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Sequential Asymmetric Catalysis in Michael–Michael–Michael–Aldol Reactions: Merging Organocatalysis with Photoredox Catalysis in a One-Pot Enantioselective Synthesis of Highly Functionalized Decalines Bearing a Quaternary Carbon Stereocenter

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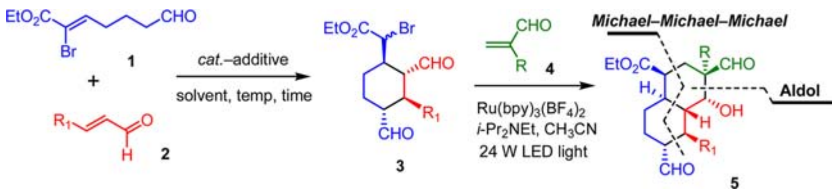
ABSTRACT



An expedited method has been developed for the enantioselective synthesis of highly functionalized decaline systems containing seven contiguous stereogenic centers with high enantioselectivities (>99% ee). The one-pot methodology comprises a cascade of organocatalytic double Michael–photocatalyzed Michael–aldol reactions of ethyl 2-bromo-6-formylhex-2-enoate, β-alkyl-α,β-unsaturated aldehydes, and α-alkyl-α,β-unsaturated aldehydes. The structure and absolute configuration of an appropriate product were confirmed by X-ray analysis.

Visible light photoredox catalysis has attracted much attention due to its use of the abundant and renewable source of light and its incorporation of green operation chemistry.[1] Accordingly, many promising methodologies and synthetic applications have been developed; indeed, rare examples have been reported for the photoredox catalyzed Michael reaction.[2] Furthermore, organocatalyzed asymmetric conjugate additions of α,β-unsaturated aldehydes have received extensive interest over recent decades, resulting in significant advances.[3] Most examples have been devoted to the reactions with β-alkyl-α,β-unsaturated aldehydes, but the organocatalyzed conjugate addition reactions involving the α-alkyl-α,β-unsaturated aldehydes, especially those that feature asymmetric amino catalysis, have been rare due to the inherent difficulty in generating the congested iminium intermediate.[4] The successful examples of organocatalyzed conjugated additions to

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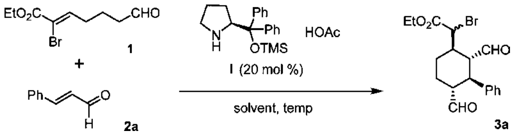
Scheme 1. Retrosynthetic Analysis

α-alkyl-α,β-unsaturated aldehydes have usually involved strong nucleophiles such as indoles,[5] nitromethane,[6] or NHC catalysis.[7] Alternative asymmetric metal-catalyzed strategies for the conjugate addition to α-alkyl-α,β-unsaturated aldehydes have also been lacking and remain a compelling area of investigation.[8]

In an effort to extend our earlier studies on organocatalyzed annulations[9,10] and to merge photoredox catalysis and organocatalysis,[11] we envisioned a cascade of organocatalytic double Michael and photoredox catalyzed Michael–aldol reactions[12] involving ethyl 2-bromo-6-formylhex-2-enoate, β-alkyl-α,β-unsaturated aldehydes, and α-alkyl-α,β-unsaturated aldehydes that might provide a useful protocol for the formation of the highly functionalized decaline system containing multiple contiguous stereogenic centers and bearing a quaternary stereocenter, as illustrated in Scheme 1.

Table 1. Screening of the Solvent and Reaction Conditions for the Double Michael Reaction[a]



entry	solvent	temp (°C)	time (h)	yield[b](%)	dr[c]
1	CH_2Cl_2	28	16	66	9.4:1
2[d]	MeCN	28	5	69	7.1:1
3[e]	H_2O	24	1	56	5.4:1
4	CH_2Cl_2	0	16	82	9.0:1
5	MeCN	0	17	87	13.6:1
6	EtOH[f]	0	20	78	2.4:1
7	toluene	0	49	50	4.2:1

[a] Unless otherwise noted, the reactions were performed with *cat.* **I**–HOAc (20 mol %) in 0.1 M of **1** with a ratio 1.5/1 of **2a**/**1**. [b] Isolated yield. [c] Determined by the ^{1}H NMR of the crude product. [d] Reaction proceeded with 30 mol % of catalyst; the reaction with less catalyst gave an incomplete reaction. [e] Reaction with a ratio of 6/1 of **2a**/**1**. [f] 99% EtOH.

At the outset of the study, the reaction of **1** with 1.5 equiv of cinnamaldehyde (**2a**) in the presence of the Jørgensen–Hayashi catalyst **I**–AcOH (20 mol %)[13] in CH_2Cl_2 at ambient temperature for 16 h afforded a 66% yield of the expected double Michael adduct **3a** with a 9.4:1 ratio of diastereomers, arising from the CH–Br center (Table 1, entry 1). Perhaps due to the rapid consumption of the catalyst in the CH_3CN media, the reaction with 20 mol % of catalyst **I**–AcOH in CH_3CN at ambient temperature was halted after 9 h and even after 2 days was not complete. By increasing the catalyst loading to 30 mol %, the reaction in CH_3CN was completed in 5 h and gave a 69% yield of **3a** with 7.1:1 dr (Table 1, entry 2). The reaction in aqueous media with an excess of **2a** (6 equiv) was facilitated and was completed in 1 h, but afforded a lesser yield of **3a** with less selectivity, 56% yield, 5.4:1 dr (Table 1, entry 3). Subsequently, the reaction at a lower temperature (0 °C) gave higher yields and better diastereoselectivity (Table 1, entries 4 and 5). The best conditions for this reaction were obtained in CH_3CN for 17 h to give an 87% yield of **3a** with 13.6 dr. The reactions in other solvents (e.g., EtOH, toluene), however, afforded lower yields of **3a** (entries 6–7).

With **3a** in hand, we began our investigation employing the photoredox catalysis by irradiating a mixture of **3a** (0.03 M)[14] and methacrolein (4 equiv) in the presence of catalytic amounts of $Ru(bpy)_3(BF_4)_2$ (5 mol %) and

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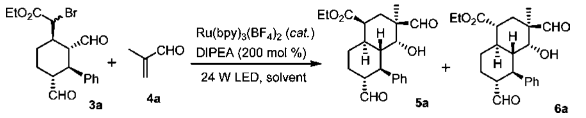
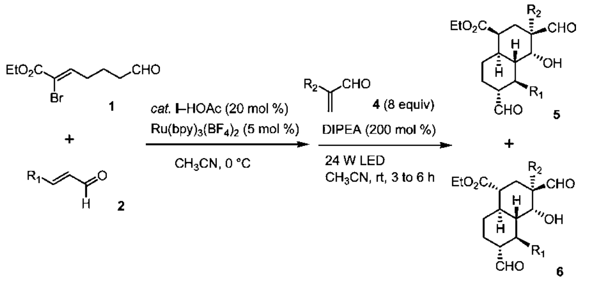
Table 2. Screening of the Solvent and Reaction Conditions for the Photoredox Catalyzed Michael–Aldol Reaction[a]



entry	solvent	cat. (mol %)	time (h)	yield[b] (%)	dr
1	MeCN	5	3	30	83:17
2	DMF	5	2	13	81:19
3	CH_2Cl_2	5	32	trace	
4[c]	CH_2Cl_2	5	1	trace[d]	
5	MeCN	2.5	10	26	81:19
6	MeCN	1	21	20	80:20
7	MeCN[e]	5	4	56	84:16
8	MeCN[f]	5	2	27	82:18
9[g]	MeCN[e]	5	2	66	81:19

[a] Unless otherwise noted, the reactions were performed in 0.03 M of **3a** with a ratio 4/1 of **4a**/**3a** at ambient temperature with a 24 W LED lamp. [b] Isolated yield. [c] Reaction with the addition of Hantzsch ester (150 mol %). [d] Reductive bromination of **3a** was predominately obtained. [e] 0.1 M of **3a**. [f] 0.3 M of **3a**. [g] A ratio 8/1 of **4a**/**3a**.

Table 3. Scope of Organocatalytic Double Michael–Photoredox Catalyzed Michael–Aldol Reactions[a]



entry	R_1, R_2	time (h)[b]	yield (%)[c]	dr[d] **5/6**	*ee*[e] (%)
1	**a** R_1 = Ph, R_2 = Me	16	55 (54)[f]	83:17	>99
2	**b** R_1 = Ph, R_2 = Et	16	51(50)[f]	82:18	>99
3	**c** R_1 = Ph, R_2 = Bn	16	47(43)[f]	81:19	>99 (>99)[g]
4	**d** R_1 = Ph, R_2 = n-C_5H_{11}	16	49(49)[f]	73:27	99
5	**e** R_1 = Ph, R_2 = OBn	16	53	84:16	99
6	**f** R_1 = 4-OMeC_6H_4, R_2 = Me	83	52	84:16	98
7	**g** R_1 = 4-MeC_6H_4, R_2 = Me	37	53	85:15	98
8	**h** R_1 = 4-BrC_6H_4, R_2 = Me	16	54	83:17	>99
9	**i** R_1 = 4-BrC_6H_4, R_2 = Bn	16	53	83:17	>99
10	**j** R_1 = 4-ClC_6H_4, R_2 = Me	7	48	82:18	99
11	**k** R_1 = 4-FC_6H_4, R_2 = Me	5	38	81:19	98
12	**l** R_1 = 4-$NO_2C_6H_4$, R_2 = Me	5	0[h]	na	na

[a] Unless otherwise noted, the reactions were performed in 0.1 M of **1**, in a ratio of 1:1.5 for **1**/**2**, with a 24 W household LED lamp (method A). [b] Reaction time for the formation of **3**. [c] Isolated yields of **5** and **6**. [d] Determined by the ^{1}H NMR of the crude reaction mixture. [e] *ee* of **5**, determined by HPLC with chiral column Chiralpak IC. [f] Isolated yield in parentheses for the addition of enal **4** with **1** and **2a** (in a ratio of 8:1:2.5) in the beginning of the reaction (Method B). [g] *ee* of **6**, determined by HPLC with chiral column Chiralpak IC. [h] Reductive debrominations of **3l** and other unknown mixtures were observed during the photocatalysis.

Hünig's base (200 mol %) in degassed acetonitrile (0.03 M), with a household LED lamp (24 W). We obtained a 30% yield of the Michael-aldol product **5a** and **6a** in a ratio of 83:17 (Table 1, entry 1). It is noteworthy that the reaction without the Hünig base provided no product, but resulted in recovery of the starting compounds. The same reaction conditions in other solvent media, *e.g.*, DMF, CH_2Cl_2, gave no observable product or afforded a lower yield (Table 2, entries 2–3). With the addition of the Hantzsch ester, the reaction resulted in the formation of reductive debromination of bromide **3a** (Table 2, entry 4). The reaction with 2.5 mol % of $Ru(bpy)_3(BF_4)_2$ gave a slightly lower yield than the reaction with 5 mol % catalyst. The yield decreased substantially when the amount of the ruthenium catalyst was lowered to 1 mol % and required prolonged irradiation for the completion of reaction for **5a** (Table 2, entries 5–6). The reaction yield was increased to 56% when the amount of **3a** was increased to 0.1 M, but gave no further improvement with 0.3 M of **3a** (Table 2, entries 7–8). Finally, the yield of the reaction was increased to 66% with 8 equiv of methacrolein (Table 2, entry 9).

After establishing the optimal reaction conditions (Table 1, entry 5 and Table 2, entry 9), we next examined the scope and limitations of the organocatalytic double Michael–photocatalyzed Michael–aldol reaction sequence in a one-pot process with variants of **1**, **2**, and **4**. Reaction of **1** and **2** in the presence of catalyst **I**–HOAc in CH_3CN at 0 °C provided the corresponding **3**, followed by the addition of **4**, $Ru(bpy)_3(BF_4)_2$, and Hünig's base with exposure to a household LED lamp (24 W) for 3–6 h at ambient temperature. The reaction appeared quite general with respect to the substrates tested, providing the corresponding adducts (dr ~80:20) with excellent *ee* values and in good yields (Table 3).[15] After the one-pot four-step reaction sequence, the overall yields were ~55%, i.e., an average 86% yield for each C–C bond formation reaction. In an alternative operation, addition of enal **4** at the beginning of the reaction, *i.e.*, initial mixing of the reactant **1**, **2**, and **4**, followed by the same reaction conditions described above afforded similar yields, as indicated in parentheses and the description in footnote f, entries 1–4, Table 3.

When DIPEA was added at the beginning of the reaction with the mixture of **1** and **2**, the first-step double Michael reaction did not take place and did not provide **3**. The dr ratio of **5**/**6** decreased slightly to 73:27 in the reaction with **4d**, with the enal bearing the aliphatic long chain on R_2 (Table 3, entry 4). With the electron-donating groups on R_1, *e.g.*, methoxy and methyl groups, the double Michael reaction of **1** and **2** to **3** required a longer time for completion (Table 3, entries 6 and 7). In contrast, the reaction

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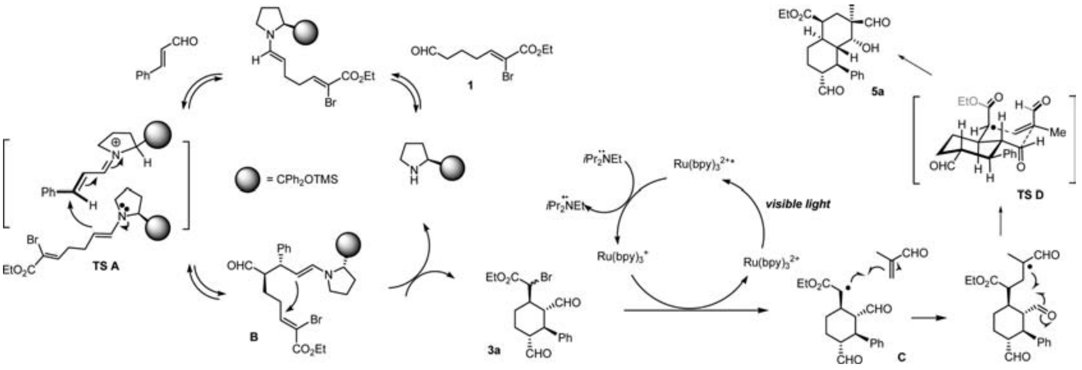
(14) Regardless of the diastereomeric ratio of **3a**, the obtained ratios of **5a**/**6a** remained the same. For routine operation, **3a** with the dr ~5:1 was used.

(15) Unfortunately, the reactions with enal **4** having a β-substituent, *e.g.*, cinnamaldehyde or 2-methylbut-2-enal, were fruitless and provided the reductive debromination of **3** as the major products. The problem may be due to an increase in the steric congestion around the neopentyl centers of products **5** and **6** which hampered the reaction progress.

Scheme 2. Proposed Mechanism for the One-Pot Transformation



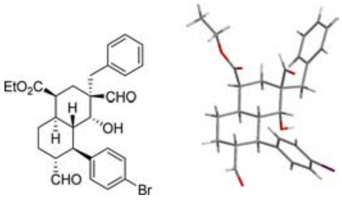


Figure 1. Stereoplots of the X-ray crystal structures of (−)-**5i**: C, gray; O, red; Br, purple.

with electron-withdrawing groups on R_1, *e.g.*, fluoro, chloro, and nitro groups, provided lesser yields (Table 3, entries 10−12).

Notably, the formation of **3l** was relatively fast and completed in 5 h, but the reductive debrominations of **3l** and other unknown mixtures were observed as the major products during the subsequent photocatalysis (Table 3, entry 12).[16] The structure and absolute configuration of the product (−)-**5i** were assigned unambiguously by the single-crystal X-ray analysis (Figure 1).

The advantage of this protocol is that in a one-pot operation the three components have been converted into a highly functionalized decaline with control over the seven stereocenters including a quaternary carbon. In addition, the high stereoselectivity of the second step photocatalyzed-Michael−Aldol reaction is noteworthy, since the 6-*exo*-trig radical cyclization would generate three new chiral centers, leading to a maximum of eight possible stereoisomers. To account for the stereoselectivity of the transformation, we propose a plausible mechanism (Scheme 2). Initially, iminium formation of the enamine **1a** from bromoenal **1** occurs, followed by the nucleophilic attack on the iminium-activated cinnamaldehyde from the *Re* face under the control of the catalyst (TS **A**), giving intermediate **B**, which subsequently undergoes the Michael reaction to afford **3a**. Under the regular photoredox procedures, reductive quenching of $^*Ru(bpy)_3^{2+}$ by Hünig's base generates $Ru(bpy)_3^{+}$, which is reduced to donate an electron to bromide **3a**, thereby generating the ester radical **C**. Subsequently, conjugate addition of the alkyl radical **C** to methacrylaldehyde, followed by aldol cyclization via the preferable transition state **TS D**, affords the decaline adduct **5a** as the major isomer. In the transition state **TS D**, the sterically demanding phenyl group preferentially adopts sites in equatorial positions in cyclohexane. The methacrylaldehyde is furthermore expected to reside in a location with the methyl group in an equatorial orientation during the 6-*exo*-trig radical cyclization.[17]

In summary, we have described a concise synthesis of an optically active, highly functionalized decaline system containing seven contiguous stereogenic centers with a quaternary carbon stereocenter with high enantioselectivities (>99% *ee*) by a cascade organocatalytic double Michael and visible light driven photocatalytic Michael−aldol reaction. Particularly noteworthy is the synergistic use of organo- and photocatalysis with highly stereoselective cascade reactions under mild reaction conditions in a one-pot process. The structures and the absolute configuration of the product were unambiguously confirmed by single crystal X-ray crystallographic analysis of the appropriate adducts. Further applications of this protocol in the synthesis of elaborated natural products, *e.g.*, cadinene derivatives, are currently underway.

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Supporting Information Available. Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for compound (−)-**5i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A computational investigation conducted by SPARTAN'10 on the origin of the stereoselectivity of the 6-*exo*-trig radical cyclization has revealed the lowest-energy transition state **TS D**, as depicted in Scheme 2.

The authors declare no competing financial interest.