CuBr-catalyzed selective oxidation of *N*-azomethine: highly efficient synthesis of methine-bridged bis-indole compounds†

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An efficient CuBr catalyzed cleavage of C–N bonds in the oxidative cross-dehydrogenative-coupling (CDC) of *N*-benzyl amines with indoles mediated by *tert*-butyl hydroperoxide (TBHP) was reported. A series of methine-bridged bis-indole derivatives were successfully synthesized under the optimized reaction conditions.

Introduction

Formation of new bonds (such as C–C, C–O and C–N) by direct and selective activation of C–H bonds is one of the most challenging research areas in organic chemistry, because it is unique organic transformations that are hard to achieve by classical methods.[1] It has attracted great interest in recent years since it avoids the preparation of functionalized starting materials and makes synthetic schemes shorter and more efficient.[2] The C–H activation process can be completed by several methods. Oxidative C–H functionalization catalyzed with[3,5a–e,6] or without[4] metallic catalysts is one of the most effective and versatile methodologies. Activation of the C–H bond adjacent to a heteroatom (such as N, O or S) has been widely investigated and a number of excellent results have been obtained.[5,6] In the published works, functionalizations of sp^3 C–H adjacent to nitrogen are most common. Many pioneering works have been done.[6]

The C–N bond is one of the most abundant and unreactive bonds in organic molecules.[7–10] The cleavage of the C–N bond in the oxidative C–H bond activation is rare. However, an interesting example of the cleavage of the C–N bond after the functionalization of the adjacent carbon was reported by Zhi-ping Li.[11] In their report, methylene-bridged bis-1,3-dicarbonyl derivatives were formed by the coupling of *N*,*N*-dimethyl aniline with 1,3-dicarbonyl compounds and thereafter cleavage of the C–N bond.

Herein, we report a highly efficient CuBr catalyzed cleavage of C–N bonds in the oxidative cross-dehydrogenative-coupling (CDC) of *N*-benzyl amines with indoles, mediated by *tert*-butyl hydroperoxide (TBHP). A series of methine-bridged bis-indole compounds were formed. The indole framework represents a privileged structural motif of established value in biologically natural products and pharmaceutical compounds.[12] Introducing or functionalizing indole derivatives to complex molecules[13] is important for not only the medical application but also the development of synthetic methodologies.[6d]

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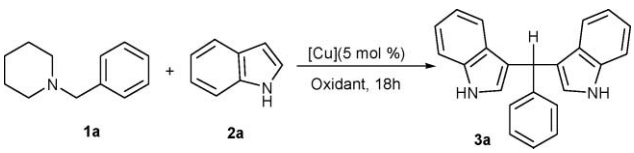
Table 1 Optimization of the reaction conditions.[a]



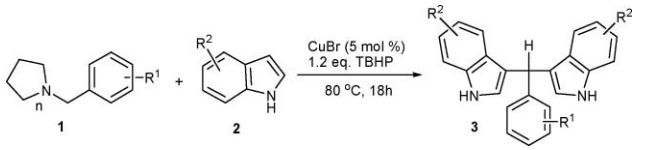
Entry	Catalyst	T °C	**1a** (equiv.)	Oxidant/mmol	yield [b](%)
1	CuBr	50	1.0	*t*-BuOOH (0.8)	32
2	CuBr	70	1.0	*t*-BuOOH (0.8)	48
3	CuBr	80	1.0	*t*-BuOOH (0.8)	52
4	CuBr	80	0.6	*t*-BuOOH (0.8)	42
5	**CuBr**	**80**	**1.0**	***t*-BuOOH (0.6)**	**62**
6	$CuCl_2$	80	1.0	*t*-BuOOH (0.6)	34
7	CuCl	80	1.0	*t*-BuOOH (0.6)	38
8	$CuBr_2$	80	1.0	*t*-BuOOH (0.6)	34
9	CuI	80	1.0	*t*-BuOOH (0.6)	46
10	$Cu(OTf)_2$	80	1.0	*t*-BuOOH (0.6)	41
11	$Cu(OAc)_2$	80	1.0	*t*-BuOOH (0.6)	41
12	CuBr	90	1.0	*t*-BuOOH (0.6)	47
13	CuBr	80	1.0	*t*-BuOOH (0.6)	58[c]
14	no	80	1.0	*t*-BuOOH (0.6)	<5
15	CuBr	80	1.0	*t*-BuOOH (0.6)	50[d]
16	CuBr	80	1.0	$(t\text{-BuO})_2$ (0.6)	26[e]

[a] 0.5 mmol indole, 0.025 mmol [Cu], t-BuOOH (5~6 M in decane). [b] Isolated yields and based on indole. [c] Reaction time: 26 h. [d] 10% CuBr was used. [e] Di-*tert*-butyl peroxide in 0.5 mL toluene was used as oxidant.

Results and discussion

In the initial study, *N*-benzyl piperidine **1a** and indole **2a** were subjected for the desired transformation at the presence of CuBr/*t*-BuOOH. We were glad to find that the target methine-bridged bis-indole **3a** was formed and isolated in 32% yield after 18 h at 50 °C (Table 1, entry 1). This result encouraged us to optimize the reaction parameters to enhance the yield of **3a** on this template reaction. Various reaction temperatures, the copper salts, the reaction time and the amount of catalysts for the desired CDC reaction were examined (Table 1). Among the reaction temperature tested, 80 °C was the best one (Table 1, entries 1–3 and 12). The amount of oxidant obviously affects the reaction result. Decreasing the amount of *tert*-butyl hydroperoxide (TBHP) from 0.8 to 0.6 mmol can improve the yield (Table 1, entries 3 and 5). Subsequently, various copper salts were tested, obviously, CuBr was the most efficient one and the yield was 62% (Table 1, entry 5).

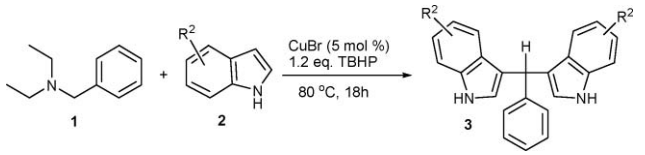
Table 2 Reaction of benzylamine with indoles[a]



Entry	n	R^1	R^2	Products	Yield (%)[b]
1	2	H	H	**3a**	62
2	2	H	6-Cl	**3b**	60
3	2	H	6-F	**3c**	56
4	2	H	5-CH_3	**3d**	50
5	1	H	H	**3a**	70
6	1	H	6-Cl	**3b**	76
7	1	H	6-F	**3c**	80
8	1	H	5-CH_3	**3d**	63
9	1	4-Cl	H	**3e**	57
10	1	4-Cl	6-F	**3f**	59
11	1	4-Cl	5-Br	**3g**	70
12	1	4-Cl	5-CH_3	**3h**	55
13	1	3-CH_3	5-Br	**3i**	60
14	1	3-CH_3	6-F	**3j**	53
15	1	3-CH_3	5-CH_3	**3k**	51

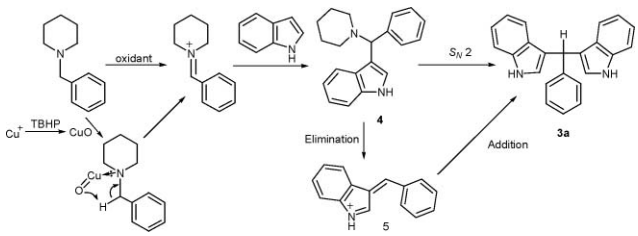
[a] 0.5 mmol Indole, 0.5 mmol benzylamine, 0.025 mmol CuBr, and 0.6 mmol of *t*-BuOOH (5~6 M in decane). [b] Isolated yields and based on indole.

Table 3 Reaction of *N*,*N*-diethyl benzylamine with indoles[a]



Entry	R^2	Products	yield (%)[b]
1	H	**3a**	52
2	6-Cl	**3b**	65
3	6-F	**3c**	66

[a] 0.5 mmol Indole, 0.5 mmol *N*,*N*-diethyl benzylamine, 0.025 mmol CuBr, and 0.6 mmol of *t*-BuOOH (5~6 M in decane). [b] Isolated yields and based on indole.



Scheme 1 Possible pathways for the formation of **3a**.

As for the dosage of CuBr, increasing the amount of CuBr, the yield was declined (Table 1, entry 15). Prolonged reaction time resulted in slightly decreasing in yields (Table 1, entry 13). In the absence of any metal catalyst, the desired product generated in a low yield (<5%) (Table 1, entry 14). By replacing the *tert*-butyl peroxide with di-*tert*-butyl peroxide, the reaction conducted smoothly, however, the yield of the desired product was not high (Table 1, entry 16). So the best reaction conditions is using 0.6 mmol TBHP and 5% mol CuBr under 80 °C.

Under the optimized reaction conditions, various indoles were used to react with *N*-benzyl piperidine and *N*-benzyl pyrrolidine derivatives, and representative results are listed in Table 2. Both *N*-benzyl piperidine and *N*-benzyl pyrrolidine derivatives are effective for this CDC reaction. Indoles with electron-withdrawing groups or electron-donating groups on C5 and C6 also worked well with substrates under the present reaction conditions (Table 2, entries 2–4, 6–8 and 10–15). The reactions selectively occur at the C3 position of indoles if both C2 and C3 positions of indoles are unoccupied. Interestingly, *N*-benzyl pyrrolidine reacted with various indoles to give the desired products in 61–80% yields which are higher than *N*-benzyl piperidine (Table 2, entries 1–8). *N*-(3-methylbenzyl) pyrrolidine and *N*-(4-chlorobenzyl) pyrrolidine could also react with various indoles, however, the yield were slightly less than *N*-benzyl pyrrolidine (Table 2, entries 5–15). This may be due to sterically hindered. *N*,*N*-diethyl benzyl amine could also react with the indole derivatives and give the satisfactory results (Table 3, entries 1–3). When *N*-ethyl pyrrolidine was used as substrate, no corresponding product was found.

Based on these results, a tentative mechanism for the formation of methine-bridged bisindole compounds is proposed in Scheme 1. Suggested by S.-I. Murahashi *etc.*,[6f,14] the first step is most likely the formation of an iminium ion *via* a copper coordinated complex through hydrogen abstraction of the sp^3 C–H adjacent to nitrogen. Then a Friedel–Crafts-type reaction is followed to give the intermediate **4**. There are two possible paths for the transform from **4** to product **3**. Either an S_N1 nucleophilic substitution reaction or a tandem reaction of Cope elimination and Michael addition was possible. However, both intermediate **4** and **5** were found in the reaction solution after the reaction was carried out for one hour. So the S_N1 route was more possible.

Conclusions

In summary, we developed a novel and efficient method for the synthesis of bis(indolyl)methane derivatives *via* the reaction between sp^3 C–H bonds and sp^2 C–H bonds catalyzed by copper bromide. This novel methodology not only provides a valid way to construct bisindoles derivatives but also opens a new way to study and construct more complex molecules since indole fragment widely featured in a variety of pharmacologically and biologically active compounds. The scope, mechanism, and synthetic application of this reaction are under investigation.

Experimental Section

Typical experimental procedure

To a mixture of CuBr (3.6 mg, 0.025 mmol) and indole (59 mg, 0.5 mmol), N-benzyl piperidine (88 mg, 0.5 mmol) was added. Then *tert*-butyl hydroperoxide (0.6 mmol, 5–6 M in decane) was added dropwise into the mixture under nitrogen at room temperature. The resulting mixture was stirred at 80 °C for 18 h. Then, the cooled reaction mixture was dissolved in water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried with anhydrous $MgSO_4$, and the product was further purified by silica gel column chromatography and eluted with cyclohexane and petroleum ether mixture to afford the product.

3,3′-(Phenylmethylene)bis(1*H*-indole) (3a)

Pink solid; mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (br s, 2H, NH), 7.34–7.39 (m, 6H), 7.25–7.29 (m, 2H), 7.14–7.17 (m, 3H), 7.00 (t, J = 6.8 Hz, 2H), 6.66 (s, 2H), 5.88 (s, 1H, Ar–CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.2, 136.9, 128.9, 128.4, 127.3, 126.3, 123.8, 122.1, 120.1, 120.0, 119.5, 111.2, 40.4; IR (KBr) ν_{max}/cm^{-1} 3410, 3051, 2924, 2858, 1612; HRMS (EI) calcd for $C_{23}H_{18}N_2$: 322.1470; found 322.1472.

Bis(6-chloroindol-3-yl)(phenyl)methane (3b)

Pink solid; mp 128–130 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (br s, 2H, NH), 7.34 (s, 2H), 7.28–7.30 (m, 4H), 7.23–7.26 (m, 3H), 6.96 (d, J = 8.4 Hz, 2H), 6.61 (s, 2H), 5.78 (s, 1H, Ar–CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.5, 137.2, 128.8, 128.6, 128.2, 126.7, 125.8, 124.3, 120.9, 120.3, 119.8, 111.2, 40.3. IR ν_{max}/cm^{-1} 3423, 3026, 2927, 2858, 1610; HRMS (EI) calcd for $C_{23}H_{16}N_2Cl_2$: 390.0691; found 390.0694.

Bis(6-fluoroindol-3-yl)(phenyl)methane (3c)

Pink solid; mp 133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (br, s, 2H, NH), 7.19–7.31 (m, 7H), 6.98–7.00 (dd, J = 1.8, 9.8 Hz, 2H), 6.74(dt, J = 2.0, 9.2 Hz, 2H), 6.58 (s, 2H), 5.78 (s, 1H, Ar–CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.5, 157.8, 143.8, 136.9, 136.7, 128.8, 128.6, 126.6, 124.0, 123.9, 123.8, 120.9, 120.7, 119.8, 108.5, 108.0, 97.8, 97.3, 40.4. IR ν_{max}/cm^{-1} 3421, 3064, 3030, 2929, 1624; HRMS (EI) calcd for $C_{23}H_{16}N_2F_2$: 358.1282; found 358.1284.

Bis(5-methylindol-3-yl)(phenyl)methane (3d)[15]

Red solid; mp 193–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br, s, 2H, NH), 7.32 (d, J = 7.2 Hz, 2H), 7.26 (t, J = 7.2 Hz, 2H), 7.20–7.22 (m, 3H), 7.18 (s, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.54 (s, 2H), 5.81 (s, 1H, Ar–CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.4, 135.3, 128.9, 128.7, 128.4, 127.5, 126.3, 124.1, 123.8, 119.7, 119.5, 110.9, 40.3, 21.7. IR ν_{max}/cm^{-1} 3408, 3022, 2920, 2856, 1597; HRMS (EI) calcd for $C_{25}H_{22}N_2$: 350.1783; found 350.1786.

Bis(indol-3-yl)(4-chlorophenyl)methane (3e) [16]

Pink solid; mp 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br, s, 2H, NH), 7.35 (t, J = 7.2 Hz, 4H), 7.21–7.27 (m, 4H), 7.17 (t, J = 7.4 Hz, 2H), 7.01 (t, J = 7.4 Hz, 2H), 6.61 (s, 2H), 5.85 (s, 1H, Ar–CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.8, 136.9, 132.0, 130.3, 128.6, 127.1, 123.8, 122.3, 120.1, 119.6, 119.4, 111.4, 39.8. IR ν_{max}/cm^{-1} 3410, 3051, 2923, 2858, 1614; HRMS (EI) calcd for $C_{23}H_{17}ClN_2$: 356.1080; found 356.1075.

Bis(6-fluoroindol-3-yl)(4-chlorophenyl)methane (3f)

Pink solid; mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (br, s, 2H, NH), 7.21–7.24 (m, 6H), 7.02 (d, J = 9.6 Hz, 2H), 6.77 (dt, J = 1.1, 9.2 Hz, 2H), 6.60 (s, 2H), 5.77 (s, 1H, Ar–CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.6, 157.8, 142.3, 136.9, 136.7, 132.3, 130.2, 128.7, 124.1, 124.0, 123.6, 120.8, 120.6, 119.3, 108.7, 108.2, 98.0, 97.4, 39.8. IR ν_{max}/cm^{-1} 3427, 3066, 2864, 1624; HRMS (EI) calcd for $C_{23}H_{15}F_2ClN_2$: 392.0892; found 392.0892.

Bis(5-bromoindol-3-yl)(4-chlorophenyl)methane (3g) [17]

Pink solid; mp 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 2H), 7.44 (s, 2H), 7.18–7.24 (m, 8H), 6.59(d, J = 1.6 Hz, 2H), 5.71 (s, 1H) ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.8, 135.5, 132.4, 130.1, 128.8, 128.7, 125.3, 125.1, 122.4, 118.7, 113.0, 39.5. IR ν_{max}/cm^{-1} 3431, 3130, 2856, 1616; HRMS (EI) calcd for $C_{23}H_{15}Br_2ClN_2$: 511.9291; found 511.9297.

Bis(5-methylindol-3-yl)(4-chlorophenyl)methane (3h)

Pink solid; mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (br, s, 2H, NH), 7.21–7.23 (m, 6H), 7.15 (s, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.54 (s, 2H), 5.78 (s, 1H, Ar–CH), 2.35 (s, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.0, 135.2, 131.9, 130.3, 128.8, 128.6, 127.3, 124.1, 123.9, 119.6, 119.0, 111.0, 39.7, 21.7. IR ν_{max}/cm^{-1} 3408, 3026, 2922, 2858, 1622; HRMS (EI) calcd for $C_{25}H_{21}N_2Cl$: 384.1393; found 384.1389.

Bis(5-bromoindol-3-yl)(3-methylphenyl)methane (3i)

Pink solid; mp 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.97 (br, s, 2H, NH); 7.47 (s, 2H), 7.14–7.23 (m, 6H), 7.09 (s, 1H), 7.02–7.05 (m, 3H), 6.58 (s, 2H), 5.68 (s, 1H, Ar–CH), 2.28 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.2, 138.2, 135.5, 129.5, 128.9, 128.5, 127.6, 125.8, 125.1, 125.0, 122.5, 119.3, 112.8, 40.0, 21.8. IR ν_{max}/cm^{-1} 3421, 3024, 2922, 2864, 1602; HRMS (EI) calcd for $C_{24}H_{18}N_2Br_2$: 491.9837; found 491.9840.

Bis(6-fluoroindol-3-yl)(3-methylphenyl)methane (3j)

Pink solid; mp 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br, s, 2H, NH), 7.23–7.27 (m, 2H), 7.14–7.18 (m, 2H), 7.09 (d, J = 8.0 Hz, 1H), 6.98–7.03 (m, 3H), 6.75 (dt, J = 1.2, 9.1 Hz, 2H), 6.60 (s, 2H), 5.75 (s, 1H, Ar–CH), 2.28 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.5, 157.8, 143.7, 138.1, 136.9, 136.6, 129.6, 128.4, 127.4, 125.8, 124.0, 123.8, 120.9, 120.7, 119.9, 108.5, 108.0, 97.8, 97.3, 40.3, 21.8. IR ν_{max}/cm^{-1} 3419, 3061, 2920, 2858, 1624; HRMS (EI) calcd for $C_{24}H_{18}N_2F_2$: 372.1438; found 372.1435.

Bis(5-methylindol-3-yl)(3-methylphenyl)methane (3k)

Pink solid; mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (br, s, 2H, NH), 7.09–7.21 (m, 8H), 6.96–7.01 (m, 2H), 6.52 (s, 2H), 5.77 (s, 1H, Ar–CH), 2.34 (s, 6H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.3, 137.8, 135.2, 129.7, 128.6, 128.3, 127.6, 127.1, 125.9, 124.1, 123.7, 119.7, 110.9, 40.1, 21.8, 21.7. IR ν_{max}/cm^{-1} 3408, 3022, 2918, 2858, 1601; HRMS (EI) calcd for $C_{26}H_{24}N_2$: 364.1940; found 364.1945.

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