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Radical Cyclization of Olefinic Amides through α-C(sp³)–H Functionalization of Ketones under Catalyst-, Ligand-, and Base-Free Conditions

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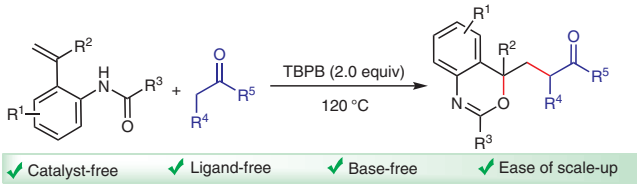

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Abstract A new, efficient, and practical radical cyclization of olefinic amides with ketones through α-C(sp³)–H functionalization in the presence of *tert*-butyl peroxybenzoate (TBPB) is described for the first time. This protocol assembles a wide range of pivotal and useful benzoxazines in good to excellent yields under mild, catalyst-free, ligand-free, and base-free conditions with wide functional group tolerance. Moreover, the mechanistic study indicates that the α-carbonyl radical is involved in this transformation.

Key words green synthesis, catalyst-free, ligand-free, base-free, radical cyclization, α-C(sp³)–H functionalization

The C(sp³)–H functionalization has changed the logic of chemical synthesis and attracted significant attentions by enabling the direct transformation of simple and easy available starting materials to complex and valuable compounds.[1] The C(sp³)–H functionalization strategies based on transition-metal catalysis, metal-catalyzed carbene transfer, hydrogen atom transfer, and radical coupling have been explored, alongside the development of various methods for balancing the reactivity and selectivity in these transformations.[2] Regardless of the great advancements in this field, the α-C(sp³)–H functionalization of ketones still remains a formidable but promising challenge, obviously attributed to the high bond dissociation energy.[3] In this context, a number of ketones with carbon–carbon double bonds, promoted by radical C(sp³)–H functionalization, have been reported.[4] However, these processes are still plagued by some limitations, such as the use of transition metal or acid catalysts, the necessity of stoichiometric bases, and relatively poor selectivity. Therefore, the continuous exploration of mild and high selectivity radical C(sp³)–H functionalization of ketones with other types of carbon–carbon double bonds is still highly desirable.

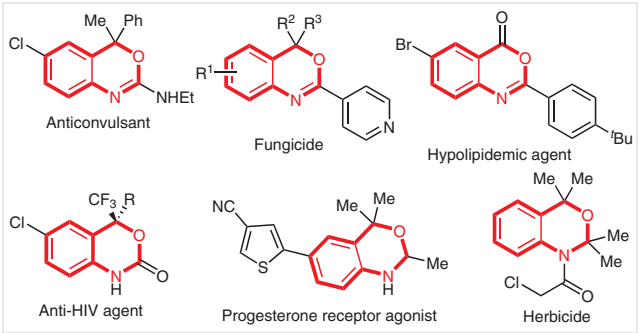
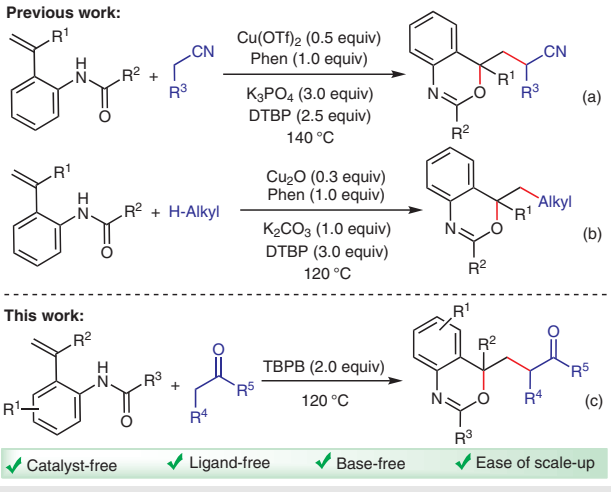


Figure 1 Representative bioactive molecules of benzoxazines

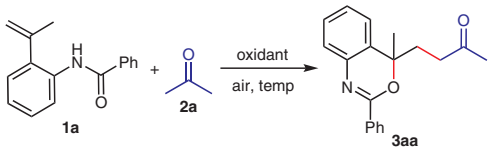
Benzoxazines are a class of pivotal and versatile structures that widely present in several pharmaceuticals and biologically active compounds.[5] They have extensive applications as anticonvulsant,[5a] fungicide,[5b] hypolipidemic,[5c] anti-HIV agent,[5d] progesterone receptor agonist,[5e] and herbicide[5f] (Figure 1). Due to their vital importance, the preparation of benzoxazines has captured long-term interest from the chemical community. Traditionally, the synthesis of benzoxazines strongly depends on the condensation of 2-aminobenzyl alcohols with aldehydes or ketones under harsh reaction conditions.[6] Recently, the electrophilic or radical cyclization of olefinic amides has emerged as a powerful and convenient tool to provide diverse benzoxazines.[7] Notably, there were two examples of radical cyclization of olefinic amides for the synthesis of benzoxazines involving α-C(sp^3)–H functionalization that have been reported.[8] One elegant example is the copper-catalyzed oxycyanomethylation reaction of olefinic amides with acetonitrile using ligand 1,10-phenanthroline (phen), base K_3PO_4, and oxidant di-*tert*-butylperoxide (DTBP) at 140 °C was reported by Xu, Ji, and co-workers (Scheme 1a).[8a] The other wonderful example is the oxyalkylation of olefinic amides with simple alkanes under similar Cu_2O/phen/K_2CO_3/DTBP system at 120 °C developed by Zhao and co-workers (Scheme 1b).[8b] Without a doubt, if such processes could be directly realized without using additional catalysts, ligands, or bases, it would be greatly appreciated. Our interest toward the construction of valuable heterocyclic compounds under mild conditions[9] provoked us to explore a new and sustainable approach for the synthesis of benzoxazines. Herein, we disclose a radical cyclization of olefinic amides through α-C(sp^3)–H functionalization of ketones (Scheme 1c). This methodology has the following prominent advantages: (a) catalyst-free, (b) ligand-free, (c) base-free, and (d) ease of scale-up.



Scheme 1 Radical cyclization of olefinic amides involving α-C(sp^3)–H functionalization

To test our hypothesis, we began to screen the optimal reaction conditions using *N*-[2-(prop-1-en-2-yl)phenyl]benzamide (**1a**) as a substrate, acetone (**2a**) as the source of radical, and Oxone as an oxidant sealed in air at 120 °C (Table 1). The choice of Oxone is guided by two important reasons: (a) Oxone is an economical and stable inorganic oxidant, and (b) we have reported the α-C(sp^3)–H functionalization of ketones using Oxone as the oxidant previously.[10] Unfortunately, only a trace of the expected cyclization product **3aa** was detected by GC–MS analysis with the generation of byproduct **4a** *via* oxidation of the C=C bond of **1a** (entry 1). Another commonly used inorganic oxidant is $K_2S_2O_8$ which also performed badly in this reaction, and trace of **3aa** was obtained (entry 2).

Table 1 Screening of Optimal Reaction Conditions[a]



Entry	Oxidant	Temp (°C)	Yield (%)[b]
1[c]	Oxone (2.0 equiv)	120	trace
2[c]	$K_2S_2O_8$ (2.0 equiv)	120	trace
3	TBHP (2.0 equiv)	120	18
4	BPO (2.0 equiv)	120	33
5	DTBP (2.0 equiv)	120	52
6	TBPB (2.0 equiv)	120	85
7	TBPB (1.2 equiv)	120	41
8	TBPB (3.0 equiv)	120	77
9[d]	TBPB (2.0 equiv)	120	84
10[e]	TBPB (2.0 equiv)	120	85
11	TBPB (2.0 equiv)	100	41
12[f]	TBPB (2.0 equiv)	100	40

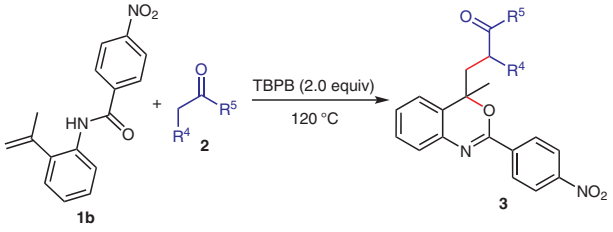
[a] Unless otherwise specified, the reactions were carried out in a Schlenk tube sealed in air in the presence of **1a** (0.2 mmol), **2a** (1.0 mL), and oxidant for 20 h. TBHP = *tert*-butyl hydroperoxide; BPO = benzoyl peroxide; DTBP = di-*tert*-butyl peroxide; TBPB = *tert*-butyl peroxybenzoate.
[b] Isolated yields based on **1a**.
[c] >80% yield of byproduct *N*-(2-acetylphenyl)benzamide (**4a**) was obtained.
[d] 10 mol% of $FeCl_3$ was added.
[e] 10 mol% of $CuCl_2$ was added.
[f] 10 mol% of *p*-TsOH was added.

We then turned our attention to screen organic oxidants. The results showed that the use of TBPB led to 85% yield, while other tested organic oxidants resulted in incomplete cyclization transformation, leading to the obtainment of **3aa** in 18–52% yields as well as the recovery of **1a** (entries 3–6). The loading amount of oxidant seemed to be essential to the reaction. When 1.2 equiv TBPB were used, the yield of **3aa** decreased dramatically to 41% (entry 7). The yield of **3aa** also decreased with the increase in the lev-

el of TBPB as a little of compound **1a** was oxidized (entry 8). Furthermore, the addition of an external catalyst $FeCl_3$ or $CuCl_2$ did not significantly affect this process (entries 9 and 10). Only 41% yield of **3aa** was produced when the reaction was carried out at 100 °C (entry 11). Finally, the addition of catalytic Brønsted acid *p*-TsOH could not lower the reaction temperature and afforded **3aa** in 40% yield at 100 °C (entry 12). Thus, this transformation proceeded efficiently in the presence of 2.0 equiv of TBPB at 120 °C as listed in entry 6.

With the optimized reaction conditions established, we next investigated the substrate scope of the ketones. As shown in Table 2[11] a broad range of ketones underwent this reaction, affording their corresponding products in moderate to good yields. Cyclopropyl methyl ketone (**2b**) could undergo this cyclization process, and a mixture of products **3bb** and **3bb′** were obtained in 62% yield with a ratio of 2:1. The cyclic ketones cyclobutanone (**2c**) and cyclopentanone (**2d**) produced the corresponding products **3bc** and **3bd** in 58% and 56% yields, respectively. This strategy was also compatible with acetylacetone (**2e**), affording the desired product in acceptable yield (**3be**). However, acetophenone (**2f**) and ethyl acetate (**2g**) were not suitable partners for this reaction (**3bf–bg**), which is presumably attributed to the inertness of α-C(sp^3)–H bond of **2f** and **2g**.

Table 2 Scope of Ketones[a]



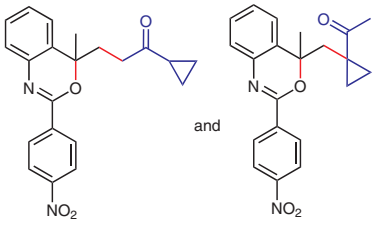
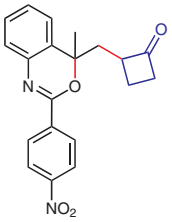
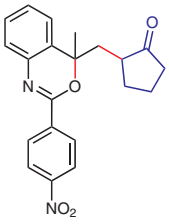
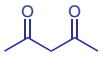
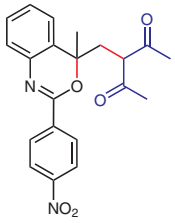
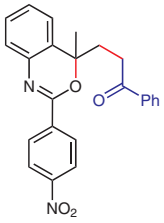
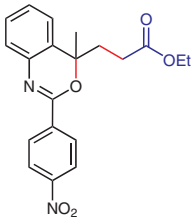
Entry	Substrate **2**	Product **3**	Yield (%)
1	 **2b**	 **3bb** and **3bb′**, **3bb**/**3bb′** = 2:1	62
2	 **2c**	 **3bc**	58, d.r. = 1:1
3	 **2d**	 **3bd**	56, d.r. >20:1

Table 2 (continued)

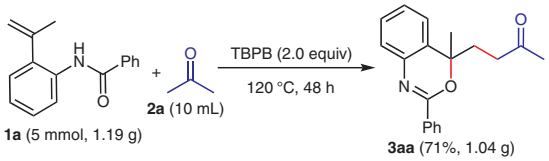
Entry	Substrate **2**	Product **3**	Yield (%)
4	 **2e**	 **3be**	71
5	 **2f**	 **3bf**	trace
6	 **2g**	 **3bg**	no reaction

[a] Unless otherwise specified, the reactions were carried out in a Schlenk tube sealed in air in the presence of **1b** (0.2 mmol), **2** (1.0 mL), and TBPB (2.0 equiv) at 120 °C for 20 h.

To further expand the scope of this methodology, we then focused our attention on various substituted olefinic amides **1** (Table 3). The current reaction showed good tolerance to olefinic amides with *para*-Br, or F substituents at the *N*-aryl ring, giving **3ca** and **3da** in 76% and 74% yield, respectively. The substrate having a phenyl group at the α-position of the styrenyl system also furnished the desired benzoxazines in 64% yield (**3ea**). To further evaluate the scope of **1**, we also investigated the reactivity of substituents on acyl moiety (R^3). The incorporation of both electron-donating (OMe, Me, *n*-Bu, and *t*-Bu) and electron-withdrawing (F, Cl, Br, CF_3, and NO_2) groups on the *para* position of the benzene scaffold in R^3 can afford the corresponding products in generally good yields (**3fa–ma** and **3ba**). Moreover, R^3 bearing the Me, OMe, and Cl groups at the *meta* or *ortho* position of benzene led to the cyclization products in 80–86% yields (**3na–ra**). Finally, the attempt to implement this cyclization by using *N*-[2-(prop-1-en-2-yl)phenyl]pivalamide (**1s**) as a partner was unsuccessful (**3sa**), and 76% of oxidation byproduct **4s** was obtained.

To demonstrate the practicality and scalability of this protocol, a gram-scale reaction with **1a** and **2a** (10 mL) as model substrates was performed under standard conditions, and 71% of **3aa** was obtained after prolonging the reaction time to 48 hours (Scheme 2).

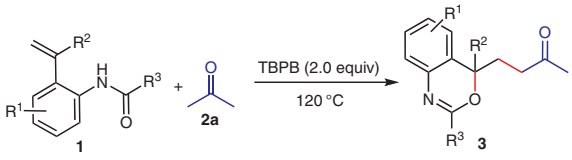
To probe the plausible reaction mechanism, some preliminary mechanistic experiments were conducted, as shown in Scheme 3. First, subjecting **1a** to the optimal conditions in the absence of **2a** failed to produce any cyclization product (Scheme 3a). This result suggests that in situ generated α-carbonyl radical enabled this transformation. Subsequently, it was found that this cyclization was completely shut down when 2.2 equiv of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) was added, indicating that a radical sequence was involved in the reaction, and the α-carbonyl

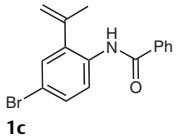
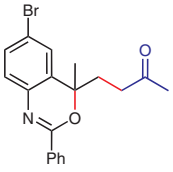
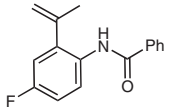
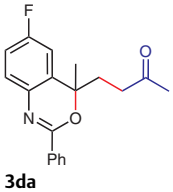
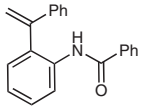
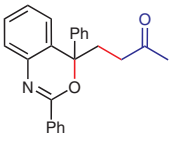
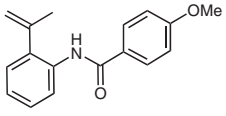
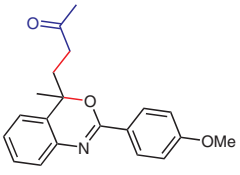
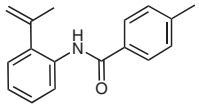
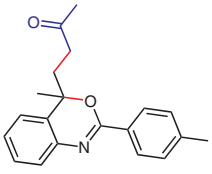


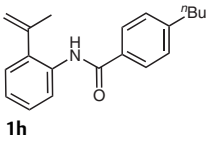
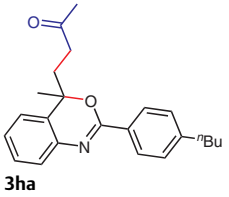
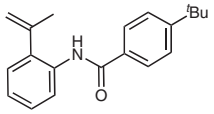
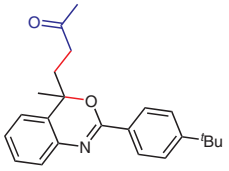
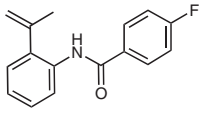
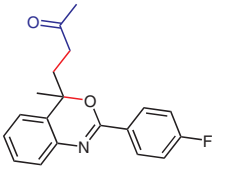
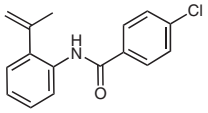
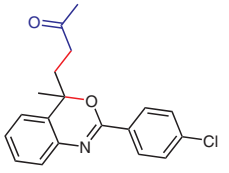
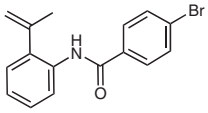
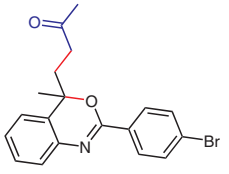
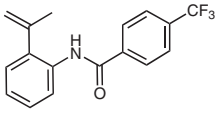
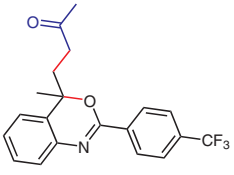
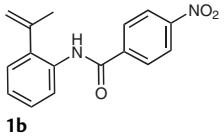
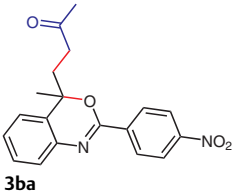
Scheme 2 Gram-scale reaction

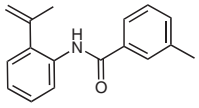
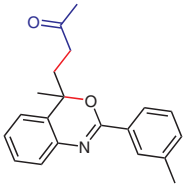
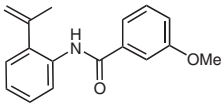
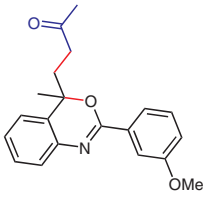
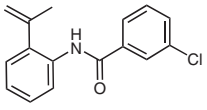
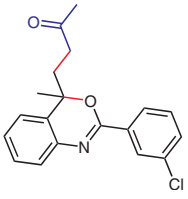
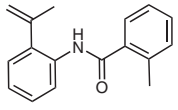
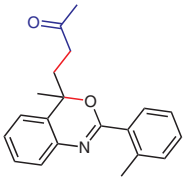
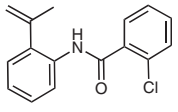
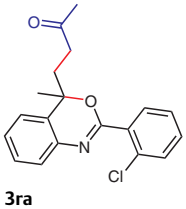
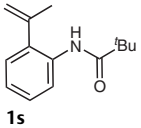
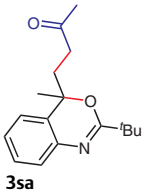
radical with BHT adduct **6a** could be obtained in 64% yield (Scheme 3b). The radical clock experiment with 2.5 equiv of (1-cyclopropylvinyl)benzene as the probe gave the ring-expanded product **7a** in 37% yield (Scheme 3c).

Table 3 Scope of Olefinic Amides[a]



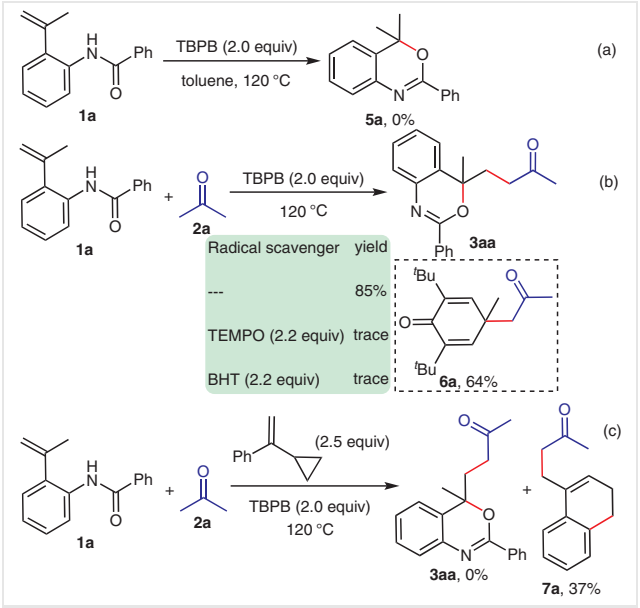
Entry	Substrate **1**	Product **3**	Yield (%)
1	 **1c**	 **3ca**	76
2	 **1d**	 **3da**	74
3	 **1e**	 **3ea**	64
4	 **1f**	 **3fa**	89
5	 **1g**	 **3ga**	88

Entry	Substrate **1**	Product **3**	Yield (%)
6	 **1h**	 **3ha**	87
7	 **1i**	 **3ia**	86
8	 **1j**	 **3ja**	83
9	 **1k**	 **3ka**	82
10	 **1l**	 **3la**	82
11	 **1m**	 **3ma**	71
12	 **1b**	 **3ba**	73

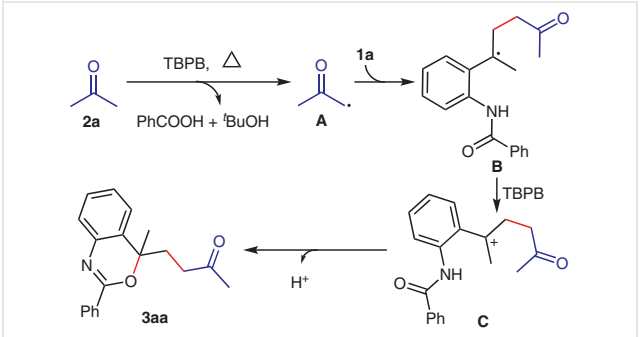
Entry	Substrate **1**	Product **3**	Yield (%)
13	 **1n**	 **3na**	85
14	 **1o**	 **3oa**	86
15	 **1p**	 **3pa**	81
16	 **1q**	 **3qa**	84
17	 **1r**	 **3ra**	80
18[b]	 **1s**	 **3sa**	trace

[a] Unless otherwise specified, the reactions were carried out in a Schlenk tube sealed in air in the presence of **1** (0.2 mmol), **2a** (1.0 mL), and TBPB (2.0 equiv) at 120 °C for 20 h.
[b] 76% of byproduct *N*-(2-acetylphenyl)pivalamide (**4s**) was obtained.

The proposed plausible mechanism for the conversion of **1** and **2** into **3** is illustrated in Scheme 4. First, in the presence of TBPB, α-carbonyl radical **A** is formed from **2a** under



Scheme 3 Control experiments



Scheme 4 Proposed mechanism

heating conditions.[12] Then, the addition of resulting radical **A** to C=C bond of **1a** forms radical intermediate **B**, which is further oxidized by TBPB to give the carbon cation intermediate **C**.[7a–f,8b] Finally, after the nucleophilic attack and deprotonation, the desired product **3aa** was generated.[7a–f,8b]

In summary, we have reported a versatile radical cyclization of olefinic amides with ketones for producing a wide range of benzoxazines. This simple method avoids the use of catalysts, ligands, and bases, including good functional group tolerance and ease of scale-up. Control experiments demonstrated that this cyclization was initiated by the α-C(sp^3)–H functionalization of ketones and a radical process was involved. Further investigation on the application of this strategy to synthesize biologically important benzoxazines is ongoing in our group.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1468-5962.

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(11) **General Procedure**

To a Schlenk tube were added olefinic amides **1** (0.2 mmol), ketones **2** (1.0 mL), and TBPB (2.0 equiv). Then the tube was stirred at 120 °C sealed in air for the indicated time until complete consumption of starting material as monitored by TLC and/or GC–MS analysis. After the reaction was finished, the solution was concentrated under reduced pressure, and the mixture was purified by flash column chromatography over silica gel (hexane/ethyl acetate = 10:1) to afford the desired product **3** and was analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy (see the Supporting Information).

Typical Data for Representative Compound 4-(4-Methyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-yl)butan-2-one (3aa)

Yellow oil (0.0500 g, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13–8.12 (m, 2 H), 7.52–7.49 (m, 1 H), 7.46–7.43 (m, 2 H), 7.31–7.30 (m, 2 H), 7.21–7.18 (m, 1 H), 7.07 (d, *J* = 7.5 Hz, 1 H), 2.66–2.59 (m, 1 H), 2.48–2.42 (m, 1 H), 2.39–2.31 (m, 2 H), 2.05 (s, 3 H), 1.67 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.8, 156.4, 139.1, 132.8, 131.4, 128.7 (2),128.3, 127.8, 126.8, 125.5, 122.7, 80.4, 38.4, 35.0, 30.1, 28.7.

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