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Highly diastereoselective synthesis of bicyclo[4.2.0]octanone derivatives by the [2+2] photocycloaddition of chiral cyclohexenonecarboxylates to ethylene

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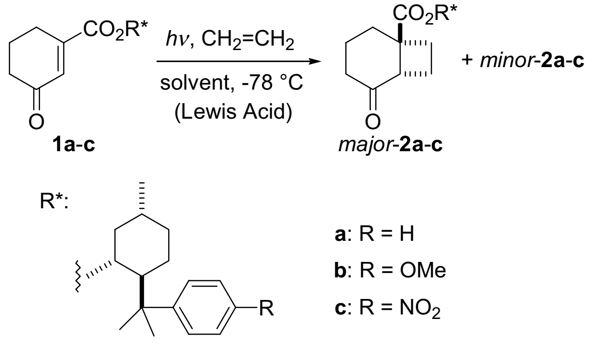
Abstract—The diastereoselective [2+2] photocycloaddition of a cyclohexenonecarboxylate containing (−)-8-(4-nitrophenyl)menthyl as a chiral auxiliary to ethylene gave the photocycloadduct, a bicyclo[4.2.0]octanone derivative, with a high degree of diastereoselectivity. A photoreaction, conducted in CH_2Cl_2 at −78 °C gave the corresponding photocycloadduct in 88% de. In the presence of $Ti(OR)_4$ or Me_3SnCl, the diastereoselectivity was increased up to 92% de.

It is well known that [2+2] photocycloaddition reactions of conjugated cycloalkenones to olefin give bicyclic cyclobutyl ketones, which are potentially versatile building blocks for the syntheses, not only of natural products but also structurally intriguing compounds.[1] We previously reported on the use of cyclobutyl ketones as starting materials for synthesis of some natural products and cyclopentenoids.[2] While the photoreaction is a useful method for the synthesis of bicyclic compounds, the products are racemic, due to the starting achiral cycloalkenones. Therefore, much attention has been focussed on the development of asymmetric [2+2] photocycloadditions to produce optically active cyclobutyl ketones.[3] We previously investigated diastereoselective [2+2] photocycloaddition reactions of cyclohexenones containing various chiral auxiliaries to the smallest olefin, ethylene, and found that menthyl derivatives are effective for achieving a higher degree of asymmetric induction.[4] However, a sufficiently high selectivity for its application to asymmetric syntheses has not been obtained, because it is generally difficult to control the stereochemistry of a compound in a highly energetic and short-lived photoexcited state in photoreactions in comparison with thermal reactions.

In this study, we report that the (−)-8-(4-nitrophenyl)menthyl group[5] is sufficiently effective as chiral auxiliary to give a high selectivity in the [2+2] photocycloaddition of cyclohexenones to ethylene, among the menthyl derivatives examined (Scheme 1). Moreover, the high selectivity as well as the effect of solvents and Lewis acids can be attributed to the most stable conformation, based on X-ray analysis and computational modeling.



Scheme 1.

Keywords: [2+2] Photocycloaddition; Cyclohexenone; Chiral auxiliary; Menthyl; Lewis acid; Diastereoselectivity.

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Table 1. Photocycloaddition reaction of **1** with ethylene[a]

Entry	Subs.	Lewis acid[b]	Solvent	Yield (%)[c]	de (%)[d]
1[e]	**1a**	—	CH_2Cl_2	84	40
2[e]	**1b**	—	CH_2Cl_2	95	50
3[e]	**1b**	—	Toluene	99	75
4[e]	**1b**	—	MCH[f]	96	81
5	**1c**	—	Toluene	92	81
6	**1c**	—	CH_2Cl_2	94	88
7	**1a**	Me_3SnCl	CH_2Cl_2	93	48
8	**1a**	$Ti(O^iPr)_4$	CH_2Cl_2	90	41
9	**1b**	Me_3SnCl	MCH[f]	71	52
10	**1b**	$Ti(O^iPr)_4$	MCH[f]	65	84
11	**1b**	$Ti(O^nBu)_4$	MCH[f]	88	83
12	**1b**	$Ti(OEt)_4$	MCH[f]	84	82
13	**1c**	Me_3SnCl	CH_2Cl_2	93	91
14	**1c**	$Ti(O^iPr)_4$	CH_2Cl_2	80	90
15	**1c**	$Ti(O^nBu)_4$	CH_2Cl_2	73	91
16	**1c**	$Ti(OEt)_4$	CH_2Cl_2	73	92

[a] A 0.05 M solution of **1** (and Lewis acid) in each solvent was purged with ethylene at 25 °C for 5 min and then irradiated under an ethylene atmosphere at −78 °C in a Pyrex flask (>280 nm) using a 500-W Hg high-pressure UV lamp as the light source.

[b] Lewis acid was added 2.0 equiv (entries 7–12), 6.0 equiv (entry 13), and 3.0 equiv (entries 14–16) based on **1**.

[c] Isolated yield by column chromatography on SiO_2.

[d] Determined by ^1H NMR and HPLC (CHIRALDEX OD-H).

[e] Ref. 4a.

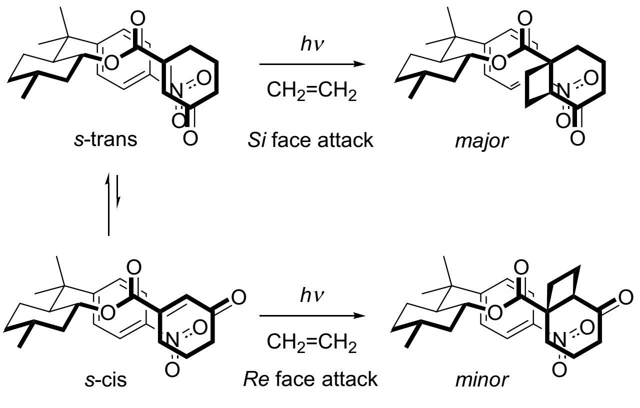
[f] MCH: methylcyclohexane.

The photoreactions were carried out by irradiating a solution of **1**, saturated with ethylene, with a Pyrex filtered light from a high-pressure mercury lamp (>280 nm) at −78 °C as reported previously (Table 1).[4a] For comparison some previous results for **1a** and **1b**, in which (−)-8-phenylmenthyl and (−)-8-(4-methoxyphenyl)menthyl groups were used, are also shown in Table 1 (entries 1–4). The [2+2] photoreaction of **1c** containing an (−)-8-(4-nitrophenyl)menthyl group in toluene at −78 °C proceeded in excellent yield with good diastereoselectivity (entry 5). The reaction was not carried out in methylcyclohexane (MCH), because of the poor solubility of the new chiral cyclohexenone **1c** to MCH. When a polar solvent, dichloromethane, was used, a higher de value (88%) was obtained compared with **1a** and **1b** (entries 1, 2, and 6). These results suggest that the (−)-8-(4-nitrophenyl)menthyl group was the most effective chiral auxiliary of the menthyl derivatives tested and **1c** involved a different solvent effect in contrast with **1b**.

Further, the reactions were carried out in the presence of a Lewis acid, to improve the selectivity of the asymmetric reactions using a phenylmenthol auxiliary.[6] When trimethyltin chloride was added to a dichloromethane solution of **1a**, the de value was increased from 40% to 48% (entry 7). However, almost no change in the de value was found by adding titanium(IV) *iso*-propoxide (entry 8). In the case of **1b**, while both the diastereoselectivity and yield were decreased in the presence of trimethyltin chloride, the de value increased slightly (84%), when titanium(IV) alkoxide was used (entries 9–12). In the reactions of **1c**, the addition of a Lewis acid resulted in an increase up to 92% de (entries 13–16). Interestingly, the use of trimethyltin chloride resulted in excellent selectivity with no decrease in yield (entry 13). These results revealed that the photoreaction of **1c** afforded a higher diastereoselectivity than of **1a** and **1b**. The effect of Lewis acids on the diastereoselectivity was not so clear in these reactions, but it may be reasonable to consider that the Lewis acid coordinates to oxygen atoms, thus stabilizing the conformation of **1** to produce the major adducts (vide infra).

The conformation of **1** was subsequently investigated, which must be related to the diastereoselectivity observed for the photoreactions. We previously reported on conformational studies of **1a** and **1b**.[4a] The distribution of conformers of **1c** was determined based on molecular mechanics calculations similar to these used for **1a** and **1b**.[7] The calculations reveal that the most stable conformation is the stacked form, in which the cyclohexenone ring and the aromatic ring are located face-to-face. There are two different possible conformers in the stacked form, that is, the *s-trans* and *s-cis* conformers between the ester carbonyl group and the double bond involved in the cyclohexane ring (Scheme 2). These results are similar to those found for **1a** and **1b**. In the addition, DFT calculations (B3LYP 6–31G*) indicate an energy difference to be about 1.60 kcal/mol in favor of *s-trans* conformer. It is reasonable to say that the major photoadduct may be produced via the *s-trans* conformer based on the shielding of the *Re* face of the enone moiety by the phenyl ring, as evidenced from the X-ray crystallography analysis of the major photoadduct.[4b] Therefore, the stability of the stacked *s-trans* conformation is crucial for achieving high diastereoselectivity.

The stacked conformation of **1** may be considered to be stabilized by the acceptor–donor interactions between the α,β-unsaturated carbonyl group and the aromatic ring.[8] **1c** contains an electron-withdrawing group (nitro group) on the aromatic ring, and, as a result, the acceptor–donor interaction would be weaker than **1b**, which contains an electron donor group (methoxy group). However, the diastereoselectivity of **1c** was higher than **1b**. To obtain additional information on the most stable conformation, a single crystal X-ray analysis of **1c** was performed (Fig. 1).[9] In the crystal state, **1c** exists in the *s-trans* stacked conformation and a computational



Scheme 2.

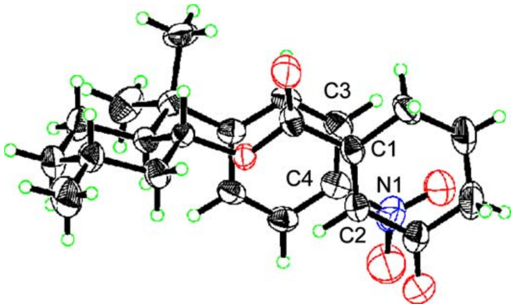


Figure 1. X-ray crystal structure of **1c**. The molecular structure is drawn with 30% thermal probability ellipsoids.

Table 2. Structural feature of **1a**–**c**

Entry	Subs.	C1–C3 (Å)	C2–C4 (Å)	Ref.
1	**1a**	4.24	3.72	4a
2	**1b**	3.71	3.68	4a
3	**1c**	3.56	3.54	This work

study supports this. In the ^{1}H NMR spectral data of **1c**, the upfield shift is observed for the alkene proton (5.92 ppm) based on the interaction of the alkene moiety with the aryl ring compared with cyclohexenone calboxylic acid methylester (6.74 ppm). X-ray crystallographic analyses of **1a** and **1b** also indicate the *s-trans* stacked conformation.[4a] These X-ray analyses show that the distance between the aromatic ring and the enone moiety of **1c** is shorter than that for **1a** and **1b** (Table 2).

This is consistent with the experiment showing that the de for **2c** is higher than those for **2a** and **2b**. The stacked *s-trans* conformation requires an additional stabilizing interaction between the aromatic ring and the enone moiety. In the case of **1b**, the electronic interactions between C═O (C, O atoms) of cyclohexenone and O–Me (O, H, atoms) of the aromatic ring may stabilize the conformation. Such interactions may be more effective in nonpolar solvents such as MCH and toluene, which explains the increased diastereoselectivity in the photoreaction of **1b** in these solvents. However, the photoreaction of **1c** did not involve such a solvent effect, suggesting a different interaction for stabilizing the conformation of **1c**. Such a stabilizing interaction on **1c** might be derived from the overlap of the molecular orbital of the nitrophenyl ring and the enone–ester moiety. Fox and co-workers reported on the intramolecular HOMO–LUMO interaction of α-carbonyl esters containing a 8-phenylmenthyl moiety.[10] A similar interaction might be effective, based on the consideration that the C1–C3 and C2–C4 distances in **1c** are short, and the nitro group and aromatic ring are located nearly on the same plane (dihedral angle between nitro group and aromatic ring = 11.91(8)°). On the basis of DFT/B3LYP 6–31G* calculations, the frontier orbitals of cyclohexenone calboxylic acid methylester and (−)-8-(4-nitrophenyl)menthol are shown in Figure 2. The HOMO orbital of the nitrophenyl ring reveals a more favorable correlation with the LUMO orbital of the *s-trans* conformation of cyclohexenone than the *s-cis* one. Therefore a HOMO–LUMO overlap may stabilize the *s-trans* stacked conformation of **1c**. In addition, the effect of a Lewis acid may involve its coordination to the carbonyl group of the enone, thus decreasing the LUMO level of the cyclohexenone moiety and enhancing the HOMO–LUMO interaction.

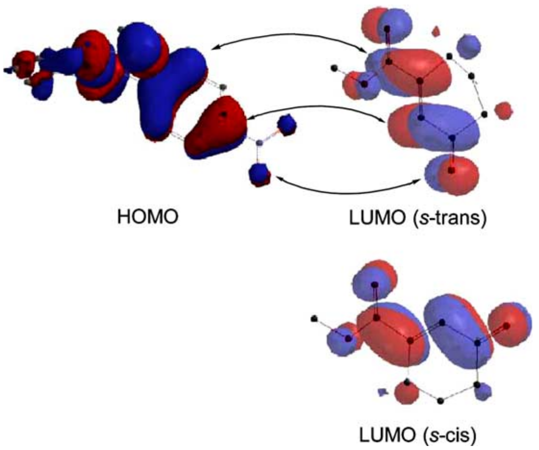


Figure 2. HOMO–LUMO interactions for (−)-8-(4-nitrophenyl)menthol and *s-trans* or *s-cis* conformer of cyclohexenone carboxylic acid ethylester. Hydrogens are omitted for clarity.

In conclusion, we report on the highly diastereoselective [2+2] photocycloaddition reaction of cyclohexenone-carboxylate having a (−)-8-(4-nitrophenyl)menthyl to ethylene and that the selectivity of the reaction is increased by adding a Lewis acid. X-ray analyses and computational modeling suggest that the origin of the diastereoselectivity can be attributed to the stability of the stacked *s-trans* conformation. Further investigations of this increase in selectivity as well as mechanistic studies are currently in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.102.

References and notes

1. (a) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453–1473; (b) Schreiber, S. L. *Science* **1985**, *227*, 857–863; (c) Crimmins, M. T.; Reinhold, T. L. In *Organic Reactions*; Paquette, L.

A., Ed.; John Wiley and Sons: New York; Vol. 44, pp 297–588; (d) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003–2020; (e) Bach, T. *Synthesis* **1998**, 683–703; (f) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485–1537; (g) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449–1483.

2. (a) Simada, Y.; Nakamura, M.; Suzuka, T.; Matsui, J.; Tatsumi, R.; Tsutsumi, K.; Morimoto, T.; Kurosawa, H.; Kakiuchi, K. *Tetrahedron Lett.* **2003**, *44*, 1401–1403; (b) Morimoto, T.; Horiguchi, T.; Yamada, K.; Tsutsumi, K.; Kurosawa, H.; Kakiuchi, K. *Synthesis* **2004**, 753–756, and references cited therein.
3. (a) Rau, H. *Chem. Rev.* **1983**, *83*, 535–547; (b) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741–770; (c) de March, P.; Figueredo, M.; Font, J.; Raya, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 2437–2447, and references cited therein.
4. (a) Tsutsumi, K.; Endo, K.; Furutani, A.; Ikki, T.; Nakano, H.; Shintani, T.; Morimoto, T.; Kakiuchi, K. *Chirality* **2003**, *15*, 504–509; (b) Tsutsumi, K.; Nakano, H.; Furutani, A.; Endou, K.; Merpuge, A.; Shintani, T.; Morimoto, T.; Kakiuchi, K. *J. Org. Chem.* **2004**, *69*, 785–789.
5. (−)-8-(4-Nitrophenyl)menthol was prepared according to the literature procedure; see: Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, M. *J. Org. Chem.* **1998**, *63*, 8397–8409.
6. Lange, G. L.; Decicco, C.; Lee, M. *Tetrahedron Lett.* **1987**, *28*, 2833–2836.
7. The calculations were performed using the SPARTAN02 software molecular modeling package for Windows available from Wavefunction, Irvine, CA.
8. (a) Maddaluno, J. F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.* **1994**, *59*, 793–802, and references cited therein; (b) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475–497.
9. Measurements were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with Mo K_α radiation at 296 K. $C_{23}H_{29}O_5N$, coloress crystal ($0.40 \times 0.17 \times 0.10$ mm), orthorhombic, space group $P2_12_12_1$ (#19), $Z = 4$, $a = 6.5573(3)$ Å, $b = 15.6471(7)$ Å, $c = 21.3024(9)$ Å, $V = 2185.7(2)$ Å^3, $\rho_{\mathrm{calcd}} = 1.214\,\mathrm{g\,cm^{-3}}$. Of 19286 reflections up to $2\theta = 54.9°$, 2810 were independent ($R_{\mathrm{int}} = 0.028$) and 2810 with $I > -10\sigma(I)$. The structure was solved with direct methods and refined with full matrix against all F^2 data. Hydrogen atoms were calculated in 'riding' positions. $wR = 0.082$ and $R = 0.074$.
10. Whitesell, J. K.; Younathan, J. N.; Hurst, J. R.; Fox, M. A. *J. Org. Chem.* **1985**, *50*, 5499–5503.