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# A Novel One-Step Synthesis of Imidazo[5,1-*a*]isoquinolines via a Tandem Pd-Catalyzed Alkylation−Direct Arylation Sequence

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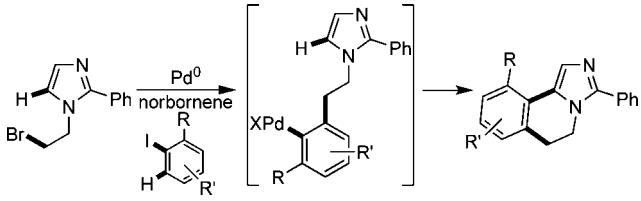


A palladium-catalyzed/norbornene-mediated one-step synthesis of highly functionalized imidazoles via a sequential alkyl−aryl and aryl−heteroaryl bond formation is devised. This method provides an efficient route to a wide variety of substituted imidazo[5,1-*a*]isoquinolines from readily accessible *N*-bromoalkyl imidazoles and aryl iodides.

Nitrogen-containing heterocycles have attracted considerable attention as they are integral components of natural products, dyes, agrochemicals, and pharmaceuticals. For instance, imidazole is known to exhibit a broad range of uses in pharmaceutical and industrial applications. This type of compound is present in important naturally occurring biological building blocks such as histidine and histamine,[1] are found in many drug cores such as angiotensin II inhibitors[2] and anti-inflammatory[3] and anticancer agents,[4] and play an important role as ligands in metalloenzymes,[5] and it is well-known that imidazolium salts can serve as excellent precursors of stable carbene ligands in various metal complexes.[6] Furthermore, vicinal diaryl-substituted imidazoles have been shown to exhibit interesting biological activities such as p38 mitogen-activated protein and B-Raf kinase inhibition, cannabinoid $CB_1$ receptor antagonism, and antimicrobial, antitumor, and cytotoxic activities.[7] Recently, increasing attention has been devoted to the imidazo[5,1-*a*]isoquinoline framework because they are important constituents in pharmaceutical drug candidates (Figure 1).[8] For instance, compounds of type **1** are considered to be of potential use in the treatment of a broad array of diseases or disorders including depression, anxiety, sleep disorders, cognitive disorders, low alertness, psychosis, obesity, pain, Parkinson's disease, Alzheimer's disease, neurodegenerative diseases, Down syndrome, and benzodiazepine overdoses (Figure 1).[8] Furthermore, a pharmaceutically acceptable salts of compounds of type **2** (Figure 1) have demonstrated pharmacological activity in processes known to be associated with one or more of cardiovascular activity, inflammatory mechanisms, oncology, and regulation of protein transport from cells and have been used in the treatment of congestive heart failure, arrhythmia, hypotension, cancer, Kaposi's sarcoma, rheumatoid arthritis, and osteoporosis.[8] Thus, several approaches have been developed for their syntheses consisting of multistep reaction processes or intermolecular cyclizations via aryl radicals.[8,9] However, these reactions often suffer from low yields and poor selectivity. One might therefore expect that general and versatile synthetic methods for the construction of this framework would find significant utility in organic synthesis.

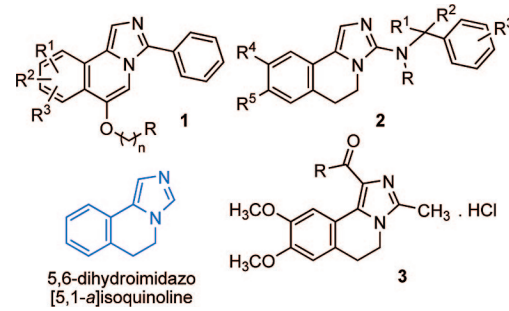


**FIGURE 1.** Biologically active compounds containing the imidazo[5,1-*a*]isoquinoline framework.

Here we report an efficient and straightforward route to annulated imidazole derivatives based on a palladium-catalyzed/norbornene-mediated sequential aromatic alkylation/aryl-heteroaryl coupling reaction. This strategy has previously been applied with success to the preparation of annulated heterocycles such as indoles, azaindoles, and pyrroles.[10] Very recently, a route very similar to that described in this Note has been applied to prepare annulated

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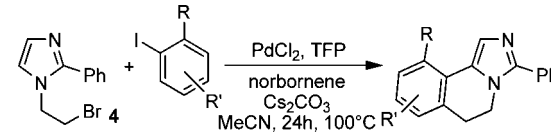
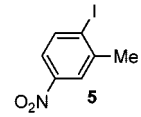
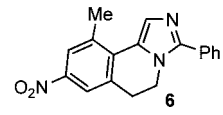
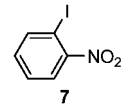
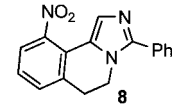
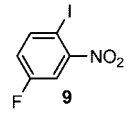
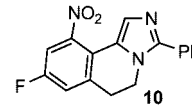
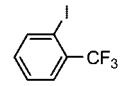
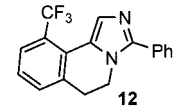
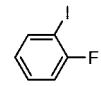
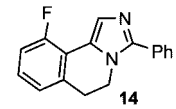
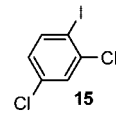
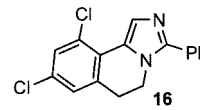
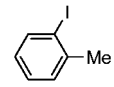
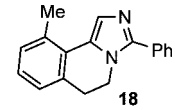
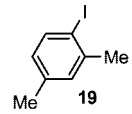
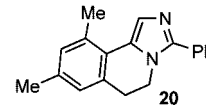
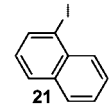
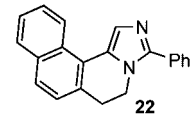
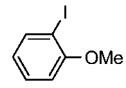
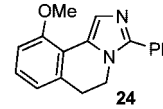
2*H*-indazoles and 1,2,3- and 1,2,4-triazoles.[10a] However, as a result of the adjacent nitrogen coordinating to one of the palladium intermediates in the catalytic cycle, only low to moderate yields of the annulated pyrazole and 7-azaindole derivatives were obtained.[10b,c] In line with this, we set out to explore the possibility of constructing imidazo[5,1-*a*]isoquinolines via selective direct C-5 arylation of imidazole, where chelation to palladium is impossible. To limit the degree of freedom in the system and avoid chemoselectivity challenges and also to overcome the catalyst poisoning obstacle, a C2-substituted imidazole with an *N*-haloalkyl tether was used. It is the first report on selective C-5 intermolecular arylation of imidazoles and one-step construction of imidazo[5,1-*a*]isoquinolines.

To test the feasibility of this reaction, we initially examined the reaction of bromoalkyl phenyl imidazole **4** with 5-nitro-2-iodotoluene under various reaction conditions. With $Pd(OAc)_2$ as the catalyst, displacement of the bromide of the *N*-bromoalkyl heterocycle with an acetate ion was observed. This reaction could be prohibited by using $PdCl_2$ instead of $Pd(OAc)_2$.[10b] We were delighted to see that under the optimized reaction conditions [iodoarene **5** (0.2 mmol, 1 equiv), $PdCl_2$ (10 mol %), TFP (22 mol %), $Cs_2CO_3$ (0.4 mmol, 2 equiv), norbornene (0.4 mmol, 2 equiv), and bromoalkyl imidazole **4** (0.6 mmol, 3 equiv) in $CH_3CN$ (0.1 M) at 100 °C in a sealed tube for 24 h] the fused tricyclic heterocycle **6** was obtained in 76% yield (Table 1, entry 1). Having successfully generated highly functionalized six-membered ring-annulated imidazole **6**, we next investigated the scope of the reaction using various substituted iodoarenes. The results showed that various electron-withdrawing and electron-donating substituents, including nitro, alkyl, methoxy, trifluoromethyl, chloride, and fluoride, were tolerated under the reaction conditions. The reactivity of aryl halides is strongly enhanced by the presence of electron-withdrawing substituents. Nitro and chloro substituents at the *ortho* and *para* positions of aryl iodide gave excellent yields, and the resulting compound **16** represents a very useful partner for further functionalizations (entries 1, 2, 3, and 6). While low yield was obtained for *ortho*-blocking $CF_3$ group, presumably due to steric effects, fluoro-substituted iodoarene resulted in the corresponding annulated imidazole in good yield (entries 4 and 5). With alkyl-substituted iodoarenes, good yields of the products **18** and **20** were obtained (entries 7 and 8). However, with iodonaphtalene partner, **22** was obtained in only 43% yield (entry 9), presumably as a result of steric hindrance between naphthalene and imidazole C−H bonds. As aryl palladium species with the palladium *ortho* to a methoxy group can undergo C−H activation with the methoxy C−H bond to form a stable five-membered palladacycle,[11] with 2-iodoanisole coupling partner the desired product **24** was isolated in only 35% yield (entry 10). We next investigated the scope of the reaction using aryliodides with *o*-carbonyl substituents (methyl 2-iodobenzoate and 2-iodobenzophenone). The results showed that the presence of carbonyl group at position 2 was not tolerated, which was in accord with the results previously reported.[12f]

The possible mechanism for the initial step is based upon the findings of Catellani and involves a Pd(II)/Pd(IV) catalytic cycle (Scheme 1).[12] A reductive elimination from the Pd(IV) species followed by extrusion of norbornene gives an aryl-Pd(II) species that then undergoes an intramolecular direct arylation reaction forming the aryl-*N*-heteroaryl bond at the 5 position of the *N*-heteroaryl compound. In fact, conflicting mechanistic interpretations of the palladium-catalyzed direct C-arylation of

**TABLE 1. Synthesis of Annulated Imidazoles via Palladium-Catalyzed/Norbornene-Mediated Tandem Alkylation−Direct Arylation Reaction**[a]




| entry | iodide | product | yield (%) |
|---|---|---|---|
| 1 |  **5** |  **6** | 76 |
| 2 |  **7** |  **8** | 68 |
| 3 |  **9** |  **10** | 74 |
| 4 |  **11** |  **12** | 45 |
| 5 |  **13** |  **14** | 63 |
| 6 |  **15** |  **16** | 76 |
| 7 |  **17** |  **18** | 61 |
| 8 |  **19** |  **20** | 60 |
| 9 |  **21** |  **22** | 43 |
| 10 |  **23** |  **24** | 35 |

[a] All reactions were run under the following conditions: iodoarene (0.20 mmol, 1 equiv), $PdCl_2$ (10 mol %), TFP (22 mol %), $Cs_2CO_3$ (2 equiv), norbornene (2 equiv), and bromoalkyl imidazole (3 equiv) in ACN (0.1 M) were heated in a sealed tube at 100 °C for 24 h.

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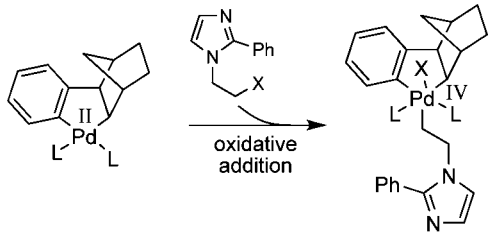
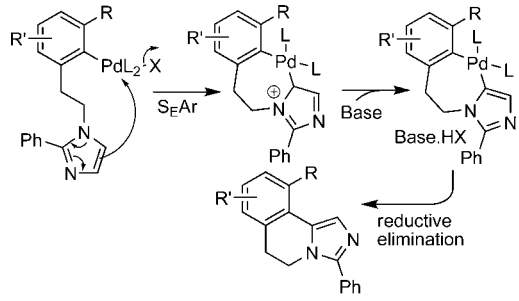
**SCHEME 1. Proposed Pd(II)/Pd(IV) Species Involved in the Catalytic Cycle**




**SCHEME 2. Electrophilic Aromatic Substitution Mechanism for Intramolecular Direct Arylation of the Imidazole Ring**




$\pi$-excessive heteroarenes have been reported in the literature.[13] Recent studies indicate that the concerted metalation−deprotonation mechanism may be much more broadly implicated than previously supposed in Pd-catalyzed direct arylation reactions of heteroarene substrates.[14] However, there is also strong evidence that most of the palladium-catalyzed arylation of $\pi$-excessive heteroarenes occurs at the site most susceptible to electrophilic attack.[15] Therefore, in this case a mechanism involving an electrophilic aromatic substitution followed by reductive elimination has to be considered as the most probable (Scheme 2).

In summary, we have developed a straightforward and efficient one-step approach to highly functionalized six-membered annulated imidazoles using readily accessible starting materials. We have explored the scope of tandem palladium-catalyzed/norbornene-mediated sequential aromatic alkylation/aryl-heteroaryl coupling reaction for construction of imidazo[5,1-*a*]isoquinoline building blocks with a wide variety of biological activities. The iodoarenes can be widely varied, which makes the method extremely versatile for the preparation of these structural motifs not easily accessible by conventional methods. Further functionalization of the annulated products via bromination of imidazole ring at C-4 and subsequent cross-coupling methodologies (Stille coupling and Suzuki coupling) are under investigation.

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(15) (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (d) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111.

## Experimental Section

**General Procedure for the Annulation of Imidazoles.** A vial equipped with a stir bar was charged with aryl iodide (0.200 mmol, 1.0 equiv), tri-2-furylphosphine (0.044 mmol, 22 mol %), norbornene (0.400 mmol, 2.0 equiv), $Cs_2CO_3$ (0.400 mmol, 2.0 equiv), $PdCl_2$ (0.020 mmol, 10 mol %), and bromoalkyl phenyl imidazole (0.600 mmol, 3.0 equiv). Dry degassed $CH_3CN$ (0.1 M) was then added, and the vial was capped and further degassed. The resulting mixture was heated in an oil bath at 100 °C for 24 h, cooled, and then filtered through a short plug of silica. Removal of the solvent gave a crude mixture, which was purified by flash column chromatography (hexane/EtOAc gradient).

**10-Methyl-8-nitro-3-phenyl-5,6-dihydroimidazo[5,1-*a*]-isoquinoline (6).** Following the general procedure for the annulation of imidazoles, 5-nitro-2-iodotoluene **5** (53.0 mg, 0.200 mmol) and bromoalkyl phenyl imidazole **4** (151.0 mg, 0.600 mmol) were reacted at 100 °C for 24 h. The crude mixture was purified by flash column chromatography on silica gel (EtOAc/hexane, 20%) to afford **6** as a yellowish solid (46 mg, 76%): mp = 215−217 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.67 (s, 3H), 3.14 (t, $J$ = 6.3 Hz, 2H), 4.30 (t, $J$ = 6.3 Hz, 2H), 7.52 (m, 3H), 7.68 (m, 3H), 8.03 (s, 1H), 8.09 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 22.9, 30.9, 42.1, 121.2, 125.3, 128.2, 129.2, 129.3, 129.7, 130.1, 131.8, 133.4, 135.5, 145.5, 148.2; IR 1326, 1506, 2919, 3074 cm$^{-1}$; MS *m*/*z* (%) 305 ($M^{\bullet+}$, 17%), 279 (25), 167 (58), 149 (100), 57 (88). Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.99; H, 5.03; N, 13.88.

**Acknowledgment.** We thank the Research Council of the University of Tehran for financial support for this project (27827/1/01).

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

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