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Synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines *via* intramolecular C–H bond functionalization

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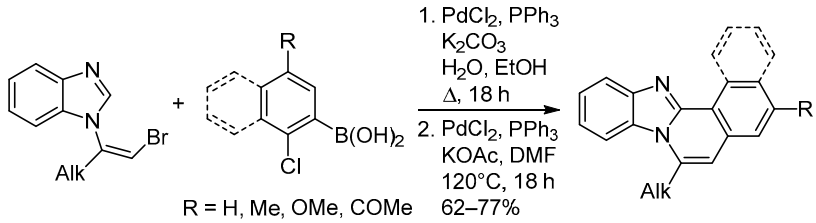


An improved procedure for the preparation of benzo[4,5]imidazo[2,1-*a*]isoquinolines using $PdCl_2$–PPh_3 as catalyst was developed, featuring simple, sequential workup, good selectivity, and compatibility with a wide range of functional groups. Various (*Z*)-2-bromovinylimidazoles and 2-chlorophenylboronic acids containing either electron-withdrawing or electron-donating groups were shown to smoothly undergo this sequence of reactions to generate the respective benzo[4,5]imidazo[2,1-*a*]isoquinolines in 62–77% yields.

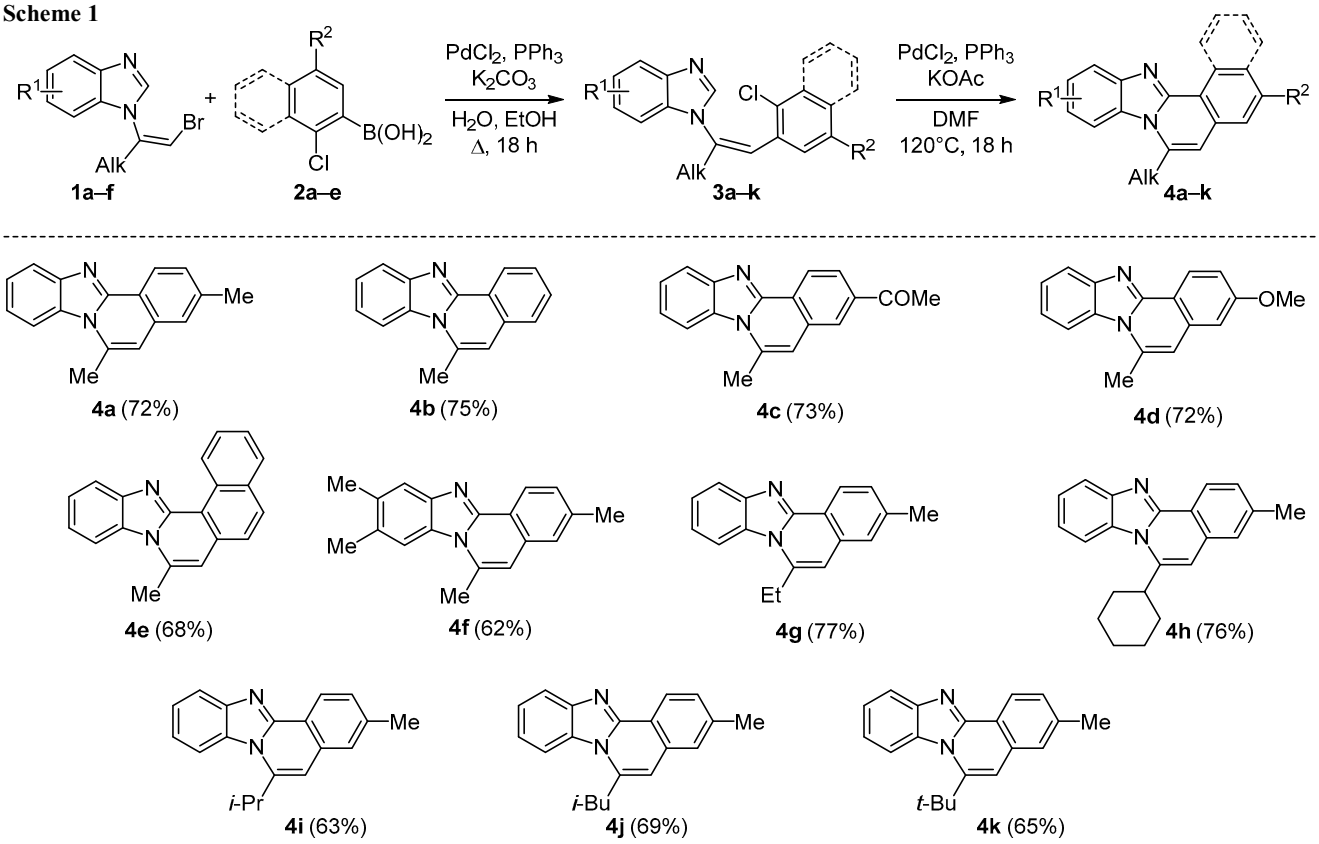
Keywords: isoquinolines, C–H functionalization, heteroannulation, intramolecular arylation, palladium catalysis.

The isoquinoline ring system is often encountered in the synthesis of biologically active compounds, including alkaloids, natural products, and therapeutic agents. Benzimidazole-fused isoquinoline framework is an especially important pharmacophore and many of its derivatives display a wide range of biological and therapeutic activities, such as anticancer, antimicrobial, antiHIV-1, and antifungal properties.[1,2] Tremendous efforts have been devoted to develop new approaches for the synthesis of isoquinolines as versatile and useful building blocks.[3] On the other hand, transition metal-catalyzed C−H functionalization has emerged as a robust and versatile tool for atom-economical assembly of heterocycles, as well as other syntheses and late-stage diversification of functional molecules in the past decade.[4] Moreover, transition metal-catalyzed intermolecular or intramolecular cyclization and heteroannulation strategy is the most useful methodology owing to its selectivity and mild reaction conditions.[5] Therefore, sequential one-pot reactions encompassing several bond-forming steps play an important role in synthetic organic chemistry.[6]

In 1975, Posner and coworkers first reported the synthesis of benzimidazole-fused ring system by reductive cyclization of aryl halides.[7] In 2009, Yanada group reported concise one-pot syntheses of benzimidazo[2,1-*a*]-isoquinolines by a microwave-accelerated tandem process.[8] Subsequently, some innovative strategies were developed for the synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines.[9–17] For example, Peng and coworkers described a protocol for the synthesis of benzimidazole-fused phenanthridines from 2-arylbenzimidazoles and 1,2-dihaloarenes. Kambe and coworkers reported rhodium-catalyzed synthesis of imidazo- and benzimidazo[2,1-*a*]isoquinolines *via* an intramolecular oxidative cross-coupling reaction.[9] Kurth and coworkers described that one-pot synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines can be achieved *via* tandem cyclization strategies.[13] However, the aforementioned protocols have certain limitations, such as tedious preparation of starting materials, harsh reaction conditions, and poor tolerance of functional groups. Hence, we set out to develop a superior procedure *via* sequential one-pot reactions to obtain benzo[4,5]imidazo[2,1-*a*]isoquinolines.

Initially, we employed (*Z*)-2-bromovinylbenzimidazoles **1** and the appropriate arylboronic acids **2** as reactants to obtain intermediates **3** (Scheme 1). The highest yield (82%) of intermediate **3a** was obtained with $PdCl_2$–PPh_3 as a catalyst, EtOH–H_2O as a solvent, and K_2CO_3 as a base, by heating at 80°C for 18 h. After synthesized intermediate **3a**, we further optimized the reaction conditions for obtaining the target product **4a**. The second step of sequential reaction was preceded by a simple fast filtration to remove solid residues. The expected product **4a** was

Scheme 1



obtained from intermediate **3a** with the highest yield of 72% in the presence of $PdCl_2$–PPh_3, DMF, and KOAc at 120°C.

After finding the best reaction conditions for both of the two steps, we explored the scope of isoquinoline derivatives that could be obtained in the intramolecular annulation reaction (Scheme 1). Initially, the acceptable range of R^2 substituents in the arylboronic acid starting material was explored. The results showed that arylboronic acids decorated with either electron-donating or electron-withdrawing groups were able to smoothly undergo the sequential process to generate the respective benzo[4,5]-imidazo[2,1-*a*]isoquinoline products **4** in good yields.

Additionally, the alkyl substituents of 2-bromovinyl-benzimidazole were evaluated. We observed that the extent of steric hindrance in substituted 2-bromovinylbenz-imidazole was not a significant factor in this intramolecular annualation process, as products **4g–j** could be isolated with good yields (Scheme 1) and identified by ^{1}H and ^{13}C NMR spectroscopy. It should be noted that even the *tert*-butyl substituent with stronger steric hindrance presented no obstacle to obtaining the desired product **4k** in a good 65% yield.

In conclusion, we have demonstrated the applicability of a novel one-pot sequential protocol for the synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines. The process is based on Suzuki coupling and palladium-catalyzed intramolecular C–H arylation, which makes it a useful and attractive method for the synthesis of these compounds. This protocol offers the advantages of simple workup, good selectivity, and tolerance for a broad range of functional groups.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 instrument (400 and 100 MHz, respectively) in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. HRMS (TOF MS EI$^+$) analyses were carried out on a Thermo MAT 95XP instrument. Melting points were measured on an Electrothemal X6 microscopic digital melting point apparatus and were corrected. Thin-layer chromatography (TLC) was performed on commercial silica gel plates (GF_{254}) with visualization under UV light (254 nm). All chemicals were purchased from commercial sources and used without additional purification.

Synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines 4a–k (General method). In a typical experiment, the appropriate (*Z*)-2-bromovinylbenzimidazole (1.0 mmol),[18] 2-chloro-arylboronic acid (1.2 mmol), K_2CO_3 (276 mg, 2.0 mmol), PPh_3 (13.1 mg, 5 mol %), and $PdCl_2$ (8.8 mg, 5 mol %) were stirred in EtOH–H_2O, 1:1 medium (3 ml) at 80°C under an argon atmosphere for 18 h. The mixture was filtered through a short silica gel column and the solvent was removed under reduced pressure. Subsequently, the obtained intermediate **3** was combined with KOAc (196 mg, 2.0 mmol), PPh_3 (13.1 mg, 5 mol %), and $PdCl_2$ (8.8 mg, 5 mol %) in DMF (3 ml) solution and stirred at 120°C under an argon atmosphere for 18 h and monitored

using TLC. After the reaction was complete, the crude products were separated by column chromatography on silica gel (petroleum ether – ethyl acetate, 5:1) to obtain the respective purified product **4**.

3,6-Dimethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4a). Yield 124 mg (72%), white solid, mp 75–77°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.67 (1H, d, *J* = 7.6); 8.03 (1H, d, *J* = 8.0); 7.92 (1H, d, *J* = 8.4); 7.48 (1H, t, *J* = 7.8); 7.41 (1H, d, *J* = 8.0); 7.36 (1H, s); 7.32 (1H, td, *J* = 8.0, *J* = 1.2); 6.62 (1H, s); 2.50 (3H, s); 2.29 (3H, s). ^{13}C NMR spectrum, δ, ppm: 148.7; 144.3; 140.1; 138.9; 131.7; 130.6; 128.6; 125.6; 124.8; 123.9; 121.3; 119.9; 119.7; 114.1; 109.4; 21.7; 20.0. Found, *m*/*z*: 246.1152 $[M]^+$. $C_{17}H_{14}N_2$. Calculated, *m*/*z*: 246.1157.

6-Methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4b). Yield 123 mg (75%), white solid, mp 76–78°C (mp 117–119°C[19]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.79 (1H, t, *J* = 7.6); 8.02 (1H, d, *J* = 8.4); 7.86 (1H, d, *J* = 8.4); 7.56–7.51 (3H, m); 7.46 (1H, td, *J* = 8.0, *J* = 0.8); 7.30 (1H, td, *J* = 8.0, *J* = 0.8); 6.64 (1H, s); 2.30 (3H, s). ^{13}C NMR spectrum, δ, ppm: 148.3; 144.1; 138.9; 131.5; 130.5; 129.7; 126.9; 125.7; 124.8; 124.0; 122.1; 121.6; 119.8; 114.1; 109.3; 20.1. Found, *m*/*z*: 231.0995 $[M]^+$. $C_{16}H_{12}N_2$. Calculated, *m*/*z*: 232.1000.

1-(6-Methylbenzo[4,5]imidazo[2,1-*a*]isoquinolin-3-yl)-ethan-1-one (4c). Yield 135 mg (73%), white solid, mp 131–133°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.67 (1H, d, *J* = 8.4); 7.97–7.93 (3H, m); 7.75 (1H, d, *J* = 8.4); 7.45 (1H, t, *J* = 7.6); 7.29 (1H, t, *J* = 7.8); 6.52 (1H, s); 2.57 (3H, s); 2.31 (3H, s). ^{13}C NMR spectrum, δ, ppm: 197.2; 147.0; 144.1; 139.7; 137.0; 130.8; 130.4; 126.3; 125.5; 124.8; 124.7; 124.3; 122.2; 120.0; 114.2; 108.9; 26.9; 20.1. Found, *m*/*z*: 274.1109 $[M]^+$. $C_{18}H_{14}N_2O$. Calculated, *m*/*z*: 274.1106.

3-Methoxy-6-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4d). Yield 144 mg (72%), white solid, mp 103–105°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.63 (1H, d, *J* = 8.8); 7.93 (1H, d, *J* = 7.6); 7.73 (1H, d, *J* = 8.4); 7.41 (1H, t, *J* = 7.6); 7.22 (1H, t, *J* = 7.4); 7.09 (1H, dd, *J* = 8.8, *J* = 2.4); 6.76 (1H, d, *J* = 2.4); 6.38 (1H, s); 3.79 (3H, s); 2.32 (3H, s). ^{13}C NMR spectrum, δ, ppm: 160.7; 148.5; 144.3; 139.3; 133.2; 130.4; 126.5; 123.8; 121.0; 119.3; 116.4; 115.7; 114.0; 108.8; 106.8; 55.2; 19.9. Found, *m*/*z*: 262.1101 $[M]^+$. $C_{17}H_{14}N_2O$. Calculated, *m*/*z*: 262.1106.

8-Methylbenzo[*h*]benzo[4,5]imidazo[2,1-*a*]isoquinoline (4e). Yield 129 mg (68%), white solid, mp 118–120°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.95 (1H, d, *J* = 8.8); 8.18 (1H, d, *J* = 8.0); 7.99–7.91 (4H, m); 7.68 (1H, t, *J* = 7.6); 7.56 (1H, t, *J* = 7.6); 7.54 (1H, d, *J* = 8.8); 7.37 (1H, t, *J* = 8.0); 6.76 (1H, s); 2.31 (3H, s). ^{13}C NMR ($CDCl_3$), δ, ppm: 148.5; 144.6; 139.7; 132.4; 131.7; 130.8; 130.1; 129.2; 128.5; 128.2; 127.9; 126.1; 124.4; 124.1; 121.3; 120.1; 116.7; 114.4; 110.1; 20.1. Found, *m*/*z*: 282.1152 $[M]^+$. $C_{20}H_{14}N_2$. Calculated, *m*/*z*: 282.1157.

3,6,9,10-Tetramethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4f). Yield 115 mg (62%), white solid, mp 123–125°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.62 (1H, d, *J* = 8.4); 7.72 (1H, s); 7.53 (1H, s); 7.36 (1H, d, *J* = 8.0); 7.29 (1H, s); 6.47 (1H, s); 2.47 (3H, s); 2.46 (3H, s); 2.42 (3H, s); 2.31 (3H, s). ^{13}C NMR spectrum, δ, ppm: 147.9; 142.8; 139.5; 138.8; 132.8; 131.5; 130.2; 129.0; 128.3; 125.5; 124.5; 119.9; 119.4; 114.1; 108.7; 21.7; 20.1; 19.1; 19.0. Found, *m*/*z*: 274.1473 $[M]^+$. $C_{19}H_{18}N_2$. Calculated, *m*/*z*: 274.1470.

6-Ethyl-3-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4g). Yield 121 mg (77%), white solid, mp 124–126°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.57 (1H, d, *J* = 8.0); 7.92 (1H, d, *J* = 8.0); 7.75 (1H, d, *J* = 8.4); 7.38 (1H, t, *J* = 7.4); 7.29 (1H, d, *J* = 8.8); 7.21 (1H, t, *J* = 7.8); 7.21 (1H, s); 6.43 (1H, s); 3.35–3.28 (2H, m); 2.39 (3H, s); 1.31 (3H, t, *J* = 6.9). ^{13}C NMR spectrum, δ, ppm: 148.5; 144.2; 140.0; 138.8; 131.6; 130.5; 128.5; 125.5; 124.7; 123.8; 121.3; 119.7; 119.6; 114.0; 109.1; 27.2; 21.2; 13.1. Found, *m*/*z*: 260.1318 $[M]^+$. $C_{18}H_{16}N_2$. Calculated, *m*/*z*: 260.1313.

6-Cyclohexyl-3-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4h). Yield 119 mg (76%), white solid, mp 167–169°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.65 (1H, d, *J* = 8.0); 8.01 (1H, d, *J* = 8.0); 7.83 (1H, d, *J* = 8.4); 7.45 (1H, t, *J* = 7.8); 7.37–7.29 (3H, m); 6.66 (1H, s); 3.38 (1H, t, *J* = 11.4); 2.45 (3H, s); 2.24 (2H, d, *J* = 12.4); 1.95 (2H, d, *J* = 13.2); 1.88 (1H, d, *J* = 13.2); 1.63–1.33 (5H, m). ^{13}C NMR spectrum, δ, ppm: 148.7; 144.3; 144.0; 140.0; 131.7; 130.2; 128.5; 125.8; 124.7; 123.8; 121.4; 119.8; 119.7; 114.3; 106.5; 39.4; 32.0; 26.3; 26.1; 21.7. Found, *m*/*z*: 314.1780 $[M]^+$. $C_{22}H_{22}N_2$. Calculated, *m*/*z*: 314.1783.

6-Isopropyl-3-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4i). Yield 86 mg (63%), white solid, mp 214–216°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.67 (1H, d, *J* = 8.4); 8.01 (1H, d, *J* = 8.0); 7.92 (1H, d, *J* = 8.4); 7.45 (1H, t, *J* = 7.4); 7.38 (1H, s); 7.37 (1H, d, *J* = 8.0); 7.29 (1H, t, *J* = 7.6); 6.73 (1H, s); 3.87–3.80 (1H, m); 2.45 (3H, s); 1.48 (3H, s); 1.47 (3H, s). ^{13}C NMR spectrum, δ, ppm: 148.7; 145.0; 144.4; 140.0; 131.6; 130.1; 128.6; 125.8; 124.8; 123.8; 121.4; 119.9; 119.7; 117.7; 106.1; 29.3; 21.7; 21.6. Found, *m*/*z*: 274.1466 $[M]^+$. $C_{19}H_{18}N_2$. Calculated, *m*/*z*: 274.1470.

6-Isobutyl-3-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4j). Yield 99 mg (69%), white solid, mp 128–130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.64 (1H, d, *J* = 8.0); 7.99 (1H, d, *J* = 8.0); 7.73 (1H, d, *J* = 8.4); 7.42 (1H, t, *J* = 7.6); 7.33 (1H, dd, *J* = 8.0, *J* = 1.2); 7.26 (1H, td, *J* = 7.6, *J* = 1.2); 7.23 (1H, s); 6.43 (1H, s); 2.87 (2H, d, *J* = 7.6); 2.40 (3H, s); 2.16–2.09 (1H, m); 0.98 (3H, s); 0.96 (3H, s). ^{13}C NMR spectrum, δ, ppm: 148.6; 144.1; 140.0; 137.2; 131.5; 130.3; 128.6; 125.6; 124.7; 123.9; 121.3; 119.8; 119.6; 113.7; 111.1; 42.2; 25.5; 22.0; 21.6. Found, *m*/*z*: 288.1622 $[M]^+$. $C_{20}H_{20}N_2$. Calculated, *m*/*z*: 288.1626.

6-(*tert*-Butyl)-3-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4k). Yield 93 mg (65%), white solid, mp 126–128°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.69 (1H, d, *J* = 8.0); 8.08 (1H, d, *J* = 8.8); 8.00 (1H, d, *J* = 7.6); 7.44–7.35 (3H, m); 7.29 (1H, td, *J* = 8.0, *J* = 1.2); 6.93 (1H, s); 2.42 (3H, s); 1.67 (9H, s). ^{13}C NMR spectrum, δ, ppm: 149.9; 146.0; 144.6; 140.2; 131.3; 129.9; 129.0; 125.9; 125.0; 123.7; 120.7; 120.3; 119.8; 118.0; 108.1; 35.1; 30.1; 21.7. Found, *m*/*z*: 288.1629 $[M]^+$. $C_{20}H_{20}N_2$. Calculated, *m*/*z*: 288.1626.

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