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Rhodium-Catalyzed Annulation of 2-Arylimidazoles and α-Aroyl Sulfoxonium Ylides toward 5-Arylimidazo[2,1-*a*]isoquinolines

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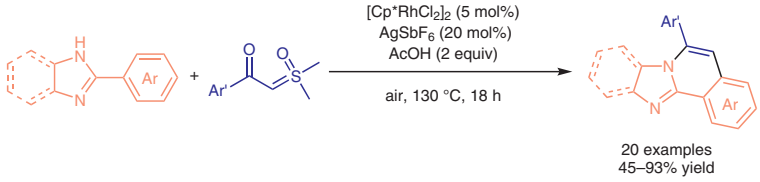

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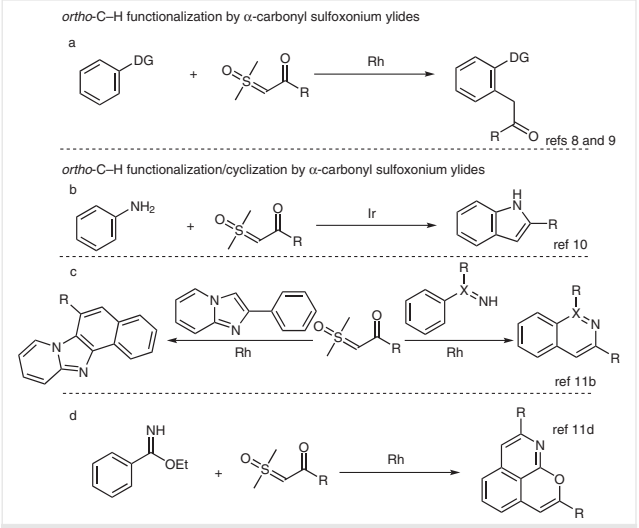
Abstract A Rh-catalyzed annulation between 2-aryl-1*H*-benzo[*d*]imidazoles and α-aroyl sulfoxonium ylides was developed, affording a series of benzimidazo[2,1-*a*]isoquinolines in moderate to excellent yields. This procedure proceeded with the sequential *ortho*-C–H functionalization and cyclization, representing a facile and straightforward pathway to access such frameworks.

Key words rhodium catalysis, annulation, sulfoxonium ylides, 2-arylimidazoles, isoquinolines

Imidazo- and benzimidazo[2,1-*a*]isoquinoline derivatives exist in a wide range of biologically active compounds, showing anticancer, anti-HIV-1, antimicrobial, and antiviral properties.[1] Consequently, many synthetic methods have been well developed to access such frameworks. For example, Zhu[2] demonstrated a direct intramolecular C–H amination reaction of *N*-aryl-2-aminopyridines leading to pyrido[1,2-*a*]benzimidazoles. Afterward, Bao reported a palladium-catalyzed oxidative procedure to access imidazole- or benzimidazole-fused isoquinolines.[3] Meanwhile, a rhodium-catalyzed intramolecular double C–H bond activation toward imidazo- and benzimidazo[2,1-*a*]isoquinolines was described by Kambe.[4]

With the development of organometallic chemistry, the insertion and further transformation of metal carbenes into X–H (X = C, N, O, S) bonds have been applied to build X–C bonds extensively.[5] Being potential safe precursors of metal carbenes,[6] sulfur ylides have attracted increasing attentions in organic synthesis. Previously, these classes of metal-carbene complexes were limited to the insertion into X–H (X = N, O, S) bonds.[7] Very recently, Li and Aïssa, respectively, reported the rhodium-catalyzed coupling of sulfoxonium ylides with C–H bond (Scheme 1, a).[8,9] Meanwhile, Hopmann developed an iridium-catalyzed cascade aniline C–H functionalization by sulfoxonium ylides/cyclization leading to indoles and pyrroles (Scheme 1, b).[10] Other examples about sulfoxonium ylides were also reported much lately(Scheme 1, c and d).[11] Based on aforementioned elegant examples and our continuous interest in the construction of heterocyclic compounds,[12] we wish to report a new strategy proceeding with the sequential 2-phenyl-1*H*-benzo[*d*]imidazole C–H functionalization by α-aroyl sulfoxonium ylides and cyclization toward imidazo[2,1-*a*]isoquinolines.

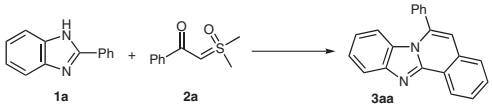


Scheme 1 The coupling of C–H bonds with sulfoxonium ylide

Based on our group report[13] and previous work,[11] we initially tested the reaction of 2-phenyl-1*H*-benzo[*d*]imidazole (**1a**; 0.2 mmol), α-aroyl sulfoxonium ylide **2a** (0.3 mmol) in THF (2 mL) at 120 °C in the presence of a catalytic amount of $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) with

AcOH (0.4 mmol) as additive. To our delight, the target product **3aa** was isolated in 47% yield (Table 1, entry 1). However, replacing THF with 1,4-dioxane (<5%), MeCN (<5%), and EtOH (<5%), inhibited the reaction (entries 2–4). Fortunately, **3aa** was isolated in 75% yield by using DCE as solvent (entry 5). In the absence of AcOH, the yield decreased to 43% (entry 8). Among the additive investigated, such as PivOH (67%, entry 6) and NaOAc (59%, entry 7), AcOH was found to be the best choice. Other metal catalysts such as $[Cp^*IrCl_2]_2$, $[Cp^*CoI_2(CO)]$, and $[Ru(p\text{-cymene})Cl_2]_2$ were incompatible in this process (entries 9–11). The reaction efficiency decreased under N_2 (73%) or O_2 (61%) and so did the reaction conducted under lower reaction temperature (entries 13). Notably, the yield further increased to 82% at 130 °C. Finally, the optimized conditions were established as follows: 2-phenyl-1*H*-benzo[*d*]imidazole (**1a**; 0.2 mmol), sulfoxonium ylide **2a** (0.3 mmol) in DCE (2 mL) at 130 °C in the presence of catalytic amount of $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) with AcOH (0.4 mmol).

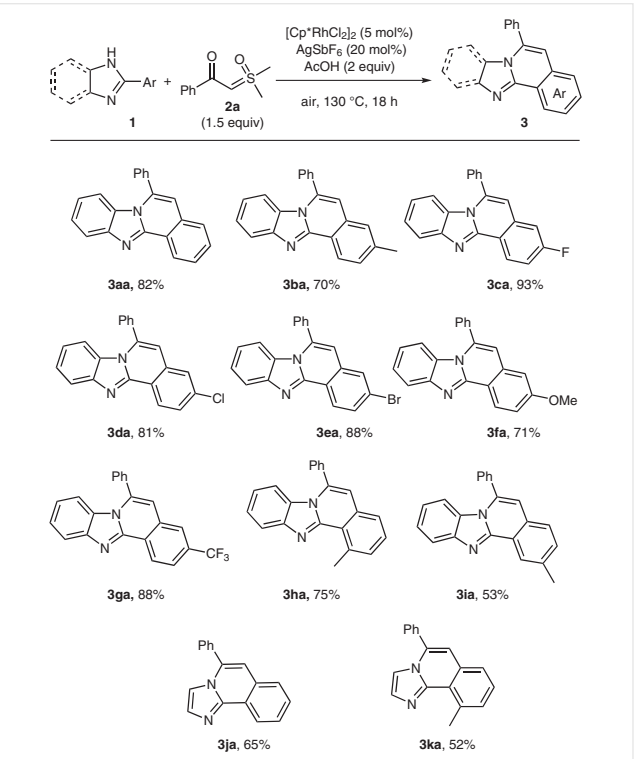
Table 1 Selected Results for Screening the Optimized Reaction Conditions[a]



Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	AcOH	THF	47
2	$[Cp^*RhCl_2]_2$	AcOH	1,4-dioxane	<5
3	$[Cp^*RhCl_2]_2$	AcOH	MeCN	<5
4	$[Cp^*RhCl_2]_2$	AcOH	EtOH	<5
5	$[Cp^*RhCl_2]_2$	AcOH	DCE	75
6	$[Cp^*RhCl_2]_2$	PivOH	DCE	67
7	$[Cp^*RhCl_2]_2$	NaOAc	DCE	59
8	$[Cp^*RhCl_2]_2$	–	DCE	43
9	$[Cp^*IrCl_2]_2$	AcOH	DCE	<10
10	$[Cp^*CoI_2(CO)]$	AcOH	DCE	0
11	$[Ru(p\text{-cymene})Cl_2]_2$	AcOH	DCE	0
12	$[Cp^*RhCl_2]_2$	AcOH	DCE	61[c], 73[d]
13	$[Cp^*RhCl_2]_2$	AcOH	DCE	0[e], 23[f], 82[g]

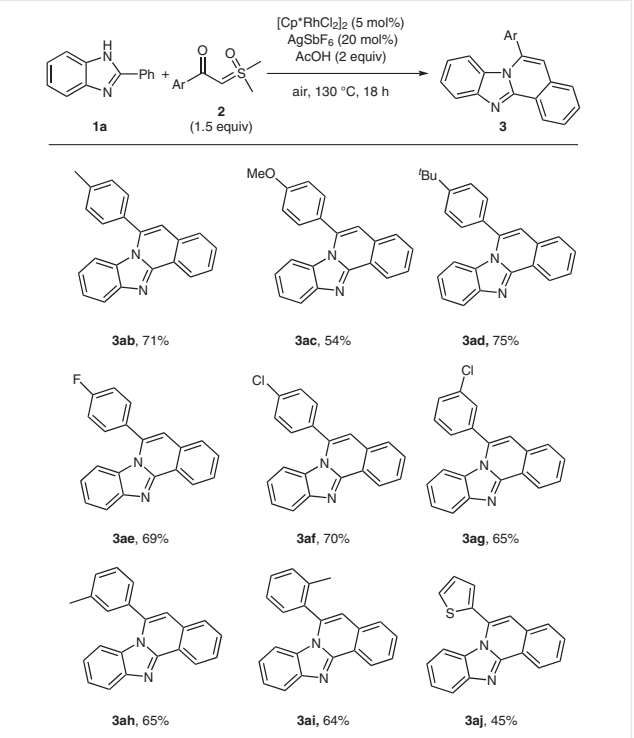
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (5 mol%), $AgSbF_6$ (20 mol%), additive (0.4 mmol), solvent (2 mL) under air at 120 °C for 18 h, in a sealed Schlenk tube, unless otherwise noted.
[b] Isolated yield.
[c] Under O_2.
[d] Under N_2.
[e] Reaction temperature: 80 °C.
[f] Reaction temperature: 100 °C.
[g] Reaction temperature: 130 °C.

With the optimized rhodium-catalyzed condition in hand, the scope and limitation of this transformation were explored. A series of 2-aryl-1*H*-benzo[*d*]imidazoles were tested, as shown in Scheme 2. For substrates with substituted aryl in 2-position, the electron-withdrawing substituents were beneficial for this transformation (**3ga** vs **3ba**, **3fa**). Halogens were compatible well in this process (**3ca**–**ea**, 81–93%). Importantly, substituents at the *ortho*-position of the aryl in 2-position did not impede the reaction (**3ha**, 75%). Notably, in the case of *meta*-substituted substrate, the cyclization preferred to take place on the *ortho*-position with less hindrance and no regioselective isomer of **3ia** was detected by GC-MS and ^1H NMR analysis. Particularly, 2-aryl-1*H*-imidazoles also reacted smoothly under this reaction condition (**3ja**, 65%; **3ka**, 52%).



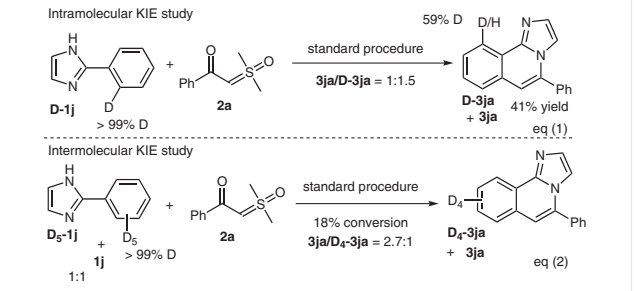
Scheme 2 The substrate scope of 2-aryl-1*H*-benzo[*d*]imidazoles. *Reagents and conditions*: 2-Aryl-1*H*-benzo[*d*]imidazoles **1** (0.2 mmol), α-aroyl sulfoxonium ylide **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), AcOH (0.4 mmol), and DCE (2 mL) under air at 130 °C for 18 h, in a sealed Schlenk tube, unless otherwise noted.

Next, the scope of the benzoyl-substituted sulfoxonium ylides was studied, as shown in Scheme 3. Substrates possessing both electron-withdrawing and electron-donating groups at the *para*-position of the phenyl ring all worked well and provided products in 54–75% yield (Scheme 3, **3ab**–**3af**). Importantly, no reactive differences were detected between substrates with substituents at *meta*-, and *ortho*-positions under this transformation (Scheme 3, **3ag**–**ai**, 65–70%). Furthermore, α-aroyl sulfoxonium with a thiophene group attached to the carbonyl was also compatible and provided **3aj** in 45% yield.



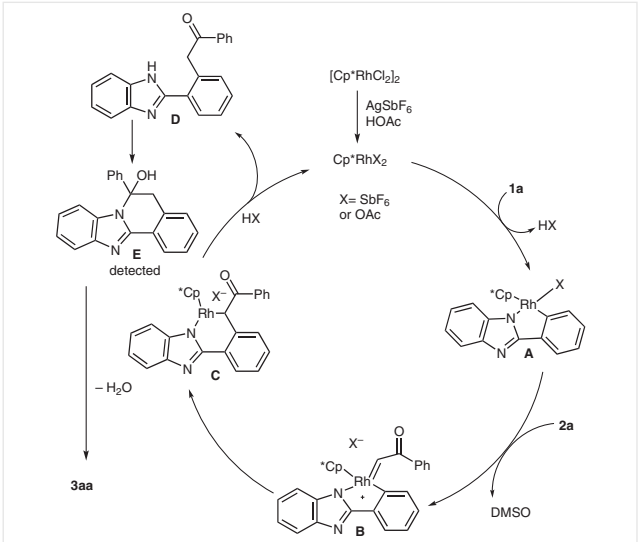
Scheme 3 The substrate scope of sulfoxonium ylides. *Reagents and conditions*: 2-phenyl-1*H*-benzo[*d*]imidazole (**1a**; 0.2 mmol), α-aroyl sulfoxonium ylides **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), AcOH (0.4 mmol), and DCE (2 mL) under air at 130 °C for 18 h, in a sealed Schlenk tube, unless otherwise noted.

The intra- and intermolecular kinetic isotope effects (KIEs) were found to be 1.5 and 2.7, respectively (Scheme 4, eqs 1 and 2). Thus, the cleavage of the *ortho*-C–H bond may be the rate-determining step during the transformation.



Scheme 4 KIE study

Based on the previous reports[14] and the aforementioned experimental results, a proposed mechanism is shown in Scheme 5. First, after the coordination of the nitrogen atom and active Rh(III) species Cp^*RhX_2 (X = SbF_6 or OAc), the cleavage of *ortho*-C–H bond takes place to afford the five-membered rhodacyclic **A**. Then, **2a** reacts with rhodacyclic **A** leading to a rhodium carbene species **B** accompanied by the elimination of DMSO. Second, a subsequent migratory insertion of rhodium carbene forms intermediate **C**. Protodemetalation of intermediate **C** releases the intermediate **D**, and regenerates the active Rh(III) species Cp^*RhX_2. Finally, an intramolecular nucleophilic reaction of **D** leads to intermediate **E**, which was observed in the reaction process. Then, the subsequent dehydration of **E** affords the product benzimidazo[2,1-*a*]isoquinoline.



Scheme 5 Proposed mechanism

In summary, we have developed a Rh-catalyzed *ortho*-C–H activation and cyclization between α-aroyl sulfoxonium ylides and 2-aryl-1*H*-benzo[*d*]imidazoles, leading to benzo[4,5]imidazo[2,1-*a*]isoquinolines. This strategy exhibits high efficiency and excellent functional group compatibility, providing a facile and straightforward pathway to access such frameworks.

Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded at ambient temperature on a 300 or 400 MHz NMR spectrometer (75 or 100 MHz for ^{13}C). NMR experiments are reported in δ units (ppm), and were referenced to $CDCl_3$ (δ = 7.26 or 77.0) or DMSO-d_6 (δ = 2.5 or 39.52) as the internal standard. The coupling constants *J* are given in Hz. High-resolution mass spectra (HRMS) were obtained using an agilent 6230 TOF focus spectrometer (ESI). Column chromatography was performed using EM silica gel 60 (300–400 mesh). All melting points are uncorrected.

5-Arylimidazo[2,1-*a*]isoquinolines 3; General Procedure

A 20 mL Schlenk tube equipped with a stir bar was charged with the respective substituted 2-aryl-1*H*-benzo[*d*]imidazole (0.2 mmol, 1.0 equiv), the corresponding α-aroyl sulfoxonium ylide (0.3 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (6.2 mg, 5 mol%), $AgSbF_6$ (13.7 mg, 20 mol%), AcOH (0.4 mmol, 2.0 equiv), and DCE (2.0 mL). The tube was sealed with a PTFE cap. The reaction mixture was stirred at 130 °C for 18 h under air in an oil bath. After the completion of the reaction, the mixture was then allowed to warm to r.t. and sat. aq $NaHCO_3$ (2 mL) was

added. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The residue obtained was purified by flash column chromatography on silica gel with a mixture of PE and EtOAc (5:1) to give the desired product **3**.

2-[2-(1*H*-benzo[*d*]imidazol-2-yl)phenyl]-1-phenylethan-1-one (E) (Scheme 5)

Yellow oil; yield: 29.3 mg (47%).

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.25–8.22 (m, 1 H), 7.72–7.70 (m, 1 H), 7.60 (s, 1 H), 7.44–7.28 (m, 6 H), 7.21–7.15 (m, 3 H), 7.03–7.01 (m, 2 H), 3.69 (s, 2 H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 149.3, 143.9, 142.6, 133.8, 133.5, 130.3, 128.5, 128.4, 128.4, 127.5, 125.7, 125.5, 124.9, 122.3, 122.1, 119.1, 113.7, 87.3, 45.3.

MS: m/z = 312 $[M]^+$.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}N_2O$ $[M + H]^+$: 313.1335; found: 313.1310.

6-Phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3aa)[15]

Yellowish solid; yield: 48.2 mg (82%); mp 178–180 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.91–8.88 (m, 1 H), 8.01–7.98 (m, 1 H), 7.71–7.58 (m, 8 H), 7.42–7.36 (m, 1 H), 7.03–6.98 (m, 1 H), 6.90 (s, 1 H), 6.50–6.48 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.2, 144.1, 137.4, 134.5, 131.5, 130.6, 130.0, 129.8, 129.3, 128.9, 127.8, 126.6, 125.0, 124.1, 122.8, 121.2, 119.6, 114.0, 112.5.

MS: m/z = 294 $[M]^+$.

3-Methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ba)[15]

Yellowish solid; yield: 43.2 mg (70%); mp 190–192 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.77 (d, J = 6.0 Hz 1 H), 7.98–7.96 (m, 1 H), 7.64–7.57 (m, 5 H), 7.51–7.49 (m, 2 H), 7.40–7.35 (m, 1 H), 7.01–6.95 (m, 1 H), 6.83 (s, 1 H), 6.48–6.45 (m, 1 H) 2.54 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.4, 144.2, 140.4, 137.4, 134.6, 131.7, 130.6, 129.8, 129.4, 129.3, 128.9, 126.4, 124.9, 124.0, 120.4, 120.5, 119.4, 113.9, 112.4, 21.8.

MS: m/z = 308 $[M]^+$.

3-Fluoro-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ca)[16]

Yellow solid; yield: 58.0 mg (93%); mp 192–194 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.90–8.86 (m, 1 H), 7.98–7.95 (m, 1 H), 7.68–7.58 (m, 5 H), 7.42–7.35 (m, 3 H), 7.03–6.97 (m, 1 H), 6.84 (s, 1 H), 6.48–6.45 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.6 (d, $J_{C,F}$ = 248.3 Hz), 147.8, 144.1, 138.7, 134.2, 133.4 (d, $J_{C,F}$ = 9.7 Hz), 130.6, 130.1, 129.2, 129.0, 127.7 (d, $J_{C,F}$ = 9.0 Hz), 124.3, 121.3, 119.6, 119.4 (d, $J_{C,F}$ = 2.3 Hz), 116.5 (d, $J_{C,F}$ = 23.3 Hz), 114.0, 111.8, 111.6 (d, $J_{C,F}$ = 18.0 Hz).

MS: m/z = 312 $[M]^+$.

3-Chloro-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3da)[15]

Yellowish solid; yield: 53.1 mg (81%); mp 186–188 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.78 (d, J = 9.0 Hz, 1 H), 7.96–7.94 (m, 1 H), 7.65–7.56 (m, 7 H), 7.40–7.35 (m, 1 H), 7.02–6.97 (m, 1 H), 6.78 (s, 1 H), 6.46 (d, J = 9.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 147.5, 144.1, 138.6, 136.0, 134.1, 132.6, 130.5, 130.0, 129.2, 128.9, 128.2, 126.5, 125.8, 124.4, 121.5, 121.1, 119.6, 114.0, 111.3.

MS: m/z = 328 $[M]^+$.

3-Bromo-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ea)

Yellowish solid; yield: 65.6 mg (88%); mp 196–198 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.70 (d, J = 8.0 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 7.81 (s, 1 H), 7.74–7.72 (m, 1 H), 7.64–7.56 (m, 5 H), 7.39–7.36 (m, 1 H), 7.01–6.98 (m, 1 H), 6.76 (s, 1 H), 6.45 (d, J = 8.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.5, 144.1, 138.6, 134.1, 132.8, 130.9, 130.5, 130.0, 129.2, 128.9, 128.9, 126.6, 124.4, 121.5, 121.4, 119.7, 114.0, 111.1.

MS: m/z = 372 $[M]^+$.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{14}BrN_2$ $[M + H]^+$: 373.0335; found: 373.0328.

3-Methoxy-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3fa)[15]

Yellowish solid; yield: 46.0 mg (71%); mp 185–187 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.80 (d, J = 8.0 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.65–7.60 (m, 5 H), 7.40–7.36 (m, 1 H), 7.30–7.27 (m, 1 H), 7.11–7.10 (m, 1 H), 7.00–6.96 (m, 1 H), 6.84 (s, 1 H), 6.47 (d, J = 8.0 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.1, 148.4, 144.3, 137.9, 134.5, 133.3, 130.5, 129.8, 129.3, 128.9, 126.8, 124.0, 120.7, 119.2, 117.2, 116.6, 113.8, 112.3, 107.9, 55.5.

MS: m/z = 324 $[M]^+$.

6-Phenyl-3-(trifluoromethyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ga)

Yellowish solid; yield: 63.7 mg (88%); mp 189–191 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.96 (d, J = 9.0 Hz, 1 H), 7.99–7.96 (m, 2 H), 7.87–7.84 (m, 1 H), 7.69–7.59 (m, 5 H), 7.42–7.36 (m, 1 H), 7.05–6.99 (m, 1 H), 6.92 (s, 1 H), 6.48 (d, J = 9.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 146.9, 144.1, 138.9, 133.9, 131.5 (q, $J_{C,F}$ = 32.3 Hz), 131.1, 130.5, 130.1, 129.2, 129.0, 125.8, 124.9 (q, $J_{C,F}$ = 0.8 Hz), 124.6, 123.8 (q, $J_{C,F}$ = 3.8 Hz), 123.78, 123.7 (q, $J_{C,F}$ = 270.8 Hz), 121.9, 119.9, 114.1, 111.8.

MS: m/z = 362 $[M]^+$.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{14}F_3N_2$ $[M + H]^+$: 363.1104; found: 363.1108.

1-Methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ha)[15]

Yellowish solid; yield: 46.2 mg (75%); mp 181–183 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.02 (d, J = 8.0 Hz, 1 H), 7.65–7.49 (m, 8 H), 7.40–7.36 (m, 1 H), 7.03–6.98 (m, 1 H), 6.88 (s, 1 H), 6.48 (d, J = 8.0 Hz, 1 H), 3.35 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.8, 144.2, 138.7, 137.1, 134.8, 132.8, 130.4, 129.7, 129.7, 129.3, 129.1, 128.9, 124.6, 123.7, 121.9, 121.1, 119.9, 113.9, 113.4, 24.6.

MS: m/z = 308 $[M]^+$.

2-Methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ia)[15]

Yellowish solid; yield: 32.6 mg (53%); mp 165–167 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.71 (s, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.63–7.57 (m, 6 H), 7.49–7.47 (m, 1 H), 7.40–7.36 (m, 1 H), 7.01–6.97 (m, 1 H), 6.86 (s, 1 H), 6.49 (d, *J* = 8.0 Hz, 1 H), 2.60 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.2, 144.1, 138.1, 136.5, 134.7, 131.6, 130.6, 129.7, 129.4, 129.2, 128.9, 126.5, 124.7, 124.0, 122.7, 121.0, 119.5, 114.0, 112.4, 21.6.

MS: *m*/*z* = 308 $[M]^+$.

5-Phenylimidazo[2,1-*a*]isoquinoline (3ja)[17]

Yellow solid; yield: 31.7 mg (65%); mp 123–124 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.67 (d, *J* = 9.0 Hz, 1 H), 7.73–7.52 (m, 10 H), 7.02 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.7, 135.9, 134.4, 130.9, 129.8, 129.6, 129.1, 128.5, 128.2, 127.9, 126.8, 123.2, 123.0, 113.1, 113.0.

MS: *m*/*z* = 244 $[M]^+$.

10-Methyl-5-phenylimidazo[2,1-*a*]isoquinoline (3ka)

Yellowish solid; yield: 26.8 mg (52%); mp 131–133 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67–7.65 (m, 3 H), 7.60–7.52 (m, 5 H), 7.46–7.45 (m, 2 H), 7.00 (s, 1 H), 3.20 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 144.2, 136.3, 135.5, 134.6, 130.9, 130.7, 130.2, 129.5, 129.1, 128.5, 127.4, 124.9, 122.0, 113.9, 112.5, 23.9.

MS: *m*/*z* = 258 $[M]^+$.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{15}N_2$ $[M + H]^+$: 259.1230; found: 259.1230.

6-(*p*-Tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ab)[15]

Yellowish solid; yield: 43.7 mg (71%); mp 150–152 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.90–8.87 (m, 1 H), 8.01–7.98 (m, 1 H), 7.71–7.64 (m, 3 H), 7.49–7.37 (m, 5 H), 7.05–6.99 (m, 1 H), 6.87 (s, 1 H), 6.59–6.56 (m, 1 H), 2.53 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.2, 144.1, 139.9, 137.5, 131.6, 131.6, 130.6, 129.9, 129.6, 129.2, 127.7, 126.5, 124.9, 124.1, 122.7, 121.1, 119.5, 114.2, 112.5, 21.5.

MS: *m*/*z* = 308 $[M]^+$.

6-(4-Methoxyphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ac)[15]

Yellowish solid; yield: 34.9 mg (54%); mp 184–186 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.89–8.87 (m, 1 H), 8.00–7.98 (m, 1 H), 7.68–7.65 (m, 3 H), 7.52–7.48 (m, 2 H), 7.42–7.38 (m, 1 H), 7.11–7.07 (m, 2 H), 7.05–7.01 (m, 1 H), 6.87 (s, 1 H), 6.61–6.59 (m, 1 H), 3.94 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.6, 148.3, 144.1, 137.3, 131.6, 130.7, 130.6, 130.0, 127.7, 126.9, 126.5, 124.9, 124.1, 122.7, 121.1, 119.6, 114.2, 114.1, 112.6, 55.4.

MS: *m*/*z* = 324 $[M]^+$.

6-[4-(*tert*-Butyl)phenyl]benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ad)[15]

Yellowish solid; yield: 52.5 mg (75%); mp 199–201 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.81–8.78 (m, 1 H), 7.91–7.88 (m, 1 H), 7.59–7.48 (m, 5 H), 7.43–7.40 (m, 2 H), 7.32–7.26 (m, 1 H), 6.94–6.89 (m, 1 H), 6.79 (s, 1 H), 6.46–6.43 (m, 1 H), 1.36 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.1, 148.2, 144.1, 137.5, 131.6, 130.7, 129.9, 128.9, 127.7, 126.5, 125.7, 124.9, 124.1, 122.7, 121.1, 119.5, 114.1, 112.5, 34.9, 31.3.

MS: *m*/*z* = 350 $[M]^+$.

6-(4-Fluorophenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ae)[15]

Yellowish solid; yield: 43.0 mg (69%); mp 145–147 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.78–8.75 (m, 1 H), 7.89–7.87 (m, 1 H), 7.61–7.54 (m, 3 H), 7.50–7.44 (m, 2 H), 7.31–7.28 (m, 1 H), 7.22–7.14 (m, 2 H), 6.95–6.90 (m, 1 H), 6.76 (s, 1 H), 6.41–6.38 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.5 (d, $J_{C,F}$ = 249.0 Hz), 148.2, 144.1, 136.3, 131.3 (d, $J_{C,F}$ = 8.3 Hz), 131.4, 130.6 (d, $J_{C,F}$ = 3.8 Hz), 130.5, 130.1, 127.9, 126.6, 125.0, 124.2, 122.8, 121.3, 119.7, 116.1 (d, $J_{C,F}$ = 21.8 Hz), 113.8, 112.9.

MS: *m*/*z* = 312 $[M]^+$.

6-(4-Chlorophenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3af)

Yellowish solid; yield: 45.9 mg (70%); mp 178–180 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.87–8.85 (m, 1 H), 8.00–7.98 (m, 1 H), 7.69–7.64 (m, 3 H), 7.57–7.51 (m, 4 H), 7.42–7.37 (m, 1 H), 7.06–7.02 (m, 1 H), 6.84 (s, 1 H), 6.58–6.56 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.1, 144.1, 136.1, 135.9, 132.9, 131.2, 130.7, 130.4, 130.1, 129.2, 128.0, 126.6, 124.9, 124.2, 122.8, 121.3, 119.7, 113.8, 112.9.

MS: *m*/*z* = 328 $[M]^+$.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{14}ClN_2$ $[M + H]^+$: 329.0840; found: 329.0834.

6-(3-Chlorophenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ag)

White solid; yield: 42.6 mg (65%); mp 182–184 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.89–8.86 (m, 1 H), 8.00–7.98 (m, 1 H), 7.71–7.66 (m, 3 H), 7.63–7.60 (m, 2 H), 7.54–7.47 (m, 2 H), 7.43–7.38 (m, 1 H), 7.07–7.03 (m, 1 H), 6.88 (s, 1 H), 6.57–6.55 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.1, 144.1, 136.1, 135.8, 134.9, 131.2, 130.4, 130.2, 130.2, 130.0, 129.4, 128.1, 127.6, 126.7, 125.0, 124.3, 122.9, 121.4, 119.8, 113.7, 112.9.

MS: *m*/*z* = 328 $[M]^+$.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{14}ClN_2$ $[M + H]^+$: 329.0840; found: 329.0846.

6-(*m*-Tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ah)

Yellowish solid; yield: 40.1 mg (65%); mp 164–166 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.91–8.88 (m, 1 H), 8.02–7.99 (m, 1 H), 7.69–7.65 (m, 3 H), 7.45–7.37 (m, 5 H), 7.05–6.99 (m, 1 H), 6.89 (s, 1 H), 6.55–6.52 (m, 1 H), 2.47 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.3, 144.2, 138.9, 137.7, 134.5, 131.6, 130.7, 130.6, 130.2, 129.9, 128.9, 127.8, 126.7, 126.5, 125.1, 124.2, 122.9, 121.3, 119.7, 114.2, 112.5, 21.6.

MS: *m*/*z* = 308 $[M]^+$.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{17}N_2$ $[M + H]^+$: 309.1386; found: 309.1380.

6-(*o*-Tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ai)

Yellowish solid; yield: 39.4 mg (64%); mp 170–171 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.94–8.92 (m, 1 H), 8.01–7.99 (m, 1 H), 7.75–7.67 (m, 3 H), 7.58–7.54 (m, 1 H), 7.47–7.37 (m, 4 H), 7.02–6.98 (m, 1 H), 6.91 (s, 1 H), 6.28–6.26 (m, 1 H), 2.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.9, 143.9, 137.8, 136.9, 134.1, 131.6, 130.6, 130.4, 130.2, 130.1, 130.0, 127.8, 126.6, 126.5, 125.0, 124.2, 122.7, 121.7, 119.5, 112.9, 111.9, 19.2.

MS: *m*/*z* = 308 $[M]^+$.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{17}N_2$ $[M + H]^+$: 309.1386; found: 309.1396.

6-(Thiophen-2-yl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3aj)[15]

Yellowish solid; yield: 27.1 mg (45%); mp 150–152 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.86–8.83 (m, 1 H), 7.97–7.95 (m, 1 H), 7.67–7.59 (m, 4 H), 7.41–7.32 (m, 2 H), 7.25–7.23 (m, 1 H), 7.08–7.03 (m, 2 H), 6.53–6.50 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.1, 144.0, 134.5, 130.9, 130.5, 130.1, 129.8, 129.7, 128.4, 128.0, 127.5, 126.7, 125.1, 124.3, 123.3, 121.5, 119.6, 115.2, 113.7.

MS: *m*/*z* = 300 $[M]^+$.

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