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Metal-free cross-dehydrogenative C–N coupling of azoles with xanthenes and related activated arylmethylenes

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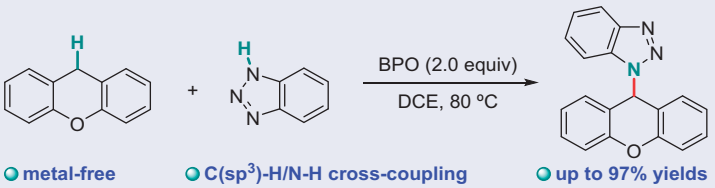
ABSTRACT

A metal-free C(sp^3)–H/N–H cross-coupling of azoles with xanthenes and related activated arylmethylenes is presented. Both the use of azoles and the activation pattern of C(sp^3)–H sources are essential for this transformation. In the presence of 2.0 equiv of benzoyl peroxide (BPO), methylenes bearing a heteroatom-bridged bisaryl group reacted with various azolic N–H sources to afford C–N bond forming products in usually excellent or quantitative yields, and the diphenylmethane and methylenes coactivated by a phenyl group and an adjacent heteroatom are less reactive. Mechanistic investigations suggest that a radical/radical cross-coupling pathway might be involved.

GRAPHICAL ABSTRACT



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KEYWORDS
Amination; C–N coupling; cross-dehydrogenative coupling; radical reaction

Introduction

Nitrogen-containing motifs are ubiquitous in natural and synthetic bioactive products,[1] and the construction of C–N bonds is of fundamental interest in organic synthesis.[2–4] Over the past decades, great progress has been made in the field of transition metal-catalyzed C–H amination reaction,[4] and advantages of this strategy include atom- and step-economy and the elimination of substrate prefunctionlization. The toxicity of heavy metal residues, however, is concerned.[5] On the other hand, whereas a plethora of methodologies for C(sp^2)–H amination have been developed, direct amination of C(sp^3)–H bonds remains more rudimentary due to their high bond energy and low acidity.[2–4]

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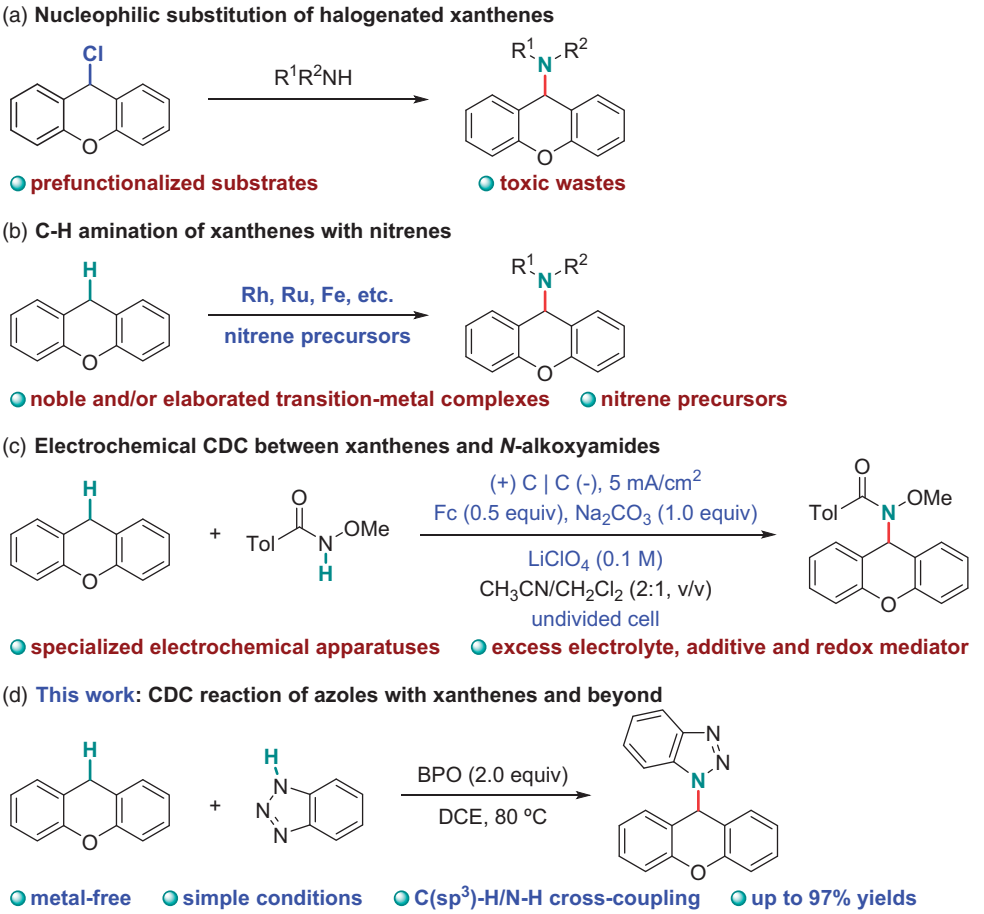
The xanthen-9-amine motif is frequently encountered in alkaloids and synthetic bioactive compounds,[6] and finding increasing applications in organic synthesis.[7] Despite the above advances in C–N bond formation, xanthen-9-amines were traditionally synthesized through nucleophilic substitution of halogenated xanthenes, which suffers from substrate prefunctionalization and toxic wastes (Scheme 1a).[6b,8] Alternatively, C–H amination of xanthenes with nitrenes could afford xanthen-9-amines, wherein a noble and/or elaborated transition-metal complex and a nitrene precursor are required (Scheme 1b).[9] The cross-dehydrogenative coupling (CDC) reaction has recently emerged as a powerful and ideal tool for the formation of C–C and C–heteroatom bonds,[10] and in 2018, Zeng and coworkers reported an electrochemical C(sp^3)–H/N–H cross-coupling of xanthenes with *N*-alkoxyamides using ferrocene as a redox mediator (Scheme 1c).[11] This is a remarkable progress, yet specialized electrochemical apparatuses, expensive electrodes, and excess electrolyte were necessary. A complementary CDC protocol using traditional chemistry is still highly desirable. In connection with our continuous efforts in radical chemistry[12] and the synthesis of bioactive molecules,[13] herein we report a metal-free cross-dehydrogenative C–N coupling of



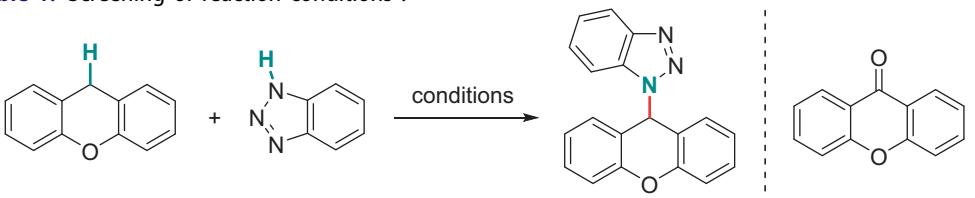
Scheme 1. Synthesis of xanthen-9-amines.

xanthenes as well as related activated arylmethylenes using azoles as N–H sources, which provides a direct and straightforward access to xanthen-9-amines and beyond with high efficiency and under simple conditions (Scheme 1d).

Results and discussion

Our studies started with the C(sp^3)–H/N–H cross-coupling of xanthene **1a** and benzotriazole **2a** (Table 1). In the presence of 10 mol% of CuBr and 2.0 equiv of benzoyl peroxide (BPO), **1a** reacted with **2a** in 1,2-dichloroethane (DCE) at 80 °C to afford xanthen-9-azole **3a** in a high yield (entry 1). A copper catalyst is not necessary, and product **3a** was formed in 89% yield in the absence of it (entry 2). While anhydrous *tert*-butyl hydroperoxide (TBHP, entry 3) is less active than BPO, the use of dicumyl peroxide (DCP, entry 4), di-*tert*-butyl peroxide (DTBP, entry 5) or *tert*-Butyl peroxybenzoate (TBPB, entry 6) as the oxidant proved fruitless. Using $K_2S_2O_8$ (entry 7) or Oxone (entry 8), coupling product **3a** was yielded in only poor yields. Other solvents were evaluated in comparison with DCE. Whereas cross-couplings carried out in tetrahydrofuran (THF, entry 13) or dimethylsulfoxide (DMSO, entry 15) were incomplete, diminished yields, ranging from 50-83%, were obtained using CH_2Cl_2 (entry 9), toluene

Table 1. Screening of reaction conditions[a].



1a **2a** **3a** **4**

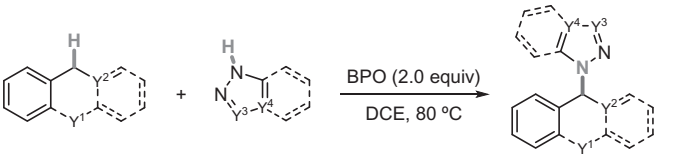
Entry	Catalyst	Oxidant (equiv)	Solvent	Temperature (°C)	Yield (%)
1	CuBr	BPO (2.0)	DCE	80	73
2	—	BPO (2.0)	DCE	80	89
3	—	TBHP[b] (2.0)	DCE	80	75 (21)[c]
4	—	DCP (2.0)	DCE	80	6 (91)[c]
5	—	DTBP (2.0)	DCE	80	trace (96)[c]
6	—	TBPB (2.0)	DCE	80	trace (94)[c]
7	—	$K_2S_2O_8$ (2.0)	DCE	80	46 (44)[c]
8	—	Oxone (2.0)	DCE	80	22 (71)[c]
9	—	BPO (2.0)	CH_2Cl_2	80	74
10	—	BPO (2.0)	toluene	80	65
11	—	BPO (2.0)	CH_3CN	80	79
12	—	BPO (2.0)	CH_3NO_2	80	78
13	—	BPO (2.0)	THF	80	53 (16)[c]
14	—	BPO (2.0)	DMF	80	50
15	—	BPO (2.0)	DMSO	80	61 (11)[c]
16	—	BPO (2.0)	EtOH	80	83
17[d]	—	BPO (2.0)	DCE	50	38 (55)[c]
18[e]	—	BPO (2.0)	DCE	80	96
19[e]	—	BPO (1.5)	DCE	80	91

aReaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), catalyst (0.05 mmol), oxidant (1.0 mmol), solvent (5 mL), 80 °C, in a sealed tube, 6 h.
b5.0–6.0 mol/L in decane.
cRecovery of **2a**.
dThe reaction time was prolonged to 12 h.
e1.5 equiv of **1a** was used.

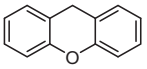
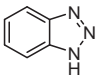
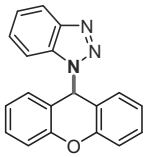
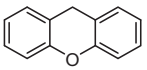
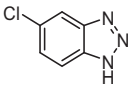
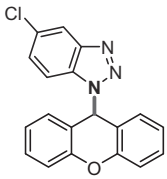
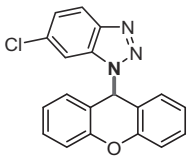
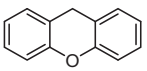
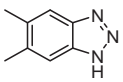
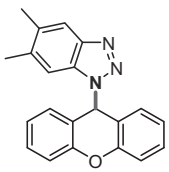
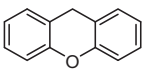
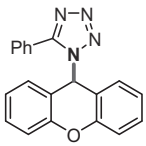
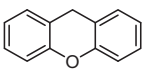
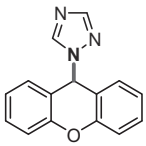
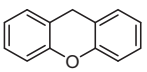
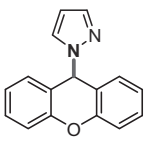
(entry 10), CH_3CN (entry 11), CH_3NO_2 (entry 12), *N*,*N*-dimethylformamide (DMF, entry 14), or ethanol (entry 16). Lowering the reaction temperature to 50 °C led to a poor yield of xanthen-9-azole **3a** (entry 17). Much to our satisfaction, **3a** was furnished in a nearly quantitative yield by using 1.5 equiv of xanthene **1a** (entry 18), while an excellent yield was still achieved with a reduced loading of BPO (entry 19). In most cases, xanthen-9-one **4** was formed.

Under optimized conditions, the C–N bond forming reaction was further explored (Table 2). It was found that the electronic nature of the substituents on the azolic benzyl ring plays a poor role in the reaction kinetics. With 5-chloro benzotriazole **2b** as the N–H source, poor N1/N3 selectivity was observed probably due to spin delocalization, and 5- or 6-chloro-substituted triazole products **3b** and **3b′** were delivered in 45% and 36% yields, respectively (entry 2). 5,6-Dimethyl benzotriazole **2c** (entry 3), 5-phenyl tetrazole **2d** (entry 4), 1,2,4-triazole **2e** (entry 5), pyrazole **2f** (entry 6), ethyl pyrazole-4-carboxylate **2g** (entry 7), 5-chloro isatin **2h** (entry 8), and 3-acetyl indole **2i** (entry 9) are all suitable N–H coupling partners, and they reacted with xanthene **1a** to give corresponding xanthen-9-amines **3c–i** in high to quantitative yields. Corresponding C–N bond forming products **3j–l** were delivered in only poor to moderate yields from acetamide **2j** (entry 10), benzamide **2k** (entry 11), or *N*-methylbenzamide **2l** (entry 12), probably due to insufficiently stabilized N-radicals. 2-Acetylxanthene **1b** (entry 13) and 2-benzoylxanthene **1c** (entry 14) are less reactive than xanthene **1a**, and their reactions with benzotriazole **2a** led to xanthen-9-azoles **3m**,**n** in high yields. Thioxanthenes **1d–f** could be alternative C(sp^3)–H coupling partners. Whereas thioxanthene **1d** reacted with benzotriazole **2a** (entry 15) or 5,6-dimethyl benzotriazole **2c** (entry 16) to afford C–N coupling products **3o**,**p** in 97% and 90% yields, respectively, thioxanthen-9-azole **3q** derived from 1,2,4-triazole **2e** was produced in a good yield (entry 17). 2-Isopropyl thioxanthene **1e** (entry 18) and 2-chloro thioxanthene **1f** (entry 19) are competent C(sp^3)-H sources as well, and corresponding xanthen-9-azoles **3r**,**s** derived from **2a** were furnished in 90% and 92% yields, respectively. The remote activating heteroatom is essential, and diphenylmethane **1g** without such a group reacted with benzotriazole **2a** (entry 20) or 5-phenyl tetrazole **2d** (entry 21) to give benzhydryl azoles **3t**,**u** in only 50% and 5% yields, respectively. The substantially lower yield of **3u** might reflect the fact that 5-phenyl tetrazole **2d** is far less active, although **2a** and **2d** reacted with xanthene **1a** with comparable ease, probably owing to the leveling effect associated with the remarkable reactivity of **1a** (entries 1 and 4). Isochromane **1h** (entry 22) and protected 1,2,3,4-tetrahydroisoquinoline **1i** (entry 23), which possess a methylene moiety coactivated by a phenyl group and an adjacent heteroatom, are less reactive than xanthene **1a** as well, and related coupling products **3v**,**w** were produced in 70–74% yields. The use of the methylene compound **1j** bearing an aryl, a remote methoxy and an adjacent benzoyloxy group furnished in 30% yield bisazole **3x**, which might arise from the further substitution by **2a** of the initial C–N coupling product (entry 24). The extraordinary performance of xanthenes and thioxanthenes as C(sp^3)–H sources might be attributed to the activation of the heteroatom-bridged bisaryl group, and the use of other diactivated methylenes, such as 2-phenylacetophenone, ethyl benzoylacetate, 1,3-benzodioxole, and 1,3-dithiane, failed to give desired C–N bond forming products (Fig. 1).

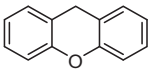
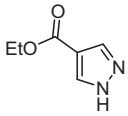
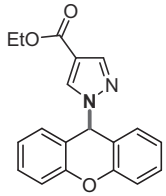
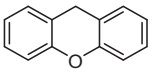
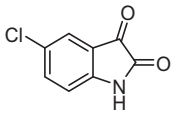
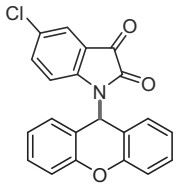
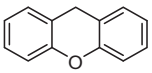
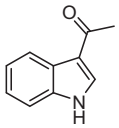
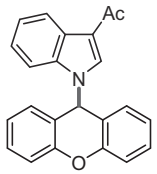
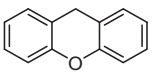
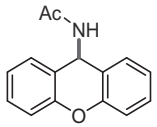
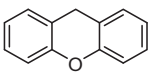
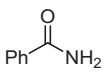
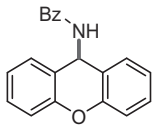
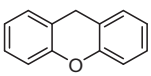
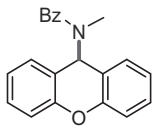
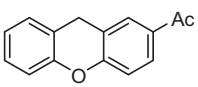
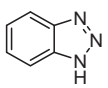
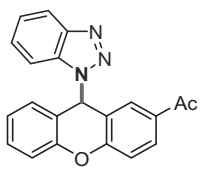
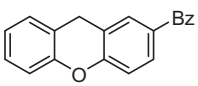
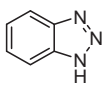
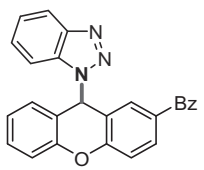
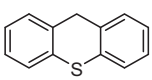
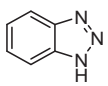
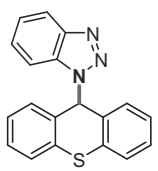
Table 2. Cross-dehydrogenative C–N coupling between azoles and activated arylmethylenes[a].



1 **2** **3**

Entry	**1**	Activated arylmethanes **1**	**2**	Azoles **2**	**3**	Products **3**	Yield (%)
1	**1a**		**2a**		**3a**		96
2	**1a**		**2b**		**3b**		45
					3b'		36
3	**1a**		**2c**		**3c**		92
4	**1a**		**2d**		**3d**		94
5	**1a**		**2e**		**3e**		97
6	**1a**		**2f**		**3f**		95

(*continued*)

7	**1a**		**2g**		**3g**		96
8	**1a**		**2h**		**3h**		85
9	**1a**		**2i**		**3i**		71
10	**1a**		**2j**		**3j**		36
11	**1a**		**2k**		**3k**		66
12	**1a**		**2l**		**3l**		44
13	**1b**		**2a**		**3m**		82
14	**1c**		**2a**		**3n**		86
15	**1d**		**2a**		**3o**		97

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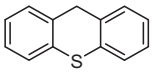
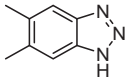
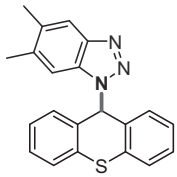
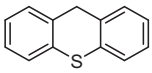
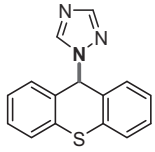
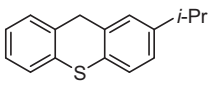
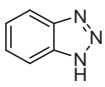
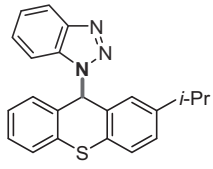
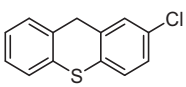
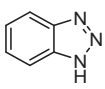
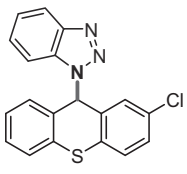
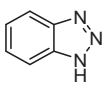
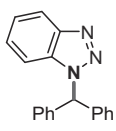
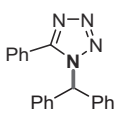
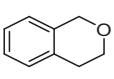
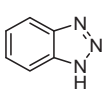
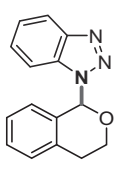
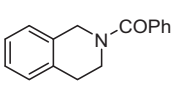
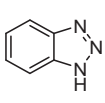
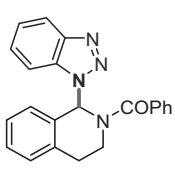
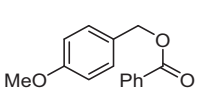
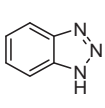
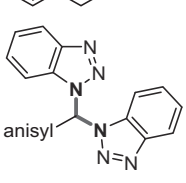
16	**1d**		**2c**		**3p**		90
17	**1d**		**2e**		**3q**		61
18	**1e**		**2a**		**3r**		90
19	**1f**		**2a**		**3s**		92
20	**1g**		**2a**		**3t**		50
21	**1g**		**2d**		**3u**		5
22	**1h**		**2a**		**3v**		70
23	**1i**		**2a**		**3w**		74
24	**1j**		**2a**		**3x**		30

aReaction conditions: **1** (0.75 mmol), **2a** (0.5 mmol), BPO (1.0 mmol), DCE (5 mL), 80 °C, in a sealed tube, 6 h.

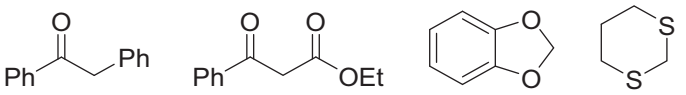
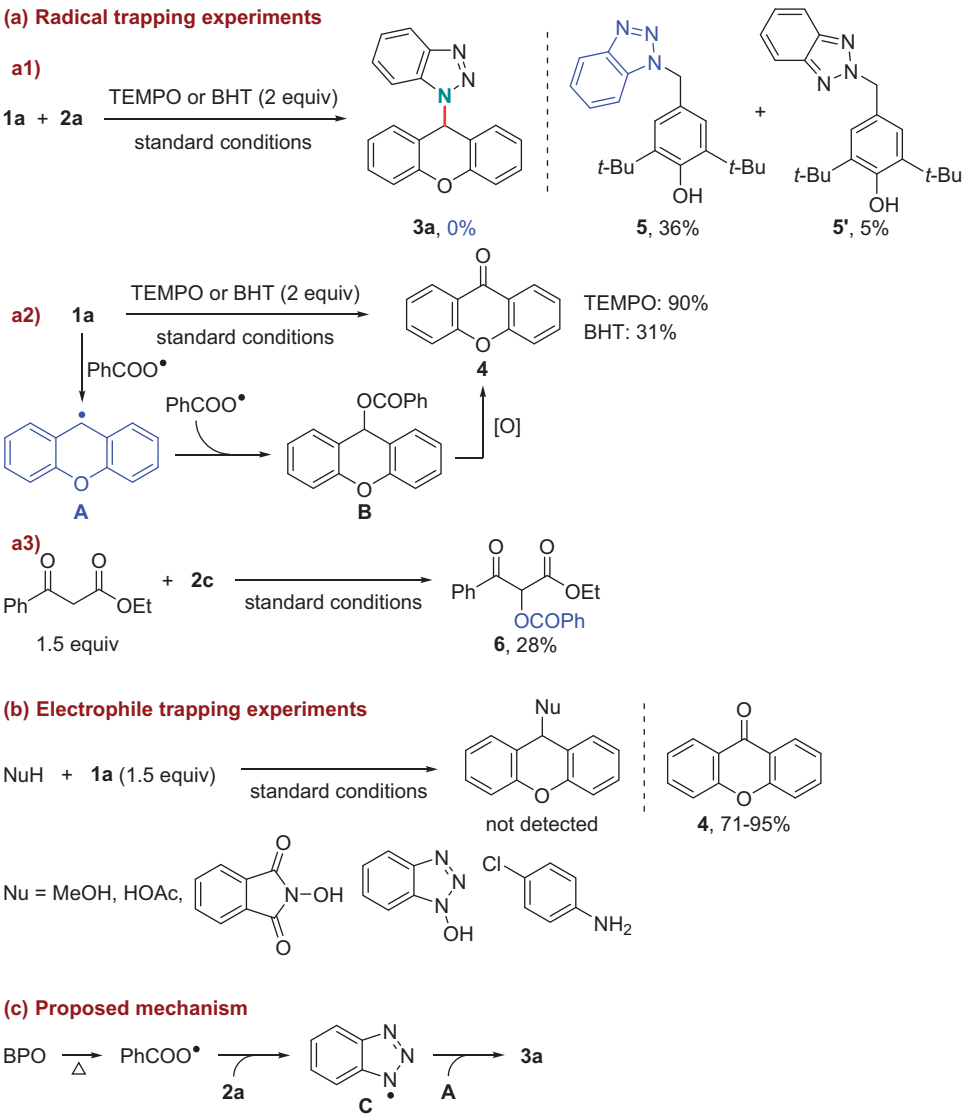


Figure 1. Diactivated methylenes failing to undergo CDC with benzotriazole **2a**.



Scheme 2. Mechanistic investigations.

To probe the reaction mechanism, radical trapping experiments were performed (Scheme 2a). Upon addition of 2 equiv of either 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) as the radical scavenger, the model reaction under otherwise standard conditions was suppressed (Scheme 2a1).

Moreover, benzotriazol-1-BHT adduct **5** was formed in 36% yield in the BHT experiment, along with regioisomeric benzotriazol-2-BHT adduct **5'** in 5% yield. Interestingly, N2-coupling product was not observed in the above cross-couplings. These results suggest that azolic N-radicals might be involved in the title reaction. On the other hand, exposure of xanthene **1a** to 2 equiv of TEMPO or BHT under otherwise standard conditions furnished xanthen-9-one **4** as the only product in 90% and 31% yields, respectively (Scheme 2a2). Though xanthen-9-TEMPO/BHT adduct was not detected, according to the abundant literature, xanthenic radical **A** does be involved in the oxidation of xanthene **1a** leading to xanthen-9-one **4**.[14] In addition, such oxidation could be catalyzed by TEMPO[15] or *N*-hydroxyphthalimide (NHPI),[16] thus it might be reasonable that xanthenic radical **A** has never been trapped by TEMPO or BHT. Upon hydrogen atom transfer from C(sp^3)–H bond of **1a** to benzoate radical, **A** is generated, and its coupling with another benzoate radical produces xanthen-9-yl benzoate **B**, which is subsequently oxidized to afford xanthen-9-one **4**. Benzoate-benzoylacetate adduct **6** was furnished in 28% yield in the reaction of ethyl benzoylacetate and 5,6-dimethyl benzotriazole **2c**, confirming the involvement of the benzoate radical[17] (Scheme 2a3).

Then, electrophile trapping experiments were conducted (Scheme 2b). Xanthene **1a** was exposed to several nucleophiles under standard conditions, and the nucleophiles include MeOH, HOAc, NHPI, 1-hydroxybenzotriazole (HOBt), and 4-chloroaniline. While cross-coupling did not proceed, again, xanthen-9-one **4** was the only product, suggesting that xanthen-9-azole products **3** might not be delivered from xanthen-9-yl benzoate **B** or xanthen-9-ylium since an acid catalyst is not involved in our protocol.[18] Though we could not completely rule out this polar possibility, a pathway of radical/radical cross-coupling is more likely.

On the basis of the above observations, a plausible mechanism is proposed (Scheme 2c). At the beginning, thermal decomposition of BPO releases the benzoate radical, hydrogen abstraction by which from benzotriazole **2a** affords benzotriazolic radical **C**. Subsequent cross-coupling of **C** with xanthenic radical **A** derived from **1a** affords xanthen-9-azole product **3a**.

Conclusions

In conclusion, we report a metal-free cross-dehydrogenative C-N coupling of azoles with xanthenes and related activated arylmethylenes. Both the use of azoles and the activation pattern of C(sp^3)–H sources are essential for this transformation. Methylenes bearing a heteroatom-bridged bisaryl group reacted with various azolic N–H sources to afford C–N coupling products in usually excellent or quantitative yields, whereas the diphenylmethane and methylenes coactivated by a phenyl group and an adjacent heteroatom are less reactive. Mechanistic investigations suggest that a radical/radical cross-coupling pathway might be involved.

Experimental

Chemicals were all purchased from commercial sources and used without treatment. Reactions were monitored by Thin Layer Chromatography (TLC) using silica gel F254

plates. Products were purified by column chromatography over 300–400 mesh silica gel under a positive pressure of air. ^{1}H NMR, ^{13}C NMR, and DEPT spectra were recorded at 25 °C on a Bruker Ascend^{TM} 400 spectrometer using tetramethyl silane (TMS) as an internal standard. High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF II Focus spectrometer (ESI).

General procedure (taking the synthesis of 3a as an example)

A 35-mL Schlenk tube, equipped with a magnetic stirring bar, was charged with 9*H*-xanthene **1a** (137 mg, 0.75 mmol), 1*H*-benzo[*d*][1,2,3]triazole **2a** (60 mg, 0.5 mmol), and BPO (242 mg, 1.0 mmol), followed by the addition of DCE (5.0 mL). The mixture was stirred at 80 °C for 6 h; then it was quenched with saturated aqueous $Na_2S_2O_3$ (2.0 mL, to react with the residual oxidant), saturated aqueous K_2CO_3 (2.0 mL), and water (20.0 mL), and extracted with CH_2Cl_2 (20.0 mL) three times. The residue obtained after evaporation of the solvent was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 12:1, v/v) to afford 1-(9*H*-xanthen-9-yl)-1*H*-benzo[*d*][1,2,3]-triazole **3a** as a colorless crystal (144 mg, 96% yield): m.p. 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.84$ (ddd, $J = 1.0$, 0.9, 8.3 Hz, 1 H), 7.01–7.05 (m, 2 H), 7.15 (ddd, $J = 1.0$, 7.0, 8.1 Hz, 1 H), 7.20–7.24 (m, 3 H), 7.28 (dd, $J = 1.2$, 8.3 Hz, 2 H), 7.35–7.39 (m, 2 H), 7.62 (s, 1 H), 8.00 (ddd, $J = 1.0$, 1.0, 8.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 151.03$, 146.98, 130.98, 130.49, 129.38, 127.37, 124.05, 123.94, 120.04, 117.06, 116.86, 110.15, 55.39; HRMS (ESI-TOF) Calcd for $C_{19}H_{14}N_3O^+$ ($[M + H]^+$) 300.1131. Found 300.1130.

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