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Communication

Alcohols controlled selective radical cyclization of 1,6-dienes under mild conditions

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ABSTRACT

An efficient procedure for the selective preparation of hydroxy-, carbonyl- and acetal-containing 2-pyrrolidinones has been developed through radical cyclization of 1,6-dienes initiated by α-C(sp^3)–H functionalization of alcohols. This protocol could be conducted at catalyst-free conditions at relatively low temperature (80 °C) by employing commercially available *tert*-butyl peroxybenzoate (TBPB) as the oxidant.

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The controllable construction of different valuable products from the same substrates has become a key goal and significant challenge in modern synthesis [1]. Moreover, the one-pot multi-bond forming strategy is a versatile platform for selectively and efficiently synthesizing complex molecules as the isolation steps, production costs and chemical waste will be reduced [2]. In this context, radical cyclization of 1,*n*-dienes has attracted great attention due to its ability to provide rapid access to complex cyclic structures through chemo- and regioselective manners with high efficiency and atom-economy [3].

Recently, the direct oxidative α-C(sp^3)–H functionalization of alcohols leading to the construction of C—C bonds is emerging as a powerful entry to assemble alcohol skeletons [4]. The group of Guo/Duan [5a] and Liang [5b] independently disclosed interesting oxidative hydroxyalkylarylation of *N*-arylacrylamides with alcohols, but selective preparation of carbonyl-containing products is limited (Scheme 1a). Lately, Han *et al.* [5c] reported the radical cyclization of *N*-allylbenzamides with alcohols using di-*tert*-butyl peroxide (DTBP) at 120 °C (Scheme 1b). However, the high reaction temperature and single product type of this process have limited its application. In 2014, a novel work was illustrated by Song, Li and co-workers [5d] to achieve 1,2-carboacylation of *N*-arylacrylamides with alcohols in the presence of $Fe(OAc)_2$ at 110 °C (Scheme 1c). However, the radical cyclization of 1,*n*-dienes initiated by α-C(sp^3)–H functionalization of alcohols in a selective mode has yet to be explored so far. In continuation of our interest in green chemistry [6], we wish to report a catalyst-free protocol for the radical cyclization of 1,6-dienes with alcohols using TBPB as an oxidant at relatively low temperature for the selective preparation of 2-pyrrolidinones (Scheme 1d), which is a crucial class of five-membered *N*-heterocycles commonly found in natural products and pharmaceuticals [7]. Notably, this discovery included three significant advances: (1) controllable construction of different products (hydroxy-, carbonyl- and acetal-containing 2-pyrrolidinones) from different alcohols under similar conditions; (2) mild reaction conditions: catalyst-free and relatively low temperature at 80 °C; (3) the realization of two to four bonds forming in one-pot.

Our studies began with the reaction of *N*-allyl-*N*-phenylmethacrylamide (**1a**, 0.2 mmol), propan-2-ol (**2a**, 1.0 mL) and *tert*-butyl hydroperoxide (TBHP, 2.0 equiv.) at 80 °C sealed in air (Table 1). As expected, the cyclization product **3aa** was obtained in 78% yield (entry 1). This serendipity encouraged us to investigate condition screenings to improve the efficiency of this novel

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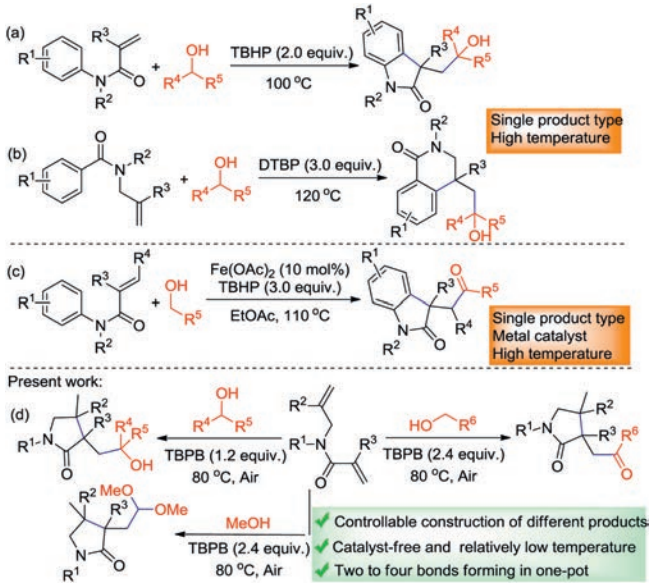
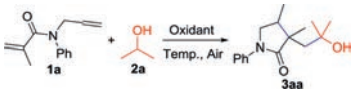


Scheme 1. Direct oxidative α-C(sp^3)–H functionalization of alcohols.

cyclization strategy. We first screened the reaction temperature. The outcomes showed that further increase of the temperature had a negative effect on the yield of **3aa**, whereas the majority of **1a** was recovered at 50 °C (entries 2 and 3). Therefore, 80 °C was selected as the reaction temperature for further screening. A control experiment indicated that an oxidant was indispensable for this transformation (entry 4). Then the screening of various oxidants, such as TBPB, DTBP, benzoyl peroxide (BPO) and $PhI(OAc)_2$, showed that TBPB was the best choice for delivering **3aa** (entries 5–8). Gratifyingly, the oxidant loading could be reduced to 1.2 equiv. without sacrificing chemical yield (94%, entry 9). Thus, we summarized the optimized reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mL) and TBPB (1.2 equiv.), at 80 °C sealed in air for 15 h.

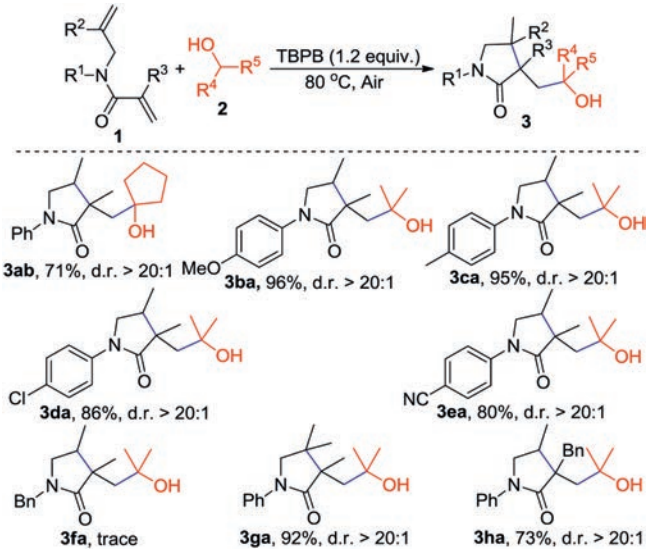
Having the optimized reaction conditions in hand, the scope of this selective cyclization with regard to 1,6-dienes **1** with secondary alcohols **2** was examined (Scheme 2). First, **1a** reacted with cyclopentanol **2b** to afford 71% of the target product **3ab**. Subsequently, 1,6-dienes **1b**–**1e** bearing OMe, Me, Cl and CN groups on the *N*-aromatic ring of 1,6-dienes were investigated, and

Table 1
Optimization of reaction conditions.[a]



Entry	Oxidant (equiv.)	Temp (°C)	Yield (%)
1	TBHP (2.0)	80	78
2[b]	TBHP (2.0)	50	8
3	TBHP (2.0)	100	71
4[c]	–	80	No reaction
5	TBPB (2.0)	80	94
6	DTBP (2.0)	80	10
7	BPO (2.0)	80	43
8[d]	$PhI(OAc)_2$ (2.0)	80	Trace
9	TBPB (1.2)	80	94

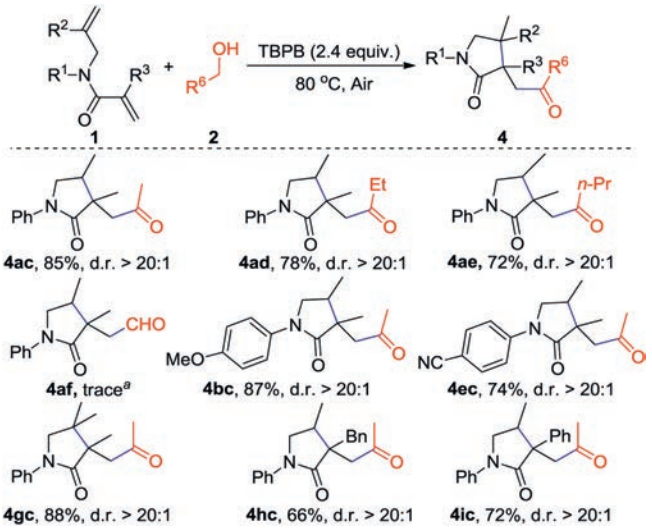
[a] Unless otherwise noted, the reactions were performed using **1a** (0.2 mmol), **2a** (1.0 mL) and oxidant sealed in air for 15 h. The d.r. of **3aa** was > 20:1.
[b] 84% of **1a** was recovered.
[c] 97% of **1a** was recovered.
[d] 89% of **1a** was recovered.



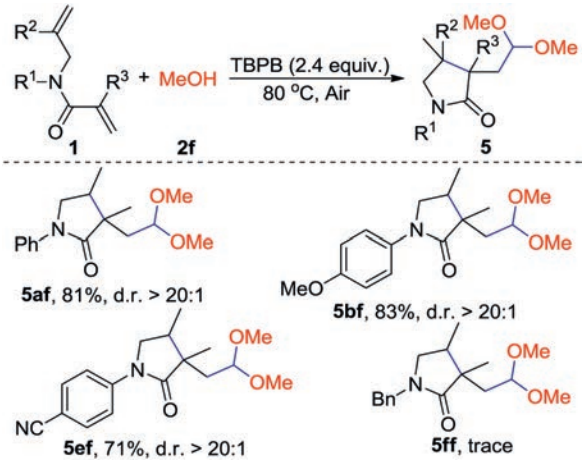
Scheme 2. Selective cyclization of 1,6-dienes with secondary alcohols. Unless otherwise noted, the reactions were performed using **1** (0.2 mmol), **2** (1.0 mL) and TBPB (1.2 equiv.) at 80 °C sealed in air for 15 h.

the corresponding products **3ba**–**3ea** were obtained in 80%–96% yields. Specifically, the results showed that electronic effect of the substituents on the *N*-aromatic ring of 1,6-dienes affected the reaction yields: The *N*-aromatic ring with electron-donating groups (**1b** and **c**) showed higher reactivities than with electron-deficient ones (**1d** and **e**). Unfortunately, when benzyl group replaced the aryl substituent on the nitrogen moiety, trace of the expected product **3fa** was afforded and 90% of **1f** was recovered. Importantly, the reaction of Me substituent at the α-position of alkenyl (R^2) with **2a** could give the desired product **3ga** in 92% yield. 1,6-Diene bearing the Bn substituent at the α-position of alkenyl (R^3) could smoothly be transformed into the corresponding cyclization product **3 ha** in 73% yield.

Next, the reaction of 1,6-dienes with primary alcohols was conducted (Scheme 3). A series of common primary alcohols such as ethanol (**2c**), *n*-propanol (**2d**), *n*-butanol (**2e**) and MeOH (**2f**) were used to react with **1a**. Notably, **2c**, **2d** and **2e** reacted smoothly



Scheme 3. Selective cyclization of 1,6-dienes with primary alcohols. Unless otherwise noted, the reactions were performed using **1** (0.2 mmol), **2** (1.0 mL) and TBPB (2.4 equiv.) at 80 °C sealed in air for 15 h. [a] 81% of 3-(2,2-dimethoxyethyl)-3,4-dimethyl-1-phenylpyrrolidin-2-one (**5af**) was obtained (d.r. > 20:1).

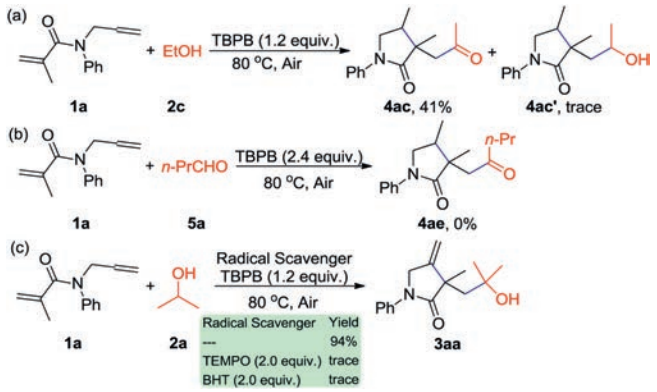


Scheme 4. Selective cyclization of 1,6-dienes with MeOH. Unless otherwise noted, the reactions were performed using **1** (0.2 mmol), **2f** (1.0 mL) and TBPB (2.4 equiv.) at 80 °C sealed in air for 15 h.

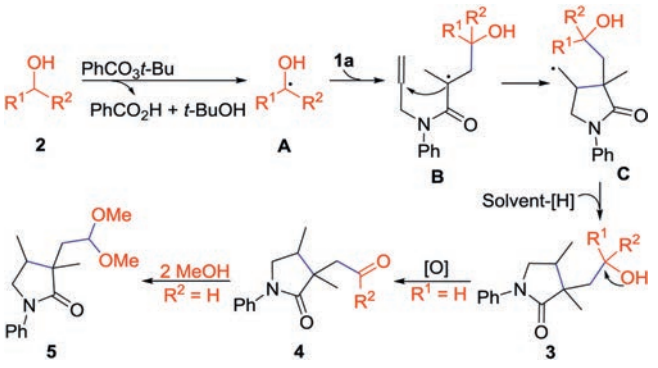
with **1a** to afford corresponding products **3ac-ae** in 72%–85% yields. To our surprise, **2f** could undergo this process and gave the acetal product 3-(2,2-dimethoxyethyl)-3,4-dimethyl-1-phenylpyrrolidin-2-one **5af** in 81% yield, but the desired product **4af** was not detected. We then chose **2c** as representative primary alcohol to react with 1,6-dienes. Two substituents, namely OMe and CN, on the *N*-aromatic ring of 1,6-dienes were well tolerated, affording the products **4bc** and **4ec** in 87% and 74% yields, respectively. This reaction was compatible with substrate bearing Me substituent at the α-position of alkenyl (R^2), leading to the formation of corresponding product **4gc** in good yield. Furthermore, 1,6-dienes bearing the Bn and pH substituents at the α-position of alkenyl (R^3) proceeded well to give the desired products **4hc-ic** in moderate yields.

As above mentioned, MeOH (**2f**) could react with **1a** and gave the acetal product **5af** in 81% yield, we then investigated the reaction between **2f** and 1,6-dienes (Scheme 4). Substrates with OMe and CN groups on the *N*-aromatic ring of 1,6-dienes were easily converted into the desired acetal products **5bf** and **5ef** in moderate to good yields. However, the reaction of **2f** with *N*-Bn substituted 1,6-diene **1f** gave trace product **5ff**.

In order to give a better understanding of this selective cyclization, several control experiments were performed (Scheme 5). Initially, when using 1.2 equiv. of TBPB in the reaction of **1a** with **2c**, the yield of desired product **4ac** was sharply reduced



Scheme 5. Control experiment.



Scheme 6. Possible mechanism for the formation of **3**, **4** and **5**.

to 41%, and only trace of **4ac'** was detected, which indicated that **4ac'** was oxidized quickly under this oxidation system (Scheme 5a). Treatment of **1a** and butyraldehyde **5a** under the standard conditions, but no **4ae** was obtained (Scheme 5b). This result implied that **5a** was not a possible intermediate and this reaction may be initiated by the α-C(sp^3)–H bond functionalization of alcohols. Moreover, we performed two radical trapping experiments with 2.0 equiv. of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT), but trace of cyclization product **3aa** was detected and nearly >90% of **1a** was recovered (Scheme 5c). This observation indicated that a radical process might be involved in the current transformation.

Based on the above experimental results and pertinent work [3b–e, 8,9], it is assumed that a radical process is involved in the formation of **3**, **4** and **5** as shown in Scheme 6. The reaction is initiated by the alkyl radical **A**, which is caused by the α-C(sp^3)–H cleavage of alcohol in the presence of TBPB under heating [8]. Then, the selective radical addition of **A** to **1a** gives intermediate **B**, which is cyclization with another C=C double bond of **1a** to produce intermediate **C**, followed by hydrogen abstraction from solvent affording product **3** [3b–e,9]. When R^1 = H, the further oxidation of hydroxyl by TBPB generates the **4**. More especially, when R^2 = H, the acetalization of **4** with MeOH under the current system to form acetal product **5**.

In conclusion, a one-pot TBPB promoted approach has been developed for the selective synthesis of hydroxy-, carbonyl- and acetal-containing 2-pyrrolidinones *via* radical cyclization of 1,6-dienes with alcohols under catalyst-free conditions. The method exhibits remarkable compatibility with a wide variety of 1,6-dienes, secondary alcohols and primary alcohols, realizing the controllable construction of different products under similar conditions. Control experiments suggested that this transformation is initiated by the α-C(sp^3)–H bond functionalization of alcohols and a radical process is involved. Further application of this radical cyclization is currently ongoing in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.04.042.

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