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Authors: Simone Stegbauer, Christian Jandl, and Thorsten Bach

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Enantioselective Lewis Acid Catalyzed *ortho* Photocycloaddition of Olefins to Phenanthrene-9-carboxaldehydes**

Simone Stegbauer, Christian Jandl, and Thorsten Bach*

Dedicated to all past and present members of the TUM family

Abstract. Visible light irradiation ($\lambda = 457$ nm) enabled the enantioselective ortho photocycloaddition of olefins to phenanthrene-9-carboxaldehydes (15 examples, 46-93% yield, 82-98% ee). A chiral oxazaborolidine Lewis acid (20 mol%) was employed as the catalyst. It operates by coordination to the aldehyde inducing a bathochromic absorption shift beyond the $n\pi^*$ absorption of the uncomplexed aldehyde. At long wavelength the Lewis acid complex is exclusively excited and within the complex one enantiotopic face of the aromatic aldehyde is efficiently shielded. Lewis acid coordination also alters the type selectivity and the simple diastereoselectivity of the photocycloaddition.

In recent years there has been a constantly increasing interest in the enantioselective catalysis of photochemical reactions. Several approaches have been reported to face the challenge of selectivity control in the excited state.^[1] Among others, it has been shown that acids can be employed to activate an α , β -unsaturated carbonyl compound by coordination to the carbonyl group and by altering its absorption properties.^[2] Important contributions include the use of chiral Brønsted acids,^[3] the use of a chiral Sc-based Lewis acid in combination with a triplet sensitizer,^[4,5] and the use of chelating Rh-based Lewis acids.^[6] Chiral AlBr₃-activated oxazaborolidines^[7] have been introduced by our group to promote enantioselective photocatalysis and have been established as very successful catalysts.^[8] They operate on α , β -unsaturated carbonyl compounds by lowering the energy of the allowed ($\epsilon \ge 10000 \text{ M}^{-1} \text{ cm}^{-1}$) $\pi\pi^*$ transition and therefore shift this UV/Vis absorption band, which typically occurs around 250-290 nm, by ca. 40-50 nm to longer wavelength (bathochromic shift $\Delta\lambda$). Since α,β -unsaturated carbonyl compounds exhibit a weak ($\varepsilon \le 100 \text{ M}^{-1} \text{ cm}^{-1}$) n π^* transition which occurs also bathochromic relative to the $\pi\pi^*$ transition, there is in solution a competition between an excitation of the respective Lewis acid complex and the uncomplexed substrate. As a consequence undesired racemic background reactions occur and the catalyst loading for an effective enantioselective photochemical reaction catalyzed by a chiral oxazaborolidine has been high (50 mol%) so far.^[8] A possible improvement would be expected if it was possible to shift the above-mentioned $\pi\pi^*$ transition bathochromically beyond the $n\pi^*$ transition of the respective substrate. Since an identical energy difference ΔE corresponds to a higher difference of $\Delta\lambda$ at longer wavelength, we

 [*] M. Sc. S. Stegbauer, Dr. C. Jandl, Prof. Dr. T. Bach Department Chemie and Catalysis Research Center (CRC) Technische Universität München Lichtenbergstr. 4, D-85747 Garching Fax: +49 (0)89 289 13315
 E-mail: thorsten.bach@ch.tum.de
 Homepage: http://www.oc1.ch.tum.de/home_en/

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reasoned that chromophores with a $\pi\pi^*$ absorption at long wavelength might allow for a selective excitation of the Lewis acid complex without interference of a racemic non-catalytic reaction. We have now shown that phenanthrene-9-carboxaldehydes fulfill the above-mentioned requirements and we report in this communication on their enantioselective catalytic photocyclo-addition to olefins.



Figure 1. UV/Vis spectrum of compound **1a** (c = 0.25 mM in CH₂Cl₂) in the presence of variable equivalents (eq.) of EtAlCl₂.

The UV/Vis spectrum of aldehyde^[9] 1a (Figure 1) revealed an absorption at 316 nm ($\varepsilon = 13780 \text{ M}^{-1} \text{ cm}^{-1}$) which is assigned to a $\pi\pi^*$ transition (¹L_b band).^[10] The shoulder at 361 nm ($\varepsilon = 1940 \text{ M}^{-1}$ $\rm cm^{-1})$ has been previously assigned to the phenanthrene $^1L_a \ band^{[10]}$ but it seems to partially overlap with the $n\pi^*$ band of the aldehyde carbonyl group. Indeed, photochemical reactions of 1a were observed (vide infra) up to an excitation wavelength of 419 nm. Upon successive addition of the Lewis acid EtAlCl₂, a strong absorption became visible with a maximum at $\lambda = 387$ nm. The absorption reached saturation upon addition of 15 equivalents of $EtAlCl_2$ indicating complete complexation of **1a**. The extinction coefficient was determined as ϵ = 16180 $M^{-1}\ cm^{-1}$ which supports an assignment of this band to a $\pi\pi^*$ transition. The band tails into the long-wavelength region of the spectrum and there is a significant absorption beyond $\lambda = 420$ nm. Photochemical experiments with achiral Lewis acids suggested a catalytic photocycloaddition reaction to be possible at $\lambda \ge 420$ nm. Experiments with chiral Lewis acids commenced with the previously reported^[8a-c] catalyst **3a**. Addition of 2,3-dimethyl-2butene to substrate 1a occurred at -78 °C in CH₂Cl₂ (Table 1) exclusively at the C9/C10 double bond and resulted in product 2a which is formally the product of an ortho photocycloaddition.^[11,12] The highest enantioselectivity was achieved at $\lambda = 457$ nm (entries 1-3) and the Lewis acid was subsequently optimized by varying the aryl substituent (Ar) at the boron atom (for the optimization studies, see the Supporting Information). Another known^[13] Lewis acid **3b** with a single substituent in ortho position of the phenyl ring gave a significant increase in ee (entry 4). Eventually, the 2,6dimethylphenyl derivative 3c turned out to be the ideal Lewis acid (entry 5) and it fulfilled our expectations with regard to catalytic turnover (entries 6, 7). A loading of 10 mol% was sufficient to provide a high yield (81%) and a high enantioselectivity (94% *ee*).

Table 1: Photocycloaddition Reaction of Phenanthrene-9-carboxaldehyde (1a) and 2,3-Dimethyl-2-butene in the Presence of Chiral Lewis acids 3



^[a] The reaction was performed at -78 °C with a substrate concentration of *c* = 20 mM in CH₂Cl₂ at the indicated wavelength (λ) and for the indicated period of time (*t*). The olefin was used in excess (30 eq.). ^[b] **3a**: Ar = 2,4,6-trifluorophenyl; **3b**: Ar = 2-(trifluoromethyl)phenyl; **3c**: Ar = 2,6-dimethylphenyl. ^[c] Yield of isolated product. ^[d] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis.

The substrate scope of the photocycloaddition was explored with some functionalized phenanthrene-9-carboxaldehydes 1. Their synthesis was best achieved by linkage of the two arene rings via a Suzuki cross-coupling and by subsequent introduction of the C9/C10 bond in an aldol condensation (see Supporting Information). In order to keep the reaction times low and in order to allow for complete conversion of all substrates a catalyst loading of 20 mol% was consistently applied (Table 2). Under these conditions the respective products were obtained in yields of 66-93% and with enantioselectivities of 82-96% ee. From the preliminary data set, it appears as if substitution at C3 and C6 is beneficial for the enantioselectivity while substituents at positions C2 and C5 (entries 2, 3, 6) lead to a slightly reduced enantioselectivity. Fluoro, chloro, methyl, and trifluoromethyl substitution was tolerated but the study on the functional group tolerance was limited by the availability of the starting materials. In general, compounds with Lewis basic sites (alkoxy, carbonyl) are not recommended due to competitive binding to the Lewis acid.

The absolute configuration of the cyclobutane products was proven by anomalous X-ray diffraction (Figure 2). Chloro derivative **2c** gave suitable crystals and the configuration at the two newly formed stereogenic centers could be unambiguously assigned. Irrespective of the mechanism of the photocycloaddition, the attack of the olefin at carbon atom C10 occurred from the *Si* face. It has been previously suggested^[7,14] that aldehydes bind to cationic oxazaborolidine Lewis acids by coordination of the carbonyl group to the boron atom and by a second non-classical hydrogen bond^[15] of the hydrogen atom to the oxazaborolidine oxygen atom.

Table 2: Lewis acid Catalyzed, Enantioselective Photocycloaddition Reactions of Phenanthrene-9-carboxaldehydes (1) and 2,3-Dimethyl-2-butene



entry ^[a]	substrate	Х	Y	product	yield ^[b] [%]	ee ^[c] [%]
1	1a	Н	Н	2a	79	94
2	1b	2-Me	Н	2b	75	84
3	1c	2-C1	Н	2c	89	88
4	1d	3-F	Н	2d	78	93
5	1e	3-Me	Н	2e	66	92
6	1f	Н	5-Me	2f	85	86
7	1g	Н	6-CF ₃	2g	92	92
8	1h	Н	6-F	2h	79	82
9	1i	2-Me	6-CF ₃	2i	89	90
10	1j	3-Me	6-CF ₃	2ј	93	92
11	1k	3-F	6-CF ₃	2k	85	96

^[a] The reaction was performed at -78 °C with a substrate concentration of *c* = 20 mM in CH₂Cl₂ at the indicated wavelength (λ) and for the indicated period of time (*t*). The olefin was used in excess (30 eq.). ^[b] Yield of isolated product. ^[c] The *ee* was determined by chiral HPLC analysis.

For substrate 1c, the respective complex $1c \cdot 3c$ is depicted in Figure 2 and the enantioface differentiation can be explained by an attack of the olefin from the face that is not shielded by the 3,5dimethylphenyl ring (in gray) of the oxazaborolidine and that is relative to carbon atom C10 on the *Si* face. Despite the fact that complex $1c \cdot 3c$ provides a rationale for the stereochemical outcome of the reaction, it cannot explain at this point the subtle differences which are caused by the choice of aryl (Ar) groups at the boron atom and by the substitution pattern at the phenanthrene substrate.



Figure 2. Absolute configuration of product **2c** as determined by anomalous X-ray diffraction and model for the association of Lewis acid **3c** to phenanthrene-9-carboxaldehyde **1c**.

In a second set of preliminary experiments, we studied the reaction of two phenanthrene-9-carboxaldehydes **1a** and **1d** with cyclopentene (Scheme 1). This olefin represents a frequently used cyclic reaction partner in [2+2] photocycloaddition chemistry^[16] and offers a first indication for the generality of the reaction. To our delight, the enantioselectivity of the Lewis acid catalyzed process remained very high. Apart from the major diastereoisomers

4a and **5a** in which the carbocyclic rings are positioned on opposite sides of the cyclobutane core (*exo*) the minor *endo* products were also detected (d.r. = diastereomeric ratio).



Scheme 1. Lewis acid catalyzed, enantioselective photocycloaddition reactions of phenanthrene-9-carboxaldehydes 1a and 1d to cyclopentene.

Similarly, cyclohexene produced the respective *exo* product **6a** as the major diastereoisomer which was formed in 90% *ee* from aldehyde **1a** (Scheme 2). Apart from the *endo* diastereoisomer, minimal amounts of a third diastereoisomer were found (*vide infra*). The reaction of aldehyde **1a** with isopropylidenecyclohexane gave mainly a single regioisomer **7** (r.r. = regioisomeric ratio) which was obtained in 84% *ee*.



Scheme 2. Lewis acid catalyzed, enantioselective photocycloaddition of phenanthrene-9-carboxaldehyde (**1a**) with cyclohexene and isopropylidenecyclohexane to products **6a** and **7**.

As previously noted for [2+2] photocycloaddition reactions,^[8d] the chiral Lewis acid governs not only the enantioselectivity but also has a significant impact on other selectivity parameters. In the current study it was found that the formation of other constitutional isomers was completely suppressed in the presence of the Lewis acid. Irradiation of aldehyde **1a** and 2,3-dimethyl-2-butene at $\lambda = 366$ nm, 398 nm, and 405 nm led consistently to the formation of oxetane *rac*-**8** (Figure 3) in a ratio of ca. 1/5 relative to *rac*-**2a**. At lower wavelength ($\lambda = 254$ nm, 350 nm, and 366 nm) decarbonylation reactions were observed. No Paternò-Büchi reaction^[17] products nor any other side products from carbonyl photochemistry were observed in the presence of the chiral Lewis acid.

Even more remarkable was the simple diastereoselectivity of the reaction which was almost completely inverted as compared to the racemic reaction. Direct excitation of **1a** and **1d** in the presence of cyclopentene at $\lambda = 366$ nm produced predominantly the *endo* diastereoisomers *rac*-**4b** (28%, d.r. = *rac*-**4a**/*rac*-**4b** = 12/88) and *rac*-**5b** (40%, d.r. = 9/91). In the case of cyclohexene, direct irradiation at $\lambda = 366$ nm led in 31% yield to the *endo* diastereoisomer *rac*-**6b** and the *trans*-configured product *rac*-**6c** in almost identical amounts. A small fraction of the *exo* isomer *rac*-**6a**/*rac*-**6b**/*rac*-**6c**) was 21/35/44.



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Figure 3. Structure of photocycloaddition products rac-8, rac-4b, rac-5b, rac-6b, and rac-6c.

Previous work on the ortho photocycloaddition of methyl phenanthrene-9-carboxylate had produced evidence that its reaction $(\lambda = 350 \text{ nm})$ with 2,3-dimethyl-2-butene proceeds via a triplet intermediate.^[18] Contrary to our results, it was found that any attempted photocycloaddition in the presence of a Lewis acid was sluggish but it was postulated that the Lewis acid mediated process occurred via a singlet-state mechanism. Indeed, a change of mechanism could explain the reversal of simple diastereoselectivity in the reaction of phenanthrene-9-carboxaldehydes with cyclopentene and cyclohexene. Preliminary fluorescence studies on the complex of **1a** with EtAlCl₂ revealed a strong fluorescence at an emission wavelength of λ_{em} = 498 nm (excitation wavelength λ_{exc} = 400 nm) which was quenched upon addition of 2,3-dimethyl-2butene. Since fluorescence quenching by energy transfer to an olefin is thermodynamically not feasible,^[19] it is likely that the excited singlet state of complex 1a AlEtCl₂ reacts with the olefin.

In conclusion, it was found that phenanthrene-9-carboxaldehydes undergo an extensive bathochromic shift upon coordination to a Lewis acid. The strong band ($\lambda_{max} = 387 \text{ nm}, \epsilon = 16180 \text{ M}^{-1} \text{ cm}^{-1}$) which is induced upon Lewis acid coordination stretches beyond all absorption bands of uncomplexed phenanthrene-9-carboxaldehydes and thus enables a selective excitation of the Lewis acid complex at long wavelength. In the presence of catalytic amounts of chiral oxazaborolidine Lewis acid 3c, an enantioselective ortho photocycloaddition was possible and a model for the complexation is suggested based on literature precedence. The result shows for the first time that the aldehyde binding motif is suitable to achieve high enantioface differentiation in photochemical reactions. Mechanistically, there is circumstantial evidence that the catalytic reaction proceeds via an excited singlet state and that this fact influences the selectivity pattern of the photocycloaddition. Further work is required to explore the subtle influence of the substituents at the oxazaborolidine and to understand the change of the selectivity pattern by the Lewis acid.

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Entry of the Table of Contents

Photochemistry

S. Stegbauer, C. Jandl, T. Bach* _____ Page – Page

Enantioselective Lewis Acid-Catalyzed *ortho* Photocycloaddition of Olefins to Phenanthrene-9-carboxaldehydes



Chromophore activation at its best: Lewis acid catalysis enables an enantioselective photocycloaddition of olefins to the C9/C10 double bond of phenanthrene-9-carboxaldehydes in which up to four stereogenic centers are created. The chromophore is significantly modified by Lewis acid coordination.