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

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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 wavelengths the Lewis acid complex is exclusively excited; 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 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 ($\varepsilon \geq 10\,000$ L mol^{-1} cm^{-1}) π–π* transition and therefore shift this UV/Vis absorption band, which typically occurs around 250–290 nm, by about 40–50 nm to longer wavelength (bathochromic shift $\Delta\lambda$). Since α,β-unsaturated carbonyl compounds exhibit a weak ($\varepsilon \leq 100$ L mol^{-1} cm^{-1}) n–π* transition which occurs also bathochromically relative to the π–π* 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 π–π* transition bathochromically beyond the n–π* transition of the respective substrate. Since an identical energy difference ΔE corresponds to a higher difference of $\Delta\lambda$ at longer wavelength, we reasoned that chromophores with a π–π* 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 herein on their enantioselective catalytic photocycloaddition to olefins.

The UV/Vis spectrum of aldehyde[9] **1a** (Figure 1) revealed an absorption at 316 nm ($\varepsilon = 13\,780$ L mol^{-1} cm^{-1}), which is assigned to a π–π* transition (¹L$_b$ band).[10] The shoulder at 361 nm ($\varepsilon = 1940$ L mol^{-1} cm^{-1}) has been previously assigned to the phenanthrene ¹L$_a$ band,[10] but it seems to partially overlap with the n–π* band of the aldehyde carbonyl group. Indeed, photochemical reactions of **1a** were observed (see below) 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 equiv of EtAlCl₂ indicating complete complexation of **1a**. The extinction coefficient was determined as $\varepsilon = 16\,180$ L mol^{-1} cm^{-1}, which supports an assignment of this band to a π–π* transition. The band tails into the long-

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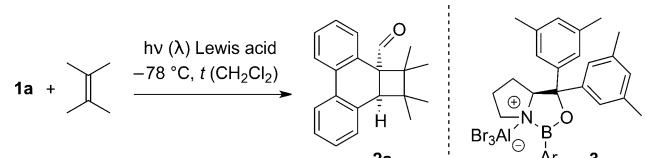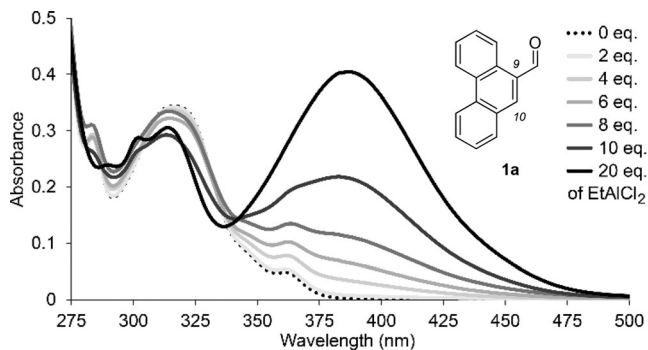   Homepage: http://www.oc1.ch.tum.de/home_en/

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

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 may be possible at $\lambda \geq 420$ nm. Experiments with chiral Lewis acids commenced with the previously reported[8a–c] catalyst **3a**. Addition of 2,3-dimethyl-2-butene to substrate **1a** occurred at −78 °C in CH$_2$Cl$_2$ (Table 1)

Table 1: Photocycloaddition reaction of phenanthrene-9-carboxaldehyde (**1a**) and 2,3-dimethyl-2-butene in the presence of chiral Lewis acids **3**.
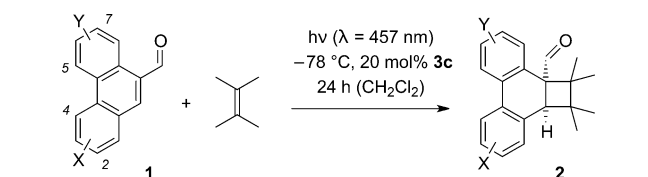

Entry[a]	λ[a] [nm]	Lewis acid[b]	Loading [mol%]	t[a] [h]	Yield[c] [%]	ee[d] [%]
1	424	**3a**	50	14	53	56
2	435	**3a**	50	9	43	70
3	457	**3a**	50	11	49	79
4	457	**3b**	50	11	54	84
5	457	**3c**	50	11	62	97
6	457	**3c**	25	19	79	94
7	457	**3c**	10	26	81	94

[a] The reaction was performed at −78 °C with a substrate concentration of $c = 20$ mM in CH$_2$Cl$_2$ at the indicated wavelength (λ) and for the indicated period of time (t). The olefin was used in excess (30 equiv). [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-phase HPLC analysis.

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 on the phenyl ring gave a significant increase in *ee* (entry 4). Eventually, the 2,6-dimethylphenyl 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*).

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 the Supporting Information). To keep the reaction times low and 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

Table 2: Lewis acid catalyzed, enantioselective photocycloaddition reactions of phenanthrene-9-carboxaldehydes (**1**) and 2,3-dimethyl-2-butene.


Entry[a]	Substrate	X	Y	Product	Yield[b] [%]	ee[c] [%]
1	**1a**	H	H	**2a**	79	94
2	**1b**	2-Me	H	**2b**	75	84
3	**1c**	2-Cl	H	**2c**	89	88
4	**1d**	3-F	H	**2d**	78	93
5	**1e**	3-Me	H	**2e**	66	92
6	**1f**	H	5-Me	**2f**	85	86
7	**1g**	H	6-CF$_3$	**2g**	92	92
8	**1h**	H	6-F	**2h**	79	82
9	**1i**	2-Me	6-CF$_3$	**2i**	89	90
10	**1j**	3-Me	6-CF$_3$	**2j**	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 CH$_2$Cl$_2$ at the indicated wavelength (λ) and for the indicated period of time (t). The olefin was used in excess (30 equiv). [b] Yield of isolated product. [c] The *ee* was determined by chiral-phase HPLC analysis.

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 owing 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
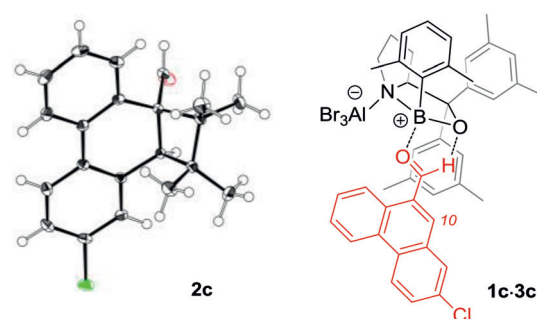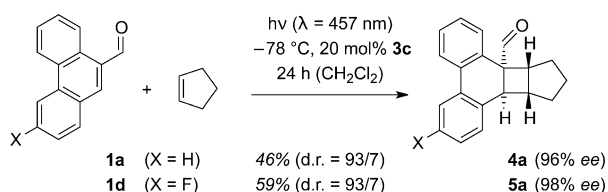

Figure 2. Absolute configuration of product **2c** as determined by anomalous X-ray diffraction and model for the association of Lewis acid **3c** to phenanthrene-9-carboxaldehyde **1c**.

by a second non-classical hydrogen bond[15] of the hydrogen atom to the oxazaborolidine oxygen atom.

For substrate **1c**, the respective complex **1c·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 3,5-dimethylphenyl ring (in gray) of the oxazaborolidine and that is relative to carbon atom C10 on the *Si* face. Despite the fact that complex **1c·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.

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 fre-

1a (X = H)   46% (d.r. = 93/7)   **4a** (96% *ee*)
1d (X = F)   59% (d.r. = 93/7)   **5a** (98% *ee*)

hv (λ = 457 nm)
−78 °C, 20 mol% **3c**
24 h (CH₂Cl₂)

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

quently 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*), minor *endo* products were also detected (d.r. = diastereomeric ratio).

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 (see below). The reaction of aldehyde **1a** with isopropylidenecyclohexane gave mainly a single regioisomer **7** (r.r. = regioisomeric ratio), which was obtained in 84% *ee*.

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
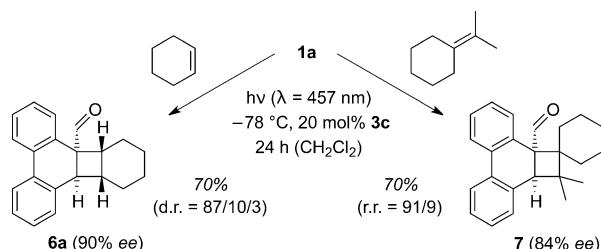
parameters. In the current study it was found that the formation of other constitutional isomers was completely suppressed in the presence of the Lewis acid. Irradiation of aldehyde **1a** and 2,3-dimethyl-2-butene at λ = 366 nm, 398 nm, and 405 nm led consistently to the formation of oxetane *rac*-**8** (Figure 3) in a ratio of about 1:5 relative to *rac*-**2a**. At lower wavelength (λ = 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.

rac-**8**   *rac*-**4b** (X = H)   *rac*-**6b** (*cis*-H)
           rac-**5b** (X = F)   *rac*-**6c** (*trans*-H)
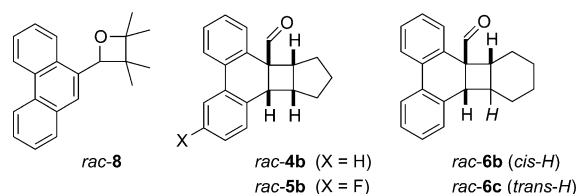
Figure 3. Structure of photocycloaddition products *rac*-**8**, *rac*-**4b**, *rac*-**5b**, *rac*-**6b**, and *rac*-**6c**.

Even more remarkable was the simple diastereoselectivity of the reaction, which was almost completely inverted compared to the racemic reaction. Direct excitation of **1a** and **1d** in the presence of cyclopentene at λ = 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 λ = 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** was also observed and the diastereomeric ratio (d.r. = *rac*-**6a**/*rac*-**6b**/*rac*-**6c**) was 21:35:44.

Previous work on the *ortho* photocycloaddition of methyl phenanthrene-9-carboxylate had produced evidence that its reaction (λ = 350 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-2-butene. 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 (λ_{max} = 387 nm, ε = 16 180 L mol⁻¹ cm⁻¹), which is induced upon Lewis acid coordination, stretches beyond all absorption bands of uncomplexed phenanthrene-9-carboxaldehydes and thus ena-

1a

hv (λ = 457 nm)
−78 °C, 20 mol% **3c**
24 h (CH₂Cl₂)

70%   70%
(d.r. = 87/10/3)   (r.r. = 91/9)

6a (90% *ee*)   **7** (84% *ee*)

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

bles 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 previous 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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