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COMMUNICATION

Metal-free, organocatalytic cascade formation of C–N and C–O bonds through dual sp^3 C–H activation: oxidative synthesis of oxazole derivatives†

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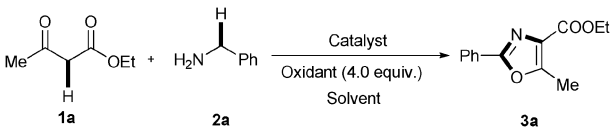
An organocatalytic cascade reaction that involves the formation of C–N, C–O and C═N bonds in one process *via* dual sp^3 C–H activation has been developed. This protocol affords a facile metal-free methodology for the synthesis of oxazole derivatives in air under mild conditions.

C–H bond activations, especially sp^3 C–H bond activations, have attracted considerable attention in recent years.[1] Avoiding prefunctionalization of the substrates, they are more valuable and straightforward than traditional synthetic strategies. However, there is one major drawback, that is, most of the reported sp^3 C–H bond activations were restricted to the metal-mediated approaches.[1] Very recently, tetra-alkylammonium iodide catalysts were found highly effective to replace transition-metal catalysts.[2] Mainly because the low valence iodide compounds could *in situ* generate the hypervalent iodine intermediate in the presence of oxidants.[3] Although some excellent results about C–O bond formations have been achieved with tetra-alkylammonium iodide catalysts,[2a–d] iodide catalytic C–N bond formations through sp^3 C–H activation have not been placed a high value.[3c,4]

Cascade reaction is one of the most powerful, efficient and atom economical methodologies in contemporary organic synthesis.[5] It usually avoids multiple processes, time-consuming and the purification of intermediates. Thus, we focused our attention on the metal-free catalytic cascade sp^3 C–H bond activations. The oxazole moieties are significant structures in many biologically natural products, such as neooxazolomycin,[6a] diazonamide A[6b] and ulapualide A.[6c] To the best of our knowledge, the available reports on catalytic synthesis of oxazole derivatives were mainly mediated by transition metals.[7] The development of an effective organocatalytic protocol for construction of oxazoles in a cascade C–H activation manner remains a challenge at the forefront of synthetic chemistry. Herein, we wish to disclose an organocatalytic cascade reaction to forge C–N, C–O and C═N bonds in one process through dual sp^3 C–H functionalization, which affords a facile metal-free approach for the synthesis of oxazole derivatives.

In our initial study, the reaction of ethyl acetoacetate **1a** with benzylamine **2a** was selected as a model reaction. The optimized results are summarized in Table 1. Initially, *n*-Bu_4NI as an organocatalyst and TBHP as an oxidant could initiate the reaction at room temperature. To our delight, when the reaction was performed at 40 °C, it resulted in a satisfactory yield of 67% (entry 1). Upon further increasing the temperature, a slightly decreased yield was obtained. Among the catalysts screened, we found *n*-Bu_4NI was the most effective (entries 1–5). It should be noted that the cascade reaction did not occur in place of *n*-Bu_4NI with *n*-Bu_4NCl or *n*-Bu_4NBr, which indicated that the iodide was necessary for the reaction (entries 2 and 3). The control experiment also demonstrated that **3a** could not be formed in the absence of a catalyst (entry 6). Then, different

Table 1 Optimization of the cascade sp^3 C–H activation reaction conditions[a]



1a 2a 3a

Entry	Catalyst	Solvent	Oxidant[b]	Time/h	Yield[c] (%)
1	*n*-Bu_4NI	EtOAc	TBHP	10	67
2	*n*-Bu_4NCl	EtOAc	TBHP	24	0
3	*n*-Bu_4NBr	EtOAc	TBHP	24	0
4	NaI	EtOAc	TBHP	10	45
5	I_2	EtOAc	TBHP	10	36
6	—	EtOAc	TBHP	24	0
7	*n*-Bu_4NI	EtOAc	T-HYDRO	8	70
8[d]	*n*-Bu_4NI	EtOAc	T-HYDRO	8	32
9[e]	*n*-Bu_4NI	EtOAc	T-HYDRO	6	nd
10[f]	*n*-Bu_4NI	EtOAc	T-HYDRO	6	61
11	*n*-BuN_4I	DCE	T-HYDRO	8	38
12	*n*-BuN_4I	DMF	T-HYDRO	8	<10
13	*n*-BuN_4I	MeCN	T-HYDRO	8	27

[a] Reaction conditions: ethyl acetoacetate **1a** (0.15 mmol), benzylamine **2a** (0.3 mmol), catalyst (20 mol%), oxidant (4.0 equiv.), solvent (1.0 mL), 40 °C. [b] TBHP = 5.5 M *tert*-butyl hydroperoxide in decane; H_2O_2 = 30% hydroperoxide in water; T-HYDRO = 70% *tert*-butyl hydroperoxide in water. [c] Isolated yields. [d] 1.0 equiv. benzylamine was used. [e] Acetic acid (20 mol%) was added as an additive. [f] $BF_3{\cdot}Et_2O$ (20 mol%) was added as an additive.

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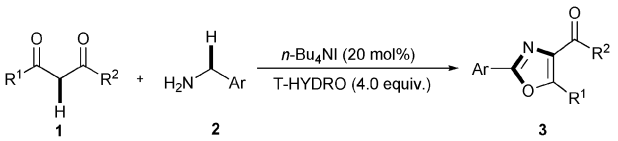
† Electronic supplementary information (ESI) available: The control experimental details and the characterization data for the products. See DOI: 10.1039/c2cc15813b

oxidants were investigated. It was important to find that when T-HYDRO was used as an oxidant instead of TBHP, the yield of **3a** can be improved to 70% (entry 7). This suggested that a small amount of water was beneficial to the reaction. Decreasing the amount of **2a** to 1.0 equiv., a lower yield was obtained (entry 8). It was reported that acidic additives favoured the C–N bond formation in oxidative condition.[2e–f] Surprisingly, when HOAc or $BF_3{\cdot}Et_2O$ was used as an additive, a less satisfactory yield was obtained (entries 9 and 10). Finally, different solvents were examined. It was found that EtOAc afforded the best result, and DCE, DMF or MeCN led to low yield (entry 7, entries 11–13). From screening of various conditions, the optimal reaction should be catalyzed by 20 mol% *n*-Bu_4NI with 4.0 equiv. T-HYDRO as an oxidant in EtOAc at 40 °C under air.

With the optimized reaction conditions in hand, we investigated the scope of this protocol between various 1,3-dicarbonyl compounds and different benzylamines. The experimental results are listed in Table 2. First, a series of 1,3-dicarbonyl compounds were examined in the cascade sp^3 C–H activation reaction. When the ethyl acetoacetate was switched to methyl or *t*-butyl acetoacetate, a satisfactory yield was obtained (entries 1–3). Moreover, β-keto esters with different alkyl substituents can also react with benzylamine **2a** smoothly, furnishing the desired products in 67–76% yield (entries 4–7). However, when 1,3-diketone was chosen as a substrate with benzylamine **2a**, a decreased yield was obtained (entries 8–10). For instance, 1,3-diphenylpropane-1,3-dione **1i** resulted in 40% yield, since the highly active methylene reactant may decompose to benzoic acid in the oxidative system.[8] It was worth mentioning that when the asymmetric 1,3-diketone **1j** was employed, excellent regioselectivity was observed (entry 10). Subsequently, different benzylamines **2a–f** were subjected to the cascade sp^3 C–H activation reaction. The results demonstrated that both electron-rich and electron-deficient benzylamines were tolerant. They can proceed readily with β-keto esters to afford the oxazoles **3k–p** in 50–73% yield (entries 11–16).

To gain insight into the cascade dual sp^3 C–H activation reaction, several control experiments were run to elucidate the mechanism. Adding a radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction system, it has almost no significant influence on the reaction of ethyl acetoacetate **1a** with benzylamine **2a**. Furthermore, no radical intermediate was trapped by radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl). These results suggested that a radical mechanism could be ruled out. Based on the study of Ishihara and co-workers, we suppose that the active iodine species ammonium hypoiodite ($[n\text{-}Bu_4N]^+[IO]^-$) or iodite ($[n\text{-}Bu_4N]^+[IO_2]^-$) plays an important role in the cascade sp^3 C–H activation reaction. When 3.0 equiv. I_2 was added into the reaction of ethyl acetoacetate **1a** with benzylamine **2a**, it hardly afforded the desired product **3a** (See ESI†). Notably, the reaction proceeded smoothly in the presence of 6.0 equiv. *n*-Bu_4NOH (25% in water) and 3.0 equiv. I_2, giving the desired product in 43% yield (See ESI†). It was acceptable that hypoiodite $[IO]^-$ might be generated from I_2 under basic conditions, subsequently disproportioned to the iodite anion $[IO_2]^-$.[9] Accordingly, a plausible mechanism is proposed in Scheme 1. Initially, intermediate **6** is formed *in situ* from ethyl

Table 2 Organocatalytic cascade sp^3 C–H bond activations for the synthesis of oxazale derivatives[a]



1 2 3

1a: R^1= Me, R^2= OEt; **1b**: R^1= Me, R^2= OMe; **1c**: R^1= Me, R^2= *Ot*-Bu; **1d**: R^1= *n*-Pr, R^2= OEt; **1e**: R^1= *i*-Pr, R^2= OEt; **1f**: R^1= *i*-Pr, R^2= OMe; **1g**: R^1= Ph, R^2= OEt; **1h**: R^1= Me, R^2= Me; **1i**: R^1= Ph, R^2= Ph; **1j**: R^1= Me, R^2= Ph.

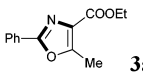
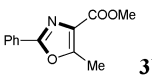
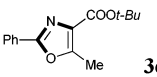
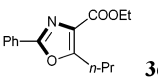
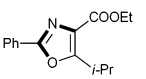
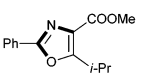
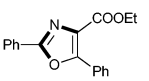
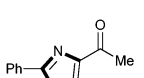
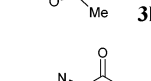
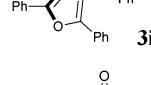
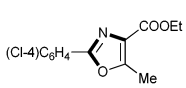
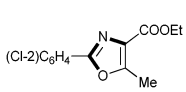
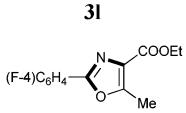
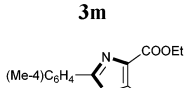
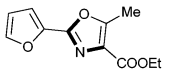
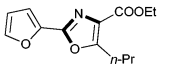
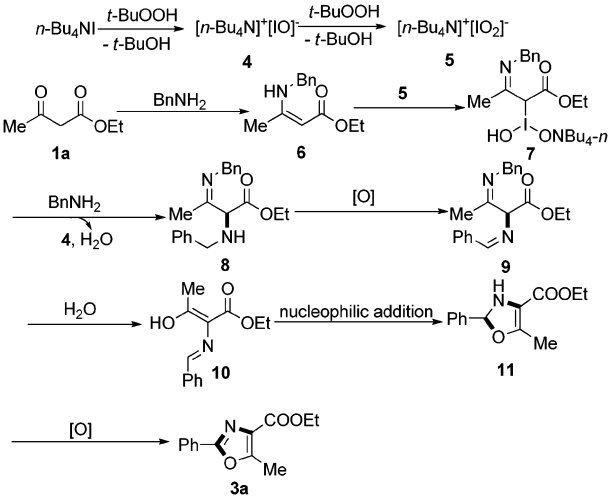
Entry	1	2	Time/h	Product	Yield[b] (%)
1	**1a**	Ar=C_6H_5, **2a**	8	 **3a**	70
2	**1b**	Ar=C_6H_5, **2a**	10	 **3b**	63
3	**1c**	Ar=C_6H_5, **2a**	12	 **3c**	72
4	**1d**	Ar=C_6H_5, **2a**	10	 **3d**	75
5	**1e**	Ar=C_6H_5, **2a**	10	 **3e**	76
6	**1f**	Ar=C_6H_5, **2a**	8	 **3f**	69
7	**1g**	Ar=C_6H_5, **2a**	8	 **3g**	67
8	**1h**	Ar=C_6H_5, **2a**	6	 **3h**	61
9	**1i**	Ar=C_6H_5, **2a**	8	 **3i**	40
10	**1j**	Ar=C_6H_5, **2a**	8	 **3j**	56
11[c]	**1a**	Ar=4-ClC_6H_4, **2b**	15	 **3k**	64
12	**1a**	Ar=2-ClC_6H_4, **2c**	10	 **3l**	73
13	**1a**	Ar=4-FC_6H_4, **2d**	8	 **3m**	65
14	**1a**	Ar=4-MeC_6H_4, **2e**	8	 **3n**	62

Table 2 (*continued*)

Entry	1	2	Time/h	Product	Yield[b] (%)
15	**1a**	Ar=Fuyl, **2f**	10	 **3o**	50
16	**1d**	Ar=Fuyl, **2f**	10	 **3p**	56

[a] Reaction conditions: **1** (0.15 mmol), **2** (0.3 mmol), *n*-Bu_4NI (20 mol%), T-HYDRO (4.0 equiv.), EtOAc (1.0 mL), 40 °C. [b] Isolated yield. [c] The reaction was carried out at room temperature.



Scheme 1 Plausible mechanism.

acetoacetate **1a** and benzylamine **2a**,[10] then it reacts with $[n\text{-}Bu_4N]^+[IO_2]^-$ **5** to form intermediate **7**. Subsequent nucleophilic attack of **7** by benzylamine **2a** gives **8**. Further oxidation of **8** to **9**, then hydrolysis of **9** generates **10**, which could undergo an intra-molecular nucleophilic addition to afford intermediate **11**. Finally, **11** may be oxidized by **4** or **5** to produce **3a** easily.

In summary, we have developed an organocatalytic cascade reaction to forge C–N, C–O and C=N bonds in one process *via* dual sp^3 C–H bond activations, which affords a facile metal-free approach for synthesis of oxazole derivatives. The presence of water and air does not have any effect to this protocol. We also proposed the possible mechanistic pathway on the basis of control experiments. Further studies for the detailed mechanism and exploration of novel oxidative coupling reactions with iodide catalytic system are under way in our laboratory.

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10 Intermediate **6** was isolated during the reaction of ethyl acetoacetate **1a** with benzylamine **2a**, and it was identified by ^1H NMR, ^{13}C NMR and MS. On the other hand, Ishihara *et al.* found that the addition of a catalytic amount of piperidine was effective for giving α-benzyloxy aldehyde, see 2*c*. The reason for it may be that piperidine could react with aldehyde to form the enamine intermediate.