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N719 Dye-Sensitized Organophotocatalysis: Enantioselective Tandem Michael Addition/Oxyamination of Aldehydes

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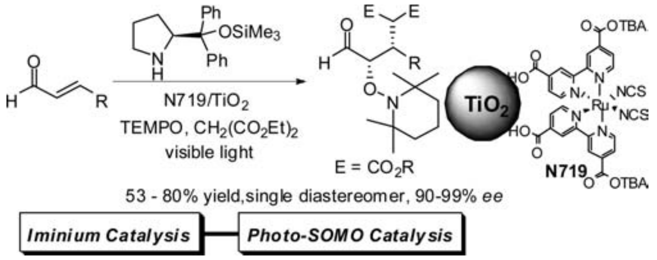
ABSTRACT



A remarkably efficient photosensitizer, N719 dye, was used in asymmetric tandem Michael addition/oxyamination of aldehydes, rendering α,β-substituted aldehydes in good yields with excellent levels of enantioselectivity and diastereoselectivity. This is the first report of a multiorganocatalytic reaction involving iminium catalysis and photoinduced singly occupied molecular orbital (SOMO) catalysis. This reaction is expected to expand the scope of tandem organocatalytic reactions.

Rapid and significant advances in organocatalysis have provided relatively simple, efficient, and environmentally benign methods of forming highly complex organic molecules with excellent stereoselectivity, resulting in numerous applications of organocatalytic reactions to natural product synthesis and in the pharmaceutical industries.[1] In recent years, organophotocatalytic reactions combining enamine-mediated organocatalysis and a photoredox reaction have been reported to broaden the scope of conventional enamine-mediated organocatalytic reactions.[2–4] In the presence of photoredox complexes (Ru and Ir complexes, TiO_2, and organic dyes), intermediates generated in the enamine-mediated organocatalytic reaction

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(3) For review articles on photoredox organocatalysis, see: (a) Renaud, P.; Leong, P. *Science* **2008**, *322*, 55–56. (b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360–1363. (c) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785–9789. (d) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859–917. (e) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102–113. (f) Ravelli, D.; Fagnoni, M. *ChemCatChem* **2012**, *4*, 169–171.

(4) For selected articles regarding enamine catalysis under photooxidation conditions, see: (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877. (c) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166–167. (d) Neumann, M.; Füldner, S.; König, B.; Zeitler, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 951–954. (e) Ho, X.-H.; Kang, M.-J.; Kim, S.-J.; Park, E. D.; Jang, H.-Y. *Catal. Sci. Technol.* **2011**, *1*, 923–926. (f) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360–2362. (g) Cherevatskaya, M.; Neumann, M.; Füldner, S.; Harlander, C.; Kümmel, S.; Dankesreiter, S.; Pfitzner, A.; Zeitler, K.; König, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 4062–4066. (h) Rueping, M.; Zoller, J.; Fabry, D. C.; Poscharny, K.; Koenigs, R. M.; Weirich, T. E.; Mayer, J. *Chem.—Eur. J.* **2012**, *18*, 3478–3481.

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undergo single-electron oxidation/reduction, which induces radical processes for novel chemical bond formation. Compared to previously reported enamine radical processes involving a large excess of chemical oxidants,[5] photoredox-catalyzed reactions require relatively small catalytic loadings of photoredox compounds (5−0.5 mol %) under light irradiation. Although enamine reactions with photoredox materials have shown advantages over chemical-oxidant-mediated reactions, there are issues to be addressed with regard to current organophotocatalytic reactions. First, the loadings of expensive photoredox materials need to be reduced by increasing the photocatalytic activity. Second, enamine-mediated organophotocatalytic reactions are confined to single-step reactions such as α-alkylation of carbonyl compounds via photoredox cleavage of C−X (X = Br and I) and α-oxyamination of carbonyl compounds in the presence of TEMPO radicals.[4] Photoinduced multiorganocatalytic one-pot reactions for installing several stereogenic centers have not yet been reported.

With the aim of developing green organocatalytic processes, our research group has tried to establish environmentally friendly oxidation protocols in enamine-mediated organocatalytic reactions; we have reported α-oxyamination of aldehydes under galvanostatic conditions and TiO_2-photocatalytic conditions and α-alkylation of aldehydes under galvanostatic conditions.[4e,6] In our research on the development of green organocatalytic reactions, we have found that TiO_2-bound N719-catalyzed organophotoreactions induce highly enantio- and diastereoselective tandem iminium/SOMO (singly occupied molecular orbital) reactions to afford α,*β*-substituted aldehydes under cost-effective, nontoxic, and visible light-induced photocatalytic conditions. Ru(II) complexes (e.g., N719) attached to TiO_2 supports have been used in dye-sensitized solar cell (DSSC) devices and in water photolysis[7] but have not been used in asymmetric organic reactions.[4h,8,9] In addition to the first use of a DSSC dye in an asymmetric organocatalytic reaction, a new type of tandem organocatalytic reaction (an iminium/SOMO combination) is achieved in this work. Although numerous combinations of iminium, enamine, Brønsted acid, Brønsted base, carbene, and transition-metal catalysts have been reported for use in multiple catalytic reactions, there has been no example of a tandem iminium catalysis/photoinduced SOMO process.[10] The optimization results are listed in Table 1. To obtain a tandem iminium-SOMO reaction, Michael additions of malonates to α,*β*-unsaturated aldehydes followed by α-oxyamination of the resulting *β*-substituted aldehydes in one pot were attempted under visible light. A mixture of **1a** (0.25 mmol), diethyl malonate (0.75 mmol), and TEMPO (0.5 mmol) in CH_3CN (0.4 M) was subjected to organophotocatalytic conditions using (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]-pyrrolidine (20 mol %) and N719/TiO_2 (25 mg) under visible light from 8 W cool white fluorescent tubes. The loading of N719 on TiO_2 (25 mg) was determined by UV spectroscopy and was 0.04 mol % of the Ru(II) complex with respect to **1a**.[11] Since the addition of acid additives promotes iminium ion formation from **1a** and a chiral amine catalyst,[12] 10 mol % of benzoic acid was added, providing the desired product **1b** in 46% yield with a diastereomeric excess (*de*) higher than 95% and an enantiomeric excess (*ee*) of 96% (entry 1). The enantiomerically enriched **1b** can be converted to biologically active chiral lactones or chiral lactams after chemical modifications, including cyclization, for further applications.[12e] The relative stereochemistry was confirmed by NMR analysis of the lactone compound derived from **1b**.[13] By increasing the amount of benzoic acid to 30 mol %, the yield of **1b** was increased to 70%, while maintaining a similar stereoselectivity (entry 2). Next, acetic acid, 2-bromobenzoic acid, *p*-toluene sulfonic acid (TsOH), adamantane carboxylic acid, perchloric acid, and NaOAc base additives were tested (entries 3−8). Among the acid and base additives, adamantane carboxylic acid gave the highest

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(6) (a) Bui, N.-N.; Ho, X.-H.; Mho, S.-i.; Jang, H.-Y. *Eur. J. Org. Chem.* **2009**, 5309–5312. (b) Ho, X.-H.; Mho, S.-i.; Kang, H.; Jang, H.-Y. *Eur. J. Org. Chem.* **2010**, 4436–4441.

(7) For review articles regarding DSSC dyes and their applications, see: (a) Grätzel, M. *Acc. Chem. Res.* **2009**, *42*, 1788–1798. (b) Youngblood, W. J.; Lee, W.-H. A.; Meada, K.; Mallouk, R. E. *Acc. Chem. Res.* **2009**, *42*, 1966–1973. (c) Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. *Chem. Rev.* **2010**, *110*, 6595–6663.

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(9) Mitkina, T.; Stanglmair, C.; Setzer, W.; Gruber, M.; Kisch, H.; König, B. *Org. Biomol. Chem.* **2012**, *10*, 3556–3561.

(10) For review articles of tandem organocatalytic reaction, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745–2755. (b) Zhou, J. *Chem.—Asian. J.* **2010**, *5*, 422–434. (c) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999–3025.

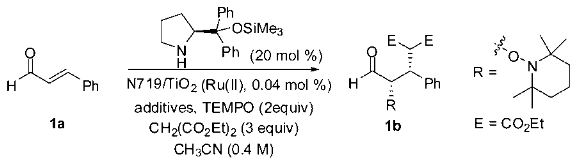
(11) The experimental details for the determination of the amount of Ru(II) species are provided in the Supporting Information.

(12) For selected articles regarding malonate addition to α,*β*-unsaturated carbonyl compounds via iminium catalysis, see: (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed.* **1993**, *32*, 1176–1178. (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520–3530. (c) Holland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661–665. (d) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66–68. (e) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305–4309. (f) Wang, Y.; Pengfei, L.; Liang, X.; Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383–1389. (g) Maltsev, O. V.; Kucherenko, A. S.; Zlotin, S. G. *Eur. J. Org. Chem.* **2009**, 5134–5137. (h) Companyó, X.; Hejnová, M.; Kamlar, M.; Vesely, J.; Moyano, A.; Rios, R. *Tetrahedron Lett.* **2009**, *50*, 5021–5024. (i) Fleischer, I.; Pfaltz, A. *Chem.—Eur. J.* **2010**, *16*, 95–99. (j) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42–53.

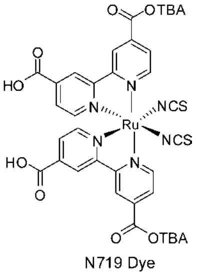
(13) The *trans* relationship between C2 and C3 was reported in ref 10e. By measuring the coupling constants of protons at C3 and C4, the relationship between C3 and C4 was determined. Detailed information and NMR spectra are provided in the Supporting Information.

yield (80%) and stereoselectivity (99% *ee* and >95% *de*) (entry 6). N719/TiO_2 was recycled and gave **1b** in 63% (first recycling) and 37% (second recycling) yields using the conditions of entry 6. In the absence of light, the addition of diethyl malonate to **1a** occurs without formation of **1b** (entry 9).

Table 1. Optimization of Tandem Michael Addition/Oxyamination of **1a**



entry	additive (mol %)	yield	*ee*	*de*
1	$PhCO_2H$ (10)	46%	96%	>95%
2	$PhCO_2H$ (30)	70%	97%	>95%
3	CH_3CO_2H (30)	52%	98%	>95%
4	2-bromobenzoic acid (30)	60%	98%	>95%
5	TsOH (30)	38%	97%	>95%
6	adamantanecarboxylic acid (30)	80%	99%	>95%
7	perchloric acid (30)	53%	98%	>95%
8	NaOAc	37%	98%	>95%
9	adamantanecarboxylic acid (30)	--[a]		--

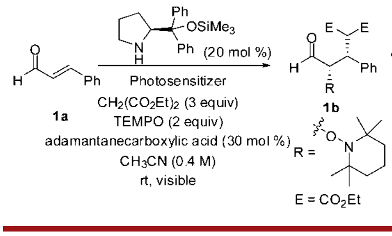


N719 Dye

[a] Experiment performed in the dark; the 1,4-addition product was observed without forming **1b**.

After optimization of the reaction using N719/TiO_2 photocatalysts, N719-catalyzed reactions were carried out in the absence of TiO_2 (Scheme 1). With 0.05 mol % N719, **1b** was formed in 62% yield. The reaction with only TiO_2 gave **1b** in 11% yield. TiO_2 may therefore function as a cooperative second photocatalyst.[4h] $Ru(bpy)_3Cl_2$ (0.05 mol %) was used in a reaction; no product was obtained. With an increased amount of $Ru(bpy)_3Cl_2$ (0.5 mol %), **1b** was isolated in 32% yield. A catalyst loading of 0.05 mol % was too low to give the desired photoredox product. The excellent catalytic activity of N719/TiO_2 may stem from both the ligand effect of the Ru complex and combining N719 with the TiO_2 photocatalyst. Accordingly, N719 on TiO_2 was chosen for the rest of the experiments.

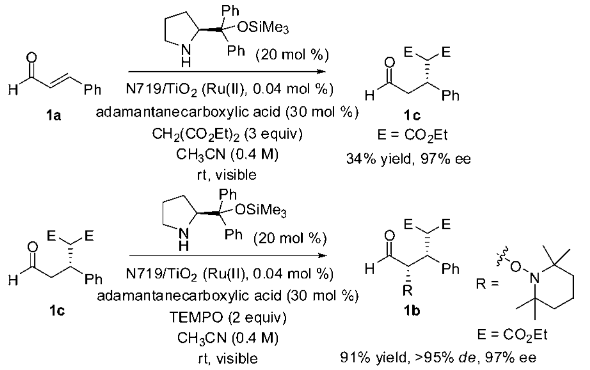
Scheme 1. Tandem Iminium/SOMO Reaction with Assorted Photocatalysts



photosensitizer	yield
N719/TiO_2 (0.04 mol %)	80%
N719 (0.05 mol %)	62%
TiO_2	11%
$Ru(bpy)_3Cl_2$ (0.05 mol %)	N.R.
$Ru(bpy)_3Cl_2$ (0.5 mol %)	32%

After optimization of the reaction conditions, stepwise reactions were conducted (Scheme 2). Compound **1a** was exposed to iminium catalysis conditions to afford **1c** in 34% yield with 97% *ee*. The photocatalyst and visible light combination is responsible for the low yield of **1c**, because the yield of **1c** is higher without photocatalysts. Then, **1c** was converted to **1b** in 91% yield with greater than 95% *de* and 97% *ee*. On the basis of these experiments, the enantioselectivity of the β-position was clearly determined at the first step (iminium catalysis). In the case of the α-position, cooperative enantiocontrol by the chiral catalyst and the chiral substrate **1c** directs remarkably high stereoselectivity during the second photoinduced SOMO catalysis.[14]

Scheme 2. Stepwise Reactions under Organophotoreaction Conditions



Using the optimized conditions listed in Table 1, a series of α,β-unsaturated aldehydes were tested with dimethyl malonate and diethyl malonate (Table 2). The reaction of dimethyl malonate, TEMPO, and **1a** afforded product **2b** in 30% yield with >95% *de* and 90% *ee* (entry 2). Compared with diethyl malonate, the addition of dimethyl malonate gave a reduced yield and selectivity. Next, a range of aromatic α,β-unsaturated aldehydes were checked. Aldehydes possessing electron-rich groups were transformed to the desired products in good yields with excellent stereoselectivities (entries 3–5). Nitro-substituted cinnamaldehyde **6a** participated in the reaction to provide **6b** in a slightly lower yield of 53% with 99% *ee* and >95% *de* (entry 6). The halogen-substituted aldehydes **7a** and **8a** were smoothly converted to **7b** and **8b** in 67% and 62% yields (98% *ee* and 99% *ee*), respectively. Heteroaromatic aldehyde **9a** also coupled with diethyl malonate and TEMPO, giving a good yield (69%) with a selectivity of >95% *de* and 98% *ee* (entry 9).

A proposed catalytic cycle for the tandem Michael addition/oxyamination is shown in Scheme 3. As proposed in the iminium catalysis mechanism of β-addition of malonates to α,β-unsaturated aldehydes,[12] iminium intermediate **I** is generated from the secondary amine catalyst and **1a** and reacts with malonates to provide enamine intermediate **II**. At this stage, intermediate **II** undergoes either hydrolysis to form β-substituted

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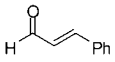
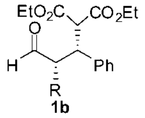
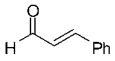
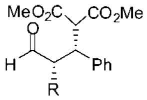
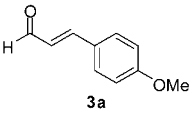
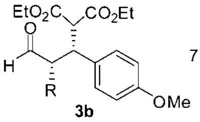
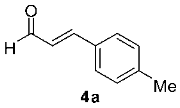
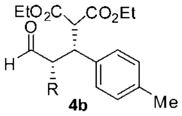
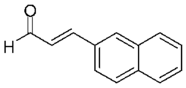
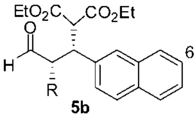
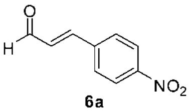
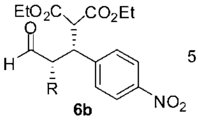
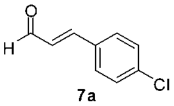
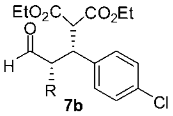
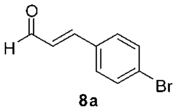
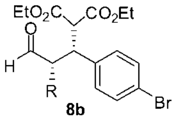
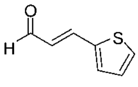
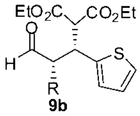
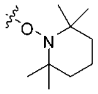
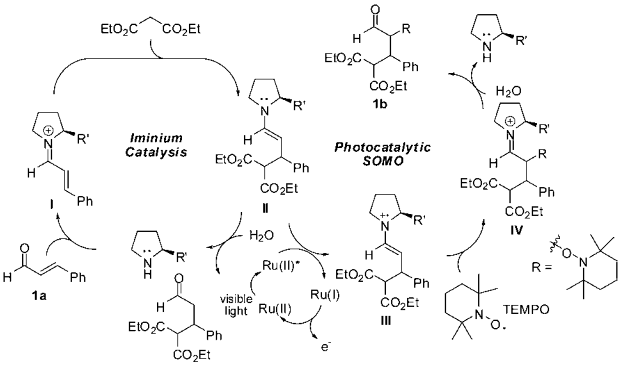
[14] Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.

Table 2. Examples of Tandem Michael Addition/Oxyamination

entry	reactant	product[a]	yield (*ee*, *de*)
1	 **1a**	 **1b**	80 % (99%, >95%)
2	 **1a**	 **2b**	30 % (90%, >95%)
3	 **3a**	 **3b**	79 % (98%, >95%)
4	 **4a**	 **4b**	73 % (98%, >95%)
5	 **5a**	 **5b**	65 % (96%, >95%)
6	 **6a**	 **6b**	53 % (99%, >95%)
7	 **7a**	 **7b**	67 % (98%, >95%)
8	 **8a**	 **8b**	62 % (99%, >95%)
9	 **9a**	 **9b**	69 % (98%, >95%)

[a] R = 

Scheme 3. Mechanism for Tandem Michael Addition/Oxyamination



aldehydes or photo-oxidation by the photoexcited Ru(II) dye to form enamine radical **III**.[4c,e,6a,15,16] The resulting Ru(I) dye is assumed to be oxidized by oxygen in the air or TEMPO in the solution.[4f,6a] Subsequent addition of TEMPO to **III** and hydrolysis afford the desired product **1b**. The organocatalyst is regenerated during the catalytic reaction, and the photocatalyst is also re-excited by visible light irradiation.

In conclusion, we have presented a highly efficient multicatalytic system for tandem Michael addition/oxyamination of aldehydes under organophotocatalytic conditions. By using a chiral amine organocatalyst along with N719/TiO_2 under visible light, asymmetric iminium catalysis was combined with photoinduced SOMO catalysis. This methodology offers cost-effective, environmentally benign, and step-economic reaction conditions for producing a variety of α,β-substituted aldehydes in good yields with excellent levels of enantio- and diastereoselectivities.

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Supporting Information Available. Detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Liu, H.; Feng, W.; Kee, C. W.; Zhao, Y.; Leow, D.; Pan, Y.; Tan, C.-H. *Green Chem.* **2010**, *12*, 953–956.

(16) During the anodic scan, the enamine derived from pyrrolidine and hydrocinnamaldehyde gave an oxidation peak at 0.72 V, and the oxidation peak of TEMPO was observed at 1.03 V (vs a silver wire pseudoreference electrode, in CH_2Cl_2, $TBAClO_4$ electrolyte).

The authors declare no competing financial interest.