

Organocatalysis

International Edition: DOI: 10.1002/anie.201612159
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Abstract: A photochemical organocatalytic strategy for the direct enantioselective β -benzylation of α,β -unsaturated aldehydes is reported. The chemistry capitalizes upon the light-triggered enolization of 2-alkyl-benzophenones to afford hydroxy-*o*-quinodimethanes. These fleeting intermediates are stereoselectively intercepted by chiral iminium ions, transiently formed upon condensation of a secondary amine catalyst with enals. Density functional theory (DFT) studies provided an explanation for why the reaction proceeds through an unconventional Michael-type addition manifold, instead of a classical cycloaddition mechanism and subsequent ring-opening.

The photoenolization/Diels–Alder sequence^[1] is an established synthetic strategy (Figure 1 a) which has found widespread application for the one-step construction of stereochemically dense benzannulated carbocyclic molecules (**2**).^[2] The approach exploits the light-triggered enolization of 2-alkyl-benzophenones (**1**) affording transient hydroxy-*o*-quinodimethanes (**A**),^[3] which are highly reactive intermediates that can serve as dienes in [4+2] cycloadditions with electron-poor alkenes of type **B**. Herein, we document that the reactivity of the photoenol **A** is not restricted to cycloaddition mechanisms, but can also participate in conjugate addition manifolds.^[4] More specifically, we have found that a chiral iminium ion intermediate (**C**),^[5] formed upon condensation of a secondary amine catalyst (**4**) and α,β -unsaturated aldehydes (**3**), can stereoselectively intercept **A** and lead to the exclusive formation of the Michael addition

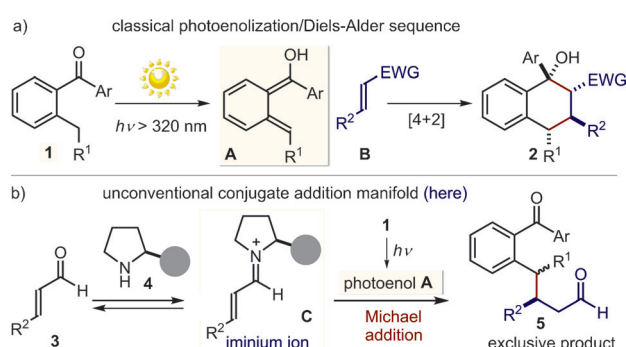


Figure 1. a) The classical photoenolization/Diels–Alder strategy for the one-pot synthesis of chiral cyclic compounds (**2**). b) The discovered Michael-type addition of the photoenol **A** to the chiral iminium ion **C** leading to the enantioenriched β -benzylated aldehyde **5**. Filled grey circle represents a bulky substituent on the chiral amine catalyst. EWG = electron-withdrawing group.

product **5** (Figure 1 b). No traces of the expected Diels–Alder adduct of type **2** were detected.

To account for this unexpected reactivity, we have conducted theoretical studies which indicate that the reaction proceeds through an unconventional direct Michael-type addition path instead of a classical cycloaddition manifold, followed by the retro-aldol-mediated ring-opening of **2**. From a synthetic perspective, the chemistry described in Figure 1 b is relevant since it provides a straightforward method for the direct β -benzylation of enals (**3**), a transformation for which there are few effective catalytic enantioselective precedents.^[6] Metal-catalyzed conjugate additions to enals are generally plagued^[7] by the intrinsic instability of the benzyl-metallic reagents and the competing 1,2-addition manifold, while organocatalytic iminium-ion-based strategies have been successful only for a specific class of highly activated nitro-toluene substrates.^[8]

The initial motivations for this study stemmed from our recent discovery that a chiral bifunctional organic catalyst, by activation of a dienophilic maleimide of type **B**, could allow the stereoselective trap of the photoenol **A**, thus leading to enantioenriched cycloaddition products of type **2**.^[9] This strategy provided the first effective enantioselective catalytic variant of the photoenolization/Diels–Alder sequence.^[10] Building on this precedent, we wondered whether the electrophilic iminium ion intermediate **C**^[5] could provide another organocatalytic tool useful for successfully intercepting **A** (Figure 1 b). The feasibility of our plan was tested by reacting the commercially available 2-methylbenzophenone (**1a**) and *trans*-2-pentenal (**3a**) in the presence of commercially available diphenylprolinol trimethylsilylether (**4a**)^[11] as the chiral amine catalyst (Table 1). The experiments were conducted over 20 hours, in toluene, and under irradiation by

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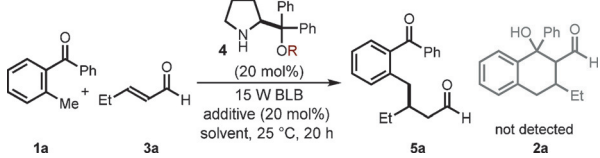
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Table 1: Exploratory studies.


Entry	Catalyst (R)	Solvent	Additive	Yield [%] ^[a]	ee [%] ^[b]
1	4a (TMS)	toluene	–	38	90
2	4a (TMS)	<i>o</i> -Cl ₂ C ₆ H ₄	–	52	83
3	4a (TMS)	<i>o</i> -Cl ₂ C ₆ H ₄	DPP	60	86
4	4b (TBS)	<i>o</i> -Cl ₂ C ₆ H ₄	DPP	61	90
5 ^[c]	4b (TBS)	<i>o</i> -Cl ₂ C ₆ H ₄	DPP	0	–
6	none	<i>o</i> -Cl ₂ C ₆ H ₄	DPP	18	–

[a] Yield of isolated **5a**. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction in the dark. BLB = black light bulb ($\lambda_{\max} = 365$ nm), DPP = diphenylphosphoric acid, *o*-Cl₂C₆H₄ = 1,2-dichlorobenzene, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.

an ordinary 15 W black light bulb (BLB; $\lambda_{\max} = 365$ nm). Initial experiments confirmed the possibility of trapping the fleeting **A**, generated from **1a**. This observation came about with an unanticipated reactivity, since the light-triggered process led to the exclusive formation of the conjugate addition product **5a** with high stereocontrol, albeit with poor chemical yield (entry 1). A screening of the reaction media identified 1,2-dichlorobenzene as the most appropriate solvent (entry 2). The addition of an acidic additive (diphenylphosphoric acid, DPP, 20 mol%) had a beneficial effect on the reactivity (entry 3), while modification of the catalyst scaffold, by introducing a bulkier silyl protecting group, resulted in a better enantioselectivity (entry 4).

We then conducted control experiments to better clarify the nature of the photochemical organocatalytic process. As expected, the reaction was completely inhibited in the dark (Table 1, entry 5). When the process was performed in the absence of the aminocatalyst **4**, the racemic adduct **5a** was isolated in 18% yield after 20 hours (entry 6). Thus, the high stereocontrol inferred by the chiral amine **4b** indicated that the rate acceleration afforded by the catalyst must be large enough to overcome a racemic background process.^[12] In all of these experiments, we could not detect any traces of the Diels–Alder adduct **2a**.^[13]

Adopting the optimized reaction conditions described in Table 1, entry 4, we then demonstrated the generality of the asymmetric organocatalytic photoenolization/conjugate addition sequence (Figure 2a) by evaluating a variety of enals (**3**). Figure 2b shows that different aliphatic groups at the β -position are viable substituents. Short (adducts **5a** and **5b**) and long alkyl chains, containing either aromatic or alkene functionalities (**5e** and **5f**), as well as a more sterically hindered isopropyl group (**5c**), are all well tolerated. The reaction of the carboxybenzyl (Cbz)-protected 5-amino-2-pentenal affords the cyclic compound **5g**, originating from a spontaneous intramolecular condensation between the aldehyde and the amino group within the β -benzylated product precursor. The method is synthetically useful, with a good efficiency maintained when running the reaction on a 1 mmol scale (**5a**). Cinnamaldehyde derivatives are also

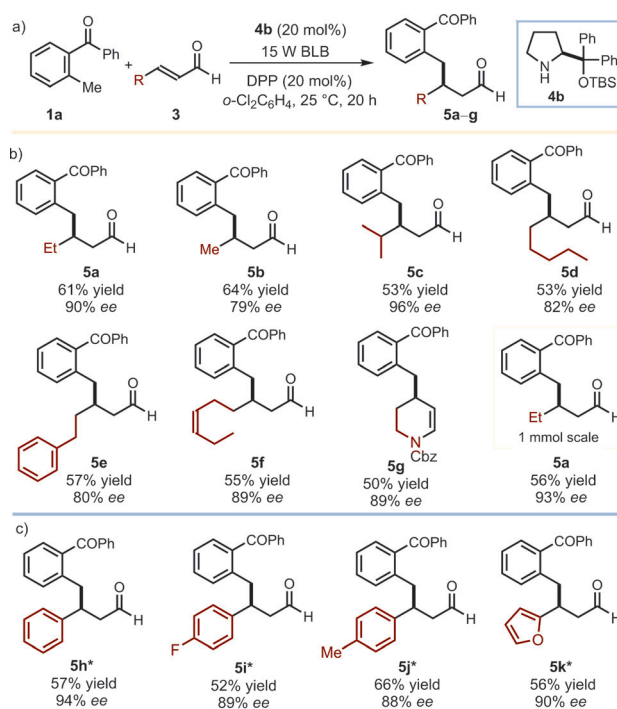


Figure 2. a) Survey of the enals **3** which can participate in the photochemical β -benzylation process. Reactions of b) aliphatic and c) aromatic β -substituted enals. Reactions performed on a 0.2 mmol scale. Yields of the isolated products **5** are given. The enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. *Performed in toluene using the catalyst **4a**.

competent substrates (Figure 2c) since different substitution patterns at the aromatic moiety of **3** are well tolerated, regardless of their electronic properties (**5h–j**). A heteroaryl framework can also be included in the product, as shown by the furyl-substituted adduct **5k**.

We then sought to explore the scope of the benzophenone substrate **1** (Figure 3a). Different substituents on both the enolizable (products **5l–o**) and the non-enolizable aromatic ring of **1** (**5p–s**) are well tolerated (Figure 3b). The presence of substituents at the benzylic position (R^2) of **1** brings about the formation of two contiguous stereogenic centers (**5t–w**). When $R^2 = \text{Ph}$, a valuable diarylmethine stereocenter is forged with very high fidelity (**5t**). Finally, as a demonstration of the synthetic versatility of the β -benzylated products, **5p**, obtained from a 1 mmol scale reaction, was easily converted into the cyclic adduct **6**, whose absolute configuration was unambiguously inferred by single-crystal X-ray analysis (Figure 3c).^[14]

After delineating its synthetic potential, we sought to shed light on the mechanism of the reported process, for the uncommon ability of the photoenol **A** to undergo a conjugate addition was mechanistically intriguing. Since we could not collect any experimental evidence supporting a [4+2] cycloaddition pathway followed by the opening of the cyclic intermediate **2**,^[13] the question remained as to why this generally preferred pathway was disabled in the present system. We investigated the mechanism using a density functional theory (DFT) computational study^[15] at the M06-

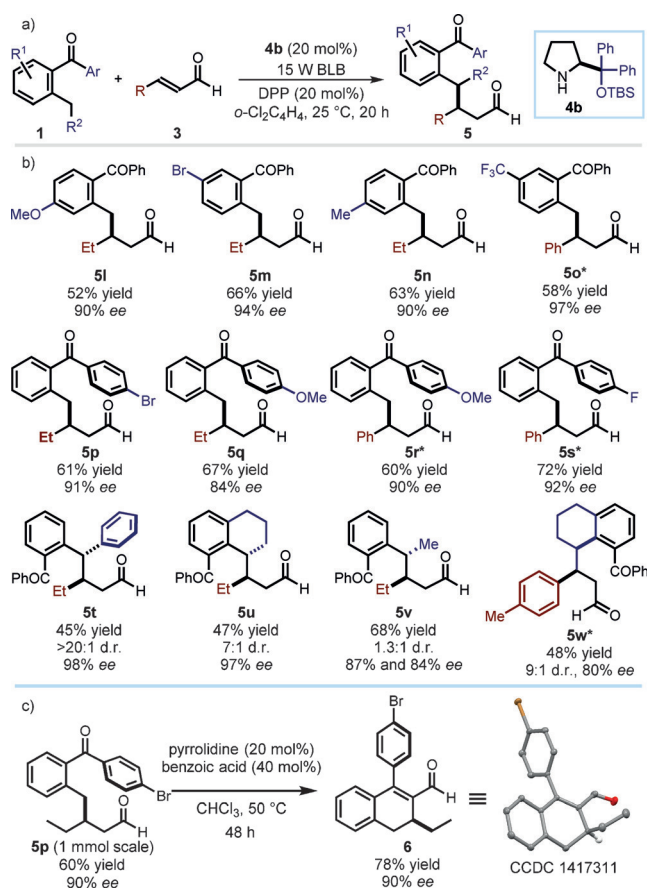


Figure 3. Substrate scope for the photoenolization/ β -benzylation sequence. a) The developed photochemical organocatalytic reaction. b) Survey of the benzophenones **1** which can participate in the reaction. c) Product manipulation and stereochemical assignment. Reactions performed on a 0.2 mmol scale. Yields of the isolated products **5** are given. The enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. *Performed in toluene using catalyst **4a**.

2X level in a toluene solvent. DFT calculations are established tools for mechanistically elucidating organocatalytic^[16] and light-triggered processes.^[17] They have recently been used to support a hetero-Diels–Alder/ring-opening sequence as the underlying mechanism of the light-driven carboxylation of benzophenones (**1**) proceeding by the trapping of **A** with CO_2 .^[17b]

The reaction of crotonaldehyde and **1a**, yielding **5b** (Figure 2b), catalyzed by **4a** was chosen as the model system. Systematic conformational analyses were carried out, and we discuss here only the results concerning the most stable conformations.^[18] We computed the reaction between the transiently generated **A** and the chiral iminium ion **C**. The results are summarized in Figure 4. We could locate two transition states, one leading to the intermediate **D** (the precursor of the cycloaddition adduct **2b**) and the other to **E** (which provided the Michael addition product **5b** upon hydrolysis). The cycloaddition transition state (**TS1**) leads to the very stable **D** ($-47.4 \text{ kcal mol}^{-1}$) through the formation of two carbon–carbon (C–C) bonds. The alternative transition state (**TS2**), which involves only one C–C bond-forming

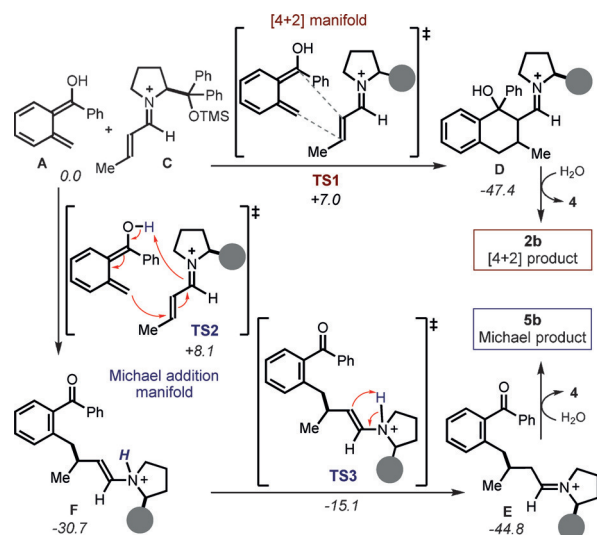


Figure 4. Reaction mechanism in the absence of a proton shuttle. Free energies in kcal mol^{-1} . Filled grey circle represents the trimethylsilyloxy group of the chiral amine catalyst **4a**.

event, leads to the intermediate **F** upon proton transfer from **A** to the iminium ion nitrogen atom. Then **F**, which is also quite stable ($-30.7 \text{ kcal mol}^{-1}$), undergoes an intramolecular proton transfer through **TS3**, ultimately leading to **E** ($-44.8 \text{ kcal mol}^{-1}$).^[19] The computed reaction pathways in Figure 4 are not surprising, as one would expect both the cycloaddition and the Michael addition to be mechanistically viable. But this data is in sharp disagreement with the experimental results. The cycloaddition transition state **TS1** ($7.0 \text{ kcal mol}^{-1}$) is $1.1 \text{ kcal mol}^{-1}$ lower in energy than the Michael addition transition state **TS2** ($8.1 \text{ kcal mol}^{-1}$), meaning that the Diels–Alder adduct **2b** should be the preferred kinetic product. In addition, since **2b** is the more stable product, there is no chance that it could evolve towards **5b** through a retro-aldol/ring-opening process.^[13]

Since we could not computationally reproduce the experimental observation, we considered the potential role of additional species in the reaction media, and how they could affect the relative energy of the transition states reported in Figure 4. The condensation of **4** and **3** to afford **C**, assisted by DPP as an acidic additive, releases water into the system.^[20] Both water and the resulting diphenylphosphate can act as a proton shuttle. Proton shuttles have been shown to lower the barrier of processes involving proton transfer,^[21] a key step underlying the Michael addition mechanism (see **TS2** in Figure 4). Since the DPP anion has no acidic protons and cannot serve as hydrogen-bonding donor, we repeated the calculations including an explicit water molecule as the most likely proton shuttle.^[22] The results are summarized in Figure 5.

A water molecule can engage in a hydrogen-bonding network with **A** to form the adduct **G**, which is only $2.0 \text{ kcal mol}^{-1}$ above the separate species. The approach of **G** to **C** has only one transition state (**TS1-H₂O**), which leads to the Michael addition product **E**. No transition state could be located for the cycloaddition manifold. Remarkably, the structure of **TS1-H₂O** is conformationally similar to that of

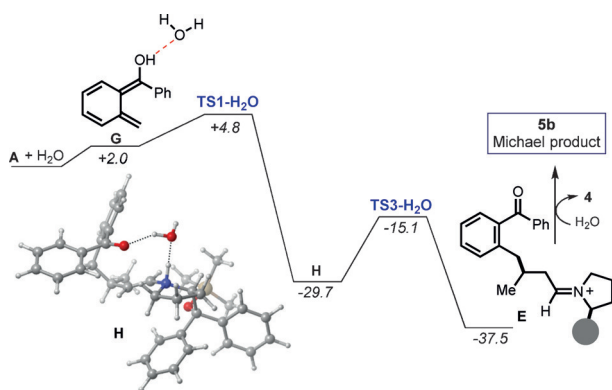


Figure 5. Free-energy profile of the reaction assisted by a proton shuttle. The optimized structure of intermediate **H** (at -29.7 kcal mol $^{-1}$) is highlighted. Free energies in kcal mol $^{-1}$.

TS1 (Figure 4), which affords the cycloaddition adduct **2b** instead. We confirmed, by an intrinsic reaction coordinate (IRC) calculation, that **TS1-H₂O** exclusively relaxes to the intermediate **H** with the proton being transferred from the photoenol to the iminium ion nitrogen atom by a water-assisted proton shuttle mechanism. The structure of **H** shows how the water molecule participates in multiple hydrogen-bonding interactions with both the H-N⁺ moiety within the enammonium ion and the O=C group of the benzophenone. From this intermediate, an intramolecular proton transfer readily forms the Michael adduct precursor **E**.^[19] The key feature of the water-assisted mechanism is the free energy of **TS1-H₂O**, which is 2.2 kcal mol $^{-1}$ lower than the free energy for **TS1** reported in Figure 4, thus explaining why the Michael addition manifold dominates over the classical cycloaddition mechanism.

In conclusion, we have demonstrated that chiral iminium ions can stereoselectively intercept photochemically generated hydroxy-*o*-quinodinomethanes. The chemistry, which provides a rare example of enantioselective catalytic β -benzylation of electron-poor olefins, proceeds through an unconventional Michael-type addition path instead of a classical cycloaddition manifold. Computational studies revealed that the intrinsic preference for the cycloaddition is offset in this system by a network of proton-transfer mechanisms facilitated by the presence of proton shuttles. Similar behaviors can be expected in related systems where such key structural elements are conserved.

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Conflict of interest

The authors declare no conflict of interest.

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