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Visible Light Enabled Formal Cross Silyl Benzoin Reaction as an Access to α-Hydroxyketones

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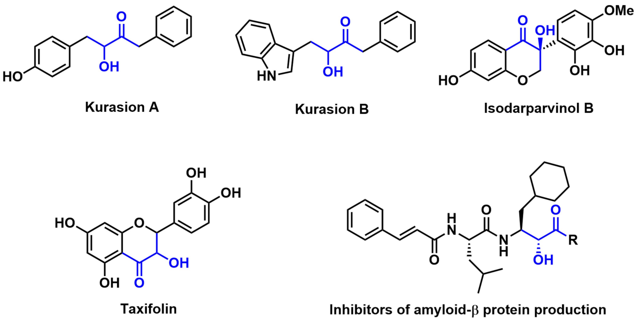
Abstract: In this work, a visible-light enabled coupling of acylsilanes with aldehydes to give a range of cross-benzoin type products α-hydroxyketones is described. The reaction could proceed at ambient temperature, with the irradiation of low energy visible light, and without addition of photosensitizer or any other additives.

Keywords: cross-benzoin reaction; visible-light; aldehydes; acylsilanes; α-hydroxyketones; additive-free

α-Hydroxyketones are ubiquitous structural motifs existing in many natural products and biologically active compounds (Scheme 1).[1,2] They are also valuable synthons for chemical synthesis. Classical approach to access these molecules normally relies on reaction of two aldehydes via benzoin condensation.[3,4] However, when two aldehydes with similar properties are employed, the reaction may lose the regiochemical control, and lead to the formation of four isomeric products.[5]

The cross silyl benzoin reaction of acylsilanes and aldehydes has been reported as regiospecific alternative to traditional benzoin condensation, while this reaction generally requires toxic cyanide salts or moisture sensitive metallophosphites as umpolung catalysts.[6] Acylsilanes are known to undergo [1,2]-Brook rearrangement to generate siloxycarbene intermediates through thermolysis or photoirradiation.[7,8]

Recently, Kusama and coworkers have reported an elegant method on ZnI_2 assisted photoinduced coupling of acylsilanes with aldehydes with an irradiation of 500 W super-high-pressure Hg lamp.[9] In line with our continuing research interests in the reaction of aldehydes with reactive carbene intermediates,[10] we have unexpectedly uncovered an efficient protocol to prepare α-hydroxyketones through formal cross silyl benzoin reaction between acylsilanes with aldehydes under extremely mild conditions. Compared with Kusama's work, the reaction described in this work could proceed well without addition of any Lewis acid catalysts or photosensitizers. Irradiation by low energy blue LEDs with a wavelength at 425 nm at room temperature is already enough to enable the reaction to occur.[11] In view of the mild reaction conditions and operational simplicity, we decide to report our prelimi-



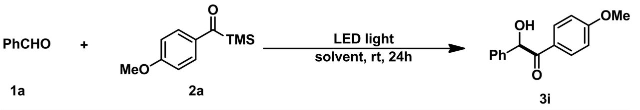
Scheme 1. Bioactive compounds containing α-hydroxyketone scaffolds.

nary results on this metal- and additive-free protocol to access α-hydroxyketones.

Initially, we selected the reaction of benzaldehyde **1 a** and (4-methoxybenzoyl)trimethyl-silane **2 a** as the model reaction to explore the conditions (Table 1). To our delight, the desired α-hydroxyketones **3 i** was obtained in 50% yield using *n*-hexane as solvent under irradiation with blue LEDs (30 W, 425 nm) (Table 1, entry 1). Encouraged by this result, we subsequently tested the effects of different solvents, including cyclohexane, toluene, THF, dioxane, DCE, DCM, CH_3CN and $PhCF_3$ (Table 1, entries 2–9). As depicted, the yield of **3 i** could be enhanced to 82%, when the reaction was carried out in DCM. In addition, we also examined the influences of the wavelengths of the light sources, and the results revealed that the blue LEDs with wavelengths of 425 nm were still the best choice (Table 1, entries 11–14). When the reaction was run in more concentrated solution, the yield of **3 i** could be enhanced to 85% (Table 1, entry 10).

With the optimal reaction conditions in hand, we then explored the substrate scope. As depicted in Table 2, the reaction of the acylsilane containing a triethylsilyl (TES) group gave the desired product **3 a** in 60% yield upon isolation. When the acylsilane bearing the more sterically hindered triisopropyl (TIPS) group was employed as carbene precursor, the reaction became sluggish and the formation of desired

Table 1. Optimization of the reaction conditions.[a]

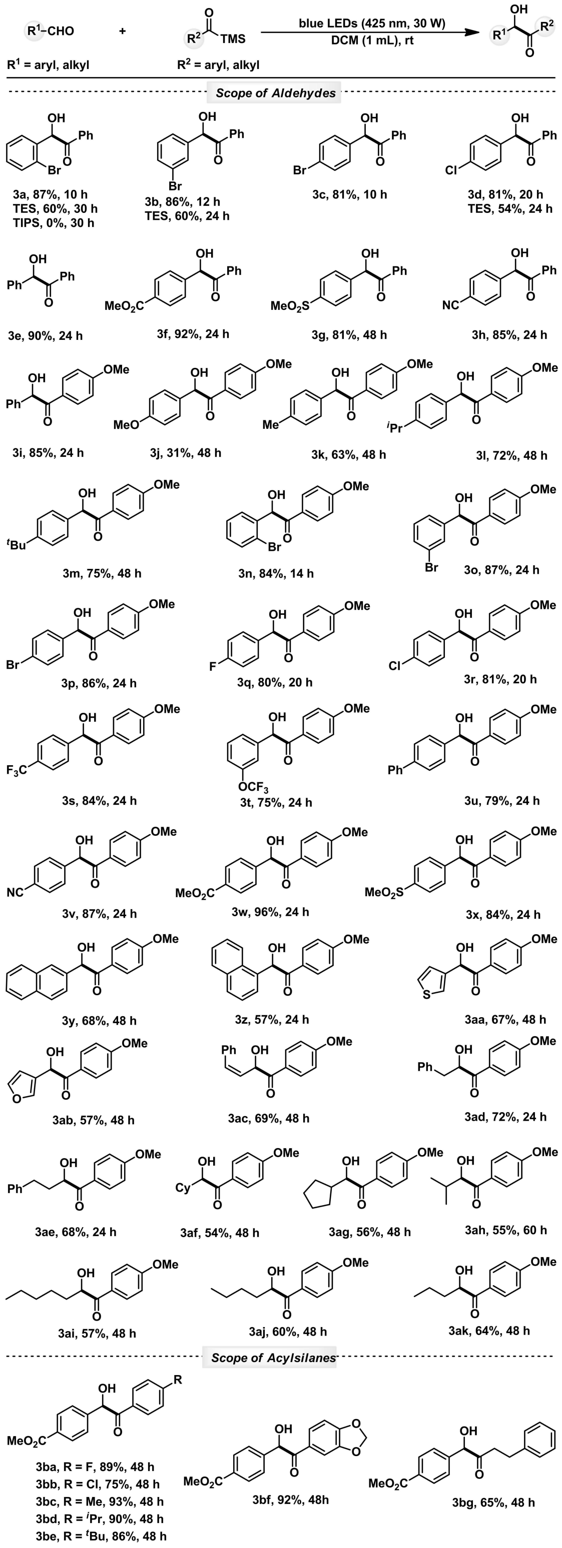


entry	solvent	λ/nm	isolated yields%
1	n-hexane	425	50
2	cyclohexane	425	44
3	$PhCH_3$	425	41
4	THF	425	39
5	dioxane	425	35
6	DCE	425	67
7	DCM	425	82
8	CH_3CN	425	77
9	$PhCF_3$	425	63
10*b*	DCM	425	85
11	DCM	445	77
12	DCM	435	80
13	DCM	415	63
14	DCM	405	62

[a] **1 a** (0.2 mmol), **2 a** (0.3 mmol) and solvent (1 mL) was stirred at room temperature with LED (30 W) irradiation for 24 h under argon.

[b] **1 a** (0.3 mmol), **2 a** (0.45 mmol) and solvent (1 mL).

Table 2. Substrate scope.[a]



[a] Aldehyde (0.3 mmol), acylsilane (0.45 mmol) and DCM (1 mL) was stirred at room temperature with LED (425 nm, 30 W) irradiation under argon.

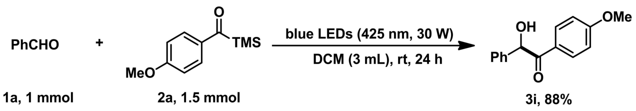
product **3a** was not observed. These results indicated that this cross- coupling reaction was sensitive to the steric nature of the silyl groups. Aldehydes ranging from aromatic to aliphatic aldehydes could react well with acylsilanes, giving a variety of substituted α-hydroxyketones in moderate to high yields. With respect to aromatic aldehydes, electron withdrawing groups on the phenyl ring seem to have positive effects on the reaction outcome. By contrast, the reactions of aldehydes bearing MeO-, Me-, *i*-Pr- or *t*-Bu- group at the *para* position of the phenyl ring gave the corresponding hydroxyketones in slightly lower yields. Functional groups including bromo, chloro, nitrile, ester and sulfone moieties were tolerated as well. Aldehydes containing heteroaromatic rings were competent reactants and longer reaction time were required to reach full conversion.

Next, we investigated reactions of benzoyltrimethylsilane with aldehydes bearing substituted groups on the phenyl ring at different positions, and the desired products **3a**–**3h** were obtained in 81–92% yields. Subsequently, the reactivities of aldehydes containing different electron-donating groups including a methoxyl group or alkyl substituents at the *para* position of the phenyl ring were examined, and the corresponding α-hydroxyketones **3j**–**3m** were obtained in 31–75% yields. For reactions of aldehydes bearing halogen atoms on the phenyl ring, **3n**–**3r** were obtained in 80–87% yields. Aldehydes bearing different substituents with different electronic properties, including trifluoromethyl, trifluoromethoxy, phenyl, nitrile, ester and sulfone, were viable substrates, and corresponding α-hydroxyketones **3s** to **3x** were obtained in up to 96% isolated yields. Naphthaldehydes are also suitable for this reaction, giving α-hydroxyketones **3y**–**3z** in 57–68% yields. Aldehydes bearing heteroaromatic rings were also tolerated under standard conditions, α-hydroxyketones bearing thiophenyl and furanyl rings could be synthesized (**3aa** and **3ab**). Moreover, cinnamaldehyde was also viable substrate for current reaction, and α-hydroxyketone **3ac** was obtained in 69% isolated yield. Interestingly, the geometry of the double bond was isomerized from E to Z upon visible light irradation. It is worth noting that aliphatic aldehydes containing open chain or cyclic rings were all compatible, giving corresponding the α-hydroxyketones **3ad**–**3ak** in moderate to high yields.

Subsequently, a variety of acylsilanes were prepared, and their reactivity was tested under standard conditions. As depicted, a range of acylsilanes could react well, regardless of the electronic characters of substituents on the aromatic ring (**3ba**–**3bf**). Pleasingly, acylsilane derived from aliphatic aldehyde was a competent carbene precursor as well, and α-hydroxyketone product **3bg** was obtained in 65% yield, which further highlight the benzoin reaction. The reaction could also be easily scaled-up to 1 mmol scale while maintaining similar reaction efficiency (Scheme 2).

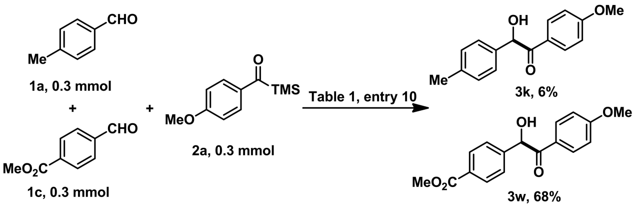
To understand the reaction mechanism, a competitive experiment was performed. As described in Scheme 3a, silane **2a** reacted with equal equivalent of aldehydes bearing methyl or ester moiety at the *para* position of the phenyl ring, giving α-hydroxyketones **3k** and **3w** in 6% and 68% NMR yields, respectively. These results indicated that aldehyde with electron-withdrawing group possessing higher reactivity. To identify the significance of irradiation with visible light, a light on-off experiment was carried out with **1a** and **2a** (Scheme 3b). The desired product yield increased significantly only during the irradiated period. By constrast, the reaction was almost shut down during the dark period.

Based on aforementioned results, a possible reaction mechanism is described in Scheme 4. First, acylsilane **A** undergoes 1,2-Brook rearrangement upon irradiation with visible-light to generate a transient

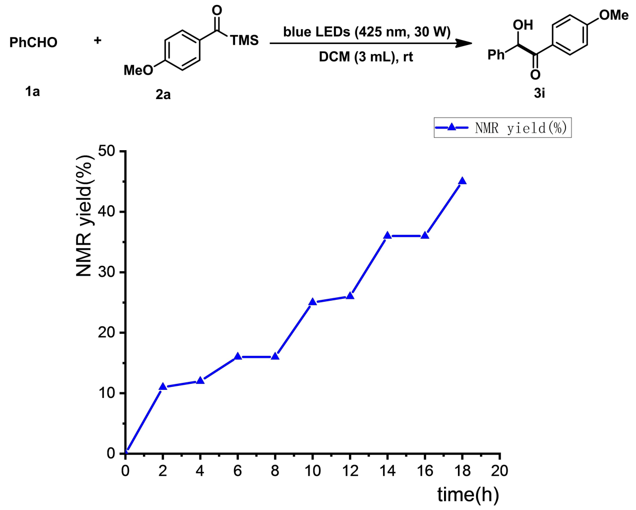


Scheme 2. Scale-up experiment

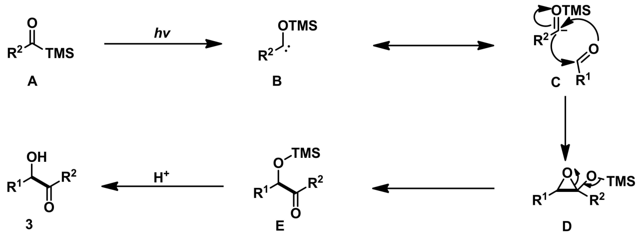
(a) competitive experiment



(b) light on-off



Scheme 3. Mechanistic studies.



Scheme 4. Proposed mechanism.

carbene species **B**. According to the competition experiments shown in Scheme 3a, the resonance form zwitterion **C** rather than the free carbene intermediate **B** would prefer to react with aldehydes to generate epoxide **D**, which is highly reactive to undergo ring-opening to produce **E**. In situ removal of the trimethylsilyl group in **E** could eventually give the desired α-hydroxyketone **3**.

In summary, we have developed a visible-light-enabled formal cross silyl benzoin reaction. The reaction could proceed under extremely mild condition while without the requirement of addition of any other reagents. The ease operational procedure and broad substrate scope may indicate a valuable synthetic potential for preparation of different α-hydroxyketones in a sustainable manner.

Experimental Section

General Procedure for Preparation of α-Hydroxyketones 3

An oven-dried Schlenk tube under argon atmosphere was charged with aldehyde **1** (0.30 mmol, 1.0 equiv), acylsilane **2** (0.45 mmol, 1.5 equiv) and DCM (1 mL). The mixture was stirred at room temperature with the irradiation of LED (425 nm, 30 W). The progress of the reaction was monitored by TLC. Upon completion, *p*-toluenesulfonic acid (0.3 mmol, 1.0 equiv) was added to the reaction mixture, then the solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel to afford the desired products.

Acknowledgements

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COMMUNICATIONS

Visible Light Enabled Formal Cross Silyl Benzoin Reaction as an Access to α-Hydroxyketones

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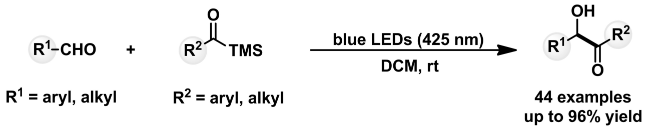

- Metal-free and additive-free
- Mild conditions and operationally simple
- Visible light irradation without photosensitizer
- Broad substrate scope