Photochemistry

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Enantioselective Lewis Acid Catalysis in Intramolecular [2+2] Photocycloaddition Reactions of Coumarins**

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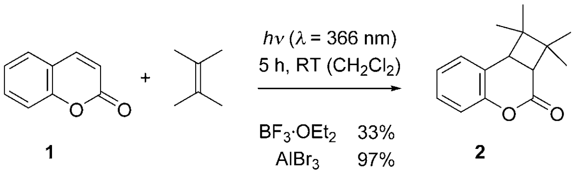
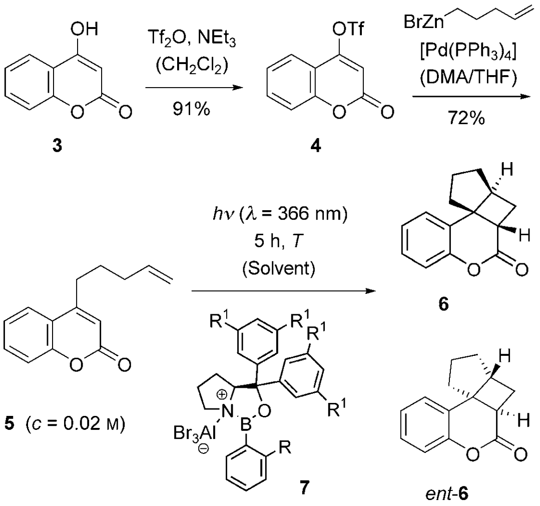
Despite increasing efforts in recent years, new methods for the enantioselective formation of chiral compounds by photochemical methods remain rare. The high energy content of an excited photosubstrate results in low activation barriers for further transformations and in rapid relaxation pathways. It is therefore intrinsically difficult to activate a photoexcited compound by a catalyst. Attempts to attain significant enantioselectivities by the use of circularly polarized light have seen little success.[1] Currently, the most frequently used method to achieve catalytic enantioselective photochemical reactions in solution relies on chiral sensitizers, which work by electron or energy transfer.[2,3] Herein we present an as yet unexplored concept for enantioselective photochemical reactions, which is based on the use of chiral Lewis acids. After some optimization we have now found a chiral cationic oxazaborolidine catalyst, which enables enantioselective intramolecular [2+2] photocycloaddition[4] reactions of 4-alkenyl-substituted coumarins. Our preliminary results are disclosed herein.

In 1989, Lewis and Barancyk reported that the [2+2] photocycloaddition of 2,3-dimethyl-2-butene to coumarin (**1**),[5] which is inefficient in the absence of an additive, was promoted by $BF_3{\cdot}OEt_2$.[6] By employing 50 mol % of the Lewis acid, product **2** was obtained in 57 % yield upon irradiation in a Pyrex apparatus with a mercury medium-pressure lamp for five hours. Similar reactions were conducted with other alkenes and—based on photochemical and photophysical data—the enhanced reactivity of complexed over uncomplexed coumarin was attributed to its increased singlet-state lifetime and electrophilicity. The observation of catalytic Lewis acid activity in the [2+2] photocycloaddition stimulated the idea to use chiral Lewis acids to achieve an enantioselective process. In search for an optimum Lewis acid catalyst,[7] the irradiation of coumarin in the presence of 2,3-dimethyl-2-butene was performed in CH_2Cl_2 with different Lewis acids at $\lambda = 366$ nm (Scheme 1). Without a Lewis acid no reaction was observed after five hours, while 50 mol % of $BF_3{\cdot}OEt_2$ gave under these conditions a yield of 33 %. The most active catalyst among the tested Lewis acids was found to be $AlBr_3$, which promoted an almost complete conversion and a high yield (97 %) of the isolated product **2**.



Scheme 1. $AlBr_3$ as an ideal catalyst for the intermolecular [2+2] photocycloaddition of 2,3-dimethyl-2-butene to coumarin (**1**).

Considering the possibility of an enantioselective Lewis acid promoted photochemical reaction it was assumed that Lewis acid coordination was weak and that the association/dissociation of the coumarin substrate was relatively fast. An intramolecular [2+2] photocycloaddition consequently seemed best suited to achieve high enantioselectivity because the enantioselectivity-determining bond-formation step is more rapid than in an intermolecular reaction. 4-(Pent-4-enyl)coumarin (**5**) was chosen as a test substrate and was readily prepared from commercially available 4-hydroxycoumarin (**3**). Conversion into triflate **4**[8] was followed by a Negishi cross-coupling to give the desired product **5**. In the absence of a Lewis acid, coumarin **5** gave, under standard photochemical irradiation conditions (Scheme 2, Table 1), a 28 % yield of racemic product **6** and *ent*-**6** after five hours of irradiation.



Scheme 2. Preparation of coumarin **5** and catalyst optimization for its enantioselective intramolecular [2+2] photocycloaddition.

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Table 1: Enantioselective catalytic [2+2] photocycloaddition reactions of coumarin **5** (cf. Scheme 2).

Entry	Catalyst	R	R^1	mol%[a]	Solvent	T [°C]	Yield [%][b]	e.r.[c]	*ee* [%]
1	–	–	–	–	CH_2Cl_2	30	28	50:50	–
2	**7a**	Me	H	50	CH_2Cl_2	30	88	60:40	20
3	**7b**	H	H	50	CH_2Cl_2	30	77	66:34	32
4	**7b**	H	H	20	CH_2Cl_2	30	77	65:35	30
5	**7b**	H	H	20	Et_2O	30	74	50:50	–
6	**7c**	CF_3	H	50	CH_2Cl_2	30	83	72:28	44
7	**7d**	CF_3	Me	50	CH_2Cl_2	30	88	81:19	62
8	**7e**	CF_3	*t*Bu	50	CH_2Cl_2	30	82	63:37	26
9	**7d**	CF_3	Me	50	CH_2Cl_2	−75	84	91:9	82
10	**7d**	CF_3	Me	20	CH_2Cl_2	−75	82	77:23	54
11[d]	**7d**	CF_3	Me	20	$ClCH_2CH_2Cl$	−35	87	89:11	78

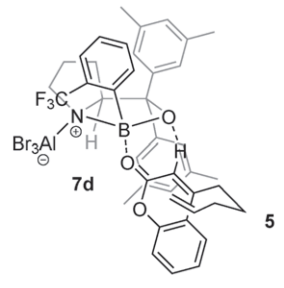
[a] The reactions were carried out in a de-aerated solvent at the indicated temperature (irradiation in a RPR-100 reactor with Philips black light blue lamps, 8 W for 5 h) and with a substrate concentration of 20 mM (see Supporting Information). [b] Yield of product isolated after column chromatography. [c] The enantiomeric ratio (e.r.) was determined by chiral GC. [d] The reaction was run at a substrate concentration of 50 mM.

An extensive study was subsequently conducted employing a broad variety of chiral aluminum-based Lewis acids as potential enantioselective catalysts. Among the few lead structures we discovered—most Lewis acids gave only racemic products—the $AlBr_3$-activated oxazaborolidines[9,10] **7** appeared to be a promising class of combined acid catalysts[11] for further optimization. The known catalyst **7a**[10] (Table 1, entry 2) facilitated the preferred formation of **6** in an enantiomeric ratio (e.r.) **6**/*ent*-**6** = 60:40, which corresponds to an enantiomeric excess (*ee*) of 20%. The parent triphenyl-substituted catalyst **7b** gave an even higher excess (32% *ee*, Table 1, entry 3) and was used to show that high selectivities and a chirality turnover can be achieved with only 20 mol% of catalyst (Table 1, entry 4) and that CH_2Cl_2 was indeed the preferred solvent. The use of diethyl ether, for example, resulted in no selectivity (Table 1, entry 5).

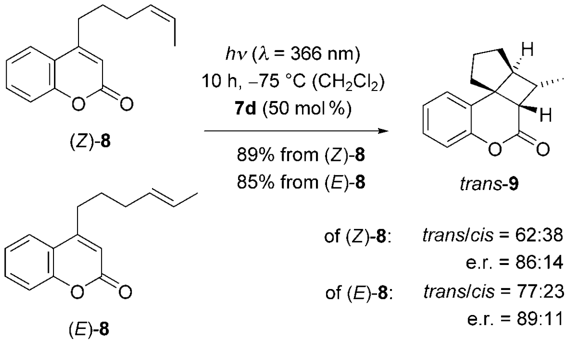
Further variations of the catalyst structure were most successful at the *ortho* position (R) of the phenyl substituent at boron and at the *meta* positions (R^1) at the two other phenyl groups (Table 1, entries 6–11). Replacing the methyl group in **7a** by a trifluoromethyl group led to a twofold increase of the *ee* value (catalyst **7c**, 44% *ee*, Table 1, entry 6). Introduction of *meta*-methyl substituents (R^1) at the pyrrolidine phenyl groups increased this value further (catalyst **7d**, Table 1, entry 7), while the bulkier *tert*-butyl groups led to a decrease in selectivity (catalyst **7e**, Table 1, entry 8). Indeed, among a total of 26 oxazaborolidines tested, compound **7d** was the most selective catalyst, providing the desired product at −75 °C with 82% *ee* (Table 1, entry 9). With less catalyst, the enantioselectivity decreased because of the competitive background reaction (cf. Table 1, entries 10 and 1). Catalytic reaction conditions employing only 20 mol% of catalyst **7d** (Table 1, entry 11) were found which delivered results, which almost completely paralleled the results achieved with 50 mol% of catalyst **7d**.

The absolute configuration of products **6** and *ent*-**6** was proven by converting both enantiomers into the corresponding monobromo derivatives, the absolute configurations of which were in turn elucidated by anomalous X-ray diffraction studies (see the Supporting Information). The stereochemical outcome of the photochemical reaction can be preliminarily explained by assuming a 1:1 complex **5·7d**, in which one of the two enantiotopic faces of coumarin is shielded (Scheme 3). As previously suggested,[9] coordination to the boron is assumed to be further enhanced by an electrostatic interaction of the hydrogen atom at C3 with the oxygen atom of the oxazaborolidine.[12]

Experiments with the diastereomerically enriched 4-(hex-4-enyl)-coumarins (*Z*)-**8** (diastereomeric ratio = d.r. = 98:2) and (*E*)-**8** (d.r. = 98:2) were conducted to acquire additional information about the nature of the excited state, from which the reaction occurs (Scheme 4). The compounds were prepared analogously to **5** by using a Negishi cross-coupling reaction (see the Supporting Information). It was found that the photochemical reactions proceeded in a stereoconvergent fashion with almost complete loss of the relative configuration.[13] The *trans*-product *trans*-**9** was the predominant product. If the reaction was interrupted before the substrate was completely consumed, the starting



Scheme 3. Model of the complex **5·7d** explaining the observed enantioselectivity in the intramolecular [2+2] photocycloaddition of coumarin **5**.



Scheme 4. Lewis acid catalyzed intramolecular [2+2] photocycloaddition of the two diastereoisomeric coumarins (*E*)-**8** and (*Z*)-**8**.

coumarins showed a change in their relative configuration. After 30 min irradiation time the d.r. of (*E*)-**8** changed to 80:20 and the d.r. of (*Z*)-**8** to 60:40. Irradiation of the substrates in the absence of a catalyst did not lead to a double-bond isomerization, however. From this result it can be concluded that the loss of the stereochemical information occurs in the catalytic process.[14] While a stereospecific reaction course would have indicated a reaction on the singlet hypersurface, the result supports a triplet mechanism with intermediate formation of a 1,4-biradical, in which free rotation around the former carbon–carbon double bond can occur.[15] As the reaction is not completely stereoconvergent, minor quantities of the product may be formed via singlet intermediates. The fact that recovered starting material has undergone partial isomerization appears to indicate that retrocleavage of the intermediate 1,4-biradical competes efficiently with its ring closure.[13] The enantioselectivity as determined for the major diastereoisomer *trans*-**9** was comparable to the enantioselectivity achieved in the reaction **5**→ **6**.

In summary, chiral Lewis acid catalysis is shown to be a promising, yet unexplored area of enantioselective photochemistry. A significant catalytic effect was achieved with AlBr$_3$-activated oxazaborolidines. Enantioselectivities up to 78% *ee* were recorded with 20 mol% catalyst. Further work is in progress aiming at new catalytic photoreactions based on this concept.

Experimental Section

Typical procedure for the enantioselective [2+2] photocycloaddition: 4-(Pent-4-enyl)coumarin (**5**, 43.0 mg, 0.201 mmol), anhydrous CH$_2$Cl$_2$ (4 mL), and catalyst **7d** (solution in CH$_2$Cl$_2$, 3 mL, 0.100 mmol) were added into a dried Duran tube under nitrogen atmosphere. The vessel, in which the catalyst **7d** was prepared, was washed with CH$_2$Cl$_2$ (3×1 mL), and the solvent was transferred into the Duran tube by syringe. The mixture was cooled in a bath at −75 °C for 30 min. The sample was then irradiated at $\lambda = 366$ nm at −75 °C. The photochemical reaction was completed after 5 h as monitored by TLC (silica gel; petroleum ether/ethyl acetate 10:1). The solution was extracted with water, the organic and aqueous layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic phase was dried over MgSO$_4$ and filtered, and the solvent was removed by rotary evaporation. The residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate 10:1) to afford 36.0 mg (84%) of products **6** and *ent*-**6** (82% *ee*): solid, mp: 70–72 °C (diethyl ether); $[\alpha]_D^{20} = -13.5$ deg cm^3 g^{-1} dm^{-1} ($c = 1.00$, CHCl$_3$); ^{1}H NMR (360 MHz, CDCl$_3$) $\delta = 7.28$–7.08 (m, 3H), 7.01 (d, $J = 7.9$ Hz, 1H), 3.21–3.12 (m, 1H), 2.68–2.52 (m, 2H), 2.17–2.05 (m, 3H), 2.04–1.80 (m, 3H), 1.76–1.66 (m, 1H); ^{13}C NMR (CDCl$_3$, 90.6 MHz) $\delta = 169.1$, 150.7, 128.2, 126.2, 126.0, 125.1, 117.4, 48.6, 47.2, 40.8, 37.8, 33.2, 28.7, 25.9; IR (neat) 1756, 1491, 1447 cm^{-1}; HRMS (EI): *m*/*z* calcd for C$_{14}$H$_{14}$O$_2$: 214.0994, found: 214.0995.

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