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Enantioselective Michael Addition of Photogenerated *o*-Quinodimethanes to Enones Catalyzed by Chiral Amino Acid Esters

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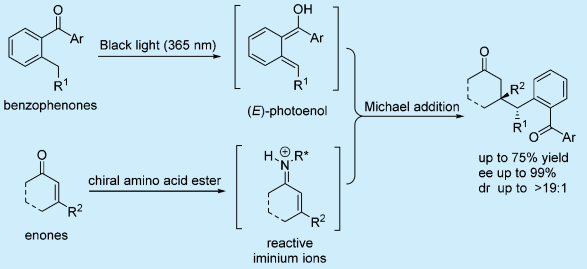
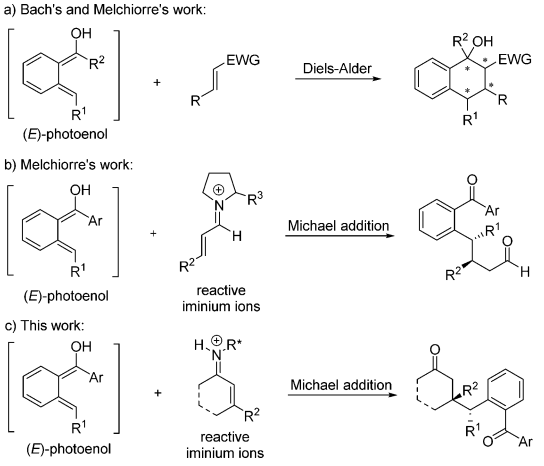
Supporting Information

ABSTRACT: The first example of a photoexcitated amine-catalyzed process for asymmetric Michael addition of *o*-quinodimethanes to enones is described. In the presence of simple chiral amino acid esters, a variety of Michael adducts were generally obtained in good yields and excellent stereoselectivities. This strategy can be successfully applied to 3-substituted-2-cyclohexenones and provides an asymmetric access to all-carbon quaternary centers. Furthermore, the high stereocontrol was explained by means of density-functional theory (DFT) calculations.



Photoexcitation of *o*-alkylphenyl ketones induces intramolecular H-abstraction followed by bond reorganization to *o*-quinodimethane species.[1] This strategy provides a powerful approach to activate the inert phenyl methane, which is usually realized by the use of a strong base or introducing an electron-withdrawing group on the aromatic ring.[2] The resulting *o*-quinodimethanes carrying a highly reactive diene functionality participating in [4 + 2] cycloaddition with various dienophiles has been extensively reported.[3,4] Among these, Bach et al. and Melchiorre et al. respectively applied this strategy to enantioselective Diels–Alder reactions of acrylonitrile, methyl acrylate, dimethyl fumarate,[4a] and maleimides (Scheme 1a).[4b] However, addition reactions of photogenerated *o*-quinodimethanes still remain challenging to date.[5] Interestingly, in 2017, Melchiorre and co-workers reported an elegant enantioselective Michael addition reaction of photogenerated *o*-quinodimethanes with enals catalyzed by a secondary amine (Scheme 1b).[6]

Scheme 1. Asymmetric Diels-Alder Reactions and Michael Addition Reaction of Photogenerated *o*-Quinodimethanes



Recently, the development of enantioselective photochemistry has garnered great attention by using photocatalysis in conjunction with metallo- or organocatalysis.[7,8] Photochemical asymmetric Michael additions of radicals or unusual nucleophiles to α,β-unsaturated carbonyl compounds have the potential to provide an efficient strategy to construct new stereogenic centers under mild reaction conditions. Notably, several research groups (e.g., Yoon,[9a] Meggers,[9b,c] and Melchiorre[9d]) reported the enantioselective radical Michael additions of α,β-unsaturated carbonyls through the combination of photoredox catalysis and metallo- or organocatalysis. To the best of our knowledge, asymmetric Michael addition of photoenols acting as nucleophiles to enones has never been explored. Based on our previous success in asymmetric conjugate addition catalyzed by primary amine catalysts[10] and photochemistry,[11] we herein report our exploration on asymmetric Michael addition of photogenerated *o*-quinodimethanes to the iminium ions generated upon condensation of chiral amino acid esters and α,β-unsaturated ketones (Scheme 1c).

We began our study by choosing 2-methylbenzophenone **1a** and 2-cyclohexenone **2a** as model substrates to screen a set of primary amine catalysts (at 20 mol % loading) in the presence of 50 mol % of benzoic acid (see Table S1 in the Supporting Information (SI)). Initially, the expected product **3a** was obtained using C_2-symmetric diamine (1*R*,2*R*)-1,2-diamino-cyclohexane **4a** as catalyst, although with only a 25% yield and 21% ee (Table 1, entry 1). The asymmetric Michael addition of **1a** with **2a** under the catalysis of chiral 9-amino(9-deoxy)epiquinine **4b** afforded the adduct in poor yield and enantioselectivity (Table 1, entry 2).

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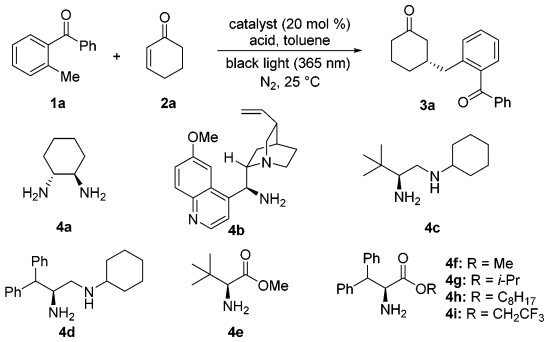
Table 1. Optimization of Reaction Conditions[a]



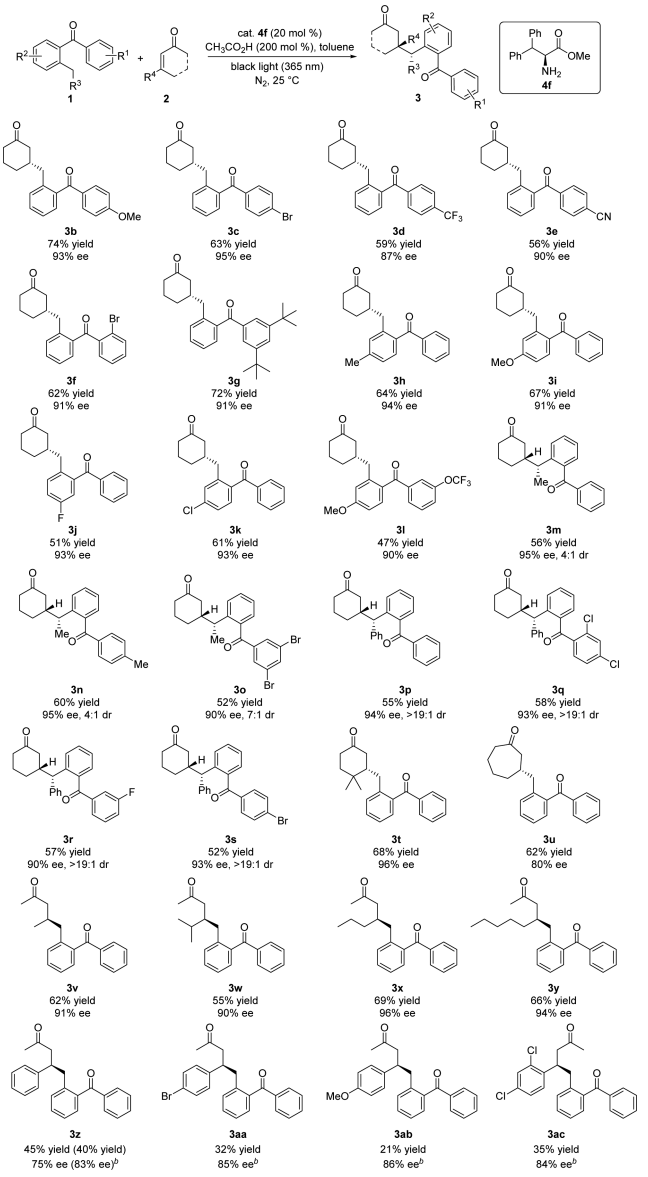
entry	catalyst	acid	t (h)	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	**4a**	$PhCO_2H$	36	28	25	21
2	**4b**	$PhCO_2H$	36	19	17	27
3	**4c**	$PhCO_2H$	24	52	49	−60
4	**4d**	$PhCO_2H$	24	18	16	−20
5	**4e**	$PhCO_2H$	24	40	36	82
6	**4f**	$PhCO_2H$	24	45	40	93
7	**4g**	$PhCO_2H$	24	40	37	81
8	**4h**	$PhCO_2H$	24	38	35	84
9	**4i**	$PhCO_2H$	24	52	49	89
10	**4f**	CH_3CO_2H	24	56	52	93
11[e]	**4f**	CH_3CO_2H	24	80	75	96
12[e]	none	CH_3CO_2H	24	18	15	0
13	**4f**	none	72	N.R.	N.R.	–
14[e,f]	**4f**	CH_3CO_2H	72	N.R.	N.R.	–

[a]All reactions were carried out using 1.0 equiv of 2a (0.2 mmol), 3.0 equiv of 1a, 20 mol % of catalyst, 50 mol % of acid, 2.0 mL toluene, black light (365 nm). [b]Determined by GC analysis. [c]Yield of the isolated product, N.R. = no reaction. [d]Determined by chiral HPLC analysis. [e]200 mol % of CH_3CO_2H was used. [f]In the absence of light source.

The primary-secondary diamine catalyst **4c** afforded the desired product **3a** in moderate enantioselectivity (Table 1, entry 3). Disappointingly, catalyst **4d** gave a similar poor result with catalyst **4b**. By evolving the catalyst scaffold, we were pleased to find that simple chiral amino acid ester catalysts were efficient for this reaction. Then a series of amino acid esters were screened (Table 1; Table S1 in the SI), and it was found that *tert*-leucine methyl ester (Table 1, entry 5) and diphenyl alanine esters (Table 1, entries 6−9) afforded the adduct in moderate yields and excellent enantioselectivities among the top catalysts. Unfortunately, further screening of solvents did not show any better results than toluene (see Table S2 in the SI). The results showed that different acidic additives had remarkable effects on the reaction (see Table S3 in the SI). When acetic acid was employed, the yield increased to 52% (entry 10). Finally, by increasing the amount of acetic acid to 200 mol %, the yield and ee values were increased (entry 11). Meanwhile, control experiments showed that amine catalysts and light were essential to the success of this reaction (entries 12, 14). The presence of acid had a significant impact on the reaction, and in the absence of acid essentially no product was formed (entry 13). In all experiments, no trace of the Diels−Alder adduct was detected.[6] It was found that the optimal reaction should be catalyzed by 20 mol % of catalyst **4f** with 200 mol % of acetic acid in toluene by irradiation with black light (365 nm) at 25 °C.

To explore the scope of this transformation, a variety of 2-alkyl benzophenones and enones were examined under the optimized reaction conditions (Scheme 2). 2-Alkyl benzophenones **1**

Scheme 2. Substrate Scope for Michael Addition Reactions[a]



[a]All reactions were carried out using 1.0 equiv of **2** (0.2 mmol), 3.0 equiv of **1**, 20 mol % of cat. **4f**, 200 mol % of acetic acid, 2.0 mL of toluene, black light (365 nm), 24 h. [b]The addition of enones in batches (0.07 mmol every 12 h, 3 times), 60 h (for details see the SI).

bearing electron-donating and -withdrawing groups on the enolizable aromatic ring all reacted with 2-cyclohexenone **2a** affording the corresponding adducts **3b−l** in good yields (47−74%) and excellent enantioselectivities (90−95% ee). With 2-ethyl substituted benzophenones as substrates, the yields and diastereoselectivities were moderate (52−60% yield, 4:1−7:1 dr), and the enantioselectivities were excellent (90−95% ee) (products **3m−o**). The benzophenone substrates bearing a phenyl group at the benzylic position worked well in this conjugate addition, affording the desired adducts **3p−s** in good yield (52−58%), excellent enantioselectivities (90−94% ee), and excellent diastereoselectivities (>19:1 dr). Notably, cyclic enones with a seven-membered ring and cyclohexenone bearing *gem*-dimethyl groups were well tolerated in this transformation. Remarkably, the reaction was not limited to cyclic enones, and it was also applied to acyclic α,β-unsaturated ketones, thus

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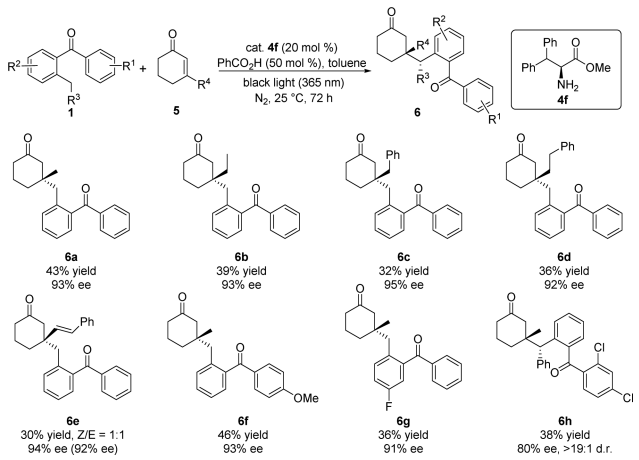
providing chain ketone products in high enantioselectivities (83%–96% ee).

Gratifyingly, this strategy can be successfully applied to 3-alkyl-2-cyclohexenones, thus building the quaternary stereogenic centers (Scheme 3). Utilizing benzoic acid instead of acetic acid

Scheme 3. Substrate Scope for Michael Addition Reactions of 3-Substituted-2-cyclohexenones[a]

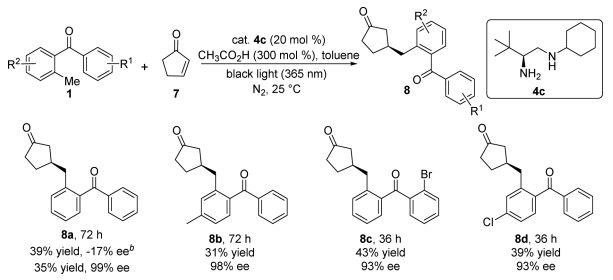


[a]All reactions were carried out using 1.0 equiv of **1** (0.2 mmol), 3.0 equiv of **5**, 20 mol % of cat. **4f**, 50 mol % of benzioc acid, 2.0 mL of toluene, black light (365 nm).

gave the best result in terms of yield and enantioselectivity. 2-Cyclohexenones with different substituents (methyl, ethyl, benzyl, phenylethyl) all proceeded smoothly in this transformation, giving the desired products **6a–d** with encouraging results (32–43% yield, 92–95% ee). 3-Styryl-2-cyclohexenone delivered the Michael product **6e** with 94% ee, albeit in low yield (30%). Electron-rich groups such as methoxy and electron-deficient groups such as fluoro, chloro on the aromatic ring proved to be adaptable for this reaction, providing the desired products **6f–h** in moderate yields (36–46%) and good enantioselectivities (80–93% ee).

Unfortunately, no expected products were obtained when 2-cyclopentenone was used as an enone substrate under the previously optimized reaction conditions. Different acidic additives were screened, and it was found that the expected product **8a** could be obtained when trifluoroacetic acid was used (Scheme 4). However, the asymmetric conjugate addition

Scheme 4. Substrate Scope for Michael Addition Reactions of 2-Cyclopentenones[a]



[a]All reactions were carried out using 1.0 equiv of **1** (0.2 mmol), 3.0 equiv of **7**, 20 mol % of cat. **4c**, 300 mol % of acetic acid, 2.0 mL of toluene, black light (365 nm). [b]20 mol % of catalyst **4f**, 50 mol % of trifluoroacetic acid.

proceeded smoothly affording product **8a** in moderate yield (39%) and poor enantioselectivity (17% ee). Extensive optimization studies involving the screening of different primary amine catalysts and acidic additives led to an improvement in the enantioselectivity of product **8a** to 99% ee by using catalyst **4c** and acetic acid. Functional groups such as methyl, bromo, chloro groups were also tolerated on the aromatic rings.

Further transformation of **3c** and **3q** afforded tricyclic compounds **9** and **10**, and the absolute configurations of **3c** and **3q** could be extrapolated by single-crystal X-ray structure analysis of **9** and **10**.[12] Furthermore, product **3a** could be selectively transformed into the corresponding 2-oxepanone **11** through a Baeyer–Villiger oxidation in 82% yield (for more details see the SI).

To understand the mechanism and origins of the high stereocontrol with a chiral amino acid ester catalyst, we investigated two possible reaction mechanisms by using DFT calculations: (i) the cationic reaction route and (ii) the neutral reaction route assisted by the acid anion. The Gibbs free energy profiles of the two reaction pathways are depicted in Figure 1, and

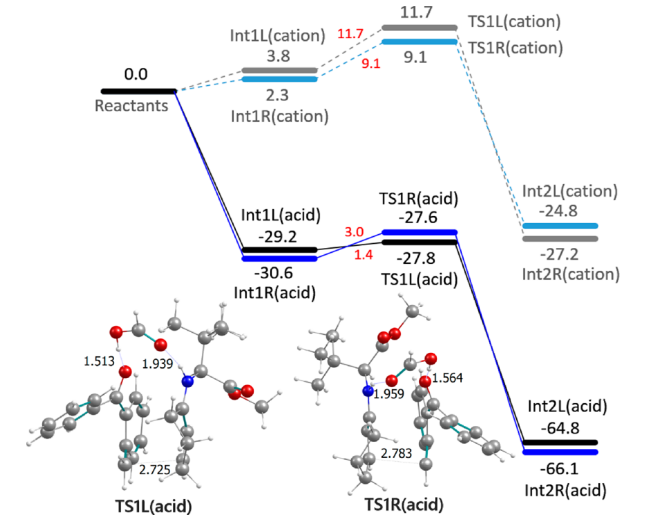


Figure 1. Gibbs free energy profile of Michael addition reaction of **1a** to **2a** catalyzed by **4e**.

the full details of the computation are provided in the SI. Apparently, in the absence of the acid anion, the enone **2a** under the catalysis of cat. **4e** in the presence of a proton results in the formation of the cationic adduct **Int1(cation)**. However, this reaction route is unlikely to be the mechanism for the Michael addition reaction catalyzed by **4e** because of the incorrect enantioselectivity as predicted by DFT calculations compared to the experimental results. Interestingly, the inclusion of the acid anion in the calculated molecular system significantly lowers the free energy of **Int1(acid)**. Thus, the formation of the neutral adduct **Int1(acid)** (ΔG = −30.6 to −29.2 kcal/mol) is thermodynamically much more favorable than the formation of the cationic adduct **Int1(cation)** (ΔG = 2.3–3.8 kcal/mol), as shown in Figure 1.

We further calculated acid-assisted proton transfer transition states which are commonly depicted as **TS1L(acid)** and **TS1R(acid)**. **TS1L(acid)** ($\Delta\Delta G$ = 1.4 kcal/mol) is favored over the other transition state **TS1R(acid)** because the activation free energy is lower than **TS1R(acid)** ($\Delta\Delta G$ = 3.0 kcal/mol). Although the "exact" enantioselectivity was not calculated based on the present DFT calculations, however, the predicted

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enantioselectivity was in good agreement with the experiment. The necessity of an acid and anion was also observed in the experiments (Table 1, entry 13; Table S4 in the SI). Based on this mechanistic understanding, the acid in the Michael addition reactions plays two important roles: (i) the protonation of the amino acid ester catalyst and then (ii) the extraction of the proton of the enone by the acid anion in the process of the C−C coupling reaction. This characteristic of proton shuttling by the acid molecule was also proposed for another Michael addition reaction in our recent study.[10c]

In conclusion, we have presented the first example of asymmetric Michael addition of photogenerated *o*-quinodimethanes to *α,β*-unsaturated ketones employing simple chiral amino acid esters as the catalyst. This reaction can be successfully applied to 3-substituted-2-cyclohexenone and provides an efficient protocol for constructing the quaternary carbon centers. A variety of different enones were well tolerated, providing Michael adducts in good yields (up to 75%) and excellent stereoselectivities (ee up to 99% ee, dr up to >19:1). The stereoselectivity was explained by DFT calculations for transition states of the C−C bond formation between the iminium intermediate and *o*-quinodimethanes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00862.

Detailed experimental procedures, characterization data of products (NMR, HRMS, etc.), spectra of products (PDF)
X-ray crystal structure of **10** (CIF)
X-ray crystal structure of **14** (CIF)
X-ray crystal structure of **9** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) CCDC 1533803 and CCDC 1533804 contain the supplementary crystallographic data for this paper.

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