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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.

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 isoqinoline 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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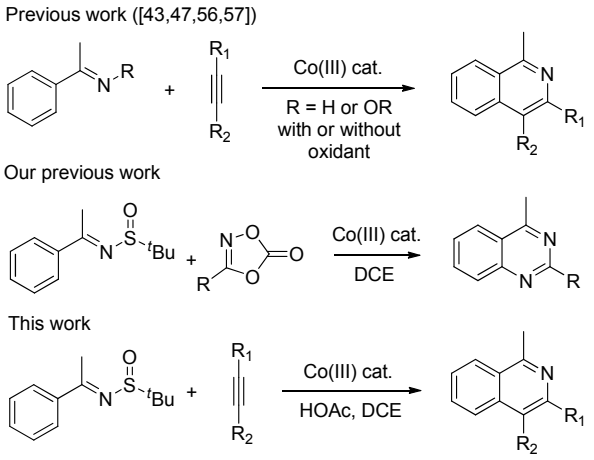


Scheme 1. C–H activation of imines for heterocycle synthesis.

plementary activity to the rhodium congeners [58,59]. In particular, Sun et al. [43], Kornhaaß 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. ^{1}H 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 ^{1}H 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), CoCp*(CO)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 Rf 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. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H 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). 13C NMR (101 MHz, CDCl3) 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. ^{1}H 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, $J_{C\text{-}F}$ = 245.6 Hz), 162.0 (d, $J_{C\text{-}F}$ = 245.4 Hz), 160.1, 148.8, 139.6, 136.9, 136.8 (d, $J_{C\text{-}F}$ = 3.2 Hz), 133.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 132.9 (d, $J_{C\text{-}F}$ = 7.9 Hz), 132.1(d, $J_{C\text{-}F}$ = 8.1 Hz), 130.2, 130.1, 128.7, 128.6, 128.3, 127.6, 126.8, 125.7, 125.4, 115.7 (d, $J_{C\text{-}F}$ = 21.3 Hz) , 114.6 (d, $J_{C\text{-}F}$ = 21.2 Hz).

3ga. ^{1}H 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. ^{1}H 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, $J_{C\text{-}F}$ = 245.8 Hz), 162.4 (d, $J_{C\text{-}F}$ = 245.8 Hz), 160.4, 148.2 (d, $J_{C\text{-}F}$ = 2.4 Hz), 142.8 (d, $J_{C\text{-}F}$ = 7.6 Hz), 139.5 (d, $J_{C\text{-}F}$ =3.0 Hz) , 139.4, 136.6, 130.4, 130.1, 130.0, 129.0 (d, $J_{C\text{-}F}$ = 8.0 Hz) , 128.74, 128.70, 128.4, 127.7, 127.1 (d, $J_{C\text{-}F}$ = 3.0 Hz), 127.0, 126.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 125.7, 125.6, 118.2 (d, $J_{C\text{-}F}$ = 21.3 Hz) , 117.2 (d, $J_{C\text{-}F}$ = 22.4 Hz), 114.6 (d, $J_{C\text{-}F}$ = 20.9 Hz), 114.2 (d, $J_{C\text{-}F}$ = 21.0 Hz).

3ia. ^{1}H 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, $J_{C\text{-}F}$ = 245.4 Hz), 160.7, 159.7 (d, $J_{C\text{-}F}$ = 245.8 Hz), 146.7, 139.4, 136.3, 132.7 (d, $J_{C\text{-}F}$ = 3.5 Hz), 131.8 (d, $J_{C\text{-}F}$ = 3.3 Hz), 130.4, 130.2, 129.9 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.5, 129.49 (d, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 3.5 Hz), 123.6 (d, $J_{C\text{-}F}$ = 3.4 Hz), 115.4 (d, $J_{C\text{-}F}$ =21.9 Hz), 115.2 (d, $J_{C\text{-}F}$ = 22.0 Hz).

3ja. ^{1}H 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. ^{1}H 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. ^{1}H NMR (400 MHz, CDCl3) 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'. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H 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. ^{1}H NMR (400 MHz, CDCl3) 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. ^{1}H 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 3.7 Hz), 125.0, 124.0 (q, $J_{C\text{-}F}$ = 4.5 Hz), 122.8, 122.6 (q, $J_{C\text{-}F}$ = 3.1 Hz), 122.3.

3ae. ^{1}H 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. ^{1}H 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 ($J_{C\text{-}F}$ = 2.1 Hz), 161.9 ($J_{C\text{-}F}$ = 5.7 Hz), 158.5, 150.6, 140.4, 139.0 ($J_{C\text{-}F}$ = 9.7 Hz), 137.0, 135.6 ($J_{C\text{-}F}$ = 3.3 Hz), 131.9 ($J_{C\text{-}F}$ = 8.2 Hz), 131.1, 130.4 ($J_{C\text{-}F}$ = 5.3 Hz), 130.3, 129.5 ($J_{C\text{-}F}$ = 5.4 Hz), 128.5, 127.6, 127.3, 122.6, 117.0 ($J_{C\text{-}F}$ = 25.1 Hz), 115.5, 115.3, 109.8 ($J_{C\text{-}F}$ = 22.2 Hz),.

3ag. ^{1}H 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'. ^{1}H 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 ($J_{C\text{-}F}$ = 14.1 Hz), 140.4, 139.0, , 136.6, 136.4 ($J_{C\text{-}F}$ = 3.6 Hz), 131.6, 131.3, 131.26, 130.5 ($J_{C\text{-}F}$ = 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 ($J_{C\text{-}F}$ = 4.9 Hz), 122.5, 122.1 ($J_{C\text{-}F}$ = 3.0 Hz), 22.2, 21.4.

3ai. ^{1}H 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.

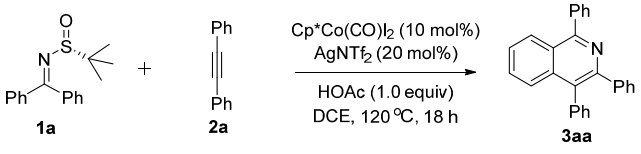
3aj. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30–8.28 (m, 1H), 7.68–7.65 (m, 1H), 7.61–7.51 (m, 2H), 7.58–7.52 (m, 2H), 7.46–7.44 (m, 2H), 7.39–7.34 (m, 3H), 7.26–7.23 (m, 2H), 7.20–7.16 (m, 3H), 4.03 (dt, J = 13.5, 6.8 Hz, 1H), 1.53 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 148.5, 141.3, 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. ^{1}H 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 studied with the optimization of reaction conditions of the coupling between *N*-sulfinyl imine **1a** and diphenylacetylene with Cp*Co(CO)I_2/$AgNTf_2$ 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).

Table 1
Optimization studies.



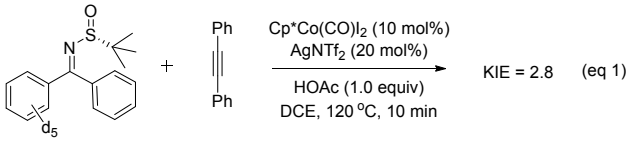
Entry	Additive (equiv.)	Solvent	Yield [a] (%)
1	—	DCE	54
2	KOAc (0.2)	DCE	64
3	KOAc (0.2)	HFIP	62
4	KOAc (0.2)	TFE	<5
5	KOAc (0.2)	Acetone	30
6 [b]	KOAc (0.2)	DCE	Trace
7	KOAc (0.4)	DCE	50
8	NaOAc (0.2)	DCE	43
9	HOAc (2)	DCE	66
10	HOAc (1)	DCE	73
11	HOAc (0.5)	DCE	68

Reaction conditions: imine **1a** (0.2 mmol), **2a** (0.24 mmol), Cp*Co(CO)I_2 (10 mol%), $AgNTf_2$ (20 mol%), solvent (3 mL), 120 °C, 18 h, sealed tube under nitrogen.
[a] Yields of isolated products.
[b] 4A molecular seives (200 mg) were added.

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 symetrically 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 product should readily allow further chemical functionalizations. The symetric alkyne substrate has been extended to a dialkyl-substituted alkyne such as 4-octyne albeit in moderate yield (**3la**). Extension of the alkyne to unsymetrical ones proved successful. Thus, 1-phenyl-1-propyne coupled to afford product **3ma** (major) and **3ma'** (mnior) as a mixture of inseperable 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 toal yield of 69% that are chromatograpohycally seperated. Terminal akynes also proved viable as a coupling partner. The reaction of phenylacetylene afforded the corresponding isoquoniline in 40% yield (**3na**), and a higher isolated yield (63%) was obtained when tri(iso-propyl)acetylene was used (**3oa**).

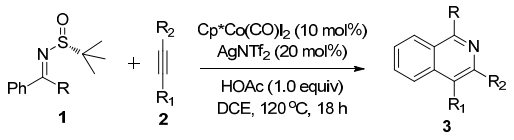
We next examined the scope with respect to the imine substrate in the coupling with diphenylacetylene. Symmetrically substituted benzophenone imines all coupled smoothly, where both electron-donating, -withdrawing, and halogen groups were tolerated (**3ac**–**3af**). The reaction occurred at the less 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)):

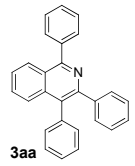
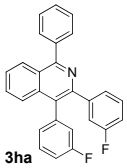
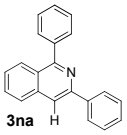
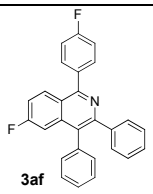
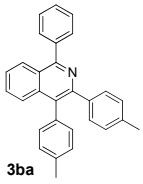
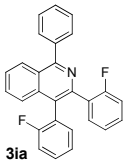
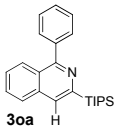
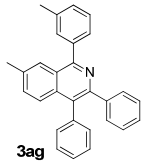
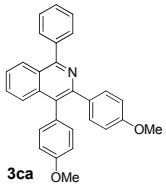
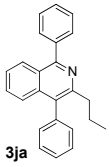
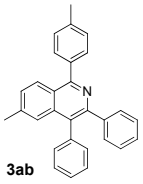
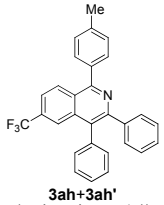
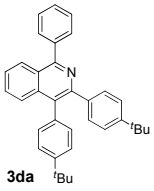
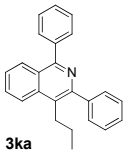
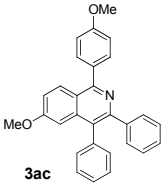
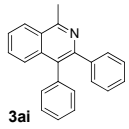
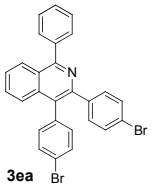
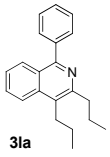
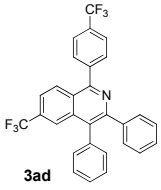
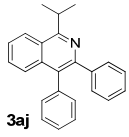
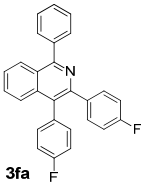
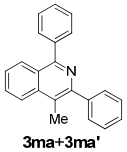
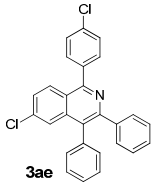
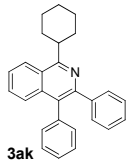
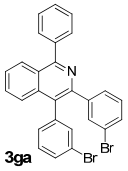


The coupling of **1a**-d_5 with diphenylacetylene afforded a mixture of isotologues, ^{1}H NMR analysis of which revealed a KIE = 2.8. Although no solid conclusion can be drawn for the turnover-limiting step using a intramolecular experiment, this

Table 2
Scope of Co-catalyzed synthesis of isoquinolines.



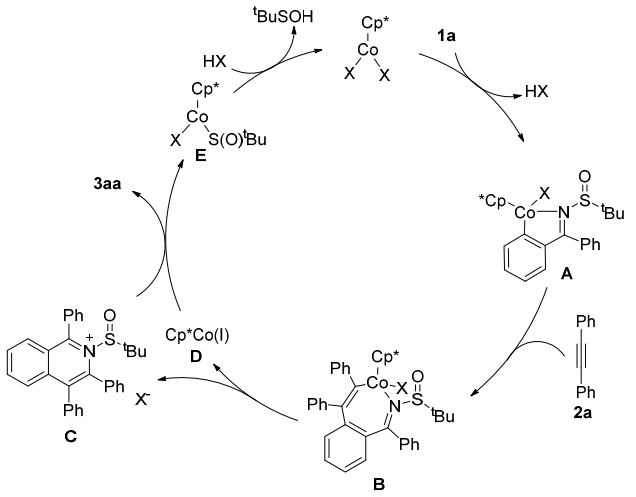
1 2 3

Entry	Product	Yield * (%)	Entry	Product	Yield * (%)	Entry	Product	Yield * (%)	Entry	Product	Yield * (%)
1	 **3aa**	73	8	 **3ha**	64	14	 **3na**	26	20	 **3af**	87
2	 **3ba**	75	9	 **3ia**	66	15	 **3oa**	43	21	 **3ag**	54
3	 **3ca**	68	10	 **3ja**	26	16	 **3ab**	44	22	 **3ah+3ah'** (major:minor = 4:1)	80
4	 **3da**	26	11	 **3ka**	43	17	 **3ac**	76	23	 **3ai**	54
5	 **3ea**	43	12	 **3la**	44	18	 **3ad**	26	24	 **3aj**	66
6	 **3fa**	44	13	 **3ma+3ma'** (major:minor = 1.3:1)	76	19	 **3ae**	71	25	 **3ak**	78
7	 **3ga**	50									

Reaction conditions: imine **1a** (0.2 mmol), **2** (0.24 mmol), Cp*Co(CO)I_2 (10 mol%), $AgNTf_2$ (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 Cp*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 Cp*CoX(SO^{t}Bu) species (**E**), protonolysis of which regenerates the active Cp*CoX$_2$ species and the ^{t}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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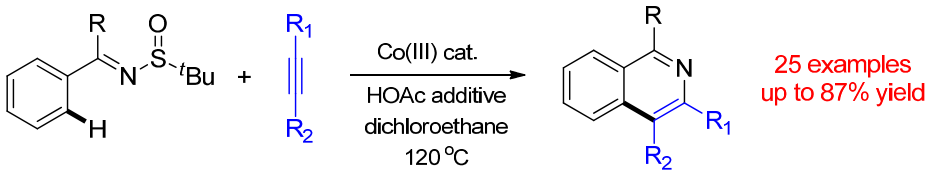

A redox-neutral avenue to access isoquinolines has been realized by a Co(III)-catalyzed C–H activation process. Starting from readily available N-sulfinyl imine substrates and alkynes, the reaction occurred via N–S cleavage with broad substrate scope and functional group compatibility in the presence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

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