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Metal-free TEMPO-catalyzed oxidative C–C bond formation from Csp^3–H bonds using molecular oxygen as the oxidant†

Bo Zhang,[a] Yuxin Cui[a] and Ning Jiao*[ab]

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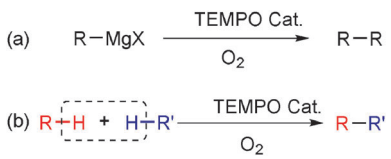
An efficient TEMPO-catalyzed oxidative C–C bond formation with two Csp^3–H bonds using molecular oxygen as the oxidant has been developed. The novel transformation provides a new strategy for the TEMPO–O_2 catalysis to construct C–C bonds. The advantages of this method include: (1) relatively mild and neutral conditions; (2) simplicity and safety of operation; (3) a stoichiometric amount of dangerous oxidants, any transition metals, additives, even solvent, is not required.

The construction of C–C bonds is one of the most useful and fundamental processes in organic synthesis. Recently, the utilization of a TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) radical as a mild organic oxidant for C–C bond formation has attracted considerable attention.[1] In the reported methods, the introduction of a stoichiometric amount of TEMPO, functionalized starting materials, or transition metal was usually required. Therefore, the development of a more environmentally benign and catalytic oxidation process for C–C bond formation is highly desirable.

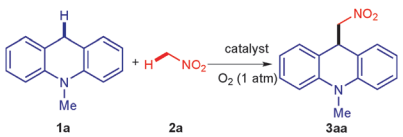
On behalf of green and sustainable chemistry,[2] molecular oxygen has been considered as an ideal oxidant, and received considerable attention in modern oxidative chemistry.[3] Although TEMPOH can be reoxidized to a TEMPO radical by O_2, the mild TEMPO-catalyzed oxidative reactions employing molecular oxygen as the oxidant are rarely reported.[4,5] Recently, Studer and coworkers disclosed a TEMPO-catalyzed homocoupling reaction of various organomagnesium compounds for C–C bond formation using molecular oxygen as the terminal oxidant (a, Scheme 1).[4] Despite its significant breakthrough in the TEMPO–O_2 catalytic system for C–C bond formation, the use of organomagnesium compounds as the substrates may limit the further application of such a method. In recent years, the cross dehydrogenative coupling of C–H bonds for C–C bond formation has become a powerful strategy.[6] However, the direct C–C coupling from Csp^3–H bonds using molecular oxygen as the oxidant is still a challenging task.[7,8] Herein, we describe an unprecedented TEMPO-catalyzed cross-coupling reaction for C–C bond formation from two different Csp^3–H bonds using molecular oxygen as the oxidant under mild and neutral conditions (b, Scheme 1).



Scheme 1 TEMPO-catalyzed oxidative C–C bond formation using oxygen as the oxidant.

Acridine derivatives are important skeletons which display a range of distinctive biological activities.[9] As part of our continuing interest in TEMPO assisted aerobic oxidation,[10] we want to try the TEMPO catalyzed C–C bond coupling reaction with Csp^3–H. The study was initiated by investigating the reaction of 10-methyl-9,10-dihydroacridine **1a** with nitromethane **2a** in the presence of 10 mol% of TEMPO at room temperature under 1 atmosphere of O_2. Fortunately, the desired coupling product **3aa** was obtained in 47% yield (Table 1, entry 1). Encouraged by this

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Temp/°C	Time/h	Yield of **3aa**[b] (%)
1	TEMPO (10)	RT	36	47
2	TEMPO (10)	40	36	90
3	NHPI (10)	40	36	71
4[c]	TEMPO (10)	40	36	56
5	TEMPO (5)	40	36	64
6	**TEMPO (10)**	**60**	**18**	**92**
7	—	60	18	Trace
8	CH_3SO_3H (10)	40	62	20
9	TFA (10)	40	62	43
10[d]	—	40	13	11
11[e]	—	40	13	0
12[f]	—	40	13	36

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mL), catalyst (0.02 mmol), stirred at the appointed temperature under O_2 (1 atm). [b] Isolated yields. [c] The reaction was carried out in air. [d] DDQ (1.0 eq.) was employed instead of TEMPO as the oxidant under Ar. [e] CAN (2.0 eq.) was employed instead of TEMPO as the oxidant under Ar. [f] PIDA (2.0 eq.) was employed instead of TEMPO as the oxidant under Ar.

[a] *State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Xue Yuan Rd. 38, Beijing 100191, China. E-mail: jiaoning@bjmu.edu.cn; Fax: +86 010 8280 5297; Tel: +86 010 8280 5297*
[b] *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, East China Normal University, Shanghai 200062, China*
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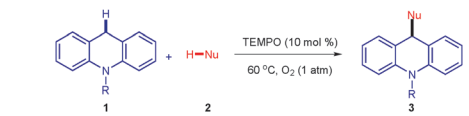
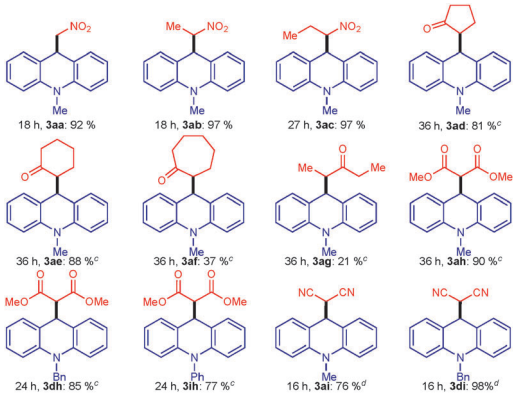
result, we decided to screen the reaction conditions. Gratifyingly, when the reaction was performed at 40 °C, the yield of **3aa** was improved to 90% (Table 1, entry 2). However, another aminoxyl radical precursor NHPI (*N*-hydroxy-phthalimide) exhibited lower efficiency than TEMPO in this transformation (Table 1, entry 3). When the reaction was carried out in air, the yield was decreased to 56% (entry 4). Lowering the catalytic amount of TEMPO to 5 mol% decreased the yield to 64% (entry 5). It is noteworthy that higher reaction temperature can accelerate the reaction and produce **3aa** in 92% yield (Table 1, entry 6). Only a trace amount of the desired product **3aa** was obtained in the absence of a TEMPO catalyst (entry 7, Table 1). When a strong acid such as CH_3SO_3H or TFA was employed as the catalyst,[8] the results were unsatisfactory in view of the low yields and long reaction time (Table 1, entries 8 and 9). Other stoichiometric oxidants such as 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ), ammonium nitrate (CAN), phenyliodonium diacetate (PIDA) were also investigated, the reactions did not execute well under these conditions (Table 1, entries 10–12).

With the optimized conditions in hand, we applied this strategy to the aerobic oxidative C–C bond formation of 9,10-dihydroacridine **1** with a variety of nucleophilic Csp^3–H substrates **2** (Table 2). When nitroethane and 1-nitropropane were used as the nucleophiles, the desired products **3ab** and **3ac** were obtained in excellent yields (97%, Table 2). Intriguingly, some cyclic ketones smoothly underwent this transformation generating the desired products **3ad–3af** in moderate to good yields (37–88%, Table 2). Compared to the reported method,[8] **3ad** could be obtained under 1 atm of molecular oxygen with shorter reaction time by this protocol. In addition, the noncyclic ketones also provided the desired products with a low yield which was attributed to the formation of 10-methylacridin-9(10*H*)-one **5** (for example **3ag**). Notably, malonate and malononitrile could be used to construct C–C bonds, affording **3ah-3di** with good to excellent yields (76–98%, Table 2).

Table 2 TEMPO-catalyzed aerobic oxidative C–C coupling of 9,10-dihydroacridines **1** with various carbon nucleophiles **2**[a,b]





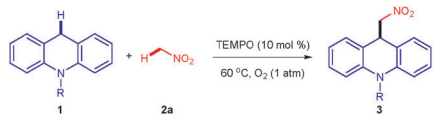
[a] Reaction conditions: see entry 6, Table 1. [b] Isolated yields. [c] The reaction was carried out at 80 °C. [d] Reaction conditions: **1** (0.2 mmol), **2i** (1.0 mmol), TEMPO (0.02 mmol) in DCE 0.3 mL, stirred at 80 °C under O_2 (1 atm).

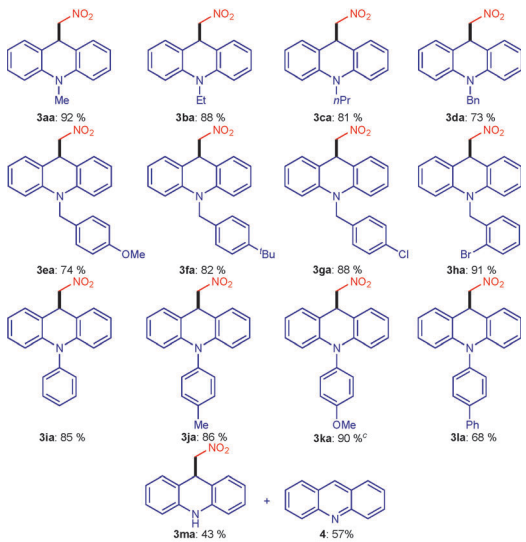
We then investigated the scope of 9,10-dihydroacridine (Table 3). Initially, the alkyl substituents on the nitrogen of the 9,10-dihydroacridine backbone were examined. Besides methyl, ethyl and propyl were compatible under the reaction conditions. They provided the desired products in excellent yields (**3ba**: 88% and **3ca**: 81%). Moreover, the benzyl substituents on the nitrogen containing electron-rich or electron-deficient groups were tolerant, affording the desired products **3da–3ha** with excellent yields (73–91%, Table 3). When phenyl substituents on the nitrogen were employed, satisfactory yields were obtained (**3ia–3la**, 68–90%, Table 3). It was noteworthy that the products **3ia–3la** contained the triphenylamine unit which was widely applied in the photoelectric material and hole-transporting material.[11] Thus, this class of compounds could have some potential performance. Interestingly, employing 9,10-dihydroacridine without N-substituents led to the desirable product **3ma** and the aromatization product **4** in 43% and 57% yield, respectively (Table 3). Unfortunately, diphenylmethane and its derivatives did not work under these conditions (see ESI†).

In addition, when the reaction was carried out in the absence of nucleophiles **2**, the reaction of **1a** in CH_3CN at 80 °C under 1 atmosphere of O_2 quantitatively produced the oxidation product **5** (eqn (1)). To the best of our knowledge, the oxidative reaction of benzyl C–H using molecular oxygen as the oxidant has been achieved by the use of NHPI and O_2, however TEMPO has no catalytic activity in the transformation.[12] This chemistry realized the oxidation of benzyl C–H for the first time by the TEMPO and O_2 catalytic system (eqn (1)).

To gain some mechanistic insights into this TEMPO-catalyzed aerobic oxidative C–C coupling reaction, the intermolecular kinetic isotopic effects (KIEs) were measured through a competition

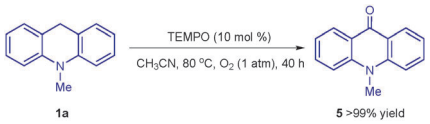
Table 3 TEMPO-catalyzed aerobic oxidative C–C coupling of 9,10-dihydroacridines **1** with nitromethane **2a**[a,b]





[a] Reaction conditions: see entry 6, Table 1. [b] Isolated yields. [c] **2a** (1.0 mL) was used.

process, by subjecting a mixture of the substrates **1a** and [D_2]–**1a** (1 : 1) to the standard conditions.



(1)

The intermolecular kinetic isotopic effect (k_H/k_D = 4.0) (eqn. 2) indicates that the cleavage of the benzyl C–H bond is involved in the rate-determining step.

(2)

The mechanism of this transformation is not clear yet.[13] We have tried to synthesize some intermediates such as hydroperoxyl or hydroxyl intermediates, but failed due to the instability of these compounds. The benzyl cations may not be involved in this transformation, because the corresponding ketone **5** (>99% yield) was obtained in the absence of a nucleophile. More detailed studies are needed to understand the mechanism.

In summary, we have developed an efficient TEMPO-catalyzed oxidative C–C bond formation with two Csp^3–H bonds using molecular oxygen as the oxidant. The novel transformation not only provides a simple and efficient approach to modify 9,10-dihydroacridine derivatives at the 9 position under mild and neutral conditions, but also discovers a new strategy for the TEMPO–O_2 catalysis to construct C–C bonds. The advantages of this method include: (1) relatively mild and neutral conditions; (2) simplicity and safety of operation; (3) a stoichiometric amount of dangerous oxidants, any transition metals, additives, even solvent, is not required. These advantages make this protocol very practical. Further studies on the scope, the mechanism, and the synthetic applications are ongoing in our laboratory.

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