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C−H Bonds as Ubiquitous Functionality: A General Approach to Complex Arylated Imidazoles via Regioselective Sequential Arylation of All Three C−H Bonds and Regioselective *N*-Alkylation Enabled by SEM-Group Transposition

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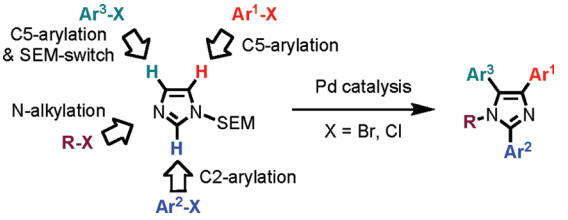

Imidazoles are an important group of the azole family of heterocycles frequently found in pharmaceuticals, drug candidates, ligands for transition metal catalysts, and other molecular functional materials. Owing to their wide application in academia and industry, new methods and strategies for the generation of functionalized imidazole derivatives are in demand. We here describe a general and comprehensive approach for the synthesis of complex aryl imidazoles, where all three C−H bonds of the imidazole core can be arylated in a regioselective and sequential manner. We report new catalytic methods for selective C5- and C2-arylation of SEM-imidazoles and provide a mechanistic hypothesis for the observed positional selectivity based on electronic properties of C−H bonds and the heterocyclic ring. Importantly, aryl bromides and low-cost aryl chlorides can be used as arene donors under practical laboratory conditions. To circumvent the low reactivity of the C-4 position, we developed the SEM-switch that transfers the SEM-group from N-1 to N-3 nitrogen and thus enables preparation of 4-arylimidazoles and sequential C4−C5-arylation of the imidazole core. Furthermore, selective N3-alkylation followed by the SEM-group deprotection (trans-*N*-alkylation) allows for regioselective *N*-alkylation of complex imidazoles. The sequential *C*-arylation enabled by the SEM-switch allowed us to produce a variety of mono-, di-, and triarylimidazoles using diverse bromo- and chloroarenes. Using our approach, the synthesis of individual compounds or libraries of analogues can begin from either the parent imidazole or a substituted imidazole, providing rapid access to complex imidazole structures.

Introduction

Imidazoles are essential components of biologically active compounds, including natural products and synthetics, and display a broad range of biological activities[1] (for example, antibacterial,[2] anticancer,[3] anti-inflammatory activity[4]). The imidazole ring serves as a rigid scaffold for the presentation of attached substituents in a fixed spatial orientation, creating

(1) Reviews: (a) Xi, N.; Huang, Q.; Liu, L. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 4, pp 143−364. (b) Luca, L. D. *Curr. Med. Chem.* **2006**, *13*, 1–23.

(2) 4,5-Diarylimidazoles showed antibacterial activity. Antolini, M.; Bozzoli, A.; Ghiron, C.; Kennedy, G.; Rossi, T.; Ursini, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1023–1028.

(3) 4,5-Diarylimidazoles were found to have strong antitubulin and cytotoxic activity. Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y.-H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697–1711.

(4) 2,4,5-Triarylimidazoles inhibit mitogen-activated protein kinase activity. Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heys, J. R.; Landvatter, S. W.; Strickler, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature* **1994**, *372*, 739–746.

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desirable motifs for high affinity protein ligands. For example, di-, tri-, and tetra-substituted imidazoles have recently emerged as potent kinase inhibitors.[5] Also, 2-arylimidazoles were found to be selective ligands for histamine receptors[6] and 1,5-diarylimidazoles to display vascular disrupting activity.[7] Moreover, imidazole-based *N*-heterocyclic carbenes have been actively pursued as transition metal ligands for the development of new catalysts,[8] and imidazolium ionic liquids are used as recyclable solvents for industrial catalytic processes, affording "green" alternatives to standard organic solvents.[9] The wide use of imidazoles generated a considerable interest in imidazole chemistry and revealed the need for more efficient synthetic strategies.[10]

There are a number of established de novo methods for the synthesis of substituted imidazoles where the imidazole ring is constructed via cyclo-condensation reactions. Although these traditional approaches have been greatly improved over the past decade, each method has its scope and efficiency limitations.[11,12] Often, the condensation methods are inefficient for the assembly of series of compounds: for example, regioisomers (2,4- versus 4,5-substitution pattern) or focused analogues (different arene rings in the 4-position). In most cases, the synthesis of each analogue of the library will require the entire de novo synthetic sequence, which translates to parallel repetition of linear synthetic sequences.

To address this problem, in part of a broad program dedicated to development of new synthetic methods and strategies based on C−H bond functionalization,[13,14] we have been developing catalytic arylation transformations, where multiple C−H bonds of heteroarenes are functionalized in a selective and sequential manner (*topologically obvious synthesis*).[13,15] We have recently reported catalytic arylation of pyrazoles and a synthetic strategy based on SEM-group transposition that enables sequential arylation and preparation of complex aryl pyrazoles.[15a] We here report a general and comprehensive strategy for the preparation of highly functionalized aryl imidazoles through direct arylation of the imidazole core (Figure 1).[16−18] *All three C−H bonds* of the imidazole ring can selectively and sequentially be replaced by arene rings using aryl bromides or aryl chlorides, and the amino group can be alkylated in a regioselective manner, providing rapid access to all regioisomers of mono-, di-, and triarylimidazoles.[19−21]

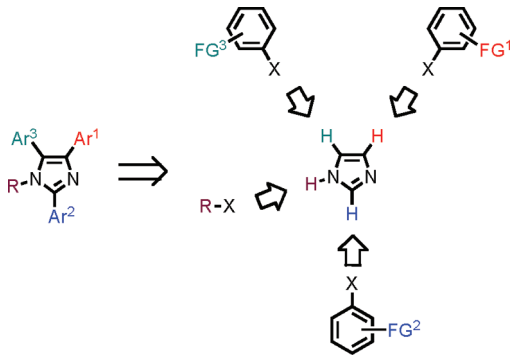


FIGURE 1. Rapid access to complex imidazoles via direct C−H arylation.

Guided by the general reactivity of imidazoles, we developed Pd-catalyzed regioselective C5- and C2-arylation protocols together with the SEM-switch and trans-*N*-alkylation. Figure 2 illustrates some of many possible synthetic pathways. Schematically, C5-arylation provides compound **I**, which can be arylated at the 2-position to give compound **II**, a protected 2,5-diarylimidazole. This compound could alternatively be prepared by C2-arylation, followed by C5-arylation (not shown), and depending on the specific structural context, one sequence may provide better yield than the other. The subsequent arylation of the 4-position in **II** is low yielding (< 10%); therefore the unreactive C-4 position is converted to a reactive C-5 position via the SEM-switch, and subsequent arylation affords **IV**, a protected 2,4,5-triarylimidazole. This compound could be deprotected or converted to **V** via selective trans-*N*-alkylation (Figure 2A). Note that all substituents of the imidazole ring are introduced in a

(5) Jackson, P. F.; Bullington, J. L. *Curr. Top. Med. Chem.* **2002**, *2*, 1011–1020.
(6) Leschke, C.; Elz, S.; Garbarg, M.; Schunack, W. *J. Med. Chem.* **1995**, *38*, 1287–1294.
(7) Bonezzi, K.; Taraboletti, G.; Borsotti, P.; Bellina, F.; Rossi, R.; Giavazzi, R. *J. Med. Chem.* **2009**, *52*, 7906–7910.
(8) Review: Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676.
(9) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692.
(10) (a) *Science of Synthesis*; Grimmett, M. R., Ed.; Thieme: Stuttgart, 2002; Vol. 12, pp 325−512. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571–4624.
(11) Murry, J. A. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 945–965.
(12) Review: (a) Kamijo, S.; Yamamoto, Y. *Chem. Asian J.* **2007**, *2*, 568–578. Recent examples: (b) Kanazawa, C.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10662–10663. (c) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050–6051. (d) Frantz, D. E.; Morency, L.; Soheili, A.; Murry, J. A.; Grabowski, E. J. J.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 843–846. (e) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516–1524.
(13) For global analysis of approaches toward C-H bond functionalization and its consequences in organic synthesis, see: Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72.
(14) Recent reviews on catalytic C−H bond functionalization: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115.
(15) (a) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042–3048. (b) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476–1479. (c) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979–1982. (d) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057. (e) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997. (f) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897–2900.
(16) (a) A comprehensive review on arylation of heteroarenes including azoles: Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310. (b) Since the publication of this review, C5-arylation of 1-alkylimidazoles with aryl bromides has been reported: Roger, J.; Doucet, H. *Tetrahedron* **2009**, *65*, 9772–9781.
(17) For recent reviews on C−H bond arylations, see: (a) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35–41. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826.
(18) For recent examples of catalytic C−H arylation of arenes and heteroarenes, see: (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597. (b) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004–3007. (c) Čerňová, M.; Pohl, R.; Hocek, M. *Eur. J. Org. Chem.* **2009**, 3698–3701. (d) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473–1476.
(19) Synthesis of diarylimidazoles via sequential arylation of *N*-benzylimidazoles has been reported: Bellina, F.; Cauteruccio, S.; Fiore, A. D.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060–6072.
(20) For sequential arylation of imidazole *N*-oxides, see: Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306.
(21) For recent examples of sequential arylation to produce highly substituted heteroarenes, see: (a) Ref 15a. (b) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622–14623. (c) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047–1060.

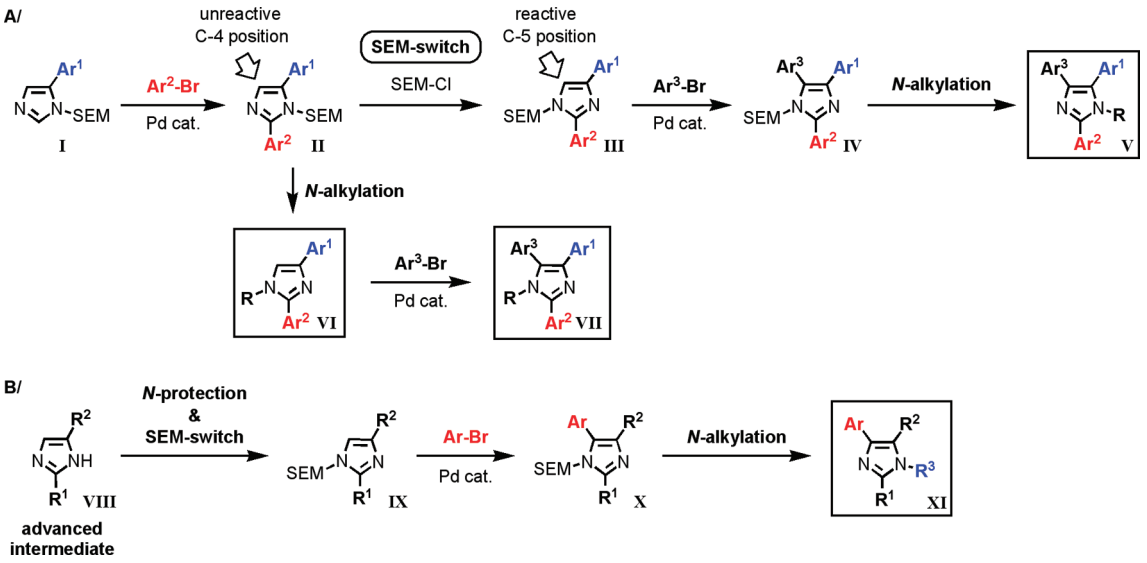


FIGURE 2. C2- and C5-arylation methods, together with the SEM-switch, provide rapid access to complex arylimidazoles with complete control of regioselectivity. The SEM group also allows for regioselective *N*-alkylation (trans-*N*-alkylation). (A) An example of sequential elaboration of SEM-imidazole to furnish 1-alkyl-2,4-diarylimidazoles and 1-alkyl-2,4,5-triarylimidazoles. (B) Advanced intermediates (accessed for example by condensation methods) may also be arylated and alkylated in a regioselective manner via the strategy based on the SEM group.

regioselective manner. Another possibility involves trans-*N*-alkylation of compound **II** to furnish **VI**, a 2,4-diaryl-1-alkyl-imidazole, which can be further arylated to give **VII**, a regioisomer of **V**. This latter pathway affords access to 2,4-diaryl-1-alkyl-imidazoles and would be the route of choice for preparation of 2,4,5-triarylimidazoles in cases where the arene ring Ar^3 is not compatible with trans-*N*-alkylation.

We also wish to point out that the C5- and C2-arylation methods and the strategy based on the SEM-switch described in this paper are applicable to arylation and *N*-alkylation of advanced imidazole intermediates with various substitution patterns and substituents other than arene rings. For example, as illustrated in Figure 2B, compound **VIII**, a 2,4(5)-disubstituted imidazole, can be protected in a regioselective manner to give compound **IX**, which can be arylated in the 5-position and alkylated to furnish product **XI**. Both the aryl group and the alkyl group are introduced in a regioselective manner in three steps. Thus, complex aryl imidazoles can be prepared from either the parent imidazole (which is readily available and inexpensive) or substituted imidazole intermediates.

Results and Discussion

Regioselectivity of the Palladium-Catalyzed Arylation of Imidazoles. The general reactivity trends of imidazole are shown in Figure 3A: the C-5 position shows high reactivity toward electrophilic substitution, the C-4 position is relatively less reactive in this respect, and the C-2 position bears the most acidic C−H bond. We have previously introduced the SEM group [SEM = 2-(trimethylsilyl)ethoxymethyl] as a suitable protecting group for azoles, including indoles, pyrroles, pyrazoles, and imidazoles, in the context of palladium-catalyzed C−H arylation.[15a,c] In this work, we developed new and practical protocols for C5- and C2-arylation of SEM-imidazoles using both aryl bromides and aryl chlorides as the arene donors (Figure 3B). With the parent SEM-imidazole, the optimized palladium protocol for C5-arylation afforded the desired product **2** in good yield along with 2,5-diphenyl-1-SEM-imidazole, in 7:1 ratio (Figure 3B). Careful examination of the reaction conditions revealed a critical role of base in the C2-arylation. Employing the stronger base sodium *tert*-butoxide in a nonpolar solvent, we developed a new protocol for C2-arylation of SEM-imidazoles that shows good selectivity for the 2-position (6:1, Figure 3B). To overcome the low reactivity of the 4-position, we developed the SEM-group transposition ("SEM-switch"), which leads to the rearrangement of the SEM-group from the N-1 to N-3 nitrogen. 4-Phenyl-1-SEM-imidazole can be accessed in one step by the SEM-switch (compound **2** → **5**, Figure 3C). Similarly, alkylation of N-3 nitrogen and SEM-group deprotection provides 4-phenyl-1-methylimidazole ("trans-*N*-alkylation", compound **2** → **6**, Figure 3C).

Mechanistic Hypothesis for Positional Selectivity: Electronic Properties of C−H Bonds and the Heteroarene Ring. The C5-arylation of imidazoles may occur via electrophilic metalation-deprotonation (EMD) or concerted metalation-deprotonation (CMD), as illustrated in Figure 4A. In both mechanisms, the carboxylate or carbonate ligand is directly involved in the intramolecular deprotonation. The EMD mechanism is a stepwise metalation process similar to S_EAr, while CMD is a concerted one-step process. In our previous work, we have demonstrated the importance of the carboxylate ligand both in the palladium-catalyzed[15b,c,f] and rhodium-catalyzed arylation[15e] of electron-rich heteroarenes. We have also provided kinetic evidence for the direct involvement of the pivalate ligand in the C−H activation step.[15e] With triarylphosphine ligands (relatively weak σ-donors), our data pointed toward the carboxylate-assisted EMD mechanism.[15e,f] Alternatively, other groups provided experimental and computational evidence for the CMD mechanism for the catalytic systems using strong σ-donor phosphines, where formation of the carbon−metal bond and breaking of the carbon−hydrogen bond take place simultaneously, while maintaining the aromaticity of arenes or heteroarenes.[22]

(22) (a) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849 and references therein.

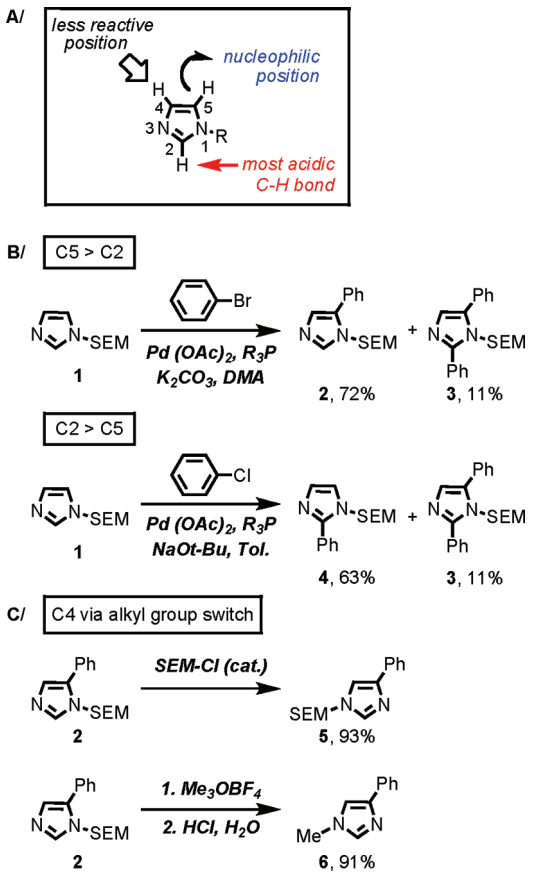


FIGURE 3. (A) General reactivity trends of imidazole. (B) Two methods for palladium-catalyzed C−H arylation of SEM-imidazoles were developed with complementary regioselectivity (C5 and C2). The C2- and C5-arylation protocols enable the use of both aryl bromides and aryl chlorides, providing a practical method for synthesis of arylimidazoles. (C) The SEM-group transposition (SEM-switch) leads to 4-arylimidazoles and allows for subsequent arylation and preparation of complex arylimidazoles. Similarly, the SEM group enables regioselective *N*-alkylation (trans-*N*-alkylation) to afford 1-alkyl-4-arylimidazoles.

The C5 selectivity can readily be explained by EMD as the 5-position is more nucleophilic than the 2- and 4-positions; standard electrophilic aromatic substitutions occur preferentially at C5. To further rationalize the high selectivity for the C-5 position, we propose that the inductive effect of the N-1 nitrogen stabilizes the carbon−palladium bond at C5 (and the partially formed carbon−palladium bond in the transition state), and thus the C5-metalation is preferred considering both thermodynamic and kinetic factors (Figure 4A). In contrast, metalation of the C-2 and C-4 positions is disfavored by the electronic repulsion between the electron lone pair on the N-3 and the carbon−palladium bond, which may be particularly important in the CMD mechanism (Figure 4B).

In the presence of a strong base (NaO*t*-Bu), deprotonation of the C-2 position becomes efficient, presumably facilitated by complexation of the palladium complex to the N-3 nitrogen (Figure 4C). The inductive effect of two nitrogen atoms renders the C−H bond most electron-deficient and most acidic. The C2-nucleophile subsequently displaces either a halide or *tert*-butanol at the palladium metal to form the C2-palladium intermediate, eventually leading to the C2-arylated product.

The electronic rationale provided above explains the low reactivity of C-4; arylation of the C-4 position gives low yields even under forcing conditions when C-2 and C-5 positions are substituted (< 10% yield). The C-5 to C-2 selectivity of the Pd/carbonate method is moderate, and so is the C-2 to C-5 selectivity of the Pd/NaO*t*-Bu system, which is attributed to relatively high reactivity of both positions (that are adjacent to the substituted nitrogen N-1) under Pd/base conditions.

Development of C5-Arylation of SEM-Protected Imidazoles. We have previously introduced the air- and moisture-stable mixed phosphine-NHC palladium complexes, exemplified by **7** (Table 1), as a new class of catalysts for the arylation of heteroarenes and reported selective C5-arylation of 1-SEM-imidazole **1** with iodobenzene using complex **7** as the catalyst.[15c] We here show that a wide range of aryl donors could be employed for the arylation of SEM-imidazole (Table 1, Method A). However, this method is not compatible with chloroarene donors and the catalyst requires a multistep synthesis.

In the hope of identifying a practical and versatile catalytic procedure, we thoroughly examined the reaction parameters including metal catalyst, ligand, base, solvent, and temperature. This search found that the treatment of SEM-imidazole **1** with 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.2 equiv of PhBr, and 2.0 equiv of K_2CO_3 in DMA (0.5 M) at 120 °C led to full conversion of the starting material, giving the desired product **2** in 72% yield along with the 2,5-diarylation product **3** in 11% yield (Table 1). Unlike our catalytic method for pyrazole *C*-arylation, where potassium carbonate and a substoichiometric quantity of pivalic acid (or potassium pivalate) were used,[15a] potassium carbonate alone proved to be an optimum base for the coupling of SEM-imidazole and bromobenzene. When we added 0.25 equiv of pivalic acid in conjunction with 3.0 equiv of potassium carbonate, a significant amount of the overarylation product **3** (21% isolated yield) was formed in addition to the monoarylation product **2** (56% yield). While the use of the carboxylic acid additive improves the performance of many palladium-catalyzed *C*-arylations of arenes and heteroarenes, the highly active catalytic system can decrease the regioselectivity of this reaction in cases where the substrate contains multiple C−H bonds susceptible to C−H arylation.[23]

Superior results to the Pd/NHC complex were achieved when the new optimized catalytic system was used (Table 1, Method B). The substituents on aryl donors did not greatly affect the coupling yields; both electron-rich and electron-poor aryl bromides coupled with SEM-imidazole, affording 5-arylimidazoles in good yields. Importantly, the optimized protocol employing the electron-rich trialkylphosphine P(*n*-Bu)Ad_2 also enables the use of aryl chlorides as arene donors with good efficiency (Table 1).[24] In addition, the reaction can be conducted on the benchtop using the air-stable phosphonium salt [P(*n*-Bu)Ad_2H]BF_4, prepared by mixing the phosphine and tetrafluoroboric acid.[25] For the C5-arylation with aryl bromides and chlorides, other sterically hindered trialkylphosphines, such as tricyclohexylphosphine and 2-(dicyclohexylphosphino)biphenyl, gave comparable results to those with *n*-butyl-di(1-adamantyl)phosphine (see Supporting Information for experimental details).

(23) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276–3277.
(24) C5-Arylation of *N*-butylimidazole with chlorobenzene (in 52% yield) was reported: Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449–1451.
(25) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.

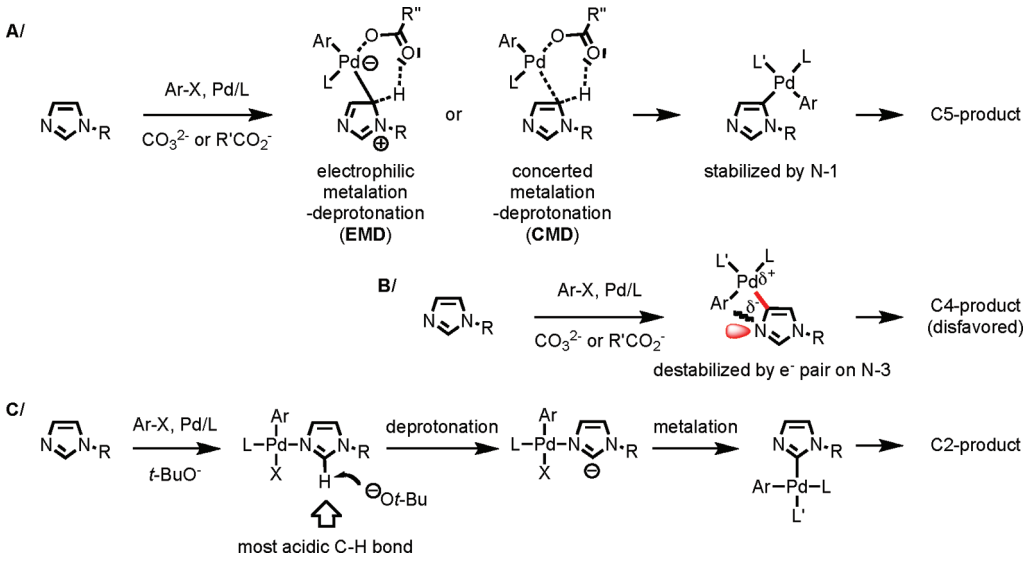
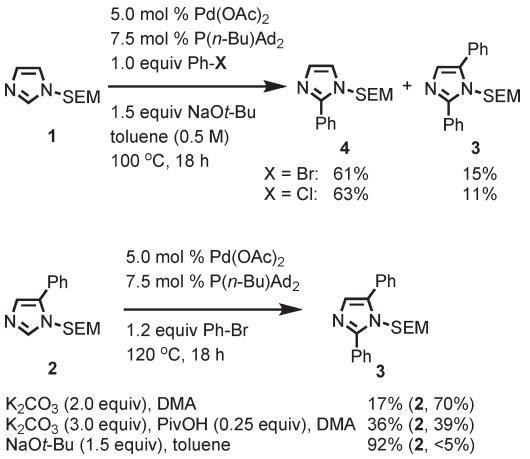


FIGURE 4. Mechanistic rationales for the observed regioselectivity of the imidazole arylation. (A) In the presence of carbonate or carboxylate base (R″ = alkyl or alkoxide), the C−H activation occurs via ligand-assisted palladation (via either EMD or CMD mechanism). The C-5 position is preferred over the C-2 and C-4 due to stabilization of the C−Pd bond by the inductive effect of N-1 nitrogen. (B) In contrast, palladation at the C-4 position is disfavored by electronic repulsion between the nitrogen e$^-$ pair and the polarized C−Pd bond. (C) In the presence of a strong base, deprotonation occurs at the C-2 position, presumably facilitated by complexation of the palladium complex to N-3. The same rationale applies to other azoles including oxazoles, thiazoles, and triazoles.

Development of New Conditions for C2-Arylation of Imidazoles. Empirical studies have found that the C-5 position of imidazoles exhibited reactivity higher than that at the C-2 position for the palladium-catalyzed arylation in the presence of weak bases, as originally demonstrated by Miura and colleagues with *N*-methylimidazole and aryl iodides.[26] It was also shown in their paper that the addition of copper(I) salts altered the bias toward the C-2 position. The latter method has subsequently been optimized by others and applied to *N*-methylimidazole and other azole heteroarenes.[19,27] Alternatively, a rhodium-catalyzed C2-arylation of 1,3-azoles has been developed; however, only arylation of 4,5-disubstituted imidazoles has been reported.[28] In sum, existing methods for C2-arylation of imidazoles are limited to aryl iodides, while aryl bromides require high temperatures (≥140 °C).[16,28,29] Furthermore, the Pd/Cu bimetallic system gave only a trace amount of the desired product with SEM-imidazole **1** (5 mol % of $Pd(OAc)_2$, 2 equiv of CuI, 2 equiv of bromoarene, DMF, 140 °C, 24 h).

Consequently, we carefully examined the palladium-catalyzed conditions and developed a versatile and practical method for C2-arylation of SEM-imidazoles with both aryl bromides and aryl chlorides. Inspired by the base-promoted tautomerization of imidazole ligands to *N*-heterocyclic carbenes,[30] we envisioned that upon coordination of the palladium complex to the N-3 nitrogen of imidazole, an alkali metal alkoxide would be sufficiently basic to produce a C2-metalated intermediate. Moreover, since an electron-rich phosphine ligand should enable the activation of chloroarenes, which are not efficient donors for the previously reported procedures as discussed above, we decided to take advantage of the palladium-phosphine pair that we identified for the C5-arylation of imidazoles (and C5-arylation of pyrazoles[15a]).

SCHEME 1. C2-Arylation of SEM-Imidazoles



Screening experiments with different bases and solvents led us to establish a new set of conditions, where imidazole **1** gave 2-phenylimidazole **4** in 61% yield after heating in toluene (0.5 M) in the presence of 1.5 equiv of NaO*t*-Bu (Scheme 1). Weaker bases were much less effective than NaO*t*-Bu. As expected, the formation of the double arylation product was not negligible, and it was isolated in 11−15% yield. Importantly, chlorobenzene gave a similar yield and higher C2:C5 selectivity (from 4:1 to 6:1) compared to that of bromobenzene. Not only the simple phenyl halides but also functionalized arene donors

(26) (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473. (b) For other examples of C2-arylation of *N*-methylimidazole using the Pd/CuI system, see the comprehensive review in ref 16a.

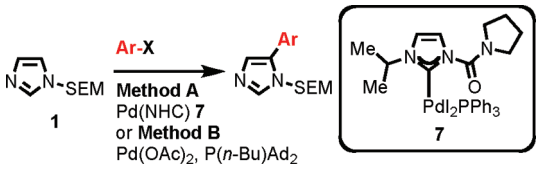
(27) Copper-catalyzed C2-arylation of *N*-methylimidazole with iodobenzene has been reported: Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185–15192.

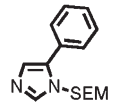
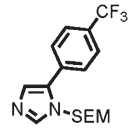
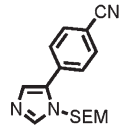
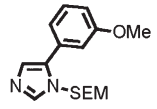
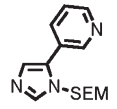
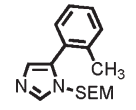
(28) (a) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493–2500. (b) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589–1591.

(29) In the following paper, the authors provide one example of C2-arylation of *N*-arylimidazole with 2-bromonaphthalene using the $Pd(OAc)_2$/CuI system in DMF at 140 °C in the presence of CsF as the base. Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 693–703.

(30) Ruiz, J.; Perandones, B. F. *J. Am. Chem. Soc.* **2007**, *129*, 9298–9299.

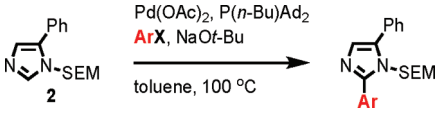
TABLE 1. C5-Arylation of 1-SEM-Imidazole

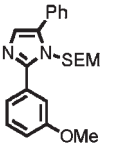
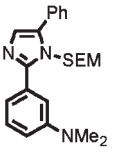
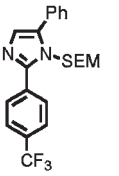
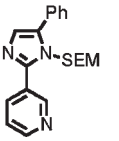
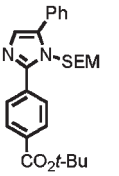
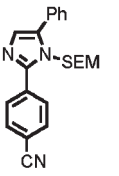


entry	product		yield (Method A)[a]	yield (Method B)[b]
1		**2**	X=Br: 59%	X=Br: 72%, 70%[c] X=Cl: 67%, 58%[c]
2		**8**	X=Br: 61%	X=Br: 64% X=Cl: 57%[c]
3		**9**	X=Br: 30%	X=Br: 59%
4		**10**	X=I: 55%	X=Br: 68% X=Cl: 56%[c]
5		**11**	X=I: 43%	X=Br: 60%
6		**12**	X=I: 29%	X=Br: 68%

[a]Method A: 5.0 mol % **7**, 2.0 equiv of ArX, 2.0 equiv of CsOAc, DMA (1.0 M), 125 °C, 16−20 h. Complex **7** can be prepared according to the protocol provided in ref 15c. [b]Method B: 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.2 equiv of ArX, 2.0 equiv of K_2CO_3, DMA (0.5 M), 120 °C, 18 h. The corresponding 2,5-diarylation product was also formed in 5−10% yield (see Supporting Information). [c]In the benchtop experiment, [P(*n*-Bu)Ad_2H]BF_4 was used, and the amount of K_2CO_3 was increased (2.5 equiv). Yields are an average of two separate isolated yields.

TABLE 2. C2-Arylation of 5-Phenylimidazole 2[a]



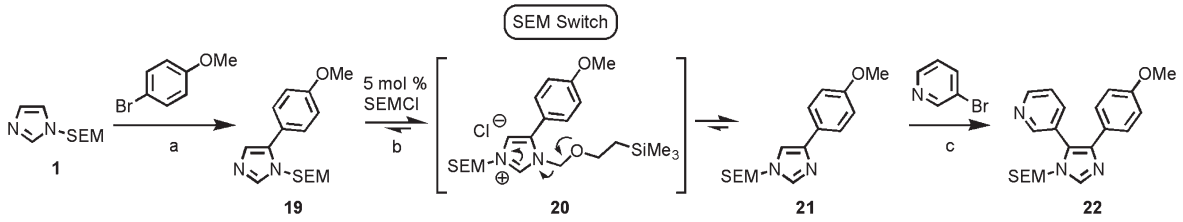
entry	product		yield[b]
1		**13**	X=Br: 88% X=Cl: 75%
2		**14**	X=Br: 77% X=Cl: 75%
3		**15**	X=Br: 78% X=Cl: 82%
4		**16**	X=Br: 45% X=Cl: 32%
5		**17**	X=Br: 70%
6		**18**	X=Br: 19% (60%)[c]

[a]Reaction conditions: 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.5 equiv of ArX, 2.0 equiv of NaO*t*-Bu, toluene (2.0 M), 100 °C, 24 h. [b]Isolated yield, average of two runs. [c]$Pd(PPh_3)_2Cl_2$ (5 mol %) was used in place of $Pd(OAc)_2$/P(*n*-Bu)Ad_2. For C2-arylation of SEM-imidazole **1**, see Supporting Information.

can be employed for the C2-arylation of imidazole **1** (e.g., 3-bromoanisole and 4-bromobenzonitrile afforded the desired products in 60% and 51% isolated yields, respectively; Scheme S1 in Supporting Information). This transformation represents an important advance as regioselective C2-arylation of imidazoles can be performed with aryl chlorides (and a single transition metal as the catalyst). Moreover, the simple switch from C5- to C2-arylation of SEM-imidazole by using the alkoxide base and the nonpolar solvent demonstrates the plasticity of palladium catalysis and suggests potential application of this method for regioselective arylation of *N*-alkyl- and *N*-arylimidazoles as well as other classes of heteroarenes.[31] While the C2/C5 regioselectivity in the reaction of the SEM-imidazole was modest, the C2-arylation of 5-phenylimidazole **2** is efficient under the newly developed conditions. Once the 5-position of imidazoles is substituted, the overarylation is no longer a problem.

(31) Compare with site-selective sp^2 and benzylic sp^3 arylation of azine *N*-oxides: (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155–3164.

SCHEME 2. Synthesis of 4,5-Diarylimidazoles[a]



[a]Reaction conditions: (a) 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.2 equiv of 4-bromoanisole, 2.0 equiv of K_2CO_3, DMA (0.5 M), 120 °C, 17 h, 63% yield; (b) 5.0 mol % SEMCl, CH_3CN, 80 °C, 22 h, 88% yield; (c) 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.2 equiv of 3-bromopyridine, 2.0 equiv of K_2CO_3, DMA (0.5 M), 120 °C, 20 h, 46% yield. Recovered starting material and 2,5-diarylation product were isolated in 17% and 11% yields, respectively. Yields are an average of two separate isolated yields.

Using the alkoxide base, we were able to obtain SEM-protected 2,5-diarylimidazoles with a variety of functional groups on the C2 aryl ring in good to excellent yields (Table 2). For example, 3-chloroanisole was coupled to 5-phenylimidazole **2**, giving **13** in 75% isolated yield. Naturally, as this method relies on the use of a strong base, there are limitations in the scope related to the presence of base-sensitive groups. We addressed two important limitations: (1) the use of a carboxylic acid ester and (2) the use of a nitrile. The method is compatible with *tert*-butyl esters of carboxylic acids as demonstrated by the efficiency of C2-arylation with *tert*-butyl 4-bromobenzoate (Table 2, entry 5). By using the *tert*-butyl ester, complications related to transesterification and hydrolysis were largely eliminated (the corresponding ethyl ester gave much lower yield). The outcome of C2-arylation with 4-bromobenzonitrile was less than satisfactory (Table 2, entry 6). However, when the air- and moisture-stable catalyst $Pd(PPh_3)_2Cl_2$ was used in lieu of $Pd(OAc)_2$ and P(*n*-Bu)Ad_2, it gave a significantly improved result, affording product **18** in 60% yield. Finding the solution to this problem was guided by the rationale that the nitrile as an electron-withdrawing group activates the aryl halide toward oxidative addition, and therefore a less active palladium system [such as $Pd(PPh_3)_2Cl_2$] would be sufficient for the aryl halide activation and at the same time less prone to inhibition by the product.[32]

Synthesis of 4-Aryl-1-SEM-imidazoles and 4,5-Diarylimidazoles via the SEM-Switch. The new methods for C2- and C5-arylation of SEM-protected imidazoles enable direct access to 5-aryl-1-SEM-imidazoles, 2-aryl-1-SEM-imidazoles, and 2,5-diaryl-1-SEM-imidazoles, as well as the corresponding free (NH)-imidazoles (via simple deprotection of the SEM group, vide infra). However, the C-4 position of SEM-imidazoles (and other *N*-substituted imidazoles) exhibits very low reactivity in the palladium-catalyzed C−H arylation described above, precluding direct *C*-arylation of this position. To address this problem, we developed and here describe the SEM-group switch that transposes the SEM group from the N-1 to N-3 nitrogen of the imidazole ring and in the process transforms the unreactive C-4 position to the reactive C-5 position. Analogous to the SEM-switch of pyrazoles,[15a] the rearrangement proceeds in the presence of a catalytic amount of SEM chloride (Scheme 2), most likely via formation of an imidazolium intermediate and subsequent loss of the SEM group through a S_N1 type process, to ultimately produce the less sterically hindered 4-arylimidazole.[33] The second arylation at the C-5 position of the resulting 4-arylimidazole then proceeds well to generate a 4,5-diarylimidazole.

In practice, 5-arylimidazole **19**, prepared by direct arylation of SEM-imidazole **1** with 4-bromoanisole, was converted in one step to 4-arylimidazole **21** in 88% isolated yield (Scheme 2). Despite the increased steric hindrance at the "new" C-5 position, remarkably, the arylation of the C-5 position was preferred over the C-2 position, furnishing 4,5-diarylimidazole **22** in 46% isolated yield, accompanied by the starting material and the double arylation product (17% and 11% yields, respectively). The second C5-arylation becomes highly efficient with C2-substituted substrates, which is discussed in the following section.

Synthesis of 2,4,5-Triarylimidazoles via Sequential *C*-Arylation and the SEM-Switch. Having established the C2-arylation, the C5-arylation, and the SEM-switch, we now can access 2,4,5-arylated imidazoles in short order. The three-step sequence consisting of direct C5-arylation, SEM-switch, and the second C5-arylation was extended to 2-substituted imidazoles. 2-Phenyl-1-SEM-imidazole **4**, prepared by C2-arylation of imidazole **1** or by protection of commercially available 2-phenylimidazole, was used to explore the efficiency of the three-step sequence (Table 3, entries 1−3). In terms of arene donor substrate scope, several functional groups, including ester, dimethylamino, pyridyl, and pyrazyl groups, were well tolerated.[34] Note that the second arylation of sterically hindered substrates is efficient, giving good to excellent yields with a variety of arene donors.

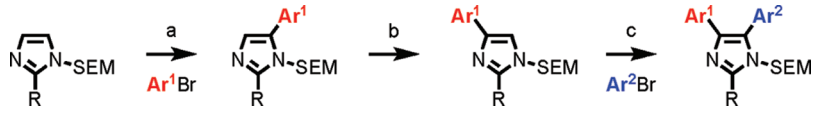
Synthesis of 2-Alkyl- and 2-Dialkylamino-Substituted 4,5-Diarylimidazoles. To further demonstrate the utility of the sequential arylation sequence, we also tested 2-alkyl- and 2-dialkylamino-imidazole derivatives. Specifically, 2-butyl-1-SEM-imidazole is an excellent substrate for the arylation and SEM-switch reactions, giving complex imidazole **34** in high yield (Table 3, entry 4). Moreover, a dialkylamino functionality on the imidazole core was compatible with not only the palladium-catalyzed arylation but also the SEM-switch; the 2-piperidylimidazole was transformed to **37** in good overall

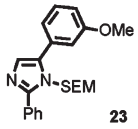
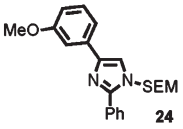
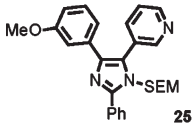
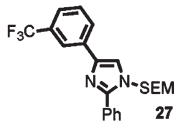
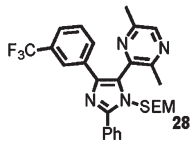
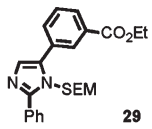
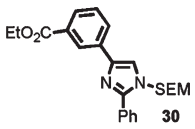
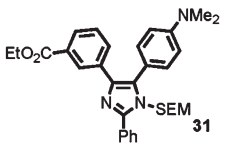
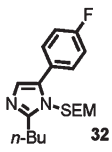
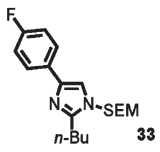
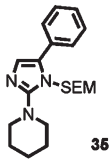
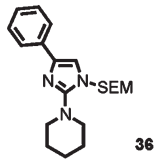
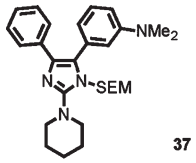
(32) Strong inhibition by electron-withdrawing substituents present in the bromoarene donors was observed in the sp^3 C-H arylation of α-methyl azine-*N*-oxides, a method that also depends on the use of NaO*t*-Bu as the base (see ref 31). The authors proposed that the catalyst was inhibited by cyclopalladation of the products containing relatively acidic benzylic groups. It is conceivable that in our case cyclopalladation of the 2′-position of the aryl ring may sequester the palladium catalyst. Inhibition by direct coordination of the nitrile group to the palladium metal is also possible; however, processes responsible for the catalyst deactivation are presently not known.

(33) He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529–5532.

(34) As long as the functional groups of the substrates are compatible with the alkoxide base and the 2-position of imidazoles is blocked, the C2-arylation conditions can be employed for C5-arylation. Namely, diarylimidazole **23** was prepared after the treatment of 2-phenylimidazole **4** with $Pd(OAc)_2$, P(*n*-Bu)Ad_2, 3-bromoanisole, and NaO*t*-Bu in toluene in 84% isolated yield.

TABLE 3. Sequential Double Arylation Enabled by SEM-Group Switch



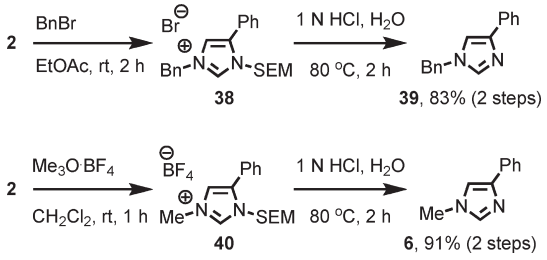
entry	R	1st arylation[a]	yield	SEM-switch[b]	yield	2nd arylation[c]	yield
1	Phenyl	 **23**	69% (71%)[d,e]	 **24**	87%	 **25**	87%
2	Phenyl	 **26**	71%	 **27**	92%	 **28**	88%[d]
3	Phenyl	 **29**	75%[e] (70%)[d,e]	 **30**	88%	 **31**	74%
4	*n*-Butyl	 **32**	90% (80%)[d,e]	 **33**	93%	 **34**	87%
5	1-Piperidyl	 **35**	76%	 **36**	74%	 **37**	84%

[a]5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.2 equiv of Ar^1Br, 2.0 equiv of K_2CO_3, DMA (0.5 M), 120 °C, 20 h. [b]5.0 mol % SEMCl, CH_3CN, 80 °C, 24 h. [c]5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.5 equiv of Ar^2Br, 2.0 equiv of K_2CO_3, DMA (0.5 M), 120 °C, 20 h. [d]ArCl was used instead of ArBr. [e]In the benchtop experiment, [P(*n*-Bu)Ad_2H]BF_4 was used and the amount of K_2CO_3 was increased (2.5 equiv).

yield (Table 3, entry 5). The SEM group of the resulting arylation products can be easily removed by either acidic hydrolysis or fluoride treatment.[35] For example, deprotection of complex imidazole **34** was performed in an aqueous HCl solution (1 N, 80 °C, 2 h) to give the corresponding free imidazole in quantitative yield.

Synthesis of 1-Alkyl-4-arylimidazoles from 1-SEM-5-Arylimidazoles via Trans-*N*-alkylation. The SEM-switch idea was extended to accomplish the trans-*N*-alkylation, which unlocks a short route to regioselective formation of 1-alkyl-4-arylimidazoles. Indeed, *N*-alkylation of **2** with benzyl bromide and subsequent acidic hydrolysis generated 1-benzyl-4-phenylimidazole **39** in excellent yield (Scheme 3).[36,37] Similarly, trimethyloxonium tetrafluoroborate produced methylimidazolium salt **40**, which underwent a SEM cleavage to give 1-methyl-4-phenylimidazole **6** in 91% yield over 2 steps. Given the fact that it is difficult to achieve regioselective *N*-alkylation of 4(5)-arylimidazoles with a small alkyl group, the procedure using SEM-imidazoles addresses this problem and enables efficient preparation of 1-alkyl-4-arylimidazoles.

SCHEME 3. Synthesis of 1-Alkyl-4-arylimidazoles

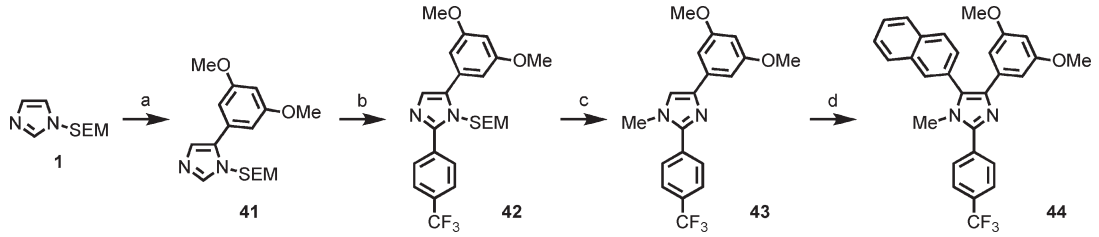


(35) (a) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891–1894. (b) Lipshutz, B. H.; Vaccaro, W.; Huff, B. *Tetrahedron Lett.* **1986**, *27*, 4095–4098.

(36) A report on the exchange of a SEM group with a benzyl group in the context of 4-arylimidazole synthesis: Nakamura, S.; Kawasaki, I.; Yamashita, M.; Ohta, S. *Heterocycles* **2003**, *60*, 583–598.

(37) The palladium-catalyzed C5-arylation of 1-benzylimidazoles has been reported (see ref 19). Similar to the SEM group transposition, the benzyl group should be transposable in the presence of a catalytic amount of benzyl bromide. In fact, 1-benzyl-5-phenylimidazole, obtained in 72% isolated yield through our protocol, underwent a benzyl switch to give 1-benzyl-4-phenylimidazole **39** in 84% isolated yield; however, the reaction required extended heating (5 days in DMF at 140 °C).

SCHEME 4. Synthesis of 1-Methyl-2,4,5-triarylimidazoles via Sequential *C*-Arylation and *N*-Methylation[a]



[a]Reaction conditions: (a) 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.2 equiv of 1-bromo-3,5-dimethoxybenzene, 2.0 equiv of K_2CO_3, DMA (0.5 M), 120 °C, 18 h (68% yield). (b) 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.5 equiv of 4-bromobenzotrifluoride, 2.0 equiv of NaO*t*-Bu, toluene (1.0 M), 100 °C, 24 h (65% yield). (c) 1.5 equiv of $Me_3O \cdot BF_4$, CH_2Cl_2, rt, 1 h; 1 N HCl, H_2O, 80 °C, 2 h (55% yield over 2 steps). (d) 5.0 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, 1.2 equiv of 2-bromonaphthalene, 2.0 equiv of K_2CO_3, DMA (0.5 M), 120 °C, 18 h (82% yield). Yields are an average of two separate isolated yields.

Programmable Synthesis of Complex 1-Alkyl-triarylimidazoles. The gathered results substantiate a general strategy for the synthesis of a broad range of mono-, di-, and triarylimidazoles from the parent imidazole as well as substituted imidazoles. For example, 2,5-diarylimidazoles can be accessed by either C5−C2 or C2−C5 sequential arylation reactions. Further, 2,4,5-triarylimidazoles can be rapidly prepared by the SEM-switch and C5-arylation of the diarylimidazoles. If the goal is to prepare free (NH)-imidazoles, SEM deprotection can be carried out under either acidic or basic (fluoride) conditions.

However, when *N*-alkyl-triarylimidazoles are desired, trans-*N*-alkylation followed by the final C5-arylation represents a good synthetic plan. This approach was implemented in a five-step synthesis of **44** (Scheme 4). In detail, the C5-arylation of imidazole **1** afforded compound **41**, from which diarylimidazole **42** was derived by C2-arylation with 4-bromo-1-trifluoromethylbenzene. The *N*-methylation and the SEM-group deprotection provided 1-methylimidazole **43**, which was subsequently subjected to the final coupling with 2-bromonaphthalene to furnish fully substituted product **44**.

In this synthesis, all four substituents including the *N*-alkyl group were introduced to the bare imidazole core in a programmable manner. This general approach based on sequential *C*-arylation and *N*-alkylation of SEM-protected imidazoles provides rapid access to complex aryl imidazoles, and it is quite apparent how series of derivatives (with different substitutions at one or more positions) can be synthesized in short order in this manner.

Conclusions

Imidazoles are an important group of the azole family of heterocycles frequently found in pharmaceuticals, drug candidates, ligands for transition metal catalysts, and other molecular functional materials. Owing to their wide application in academia and industry, a great deal of work has been dedicated to the generation of functionalized imidazole derivatives. In contrast to conventional condensation methods, catalytic C−H bond functionalization reactions enable derivatization and elaboration of the existing imidazole rings and provide new possibilities for the synthesis of complex imidazoles.

We here described a general and comprehensive approach for the synthesis of complex aryl imidazoles, where all three C−H bonds of the imidazole core can be arylated in a regioselective and sequential manner. The synthesis of individual compounds or compound libraries can commence from either the parent imidazole or advanced imidazole derivatives (accessed from ring-forming or substituent-modifying reactions). Our approach and the new C−H arylation protocols will thus complement transition-metal-catalyzed cross-coupling reactions, including the Suzuki reaction[19,38] and the catalytic *N*-arylation of imidazoles,[39,40] as well as the C−H arylation reactions developed by others.[19,20,28] The particular strength of our strategy is the flexibility with which the *N*-alkyl groups can be introduced in a regioselective manner at various stages of the arylation sequence. Another important advance this paper brings is that both C5- and C2-arylation reactions can be carried out with low-cost and readily available aryl chloride donors.

Experimental Section

General Procedure for the C2-Arylation of SEM-Imidazoles. The imidazole (0.50 mmol) was weighed into a 4-mL glass vial equipped with a magnetic stir bar. Through a Teflon-lined cap, the vial was purged with argon. The aryl halide (0.75 mmol) and toluene (0.25 mL) were added to the vial under a positive pressure of argon. The reaction vial was moved to a glovebox. $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), P(*n*-Bu)Ad_2 (13.4 mg, 0.038 mmol), and NaO*t*-Bu (96 mg, 1.0 mmol), which were stored under argon in the glovebox, were then added to the reaction mixture. The cap was replaced with a new Teflon-lined solid cap. The reaction vial was removed from the glovebox and then moved to a preheated reaction block (100 °C). After stirring for 24 h, the reaction mixture was cooled to room temperature and was directly loaded to a silica gel column. Purification by flash column chromatography provided the desired 2-arylimidazole. For a procedure that does not require the use of a glovebox, see Supporting Information.

2-(3-Methoxyphenyl)-5-phenyl-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-imidazole (13). Purification by flash column chromatography (hexanes/EtOAc = 3:1) provided **13** as a colorless oil: IR (film) 2952, 2894, 2836, 1605, 1482, 1359, 1286, 1250, 1170, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 2H), 7.49−7.43 (m, 4H), 7.42−7.35 (m, 2H), 7.22 (s, 1H), 7.02−6.97 (m, 1H), 5.14 (s, 2H), 3.87 (s, 3H), 3.45 (t, J = 8.4 Hz, 2H), 0.97 (t,

(38) (a) Primas, N.; Mahatsekake, C.; Bouillon, A.; Lancelot, J.-C.; Santos, J. S. O.; Lohier, J.-F.; Rault, S. *Tetrahedron* **2008**, *64*, 4596–4601. (b) Han, Q.; Chang, C.-H.; Li, R.; Ru, Y.; Jadhav, P. K.; Lam, P. Y. S. *J. Med. Chem.* **1998**, *41*, 2019–2028.

(39) Catalytic *N*-arylation of imidazoles with aryl halides: (a) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190–6199 and references therein. (b) Zhu, L.; Li, G.; Luo, L.; Guo, P.; Lan, J.; You, J. *J. Org. Chem.* **2009**, *74*, 2200–2202.

(40) Catalytic *N*-arylation of imidazoles with aryl boronic acids: (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944. (b) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528–1531. (c) Lan, J.-B.; Chen, L.; Yu, X.-Q.; You, J.-S.; Xie, R.-G. *Chem. Commun.* **2004**, 188–189.

J = 8.4 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 149.8, 135.4, 131.8, 129.9, 129.4, 128.7, 128.6, 128.0, 127.4, 121.0, 115.3, 113.7, 73.1, 65.3, 55.2, 17.9, −1.6; HRMS (FAB) calcd for $C_{22}H_{29}N_2O_2Si$ $[M + H]^+$ 381.1998, found 381.1991.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.