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Combining organocatalysis with photoorganocatalysis: photocatalytic hydroacylation of asymmetric organocatalytic Michael addition products†

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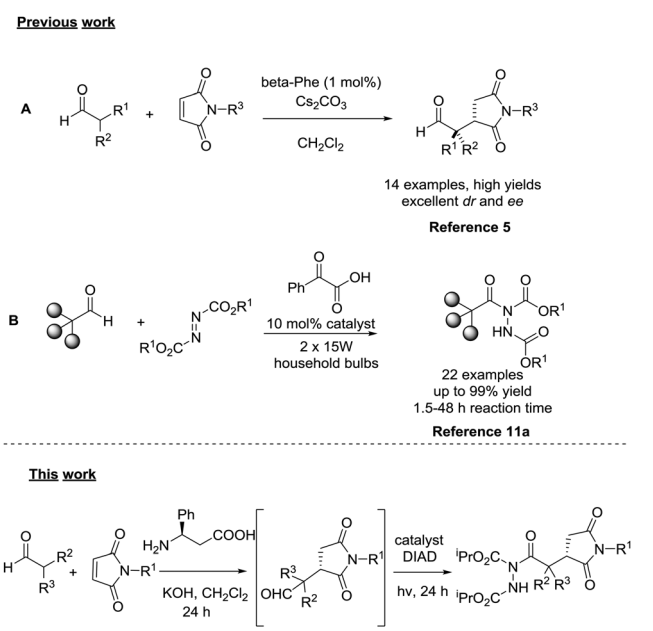
Organocatalysis and photoorganocatalysis are two areas of synthetic methodology that have found wide applications in organic synthesis. Herein, we report a combination of these two stategies, taking advantage of an organocatalytic Michael addition of α,α-disubstituted aldehydes to maleimides as the first step and a photocatalytic hydroacylation of diisopropyl azodicarboxylate as the second step. Employing an amino acid as the organocatalyst for the asymmetric organocatalytic part and an organic molecule as the photocatalyst, the combination of these two strategies led to the desired products. A number of alkyl- and aryl-substituted maleimides were successfully employed, while the protocol can be used on α,α-disubstituted aldehydes leading to products in moderate to high yields (44–84%) and excellent enantioselectivities (98–100% ee).

Introduction

Organocatalysis, the use of small organic molecules to promote asymmetric organic transformations, has become a complementary method for the synthesis of organic compounds with multiple purposes.[1,2] During the last two decades of its rebirth, organocatalysis has provided valuable solutions to unsolved problems and complementary platforms of activation modes in modern catalysis, establishing organocatalysis as one of the three pillars of asymmetric catalysis, alongside transition-metal catalysis and biocatalysis. A very well-studied reaction in organocatalysis is the Michael addition, since new C–C bonds can be forged in a highly enantioselective fashion.[3] Among the different Michael reactions, the addition of α,α-disubstituted aldehydes to maleimides represents an attractive transformation,[4,5] since the obtained products, which are substituted succinimides, are considered valuable synthetic targets and precursors of biologically interesting compounds.[6] Another interesting feature of this transformation is that this reaction leads to the formation of quaternary centers.[7] This reaction is typically catalyzed by bifunctional organocatalysts, bearing a primary amino group and a thiourea.[4] A few years ago, we have contributed in this area by introducing an organocatalytic protocol employing low catalyst loading of β-phenylalanine, in combination with Cs_2CO_3, for this reaction leading to products in high yields and selectivities, that can be employed for further product manipulations (Scheme 1, A).[5] In that study,



Scheme 1 Design plan.

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the optimum amino acid catalyst was recognized, and the substrate scope of the reaction was thoroughly examined, along with an application in the one-pot synthesis of lactones.

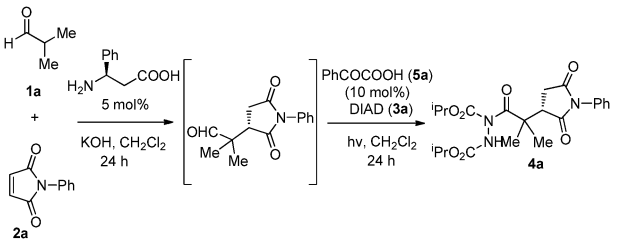
Photochemistry constitutes also a very exciting field of research, which has been known for more than a century. However, for a long time, researchers were rather preoccupied that the reactivity of radicals could not be controlled, let alone manipulated in a designed manner. In 2008, photoredox catalysis, the use of transition metal catalysts (mainly ruthenium or iridium) along with cheap household or LED lamps as the irradiation source, has emerged as a solution providing new activation modes.[8,9] Unfortunately, these types of metal complexes can be expensive, and most of them are not commercially-available. Photoorganocatalysis, the use of small organic molecules as photocatalysts, constitutes a cheaper and greener alternative.[10] We have recently introduced phenylglyoxylic acid as a potent photoorganocatalyst in a photoorganocatalytic protocol that is easy to operate, employing cheap household lamps and a cheap, organic and commercially available molecule as the photocatalyst.[11] Initially, we introduced phenylglyoxylic acid as the photocatalyst for a green and fast hydroacylation of dialkyl azodicarboxylates (Scheme 1, B).[11a] We also took advantage of this methodology to introduce visible-light induced one-pot procedures for the synthesis of hydroxamic acids[11b] and amides[11c] from aldehydes. The potential of these methodologies was highlighted in the synthesis of two commercial pharmaceuticals, vorinostat[11b] and moclobemide.[11c]

In this work, we present a novel and facile route for the combination of organocatalysis with photoorganocatalysis (Scheme 1, C). Our goal is to combine the highly versatile asymmetric Michael reaction of α,α-disubstituted aldehydes to maleimides with photoorganocatalytic hydroacylation, in order to afford products of high molecular complexity in an enantiopure fashion.

Results and discussion

We began our optimization studies employing isobutyraldehyde (**1a**), *N*-phenyl maleimide (**2a**) and diisopropyl azodicarboxylate (DIAD) (**3a**) in our previous optimized reaction conditions for both reactions (Table 1). For green chemistry and reproducibility purposes, we employed β-phenylalanine in combination with KOH for the asymmetric organocatalytic step and performed simple extractions before performing the photocatalytic step. The product was formed in a quantitative yield and high enantiomeric excess (>99% ee). All racemic samples were produced using racemic phenylalanine as the catalyst. For the second step, CH_2Cl_2 was kept as the solvent, having in mind to introduce a one-pot process in the future, although our previous studies revealed that dichloromethane is not a suitable solvent for this photocatalytic process.[11a] Previously, completion of the reaction was evident by simple observation, since the color of the solution turned from yellow to colorless,[11a] however, this did not occur even after 24 h of irradiation (Table 1, entry 1). A low yield (22%) of the desired product was isolated, albeit in high enantiomeric excess (94% ee).

Table 1 Optimization of the reaction conditions for the combination of the organocatalytic Michael addition of isobutyraldehyde with maleimide with the photoorganocatalytic hydroacylation with diisopropyl azodicarboxylate[a]



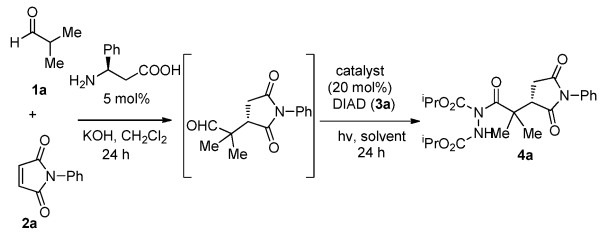
Entry	Catalyst loading (mol%)	Solvent	Yield[b] (%)	ee[c] (%)
1	10	CH_2Cl_2	22	94
2[d]	10	CH_2Cl_2	54	86
3[e]	10	CH_2Cl_2	36	96
4[f]	10	CH_2Cl_2	38	98
5	10	Pet. ether	53	88
6[e]	20	Pet. ether	42	95

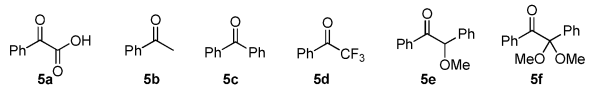
DIAD: diisopropyl azodicarboxylate.[a] **1a** (2.80 mmol), **2a** (1.50 mmol), β-Phe (0.075 mmol), KOH (0.075 mmol) in CH_2Cl_2 (2 mL) for 24 h, then diisopropyl azodicarboxylate (**3a**) (1.00 mmol), PhCOCOOH (0.10 mmol) in CH_2Cl_2 (5 mL) under household bulb irradiation for 24 h. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Reaction time 48 h. [e] **2a**:**3a** ratio: 1:1.5. [f] **2a**:**3a** ratio: 1:3.

We postulated that a prolonged reaction time could be needed for the reaction to reach completion, and the reaction time was increased to 48 h, where indeed, the yield increased significantly (54%), albeit, at the expense of the enantioselectivity (86% ee) (Table 1, entry 2). This result suggests that upon prolonged irradiation, the labile acidic proton of the product can slowly epimerize, leading to erosion of the enantioselectivity. In order to address this issue, we studied the effect of the reagent ratio for the conversion and the enantioselectivity of the reaction (Table 1, entries 3 and 4). Reversing the ratio of the reagents, a boost in the yield was observed, along with a slight boost in the enantioselectivity (Table 1, entries 3 and 4 *vs.* 1). Since the yield remained low, we decided to employ petroleum ether as the solvent for the photocatalytic step, which proved to be the solvent of choice in our previous studies.[11a] A significant increase in the yield of the product was observed, with a slight decrease in the enantioselectivity (Table 1, entry 5). Increasing the catalyst loading of phenylglyoxylic acid did not alter the yield of the product, but altered the observed enantioselectivity (Table 1, entry 6). It seems that increasing the catalyst loading pushes radicals towards the productive pathway, not letting them participate in the enantioselectivity-deteriorating pathways.

We next turned our attention to screening different photocatalysts for the second step (Table 2). Although in our previous studies, phenylglyoxylic acid (**5a**) outperformed all other activated ketones employed as the photocatalyst,[11a] it was necessary to rescreen the photocatalyst, in order to match the organocatalytic step. Replacing phenylglyoxylic acid (**5a**) by known Hydrogen Atom Transfer (HAT) photocatalysts, like acetophenone (**5b**) or benzophenone (**5c**), or other activated ketones, like 2,2,2-trifluoroacetophenone (**5d**), did not lead to higher yields, although the enantioselectivity was kept at high

Table 2 Optimization of the reaction conditions for the combination of the organocatalytic Michael addition of isobutyraldehyde with maleimide with the photoorganocatalytic hydroacylation with diisopropyl azodicarboxylate[a]





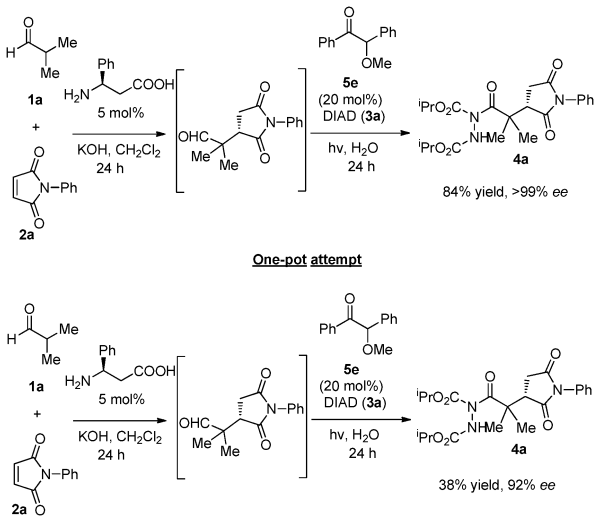
Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**5a**	CH_2Cl_2	36	96
2	**5b**	CH_2Cl_2	12	96
3	**5c**	CH_2Cl_2	16	98
4	**5d**	CH_2Cl_2	Traces	—
5	**5e**	CH_2Cl_2	67	99
6	**5f**	CH_2Cl_2	65	87
7	**5e**	Pet. ether	77	99
8	**5e**	Et_2O	52	96
9	**5e**	Pet. ether/CH_2Cl_2 1 : 1	64	98
10	**5e**	H_2O	84	>99

DIAD: diisopropyl azodicarboxylate.[a] **1a** (1.50 mmol), **2a** (1.00 mmol), β-Phe (0.05 mmol), KOH (0.05 mmol) in CH_2Cl_2 (2 mL) for 24 h, then diisopropyl azodicarboxylate (**3a**) (1.50 mmol), catalyst (0.20 mmol) in solvent (5 mL) under household bulb irradiation for 24 h. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis.

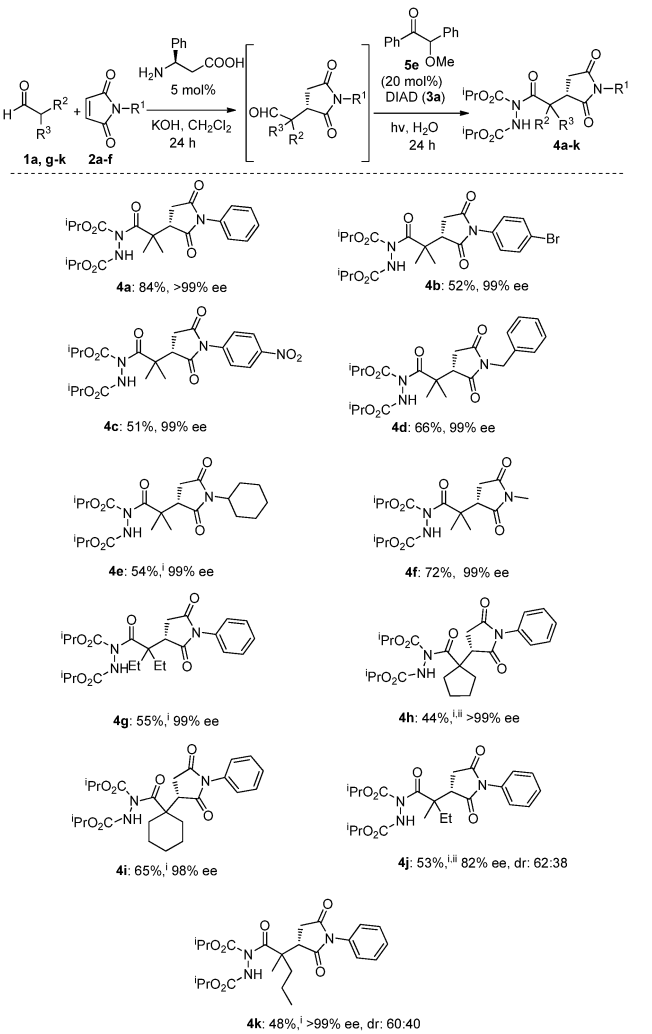
levels (Table 2, entries 1–4). Moving to commercial photoinitiators **5e** and **5f**, the yield improved significantly (Table 2, entries 5 and 6). Among these catalysts, benzoin methyl ether (**5e**) afforded the best results. Since a new photocatalyst was proved to be the optimum to match the organocatalytic step, we then performed a rapid solvent screening (Table 2, entries 7–10). Replacing dichloromethane by petroleum ether further increased the reaction yield (Table 2, entry 7). Diethyl ether or a combination of dichloromethane with petroleum ether did not improve the reaction efficiency (Table 2, entries 8 and 9). Finally, switching the organic solvent to water led to a further improvement both in the yield and the enantioselectivity (Table 2, entry 10). This can be attributed to the fact that water may bring the reactants in close proximity in hydrophobic pockets or maybe water helps the HAT process to occur faster.

In order to provide a one-pot protocol for this combination, we attempted this reaction in a sequence (Scheme 2). Unfortunately, if the intermediate extractions are omitted, a lower yield was isolated, along with decreased enantioselectivity.

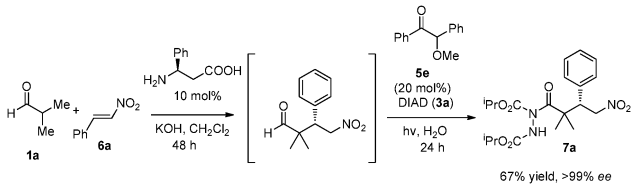
Once we have identified the optimum reaction conditions, we turned our attention to probing the substrate scope of the reaction (Scheme 3). There are many points of adding molecular complexity in the final product.[11a–c,5] Initially, we began with the moiety placed on the maleimide (R^1). Aryl moieties



Scheme 2 Attempted one-pot procedure for the combination of the organocatalytic Michael addition of isobutyraldehyde to maleimide with the photoorganocatalytic hydroacylation with diisopropyl azodicarboxylate.



Scheme 3 Substrate scope for the combination of the organocatalytic Michael addition of aldehydes to maleimides with the photoorganocatalytic hydroacylation with diisopropyl azodicarboxylate. [i]Michael addition required 48 h. [ii]In the photocatalytic reaction, a mixture of Pet ether : water 1 : 1 was employed.



Scheme 4 Expansion of the combination of the organocatalytic Michael addition of isobutyraldehyde to nitrostyrene with the photoorganocatalytic hydroacylation with diisopropyl azodicarboxylate.

bearing electron-withdrawing and electron-deficient groups can be used successfully, leading to products **4a–c** in high yields and excellent enantioselectivities. Moving from aryl- to alkyl-substituted maleimides, benzyl-maleimide or alkyl-substituted maleimides with cyclohexyl or methyl moieties reacted equally well, leading to good to high yields and excellent enantioselectivities (products **4d–f**). We next focused on the aldehyde part of the reaction. A variety of different α,α-disubstituted aldehydes can also be employed with success. 2-Ethyl-butyraldehyde afforded **4g** in good yield and excellent ee, while cyclopentane-carboxaldehyde and cyclohexane-carboxaldehyde led to **4h** and **4i** in similar good yields and excellent enantioselectivities. When non-symmetrical α,α-disubstituted aldehydes are employed, a mixture of diastereomers can be foreseen.[5] Indeed, when 2-methyl-butanal and 2-methyl-pentanal are employed, the desired products were obtained in good yield, diastereoselectivity and enantioselectivity (products **4j** and **4k**). Unfortunately, the use of 2-phenylpropanal did not lead to the desired product. We postulated that once the product of the organocatalytic step is formed,[5] radical decomposition pathways are followed, due to the stable benzyl radicals that can be formed. Also, the use of heptanal and 3-phenylpropanal failed to deliver the desired product. In these cases, we postulate that the acidic α-proton is not compatible with the second step, leading to decomposition products. Another point of diversity of the final product is the azodicarboxylate partner, but we chose not to pursue, since it seems quite straightforward.

In order to further expand the scope of this combination we decided to change the first step of the sequence (Scheme 4). Instead of employing an organocatalytic asymmetric Michael addition of α,α-disubstituted aldehydes with maleimides, we substituted the maleimide with nitrostyrene **6a**. Indeed, the combination can be expanded to nitrostyrenes, leading to the desired product **7a** in good yield and excellent enantioselectivity.

Conclusion

In conclusion, we have developed a green, cheap and easy-to-execute combination of organocatalysis with photoorganocatalysis. The first step constitutes a highly selective, low catalyst loading asymmetric organocatalytic Michael addition of α,α-disubstituted aldehydes with maleimides, while the second step is a photoorganocatalytic hydroacylation of dialkyl azodicarboxylates employing benzyl methyl ether as the photocatalyst, water as the solvent and household bulb irradiation. In order to combine these two areas of catalysis, a new optimization was required, in order to identify the appropriate photocatalyst and reaction conditions to retain high enantioselectivities and yields. The desired products were isolated in good to high yields and excellent enantioselectivities. This work constitutes a successful example of combining asymmetric organocatalysis with photoorganocatalysis, that can be the basis for further developments in the field.

Experimental section

General information

Chromatographic purification of products was accomplished using column chromatography on a Merck® Kieselgel 60 F_{254} 230–400 mesh. Thin-layer chromatography (TLC) was performed on aluminium backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using ninhydrine. Mass spectra (ESI) were recorded on a Finningan® Surveyor MSQ LC-MS spectrometer. HRMS spectra were recorded on Bruker® maxis Impact QTOF spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian® mercury (200 MHz and 50 MHz, respectively) and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant and assignment. Data for ^{13}C are reported in terms of chemical shift (δ ppm). High Performance Liquid Chromatography (HPLC) was used to determine enantiomeric excesses and was performed on Agilent 1100 Series apparatus using Chiralpak AD-H and OD-H columns. Optical rotations were measured on a Perkin Elmer 343 polarometer. The diastereomeric ratio of the crude reaction mixture was determined by ^{1}H-NMR. The configuration of the products has been assigned by comparison to literature data. All new compounds were assigned by analogy.

General experimental procedure for the combination of organocatalysis with photoorganocatalysis

In a dry flask, maleimide (1.00 mmol), L-β-phenylalanine (0.05 mmol, 8 mg), and KOH (0.10 mmol, 6 mg) were dissolved in CH_2Cl_2 (2 mL) and aldehyde (1.50 mmol) was added. The mixture was stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2 × 5 mL). The organic layer was dried over Na_2SO_4. Then, the solvent was removed *in vacuo*. The crude product was transferred to a vial, and benzoin methyl ether (**5e**) (0.20 mmol, 45 mg), diisopropyl azodicarboxylate (DIAD) (**3a**) (1.50 mmol, 303 mg) and H_2O (1 mL) were added. The reaction mixture was stirred vigorously under household bulb irradiation (2 × 80 W household lamps) for 24 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2 × 5 mL). The organic layer was dried over Na_2SO_4. Then, the solvent was removed *in vacuo*. Purification was performed by silica gel chromatography with petroleum ether/ethyl acetate.

Experimental procedure for the synthesis of (*S*)-diisopropyl 1-(2,2-dimethyl-4-nitro-3-phenylbutano-yl)hydrazine-1,2-dicarboxylate (7a)

In a dry flask, nitrostyrene (1.00 mmol, 149 mg), L-β-phenylalanine (0.10 mmol, 17 mg), and KOH (0.10 mmol, 6 mg) were dissolved in CH_2Cl_2 (2 mL) and isobutyraldehyde (1.50 mmol, 115 mg) was added. The reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2 × 5 mL). The organic layer was dried over Na_2SO_4. Then, the solvent was removed *in vacuo*. The crude product was transferred to a vial, and benzoin methyl ether (**5e**) (0.20 mmol, 45 mg), diisopropyl azodicarboxylate (DIAD) (**3a**) (1.50 mmol, 303 mg) and H_2O (1 mL) were added. The reaction mixture was stirred vigorously under household bulb irradiation (2 × 80 W household lamps) for 24 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2 × 5 mL). The organic layer was dried over Na_2SO_4. Then, the solvent was removed *in vacuo*. The product was purified by silica gel chromatography with petroleum ether/ethyl acetate.

Conflicts of interest

There are no conflicts to declare.

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