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Article

Cobalt-catalyzed redox-neutral synthesis of isoquinolines: C–H activation assisted by an oxidizing N–S bond

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ABSTRACT

A redox-neutral avenue to access isoquinolines has been realized by a Co(III)-catalyzed C–H activation process. Starting from readily available *N*-sulfinyl imine substrates and alkynes, the reaction occurred via N–S cleavage with broad substrate scope and functional group compatibility in the presence of cost-effective cobalt catalysts.

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1. Introduction

Isoquinolines are an important class of heterocycles that have found wide applications in synthetic organic chemistry and as core structures of pharmaceuticals and materials. Traditional methods to access isoquinolines suffered from employment of functionalized starting materials and strong acids [1–7]. For example, the Larock group [1–5] applied palladium catalysis to the annulative coupling between *ortho*-bromo functionalized imines and alkynes. To overcome these limitations, the past decade has witnessed significant progress in heterocycle synthesis via a C–H activation strategy [8–13], in which abundant arenes are used as readily available starting materials. Thus, a number of transition metals such as Rh, Ir, Pd and Ru have been reported to effectively catalyze the C–H activation of arenes leading to isoquinoline synthesis [14–40].

Early examples of isoquinoline synthesis via C–H activation

occurred under oxidative conditions, as demonstrated by Fagnou et al. [41] under Rh(III) catalysis. Subsequently, the groups of Chiba [18,21,23], Li [19], Hua [25], and others [20,29] have extended the arene substrate to those bearing an oxidizing N–O and N–N bond as a directing group, which allowed annulation under redox-neutral and mild conditions with high efficiency and selectivity. Besides rhodium catalysis, the employment of Ru(II) catalysts has also allowed efficient isoquinoline synthesis [33–37]. Despite the significant progress, these systems are limited to the employment of relatively costly noble metals such as rhodium and ruthenium catalysts. Very recently, the groups of Kanai [42,43], Glorius [44,45], Ackermann [46,47], Chang [48,49], Ellman [50,51], and others [52–57] have applied earth-abundant and cost-effective cobalt catalysts to the C–H activation of arenes, which allowed efficient synthesis of various heterocycles under operational simple conditions. In some cases, the Co(III) catalysts have explicitly shown com-

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Scheme 1. C–H activation of imines for heterocycle synthesis.

plementary activity to the rhodium congeners [58,59]. In particular, Sun et al. [43], Kornhaas et al. [47], and Sen et al. [57] recently independently reported the redox-neutral annulative coupling between oxime and alkynes for efficient synthesis of isoquinolines (Scheme 1). On the other hand, although oxidizing N–O, N–N, and even C–N bonds have been utilized as an internal oxidant for redox-neutral couplings [19,41,43,47,57,60,61], oxidizing N–S bonds has been rarely applied for this purpose although a N–S linkage can be readily installed to an arene [62]. We recently reported the applications of *N*-sulfinyl imines as an arene source for the coupling with olefins and dioxazolones [58]. With the cleavage of the N–S bond, isoindole and quinazoline rings have been efficiently constructed. We now report redox-neutral isoquinoline synthesis via annulative coupling between *N*-sulfinyl imine and alkynes.

2. Experimental

2.1. General

All cobalt-catalyzed reactions were carried out in a nitrogen-filled dry box. ^1H and ^{13}C NMR spectra were recorded using CDCl_3 as a solvent on a 400 MHz spectrometer at 298 K. The chemical shift is given in dimensionless δ values and is frequency referenced relative to SiMe_4 in ^1H and ^{13}C NMR spectroscopy. High-resolution mass spectra were obtained on an Agilent Q-TOF 6540 spectrometer. Dichloroethane was distilled from CaH_2 and was stored in a dry box. All other solvents were obtained from commercial sources and were used as received.

2.2. General procedure for the synthesis of compounds 3

N-Sulfinyl imine (**1a**, 57.1 mg, 0.2 mmol), $\text{CoCp}^*(\text{CO})\text{I}_2$ (9.5 mg, 10 mol%), AgNTf_2 (15.5 mg, 20 mol%), HOAc (12 mg, 1.0 equiv.), and diphenylacetylene (**2a**, 42.8 mg, 1.2 equiv.) were weighed into a pressure tube, to which was added 1,2-dichloroethane (3 mL) under N_2 . The reaction mixture was stirred for 18 h at 120 °C. After removal of 1,2-dichloroethane under reduced pressure, methanol (3 mL) was added, followed by addition of sodium borohydride (22.8 mg, 3 equiv.). The hydrolyzed

benzophenone by-product and the isoquinolines product accidentally have the same R_f in chromatography, so NaBH_4 was added to convert benzophenone to the corresponding alcohol. The mixture was stirred at room temperature for 30 min. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether to afford the desired product.

2.3. Spectral data for products

3aa. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 6.9 Hz, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.60–7.46 (m, 5H), 7.45–7.27 (m, 7H), 7.21–7.12 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.8, 149.6, 140.9, 139.8, 137.5, 136.9, 131.3, 130.4, 130.2, 129.9, 129.7, 128.5, 128.29, 128.28, 127.51, 127.47, 127.3, 127.0, 126.6, 126.0, 125.4.

3ba. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 8.3 Hz, 1H), 7.86–7.77 (m, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.58–7.43 (m, 5H), 7.35 (d, J = 8.1 Hz, 2H), 7.24–7.15 (m, 4H), 6.99 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.5, 149.5, 139.9, 138.1, 137.2, 136.8, 136.5, 134.6, 131.1, 130.3, 130.2, 129.7, 129.4, 129.1, 128.4, 128.3, 128.2, 127.4, 126.3, 126.03, 125.3, 21.3, 21.2.

3ca. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 7.0 Hz, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.60–7.42 (m, 5H), 7.39 (d, J = 8.7 Hz, 2H), 7.25–7.16 (m, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.5, 158.8, 158.7, 149.4, 140.0, 137.5, 133.7, 132.4, 131.8, 130.3, 130.0, 129.8, 128.9, 128.5, 128.3, 127.5, 126.3, 126.0, 125.3, 114.0, 113.1, 55.3, 55.2.

3da. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 6.9 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.60–7.44 (m, 5H), 7.39 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.26–7.14 (m, 4H), 1.37 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.5, 150.2, 149.7 (two overlapping signal), 140.1, 138.1, 137.2, 134.6, 131.0, 130.3, 130.1, 129.7, 129.6, 128.4, 128.3, 127.4, 126.4, 126.2, 125.3, 125.2, 124.4, 34.64, 34.4, 31.5, 31.3.

3ea. ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, J = 8.3 Hz, 1H), 7.85–7.78 (m, 2H), 7.70–7.61 (m, 2H), 7.60–7.50 (m, 6H), 7.37–7.29 (m, 4H), 7.18 (d, J = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.3, 148.4, 139.5, 139.4, 136.7, 136.2, 132.9, 132.0, 131.8, 130.9, 130.3, 130.1, 128.7, 128.5, 128.4, 127.7, 127.0, 125.6, 125.5, 121.8, 121.7.

3fa. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, J = 8.3 Hz, 1H), 7.83–7.76 (m, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.65–7.58 (m, 1H), 7.56–7.50 (m, 4H), 7.42–7.33 (m, 2H), 7.29–7.21 (m, 2H), 7.12–7.08 (m, 2H), 6.94–6.84 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.1 (d, $J_{\text{C-F}}$ = 245.6 Hz), 162.0 (d, $J_{\text{C-F}}$ = 245.4 Hz), 160.1, 148.8, 139.6, 136.9, 136.8 (d, $J_{\text{C-F}}$ = 3.2 Hz), 133.3 (d, $J_{\text{C-F}}$ = 3.5 Hz), 132.9 (d, $J_{\text{C-F}}$ = 7.9 Hz), 132.1 (d, $J_{\text{C-F}}$ = 8.1 Hz), 130.2, 130.1, 128.7, 128.6, 128.3, 127.6, 126.8, 125.7, 125.4, 115.7 (d, $J_{\text{C-F}}$ = 21.3 Hz), 114.6 (d, $J_{\text{C-F}}$ = 21.2 Hz).

3ga. ^1H NMR (400 MHz, CD_2Cl_2) δ 8.19 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 6.4 Hz, 2H), 7.70–7.65 (m, 3H), 7.63–7.53 (m, 5H), 7.51 (s, 1H), 7.38–7.25 (m, 4H), 7.09 (t, J = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 160.9, 148.5, 143.3, 140.0, 139.9, 137.2, 134.6, 133.9, 131.3, 131.0, 130.8, 130.69, 130.68, 130.65,

129.63, 129.62, 129.3, 129.2, 128.9, 128.1, 127.8, 126.2, 126.1, 123.0, 122.3.

3ha. ^1H NMR (400 MHz, CDCl_3) δ 8.21 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 6.8 Hz, 2H), 7.72–7.70 (m, 2H), 7.57–7.51 (m, 4H), 7.40 (dd, J = 14.0, 7.8 Hz, 1H), 7.25–7.00 (m, 6H), 6.95–6.86 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.8 (d, $J_{\text{C-F}}$ = 245.8 Hz), 162.4 (d, $J_{\text{C-F}}$ = 245.8 Hz), 160.4, 148.2 (d, $J_{\text{C-F}}$ = 2.4 Hz), 142.8 (d, $J_{\text{C-F}}$ = 7.6 Hz), 139.5 (d, $J_{\text{C-F}}$ = 3.0 Hz), 139.4, 136.6, 130.4, 130.1, 130.0, 129.0 (d, $J_{\text{C-F}}$ = 8.0 Hz), 128.74, 128.70, 128.4, 127.7, 127.1 (d, $J_{\text{C-F}}$ = 3.0 Hz), 127.0, 126.0 (d, $J_{\text{C-F}}$ = 3.0 Hz), 125.7, 125.6, 118.2 (d, $J_{\text{C-F}}$ = 21.3 Hz), 117.2 (d, $J_{\text{C-F}}$ = 22.4 Hz), 114.6 (d, $J_{\text{C-F}}$ = 20.9 Hz), 114.2 (d, $J_{\text{C-F}}$ = 21.0 Hz).

3ia. ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, J = 8.4 Hz, 1H), 7.83–7.80 (m, 2H), 7.69–7.62 (m, 2H), 7.61–7.48 (m, 4H), 7.46–7.41 (m, 1H), 7.38–7.31 (m, 1H), 7.25–7.19 (m, 2H), 7.13–7.05 (m, 3H), 6.91 (t, J = 9.1 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.4 (d, $J_{\text{C-F}}$ = 245.4 Hz), 160.7, 159.7 (d, $J_{\text{C-F}}$ = 245.8 Hz), 146.7, 139.4, 136.3, 132.7 (d, $J_{\text{C-F}}$ = 3.5 Hz), 131.8 (d, $J_{\text{C-F}}$ = 3.3 Hz), 130.4, 130.2, 129.9 (d, $J_{\text{C-F}}$ = 8.0 Hz), 129.5, 129.49 (d, $J_{\text{C-F}}$ = 8.0 Hz), 128.9, 128.7, 128.6, 128.3, 127.8, 127.1, 126.0, 125.7, 125.5, 124.4, 124.3, 123.8 (d, $J_{\text{C-F}}$ = 3.5 Hz), 123.6 (d, $J_{\text{C-F}}$ = 3.4 Hz), 115.4 (d, $J_{\text{C-F}}$ = 21.9 Hz), 115.2 (d, $J_{\text{C-F}}$ = 22.0 Hz).

3ja. ^1H NMR (400 MHz, CDCl_3) δ 8.09–8.07 (m, 1H), 7.77–7.75 (m, 2H), 7.58–7.47 (m, 7H), 7.46–7.42 (m, 2H), 7.37–7.35 (m, 2H), 2.81–2.70 (m, 2H), 1.84–1.70 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.6, 152.1, 140.0, 137.9, 136.8, 130.4, 130.1, 129.8, 129.6, 128.42, 128.40, 128.3, 127.4, 127.3, 125.7, 125.6, 124.7, 37.7, 23.5, 14.1.

3ka. ^1H NMR (400 MHz, CDCl_3) δ 8.17–8.10 (m, 2H), 7.79–7.70 (m, 3H), 7.62–7.57 (m, 2H), 7.57–7.43 (m, 6H), 7.43–7.37 (m, 1H), 3.13–2.98 (m, 2H), 1.88–1.69 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.2, 151.4, 141.8, 139.9, 136.2, 130.2, 129.8, 129.5, 128.24, 128.20 (two overlapping signal), 128.1, 128.0, 127.4, 126.2, 125.9, 124.0, 30.9, 24.6, 14.5.

3la. ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, J = 8.5 Hz, 2H), 7.72–7.63 (m, 3H), 7.57–7.40 (m, 4H), 3.15–2.99 (m, 4H), 1.97–1.83 (m, 2H), 1.82–1.72 (m, 2H), 1.16 (t, J = 7.3 Hz, 3H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.1, 152.2, 140.1, 136.1, 130.0, 129.4, 128.2, 128.1, 128.0, 127.1, 125.3, 125.2, 123.3, 37.4, 29.9, 24.1, 23.6, 14.7, 14.3.

3ma+3ma'. ^1H NMR (400 MHz, CDCl_3) δ 8.18–8.07 (m, 2.7H), 7.79–7.48 (m, 4.5H), 7.68 (d, J = 7.3 Hz, 2H), 7.62–7.46 (m, 12.5H), 7.45–7.36 (m, 3.3H), 2.72 (s, 3H), 2.57 (s, 2.3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.5, 158.2, 151.0, 148.2, 141.5, 139.9, 139.8, 138.0, 137.0, 136.7, 130.2, 130.1, 130.0, 129.9, 129.7, 128.6, 128.3, 128.2, 128.01, 128.0, 127.5, 127.4, 127.36, 126.3, 125.7, 125.34, 125.3, 124.8, 123.9, 123.1, 23.3, 15.7.

3na. ^1H NMR (400 MHz, CDCl_3) δ 8.28–8.22 (m, 2H), 8.15 (d, J = 8.5 Hz, 1H), 8.09 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.88–7.80 (m, 2H), 7.70–7.67 (m, 1H), 7.60–7.49 (m, 6H), 7.44–7.41 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.4, 150.2, 139.9, 139.6, 137.9, 130.3, 130.1, 128.7, 128.6, 128.5, 128.3, 127.6, 127.5, 127.1, 126.9, 125.8, 115.7.

3oa. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 8.5 Hz, 1H), 7.90–7.83 (m, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.56–7.47 (m, 4H), 1.66–1.55 (m, 3H), 1.20 (d, J = 7.5 Hz,

18H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.0, 155.7, 140.6, 135.1, 130.2, 129.3, 128.1, 128.0, 127.6, 127.14, 127.09, 127.0, 125.6, 18.8, 11.1.

3ab. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.51 (s, 1H), 7.49–7.30 (m, 10H), 7.25–7.16 (m, 3H), 2.50 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.5, 149.7, 141.1, 140.1, 138.2, 137.8, 137.2, 137.1, 131.4, 130.4, 130.1, 129.0, 128.9, 128.7, 128.2, 127.4, 127.4, 127.1, 126.8, 124.8, 123.8, 22.1, 21.3.

3ac. ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, J = 9.2 Hz, 1H), 7.83–7.72 (m, 2H), 7.48–7.34 (m, 5H), 7.33–7.30 (m, 2H), 7.24–7.13 (m, 4H), 7.12–7.05 (m, 2H), 6.98 (d, J = 2.5 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.5, 160.0, 158.8, 150.2, 141.2, 139.1, 137.9, 132.5, 131.5, 131.2, 130.4, 129.5, 128.6, 128.4, 127.4, 127.2, 126.9, 121.2, 118.7, 113.7, 104.2, 55.4, 55.2.

3ad. ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, J = 8.8 Hz, 1H), 8.07 (s, 1H), 7.95–7.83 (m, 4H), 7.72–7.70 (m, 1H), 7.44–7.40 (m, 5H), 7.30–7.28 (m, 2H), 7.24–7.18 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.3, 151.3, 142.6, 140.0, 136.4, 136.2, 133.9, 131.4 (q, $J_{\text{C-F}}$ = 32.4 Hz), 131.1, 131.0, 130.6, 130.3, 128.7, 128.2, 128.0, 127.74, 127.70, 127.6, 126.0, 125.5 (q, $J_{\text{C-F}}$ = 3.7 Hz), 125.0, 124.0 (q, $J_{\text{C-F}}$ = 4.5 Hz), 122.8, 122.6 (q, $J_{\text{C-F}}$ = 3.1 Hz), 122.3.

3ae. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 9.0 Hz, 1H), 7.80–7.74 (m, 2H), 7.73 (d, J = 2.0 Hz, 1H), 7.58–7.52 (m, 2H), 7.48 (dd, J = 9.0, 2.0 Hz, 1H), 7.46–7.37 (m, 5H), 7.32–7.27 (m, 2H), 7.25–7.18 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.4, 150.8, 140.3, 138.0, 137.7, 136.6, 136.6, 135.0, 131.5, 131.1, 130.3, 129.2, 128.9, 128.7, 128.6, 127.7, 127.68, 127.6, 127.3, 125.0, 123.5.

3af. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (dd, J = 9.2, 5.7 Hz, 1H), 7.73–7.65 (m, 2H), 7.34–7.25 (m, 5H), 7.23 (dd, J = 10.8, 2.5 Hz, 1H), 7.20–7.05 (m, 8H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.4 ($J_{\text{C-F}}$ = 2.1 Hz), 161.9 ($J_{\text{C-F}}$ = 5.7 Hz), 158.5, 150.6, 140.4, 139.0 ($J_{\text{C-F}}$ = 9.7 Hz), 137.0, 135.6 ($J_{\text{C-F}}$ = 3.3 Hz), 131.9 ($J_{\text{C-F}}$ = 8.2 Hz), 131.1, 130.4 ($J_{\text{C-F}}$ = 5.3 Hz), 130.3, 129.5 ($J_{\text{C-F}}$ = 5.4 Hz), 128.5, 127.6, 127.3, 122.6, 117.0 ($J_{\text{C-F}}$ = 25.1 Hz), 115.5, 115.3, 109.8 ($J_{\text{C-F}}$ = 22.2 Hz).

3ag. ^1H NMR (400 MHz, CDCl_3) δ 7.93 (s, 1H), 7.66–7.54 (m, 3H), 7.44–7.26 (m, 10H), 7.21–7.11 (m, 3H), 2.48 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.4, 148.9, 141.1, 140.0, 138.1, 137.8, 136.5, 135.2, 132.2, 131.4, 130.8, 130.5, 129.6, 129.2, 128.3, 128.1, 127.5, 127.3, 127.2, 126.9, 126.3, 125.9, 125.7, 21.9, 21.6.

3ah+3ah'. ^1H NMR (400 MHz, CDCl_3) δ 8.36 (d, J = 8.8 Hz, 1.04H), 8.04 (s, 1H), 8.00 (d, J = 8.6 Hz, 0.27H), 7.95 (d, J = 8.0 Hz, 0.49H), 7.82 (d, J = 8.1 Hz, 0.51H), 7.73 (d, J = 7.8 Hz, 2.03H), 7.68 (d, J = 8.8, 1.3 Hz, 1.04H), 7.51 (s, 0.3H), 7.45–7.38 (m, 8.76H), 7.31–7.29 (m, 2.57H), 7.21–7.18 (m, 3.82H), 2.49 (s, 3H), 2.46 (s, 0.75H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.9, 151.1, 140.7 ($J_{\text{C-F}}$ = 14.1 Hz), 140.4, 139.0, 136.6, 136.4 ($J_{\text{C-F}}$ = 3.6 Hz), 131.6, 131.3, 131.26, 130.5 ($J_{\text{C-F}}$ = 19.3 Hz), 130.46, 130.2, 130.1, 129.2, 129.0, 128.6, 128.4, 127.8, 127.6, 127.4, 127.1, 126.8, 126.3, 125.33, 125.30, 125.2, 125.09, 124.8, 123.7 ($J_{\text{C-F}}$ = 4.9 Hz), 122.5, 122.1 ($J_{\text{C-F}}$ = 3.0 Hz), 22.2, 21.4.

3ai. ^1H NMR (400 MHz, CDCl_3) δ 8.23–8.16 (m, 1H),

7.67–7.64 (m, 1H), 7.59–7.55 (m, 2H), 7.39–7.30 (m, 5H), 7.38–7.28 (m, 5H), 3.07 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.7, 149.4, 141.0, 137.6, 136.0, 131.4, 130.2, 129.9, 129.1, 128.2, 127.6, 127.1, 126.9, 126.5, 126.2, 126.1, 125.5, 22.7.

3aj. ^1H NMR (400 MHz, CDCl_3) δ 8.30–8.28 (m, 1H), 7.68–7.65 (m, 1H), 7.61–7.51 (m, 2H), 7.58–7.52 (m, 2H), 7.46–7.44 (m, 2H), 7.39–7.34 (m, 3H), 7.26–7.23 (m, 2H), 7.20–7.16 (m, 3H), 4.03 (dt, $J = 13.5, 6.8$ Hz, 1H), 1.53 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.9, 148.5, 141.3, 138.1, 136.5, 131.4, 130.6, 129.3, 128.4, 128.3, 127.4, 127.1, 126.8, 126.5, 126.2, 124.8, 124.5, 31.3, 22.3.

3ak. ^1H NMR (400 MHz, CDCl_3) δ 8.29–8.27 (m, 1H), 7.66–7.64 (m, 1H), 7.56–7.50 (m, 2H), 7.45–7.42 (m, 2H), 7.37–7.32 (m, 3H), 7.25–7.22 (m, 2H), 7.20–7.15 (m, 3H), 3.67–3.60 (m, 1H), 2.09–1.93 (m, 6H), 1.82 (d, $J = 12.5$ Hz, 1H), 1.58–1.51 (m, 2H), 1.45–1.34 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.4, 148.6, 141.3, 138.1, 136.5, 131.4, 130.6, 129.3, 128.3 (two overlapping signal), 127.4, 127.1, 126.8, 126.5, 126.2, 124.8, 124.5, 41.8, 32.5, 26.9, 26.3.

3. Results and discussion

We commenced our study with the optimization of reaction conditions of the coupling between *N*-sulfinyl imine **1a** and diphenylacetylene with $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2/\text{AgNTf}_2$ as a catalyst (Table 1). The coupling at 120 °C in DCE afforded the desired isoquinoline product **3aa** in 54% isolated yield together with a small amount of benzophenone (Table 1, entry 1). Introduction of KOAc as an additive further improved the yield to 64% (Table 1, entry 2). In contrast, a diminished yield was isolated when NaOAc was used (Table 1, entry 8). Screening of the solvent revealed that reactions performed in other common solvents such as HFIP, TFE, and acetone all gave inferior results (Table 1, entries 3–5). Attempts to inhibit hydrolysis of the

imine by addition of 4A molecular sieves also failed, and no reaction was observed (Table 1, entry 6). It has been reported that carboxylic acid can facilitate C–H activation and subsequent cyclization in transition metal catalysis. Indeed, switching the KOAc to HOAc under otherwise the same conditions improved the yield, and a maximum yield of 73% was secured when one equivalent of HOAc was used (Table 1, entry 10).

With the optimized conditions in hand, we next examined the scope and generality of this coupling system (Table 2). The scope of the alkyne substrate was first explored in the coupling with **1a**. It was found that symmetrically substituted diarylalkynes bearing both electron-donating and -withdrawing groups at *ortho*, *meta*, and *para* positions all coupled with good to high efficiency (**3aa–3ia**). The installed halogen groups in these coupled products should readily allow further chemical functionalizations. The symmetric alkyne substrate has been extended to a dialkyl-substituted alkyne such as 4-octyne albeit in moderate yield (**3la**). Extension of the alkyne to unsymmetrical ones proved successful. Thus, 1-phenyl-1-propyne coupled to afford product **3ma** (major) and **3ma'** (minor) as a mixture of inseparable regioisomers in 1.3:1 ratio (only the major was shown). Similarly, 1-phenyl-1-pentyne coupled to give two regioisomers (**3ja** and **3ka**) in a total yield of 69% that are chromatographically separated. Terminal alkynes also proved viable as a coupling partner. The reaction of phenylacetylene afforded the corresponding isoquinoline in 40% yield (**3na**), and a higher isolated yield (63%) was obtained when tri(iso-propyl)acetylene was used (**3oa**).

We next examined the scope with respect to the imine substrate in the coupling with diphenylacetylene. Symmetrically substituted benzophenone imines all coupled smoothly, where both electron-donating, -withdrawing, and halogen groups were tolerated (**3ac–3af**). The reaction occurred at the less hindered *ortho* site for the *N*-sulfinyl imine of di(*m*-tolyl)methanone (**3ag**). The coupling of an electronically biased imine afforded two isomeric products (**3ah** and **3ah'**) in 4:1 ratio, where C–H activation at the more electron-poor ring took preference. The imine substrate was not limited to that of benzophenone, and several acetophenone-derived imines all coupled smoothly to deliver the products in good to high yields (**3ai–3ak**).

On the basis of our previous related mechanistic studies [58], this system likely follows a C–H activation mechanism because substrate **1a** can readily undergo H/D exchange with CD_3COOD when catalyzed by Co(III) catalysts. To further probe the C–H activation process, kinetic isotope effect (KIE) has been measured by using intramolecular competition (Eq. (1)):

The coupling of **1a-d5** with diphenylacetylene afforded a mixture of isotopologues, ^1H NMR analysis of which revealed a KIE = 2.8. Although no solid conclusion can be drawn for the turnover-limiting step using an intramolecular experiment, this

Table 1
Optimization studies.

Entry	Additive (equiv.)	Solvent	Yield ^a (%)
1	—	DCE	54
2	KOAc (0.2)	DCE	64
3	KOAc (0.2)	HFIP	62
4	KOAc (0.2)	TFE	<5
5	KOAc (0.2)	Acetone	30
6 ^b	KOAc (0.2)	DCE	Trace
7	KOAc (0.4)	DCE	50
8	NaOAc (0.2)	DCE	43
9	HOAc (2)	DCE	66
10	HOAc (1)	DCE	73
11	HOAc (0.5)	DCE	68

Reaction conditions: imine **1a** (0.2 mmol), **2a** (0.24 mmol), $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10 mol%), AgNTf_2 (20 mol%), solvent (3 mL), 120 °C, 18 h, sealed tube under nitrogen.

^aYields of isolated products.

^b4A molecular sieves (200 mg) were added.

Table 2

Scope of Co-catalyzed synthesis of isoquinolines.

Entry	Product	Yield * (%)	Entry	Product	Yield * (%)	Entry	Product	Yield * (%)	Entry	Product	Yield * (%)
1		73	8		64	14		26	20		87
2		75	9		66	15		43	21		54
3		68	10		26	16		44	22		80 (3ah+3ah' (major:minor = 4:1))
4		26	11		43	17		76	23		54
5		43	12		44	18		26	24		66
6		44	13		76 (3ma+3ma' (major:minor = 1.3:1))	19		71	25		78
7		50									

Reaction conditions: imine **1a** (0.2 mmol), **2** (0.24 mmol), Cp*Co(CO)I₂ (10 mol%), AgNTf₂ (20 mol%), HOAc (1 equiv.), DCE (3 mL), 120 °C, 18 h, sealed tube under nitrogen. * Yields of the isolated products.

result suggests that a C–H activation mechanism should be involved.

On the basis of literature precedents [56,58], a plausible

mechanism of this coupling system has been proposed (Scheme 2). C–H activation of **1a** give a metalacycle **A**. Insertion of alkyne to the Co–aryl bond generates a seven-membered meta-

Scheme 2. Proposed catalytic cycle.

lacycle **B**. Subsequent C–N reductive elimination provides an isoquinolinium salt (**C**) and a $\text{Cp}^*\text{Co(I)}$ species (**D**). The N–S bond is proposed to oxidatively add to the Co(I) species to yield the isoquinoline product **3aa** together with a $\text{Cp}^*\text{CoX(SO}^t\text{Bu)}$ species (**E**), protonolysis of which regenerates the active Cp^*CoX_2 species and the $^t\text{BuSOH}$ coproduct.

4. Conclusions

We have realized a redox-neutral avenue to access isoquinolines. Starting from readily available imine substrates and alkynes, the reaction occurred with broad substrate scope and functional group compatibility in the presence of cost-effective cobalt catalysts. This represents a rare example of redox-neutral C–H activation assisted by an oxidizing N–S bond. Future studies on C–H activation and functionalization assisted by N–S bonds and other oxidizing bonds are underway in our laboratory.

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Graphical Abstract

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Cobalt-catalyzed redox-neutral synthesis of isoquinolines: C–H activation assisted by an oxidizing N–S bond

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A redox-neutral avenue to access isoquinolines has been realized by a Co(III)-catalyzed C–H activation process. Starting from readily available N-sulfinyl imine substrates and alkynes, the reaction occurred via N–S cleavage with broad substrate scope and functional group compatibility in the presence of a cost-effective cobalt catalyst.

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三价钴催化下N–S键辅助的非氧化条件下经碳氢活化合成异喹啉

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摘要: 异喹啉是非常重要的杂环化合物, 广泛应用于有机合成中, 也是构成药物和材料分子的核心骨架。很多异喹啉类的生物碱都由异喹啉基本骨架构成, 它们都有一定药理活性和生物活性, 包括抗真菌、抗癌、抗心律失常、镇痛麻醉和降血压等功效。迄今已知的含异喹啉骨架的生物碱超过1000种, 是生物碱中最的一类。传统的合成异喹啉的方法需要官能化的原料和强酸, 反应条件比较苛刻, 合成步骤繁琐。例如Larock课题组利用钯催化将邻溴官能化的亚胺与炔烃环化偶联, 合成了一系列异喹啉化合物。而过渡金属催化合成异喹啉是一种能够有效合成多种取代基异喹啉的方法。在过去的几十年中, 通过碳氢活化策略合成杂环化合物的方法得到迅猛发展, 从而使得大量的芳基化合物都能作为反应的起始原料。尤其是铑、铱、钯、钇等过渡金属都能催化芳烃的碳氢活化, 从而合成异喹啉化合物。

Fagnou课题组最早报道了氧化条件下利用三价铑催化剂经碳氢键活化与炔烃偶联合成异喹啉的方法。随后, 众多研究组利用氧化型导向基策略在无外加氧化剂条件下高效、高选择性地合成了异喹啉。除了利用三价铑催化剂之外, 利用二价钇催化剂通过碳氢活化策略也能实现类似反应。但是, 这些反应体系都必须使用铑和钇等贵金属催化剂, 极大地限制了该合成异喹啉方法的应用前景。近年来, 数个研究组将地球上储量丰富、便宜有效的钴络合物作为催化剂应用到芳烃的碳氢键活化反应中, 在简单的反应条件下合成了各种杂环化合物。对于一些反应, 三价钴催化与三价铑催化能形成互补。最近, Kanai, Ackermann和Sundararaju几乎同时报道了三价钴催化脒的碳氢键活化, 并在无外加氧化剂条件下实现了其与炔烃的偶联反应, 高效地合成了异喹啉, 在该类反应中以氮–氧键断裂作为内部氧化剂。但是在钴催化条件下氧化性的氮–硫键作为内部氧化剂辅助碳氢键活化的反应尚无报道。本课题组最近报道了芳基酮的N-亚磺酰亚胺与炔烃和胺化试剂的偶联反应, 经N–S键断裂, 高效合成了喹啉。本文利用三价钴催化剂在无外加氧化剂条件下实现了芳基酮N-亚磺酰亚胺与炔

烃的偶联, 反应经历了碳氢键活化和氮硫键断裂得到异喹啉. 此反应对端炔和内炔底物均适用.

为了初步了解反应机理, 我们利用分子内竞争的方法进行了动力学同位素效应测定, 结果表明碳氢键断裂过程可能是反应的决速步骤. 结合文献结果, 提出了可能的反应机理.

关键词: 三价钴催化剂; 碳氢活化; *N*-亚磺酰亚胺; 异喹啉

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