

Enantioselective Intermolecular [2+2] Photocycloaddition Reaction of Cyclic Enones and Its Application in a Synthesis of (–)-Grandisol

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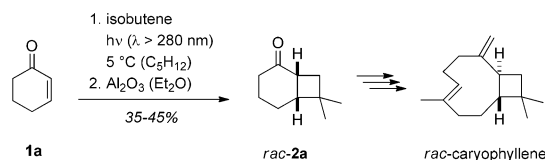
S Supporting Information

ABSTRACT: The intermolecular [2+2] photocycloaddition of typical cyclic α,β -unsaturated enones, such as 2-cyclohexenone, with olefins was performed in moderate to good yields (42–82%) and with high enantioselectivity (82%–96% *ee*). An unusual substitution pattern at the chiral oxazaborolidine- AlBr_3 Lewis acid complex that promotes the reaction was found to be crucial for the success of the reaction. The method was applied to the enantioselective synthesis of the monoterpene (–)-grandisol, which could be accomplished in six steps and with an overall yield of 13% starting from 3-methyl-2-cyclohexenone.

Although the intramolecular [2+2] photocycloaddition reaction of cyclic enones had been discovered as early as 1908,¹ it was not before the 1960s that the first intermolecular variants of this reaction were reported.² Over the last 40 years, the reaction has been employed as a key step in literally hundreds of natural product syntheses³ and it represents one of the most powerful transformations of organic chemistry.⁴ Typically, the reaction is induced by direct excitation of an enone, such as 2-cyclohexenone (**1a**), the triplet state (T_1) of which is populated by rapid intersystem crossing (ISC) from the first excited singlet state (S_1). The former state is long-lived and can be captured by a photochemically inactive alkene to generate a cyclobutane. A representative reaction is the addition of isobutene, which was employed in Corey's landmark synthesis of racemic caryophyllene (Scheme 1).⁵

Although the olefin is commonly used in excess, the reaction is not perfectly chemo- and regioselective and an extensive purification is required to obtain product *rac*-**2a** in yields of 35–45%. The treatment with basic alumina facilitates the epimerization of the stereogenic center in α -position to the ketone carbonyl group but does not remove any undesired

Scheme 1. Corey's Landmark Synthesis of Racemic Caryophyllene with an Intermolecular [2+2] Photocycloaddition Reaction of 2-Cyclohexenone (1a) as the Key Step



constitutional isomers. Most severely, there is up to this date no way to access the cyclobutane products of a typical intermolecular enone [2+2] photocycloaddition reaction in an enantioselective fashion.^{6,7} Indirect methods that rely on diastereoselective reactions require a major synthetic effort involving multistep sequences.⁸ Recently developed protocols for enantioselective intermolecular [2+2] photocycloaddition reactions⁹ are not applicable to unfunctionalized cyclic enones, such as 2-cyclohexenone (**1a**). We have now found a way to prepare cyclobutanes such as **2a** from enones with high enantioselectivity and our results are disclosed in this communication.

In preliminary work, we studied the UV/vis properties of 2-cyclohexenone (**1a**) upon treatment with Lewis acids (Figure 1). In line with previous observations,^{10,11} the strong $\pi\pi^*$

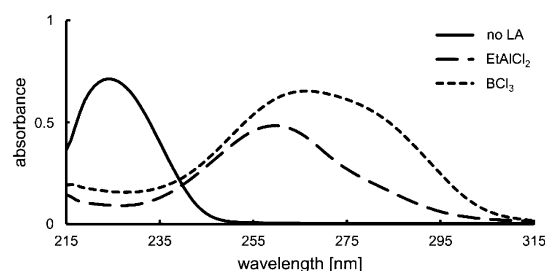


Figure 1. UV/vis spectra of 2-cyclohexenone (**1a**) in the absence (—) and in the presence of 20 equiv of either EtAlCl_2 (---) or BCl_3 (···) ($c = 0.5 \text{ mM}$ in CH_2Cl_2).

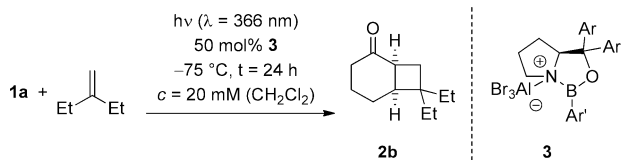
absorption of the parent compound at $\lambda = 224 \text{ nm}$ ($\epsilon = 13\,400 \text{ M}^{-1} \text{ cm}^{-1}$) was shifted bathochromically and was recorded at $\lambda = 260 \text{ nm}$ ($\epsilon = 9670 \text{ M}^{-1} \text{ cm}^{-1}$) with EtAlCl_2 and at $\lambda = 266 \text{ nm}$ ($\epsilon = 13\,080 \text{ M}^{-1} \text{ cm}^{-1}$) with the stronger Lewis acid BCl_3 . In both cases, there is still a detectable absorption of the complex at $\lambda = 330 \text{ nm}$ where the weak ($\epsilon = 70 \text{ M}^{-1} \text{ cm}^{-1}$) $n\pi^*$ absorption of uncomplexed 2-cyclohexenone is located. Because it was expected that the AlBr_3 -based oxazaborolidine Lewis acids¹² would exert an even stronger bathochromic shift than BCl_3 , it seemed possible to selectively excite the complex of cyclohexenone with a chiral Lewis acid but not the uncomplexed substrate. In this scenario, enantioselective intermolecular [2+2] photocycloaddition to an alkene should be possible as previously found for intramolecular reactions.^{10,13} However,

Received: January 26, 2018

Published: February 19, 2018

several questions remained open, e.g., whether the lifetime of the complex would be sufficiently long to allow for enantioface differentiation before dissociation and whether previously used Lewis acids would provide a reasonable enantioselectivity. It was also unclear whether the photoexcited cyclohexenone would lead to a destruction of the Lewis acid and whether the known side reactions of intermolecular [2+2] photocycloaddition reactions would be enhanced. Initial results with the previously used^{13b} Lewis acid **3a** seemed to confirm the worst concerns (Table 1, entry 1). The enantioselectivity in the reaction of **1a**

Table 1. Enantioselective Intermolecular [2+2] Photocycloaddition of 2-Cyclohexenone (1a**) and 2-Methyl-1-butene Mediated by Chiral Lewis Acids **3****



entry	Ar	Ar'	cat.	yield ^a (%)	ee ^b (%)
1			3a	27	18
2			3b	29	30
3			3c	56	88
4			3d	73	90
5			3e	65	66

^aThe crude product was purified by chromatography on silica gel (eluent: pentane/Et₂O = 4/1). The material was dissolved in CH₂Cl₂ and successively treated with basic alumina and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate. Filtration through a short pad of silica and solvent removal delivered pure compound **2b**. ^bThe enantiomeric excess was determined by chiral GLC analysis.

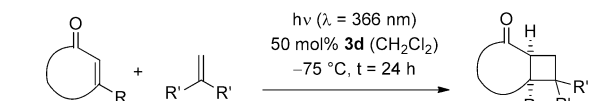
with 2-ethylbut-1-ene under typical conditions was disappointingly low and the Lewis acid seemed unstable under the reaction conditions. Variation of Ar' showed that the insufficient performance was not associated with this substituent but rather with the aryl group Ar (entry 2). Gratifyingly, an extensive screening of oxazaborolidines¹⁴ with different substituents Ar delivered Lewis acids with which the selectivity issues could be smoothly overcome. The superior substituent was a 2,3-dimethylphenyl group that was incorporated for example in Lewis acids **3c–3e**.

The 2,3,4-trifluorophenyl derivative **3c** gave already a much improved yield and enantioselectivity (entry 3) compared to **3b**. The performance was further improved when employing a 2,4,6-trifluorophenyl group as Ar' (entry 4). The last entry of the table (entry 5) illustrates that also the aryl group Ar' has a subtle influence on the enantioselectivity but not on the regio- and chemoselectivity. Indeed, apart from the high enantioselectivity,

it is notable that the yield of the [2+2] photocycloaddition significantly increased compared to the racemic reaction (see Supporting Information), which delivered a yield of only 51% for product *rac*-**2b**.

Lewis acid **3d** evolved from the optimization studies as the optimal choice to promote an enantioselective intermolecular [2+2] photocycloaddition of cyclic enones **1**. The Lewis acid was prepared in situ by addition of AlBr₃ to the respective oxazaborolidine and it was applied to a variety of enone/olefin combinations (Table 2). The reason for the high catalyst loading of 50 mol % is the racemic background reaction that can only be suppressed if the catalyst concentration is high.^{10b}

Table 2. Enantioselective Intermolecular [2+2] Photocycloaddition of Cyclic Enones (1**) and Various Terminal Olefins to Bicyclic Products **2**^a**



2a (91% ee) 60% ^b	2b (90% ee) 73% ^b	2c (87% ee) 50% ^b	2d (85% ee) 42% ^b
2e (82% ee) 59% ^b	2f (83% ee) 68%	2g (92% ee) 69% ^b	2h (90% ee) 46%
2i (82% ee) 78%	2j (93% ee) 72% ^b	2k (96% ee) 65% ^b	2l (86% ee) 71%
2m (87% ee) 69%	2n (87% ee) 81%	2o (93% ee) 60% ^c	2p (85% ee) 82% ^c

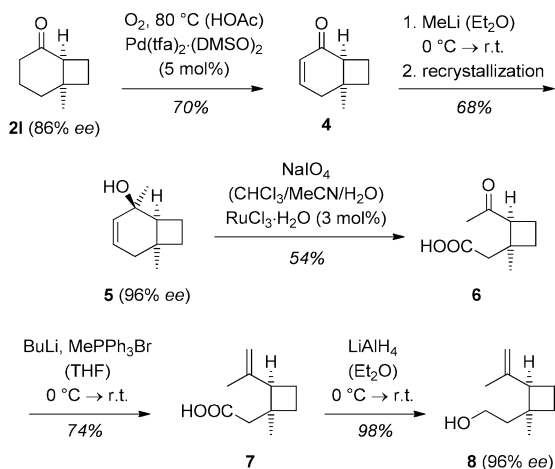
^aReactions were performed at a concentration of *c* = 20 mM in CH₂Cl₂ solution. Workup included treatment with basic alumina in CH₂Cl₂ (see Table 1). ^bThe purified material was treated with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate to remove olefinic impurities. ^cThe reaction remained incomplete and the yield is based on enone conversion.

The Lewis acid catalyzed process enabled an enantioselective access to cyclobutane **2a**, which was obtained in higher yield than racemic compound *rac*-**2a** (Scheme 1). It is known that the levorotatory enantiomer ($[\alpha]_D^{23} = -152.8$ at *c* = 1.4 in CHCl₃) *ent*-**2a** exhibits the (1*R*,6*R*)-configuration at the two stereogenic centers of the bicyclo[4.2.0]octane skeleton.¹⁵ Product **2a** was dextrorotatory ($[\alpha]_D^{25} = +162.6$ at *c* = 1.4 in CH₂Cl₂) proving unambiguously its absolute configuration as (1*S*,6*S*). The absolute configuration of the other products **2** was assigned in

analogy and matches our model for the enantioface differentiation (vide infra). Product yields were moderate to good (42–82%) and the enantioselectivity was consistently high (82%–96% *ee*). Olefinic substrates were restricted to ethylene (products **2h**, **2i**, **2l**, **2m**, **2o**, **2p**) and to symmetric 1,1-disubstituted olefins in order to avoid the formation of *cis/trans*-diastereoisomers.¹⁶ Oxygen and chlorine substituents were tolerated (products **2e**, **2f**, **2g**, **2n**) and several cyclobutanes were prepared that had previously been employed in racemic form as starting material for natural product total syntheses.^{5,17} Enone substitution was varied at the β -position (products **2l**, **2m**, **2n**, **2p**) and within the six-membered ring of 2-cyclohexenone (products **2i**, **2j**, **2k**, **2m**, **2n**). Five-membered substrates reacted with high enantioselectivity (products **2h**, **2o**) but the reaction was slower than the reaction of the respective 2-cyclohexenones.

In order to showcase the synthetic utility of the enantioselective intermolecular [2+2] photocycloaddition reaction we performed a total synthesis of (–)-grandisol (Scheme 2). Grandisol is a component of the aggregation pheromone of

Scheme 2. Enantioselective Total Synthesis of (–)-Grandisol (8)



the cotton boll weevil (*Anthonomus grandis*) and has received a lot of attention by the synthetic community.¹⁸ Although many syntheses exist and some of them provided enantiomerically enriched product,¹⁹ there is no synthesis that features an enantioselective [2+2] photocycloaddition as the key step. Our synthesis follows a known bond set^{19f} and commenced with photocycloaddition product **2l**. The introduction of the olefinic double bond was accomplished by the catalytic Saegusa oxidation protocol reported by Stahl and co-workers.²⁰ Addition of methyl lithium to enone **4** produced tertiary alcohol **5** the enantiopurity of which could be nicely increased by recrystallization. Oxidative cleavage of the double bond and further oxidation to keto acid **6** was performed with sodium periodate and RuCl₃ as the catalyst. Olefination to product **7** and the reduction of the acid to the alcohol proceeded uneventfully and delivered (–)-grandisol in 96% *ee*. Starting from 3-methyl-2-cyclohexenone, the synthesis proceeded in only six steps with an overall yield of 13% and thus represents a concise route to the enantiopure natural product.

Mechanistic considerations concerning the enantioselective intermolecular [2+2] photocycloaddition, which go beyond previously established facts,¹⁰ must account for the improved

performance of Lewis acid **3d** compared to **3a**. So far, only intramolecular Lewis acid-catalyzed [2+2] photocycloaddition reactions had been studied with substrates (dihydropyridones, β -alkoxyenones) that bear a tethered olefin in β - or γ -position. Assuming a reaction on the triplet hypersurface,²¹ the first bond formation step in these cases occurs rapidly in the β -position. Intermolecular trapping of photoexcited enones, such as 2-cyclohexenone (**1a**), in a Lewis acid complex is likely slower and it occurs with high preference in α -position (vide infra). The former fact, possibly in combination with the reactive T₁ state of **1a**, could be responsible for hydrogen abstraction²² in complex **1a**–**3a** thus leading to a decomposition of the catalyst. In complex **1a**–**3d**, the methyl groups are oriented differently (e.g., as shown in Figure 2) and not only escape hydrogen abstraction

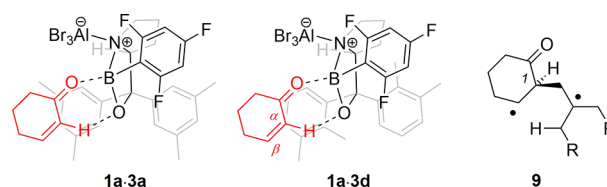


Figure 2. Suggested structure of 1:1 enone/Lewis acid complexes **1a**–**3a** and **1a**–**3d** and of putative 1,4-diradical intermediate **9**.

but also lead to an improved enantioface differentiation in α -position. Bond formation occurs from the *Si* face and establishes the first stereogenic center at the future carbon atom C₁ of the bicyclo[4.2.0]octane skeleton. Circumstantial evidence for the intermediacy of 1,4-diradicals such as **9** stems from the observation that olefinic products are formed as minor impurities in the reactions with 1,1-disubstituted alkenes. They arise likely from hydrogen abstraction, which is a side reaction competing with C–C bond formation. Synthetically, the occurrence of the byproducts is a minor issue as they can be removed by treating the crude reaction mixture with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate²³ (see Tables 1 and 2).

The improved regioselectivity of the Lewis acid-catalyzed intermolecular [2+2] photocycloaddition is associated with the above-mentioned preference of α -attack, which in turn is evidenced by the exclusive formation of head-to-tail photocycloaddition products. No head-to-head products were identified in the crude product mixture while they are formed in notable amounts in the course of racemic [2+2] photocycloaddition reactions. It appears as if the Lewis acid increases the polarity of the excited state which is opposite to the ground state polarity.⁴ In the ground state the β -position of an enone is electrophilic, whereas in the excited state the α -position is electrophilic. In a simplistic picture this polarity reversal is due to the $\pi\pi^*$ character of the triplet state with the half-filled π orbital lacking electron density in α -position.

In summary, the substitution pattern of the oxazaborolidine was found to have a strong influence on the outcome of the enantioselective intermolecular [2+2] photocycloaddition of enones which was mediated by an oxazaborolidine–AlBr₃ complex. Catalyst **3d** evolved as the catalyst of choice enabling high enantioface differentiation (82%–96% *ee*) and good chemoselectivity. Studies are ongoing to reveal its mode of action and to detect potential reaction intermediates.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01011.

Experimental procedures, analytical data and NMR spectra for all new compounds, GLC traces of products (PDF)

NMR spectra for all new compounds (ZIP)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement no. 665951 – ELICOS) is gratefully acknowledged. We thank O. Ackermann and J. Kudermann for their help with the HPLC and GLC analyses.

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