, C.-Y.; Chan, K.-T.; Tu, C.-Y.; Chang, Y.-W.; Hu, C.-H.; Lee, H. M. *Chem.—Eur. J.* **2009**, *15*, 405–417. (c) Schmidt, A.; Rahimi, A. *Chem. Commun.* **2010**, 2995–2997. (d) Kumar, M. R.; Park, K.; Lee, S. *Adv. Synth. Catal.* **2010**, *352*, 3255–3266.

(10) Examples: (a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.—Eur. J.* **2006**, *12*, 4743–4748. (b) Organ, M. G.; Çalimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383–2387. (c) Peh, G.-R.; Kantchev, E. A. B.; Er, J.-C.; Ying, J. Y. *Chem.—Eur. J.* **2010**, *16*, 4010–4017. (d) Liu, T.; Zhao, X.; Shen, Q.; Lu, L. *Tetrahedron* **2012**, *68*, 6535–6547.

(11) The procedure was modified on the basis of Orru's report: Gelens, E.; De Kanter, F. J. J.; Schmitz, R. F.; Sliedregt, L. A. J. M.; Van Steen, B, J.; Kruse, C. G.; Leurs, R.; Groen, M. B.; Orru, R. V. A. *Molecular Diversity* **2006**, *10*, 17–22.

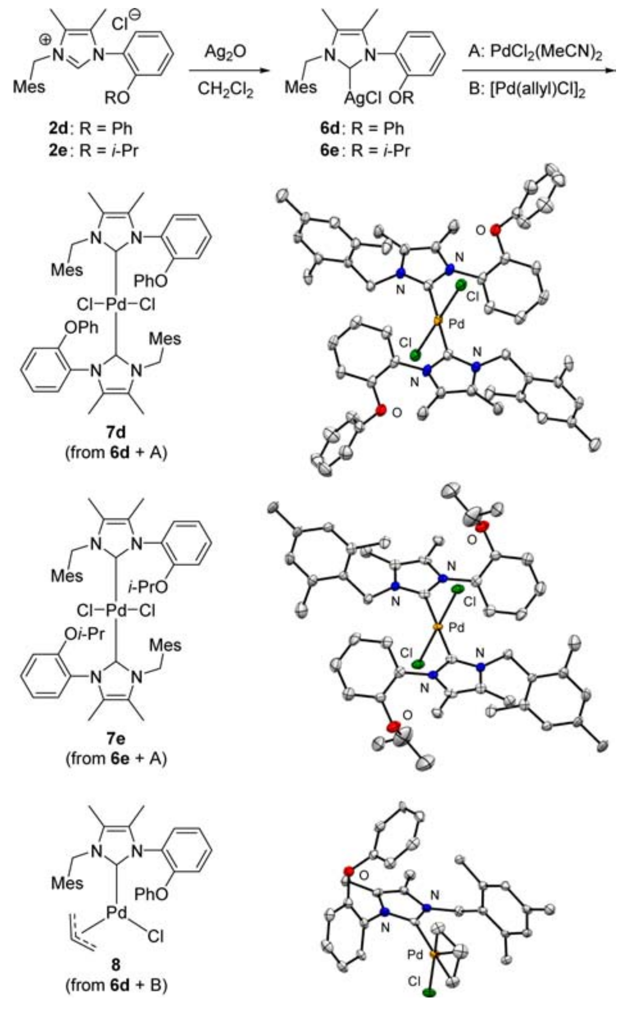
(12) The full details of carbene precursor synthesis were included in the Supporting Information.

(13) The precatalysts were prepared in situ by heating, and then the coupling reactions were carried out. See Supporting Information.

(14) The ether group could serve as a hemilabile donor: (a) Slone, C. S.; Weinberger, D. A.; Mirkin, C. A. *Prog. Inorg. Chem.* **1999**, *48*, 233–350. (b) Weng, Z.; Teo, S.; Hor, T. S. A. *Acc. Chem. Res.* **2007**, *40*, 676–684. (c) Kwong, F. Y.; Chan, A. S. C. *Synlett* **2008**, 1440–1448.

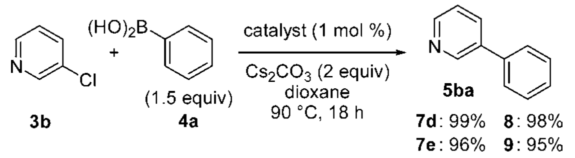
which proved that an ether moiety at the *ortho*-position was necessary for high catalytic activity.[14] In the coupling with 3-chloropyridine (**3b**), ether-imidazolium chlorides (**2b** and **2d**−**e**) were examined, and **2d** was found to be a superior ligand precursor while a significant decrease in yield was observed in the reaction with **2b** (entries 10−12). Screening of Pd sources revealed that an allylpalladium(II) chloride dimer as well as palladium(II) acetate were suitable (entries 11 and 13−16). The catalyst formed from **2d** and $Pd(OAc)_2$ in a 1:1 molar ratio led to a 4% yield (entry 17).

Scheme 2. Synthesis of Ether-Imidazolium Carbene−Palladium Complexes and X-ray Crystal Structures of **7d**−**e** and **8**



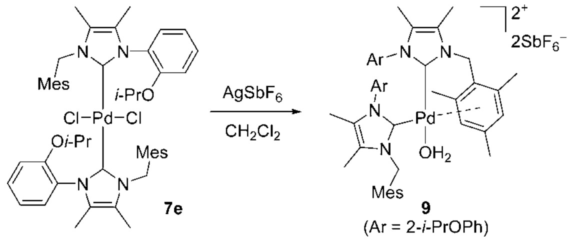
To acquire more information on the catalysts, the 1:2 and 1:1 molar ratio complexes of Pd/**2** were prepared via the Ag-NHC complexes (Scheme 2). Complexes **6**−**8** were obtained quantitatively, and the structures of **7** and **8** were determined by X-ray crystallographic analysis. The reaction with **8** in addition to that with **7d** gave desired product **5ba** in excellent yields (Scheme 3). These results suggested that the second precursor **2d** for Pd could play a key role in the formation of stable precatalysts, whereas one precursor **2d** in a complex catalyst was essential to achieve high catalytic performance.

Scheme 3. Suzuki−Miyaura Coupling with Ether-Imidazolium Carbene−Palladium Complexes



Furthermore, complex **7e** was converted with $AgSbF_6$ into the cationic complex **9** (Scheme 4), whose structure was confirmed by X-ray crystallography (Figure 1).[15] In this cationic complex **9**, the Pd−arene interaction was observed, which could stabilize catalysts and contribute to the improvement of catalyst activity and lifetime.[16] The cross-coupling using complexes **7e** and **9** also proceeded efficiently without problems (Scheme 3).

Scheme 4. Synthesis of Cationic Complex **9**



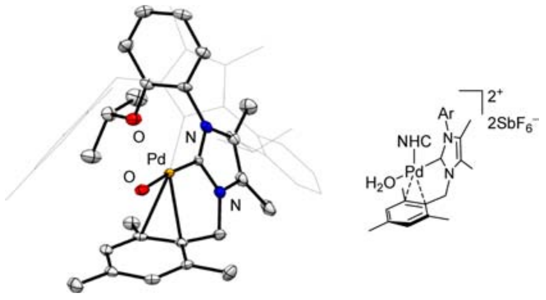


Figure 1. X-ray crystal structure of **9**. NHC with no Pd−arene interaction is displayed in a wireframe model, and two SbF_6^- are omitted for simplicity.

Investigation of heterobiaryl synthesis was conducted with 1 mol % of the palladium/ether-imidazolium chloride system (Scheme 5). Initially, a series of heteroaryl chlorides were examined using phenylboronic acid as a coupling partner. Neither the electronic influence of substituents

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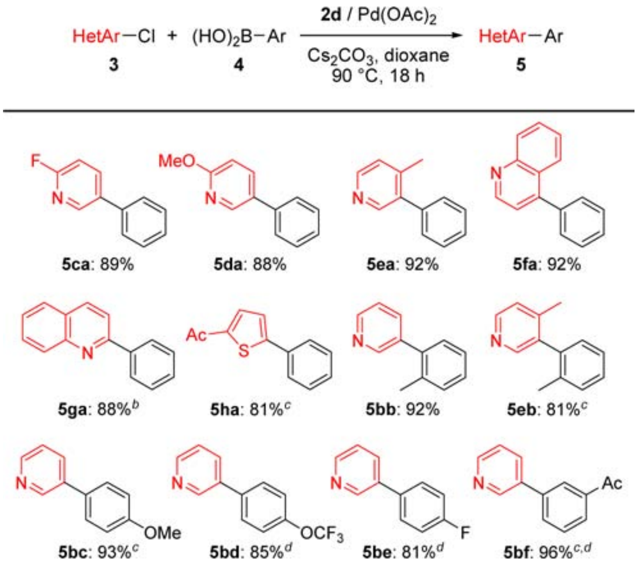
(15) The single crystals of cationic complex prepared from **7d** could not be obtained despite careful screening of recrystallization conditions.

(16) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473 and references therein.

Scheme 5. Coupling of Heteroaryl Chlorides with Arylboronic Acids Using Ether-Imidazolium Chloride[a]

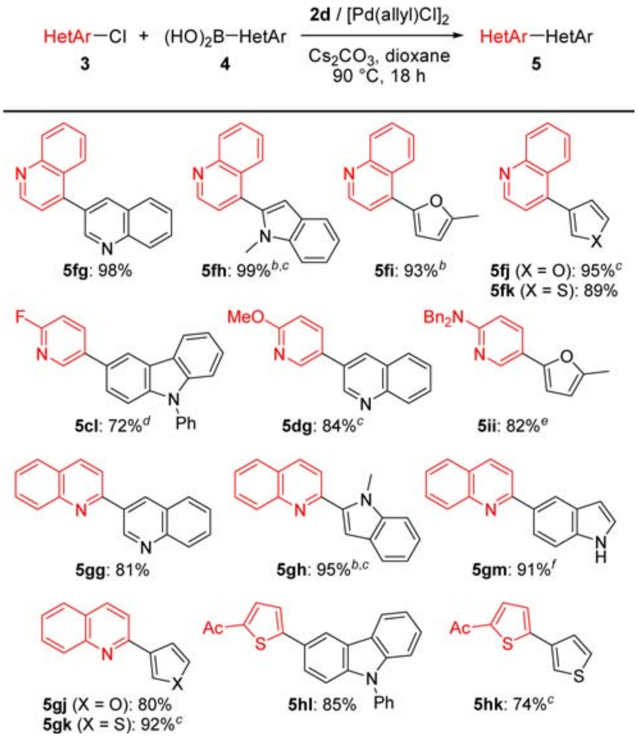


[a] Reaction conditions: **3** (1 mmol), **4** (1.5 mmol), **2d** (2 mol %), Pd (1 mol %), Cs_2CO_3 (2 mmol), dioxane (2 mL), 90 °C, 18 h. [b] $PhB(OH)_2$ (2 mmol) was used. [c] $[Pd(allyl)Cl]_2$ (0.5 mol %) was used. [d] 100 °C.

(**5ca**—**da**) nor steric hindrance (**5ea**—**fa**) led to a significant decrease in yield. The substrates bearing a heteroatom adjacent to the reactive site also proved to be good reaction partners (**5ga**—**ha**). Then, the influence of arylboronic acids was investigated in the reactions with 3-chloropyridine and its derivative. The sterically hindered reagent reacted smoothly to afford the desired products in high yields (**5bb** and **5eb**). The coupling with arylboronic acids bearing electron-donating and -withdrawing groups also proceeded with sufficient efficiency (**5bc**—**bf**).

The cross-coupling of heteroaryl chlorides with heteroarylboron reagents was examined with 1 mol % catalyst loading (Scheme 6). High catalytic activity was observed in the synthesis of biheteroaryls from sterically hindered 4-chloroquinoline and a variety of heteroarylboronic acids and esters bearing quinoline, indole, furan, and thiophene moieties (**5fg**—**fk**). A series of 3-chloropyridine derivatives with fluoro, methoxy, and amino groups showed good reactivity in the presence of heteroaryl coupling partners (**5cl**, **5dg**, and **5ii**).[17] In the coupling with 2-chloroquinoline, this catalytic system tolerated an indole NH group (**5gm**) as well as nitrogen-, oxygen-, and sulfur-containing heteroaromatic rings (**5gg**—**gh** and **5gj**—**gk**), leading to high yields. The 2-chlorothiophene derivative reacted sufficiently with heteroarylboronic acids bearing carbazole and thiophene units (**5hl** and **5hk**).

Scheme 6. Coupling of Heteroaryl Chlorides with Heteroarylboronic Acids and Esters Using Ether-Imidazolium Chloride[a]



[a] Reaction conditions: **3** (1 mmol), **4** (1.5 mmol), **2d** (2 mol %), Pd (1 mol %), Cs_2CO_3 (2 mmol), dioxane (2 mL), 90 °C, 18 h. [b] Pinacol boronate ester (1.5 mmol) was used. [c] 100 °C. [d] $Pd(OAc)_2$ (1 mol %) was used. [e] Pinacol boronate ester (2 mmol) was used. [f] H_2O (0.2 mL) was added.

In summary, the palladium/ether-imidazolium chloride system achieved high catalytic performance and substrate tolerance in the coupling reactions of heteroaryl chlorides with aryl/heteroarylboron reagents. The carbene precursor was prepared from inexpensive reagents in two steps and obtained as crystalline solids stable enough to handle and store under air. Investigation of the effects of ligand structures and the Pd—NHC complexes suggested that the ether moiety as a ligand and Pd—arene interaction could play key roles for catalytic activity. For the development of new catalytic reactions, tuning of this catalyst system is currently under investigation in our research group.

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Supporting Information Available. Full experimental details, a cif file, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[17] Instead of **2d**, IMes·HCl (2 mol %), IPr·HCl (2 mol %), and SIPr·HCl (2 mol %) were examined in the synthesis of **5ii** with the same reaction conditions, leading to 18%, 28%, and 2% yields, respectively. The reactions with [Pd(IPr)(allyl)Cl] (1 mol %) and [Pd-PEPPSI-IPr] (1 mol %) in place of **2d** and $[Pd(allyl)Cl]_2$ gave **5ii** in 22% and 18% yields, respectively.