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Enantioselective Catalysis of the Intermolecular [2+2] Photocycloaddition between 2-Pyridones and Acetylenedicarboxylates**

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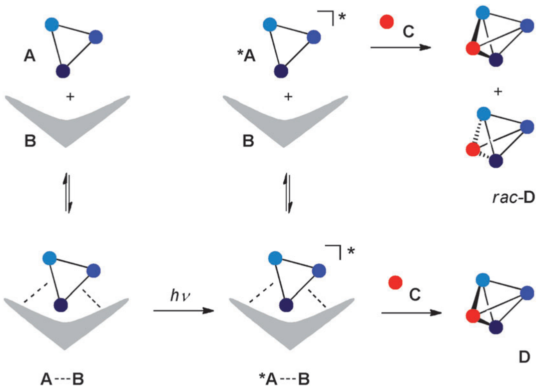
Abstract: *Intermolecular [2+2] photocycloadditions represent the most versatile and widely applicable of photochemical reactions. For the first time, such intermolecular reactions have been carried out in a catalytic fashion using a chiral triplet sensitizer, with high enantioselectivity (up to 92 % ee). The low catalyst loading (2.5–5 mol %) underlines the high efficiency of the process both in terms of reaction acceleration and differentiation of the enantiotopic faces of the substrate. The substrate is anchored to the chiral catalyst through noncovalent interactions (hydrogen bonds), thus providing a chiral environment in which the enantioselective photocycloaddition proceeds. The densely functionalized products present numerous possibilities for further synthetic transformations.*

Under thermal conditions, the main challenge in enantioselective catalysis involves the stabilization of a transition state that arises from a relatively unreactive prochiral starting material, and which leads subsequently to a defined product enantiomer.[1] In contrast, such an approach is not applicable to the enantioselective catalysis of photochemical reactions. After excitation through irradiation with a light source, further reaction of the substrate is generally very fast, such that no additional catalyst is required. Thus it is generally difficult to stabilize consecutive transition states of an already excited substrate and to channel it into an enantioselective reaction pathway. Instead, the chiral catalyst must maintain communication with the substrate in the excitation step, so that formation of an enantiomerically pure or enantiomerically enriched product is made possible through the formation of diastereoisomeric transition states.[2,3] In line with this approach, the idea of using chiral sensitizers for the enantioselective catalysis of photochemical reactions was introduced in the 1960s. The first studies in this area were published by Hammond and Cole, and dealt with the isomerization of achiral 1,2-*cis*-diphenylcyclopropane into chiral *trans*-1,2-diphenylcyclopropane.[4]

As shown in Scheme 1, in an idealized catalytic process there is no direct excitation of the substrate **A**→**A*** at a given wavelength $\lambda = c/\nu$. Instead, only sensitized excitation of the type **A**-**B**→***A**-**B** occurs, which can take place only within the complex of the substrate and chiral sensitizer **B**. This prerequisite is not at all trivial, and the situation is further complicated since the sensitizer must also ensure excellent differentiation of enantiotopic faces or groups, and since conversion of the substrate to product must occur faster than the dissociation of the substrate–sensitizer complex ***A**-**B**→**A*** + **B**. The former complication is the main reason that many viable sensitizers (e.g. chiral ketones for triplet energy transfer)[5] do not deliver high enantioselectivities, despite being catalytically active. The latter complication is most likely the reason that a recently described chiral triplet sensitizer delivers high enantioselectivites in some cases but low enantioselectivities in other cases in the intramolecular [2+2] photocycloaddition of closely related substrate classes.[6]



Scheme 1. Photochemical reaction of the prochiral substrate **A** in the presence of chiral sensitizer **B**. It is assumed that sensitization occurs exclusively in complex **A**-**B**, whereas the reaction with a reagent **C** can occur either in the complex or after its dissociation. In the latter case, the reaction is not enantioselective, and products **D** and *ent*-**D** are obtained as a racemic (*rac*-**D**) mixture (top), whilst in the former case, the reaction can proceed with enantioselective product formation (bottom).

In the case of an intermolecular reaction involving a reagent **C**, the dissociation of the excited species **A*** becomes a critical factor, because high enantioselectivities can only be achieved if the reaction with **C** is very fast, or if the complex ***A**-**B** is very stable. For a long time, it seemed that the intermediacy of singlet exciplexes represented the only approach capable of generating significant enantiose-

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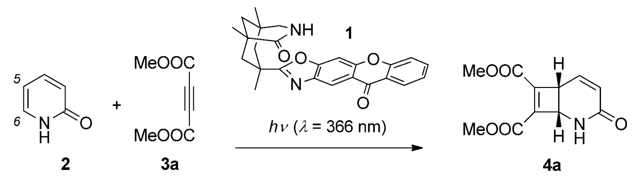
lectivities in a catalytic intermolecular photochemical reaction.[7] Herein, we now show that by the appropriate choice of reaction partner and catalyst, triplet reactions that proceed with high enantioselectivities are indeed possible.[8]

Our interest in triplet-sensitized intermolecular [2+2] photocycloaddition reactions led us to the work of Somekawa et al., which dealt with the reaction between 2-pyridones and acetylenedicarboxylates.[11] Upon irradiation of 2-pyridones in acetonitrile with a high-pressure mercury lamp (pyrex filter) in the presence of benzophenone as a triplet sensitizer, the authors obtained poor yields of the [2+2] and [4+2] adducts (12–18%). We repeated these experiments under modified conditions, using chiral triplet sensitizer **1**[12] (Table 1). Starting with the reaction between 2-pyridone (**2**) and dimethyl acetylenedicarboxylate (**3a**), which was previously studied by Somekawa et al., we observed no background reaction upon irradiation at $\lambda = 366$ nm (Table 1, entry 1). Under otherwise identical conditions, we were pleased to note that in the presence of the catalyst, a catalytic enantioselective photoreaction took place (Table 1, entry 2), forming the photoproduct **4a** with high selectivity, through addition to the 5,6 double bond of the pyridone.

Table 1: Reaction optimization for the enantioselective, intermolecular [2+2] photocycloaddition of pyridone **2** with alkyne **3a** in the presence of chiral xanthone **1**.

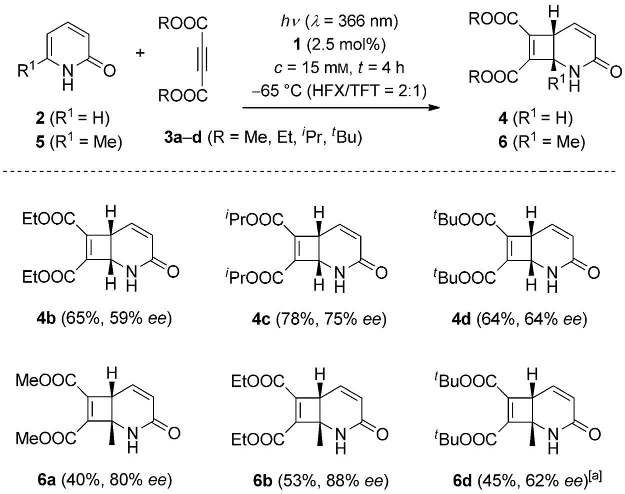


Entry	c [mM]	**1**[a] [mol%]	**3a** [equiv]	Solvent[b] [%TFT]	T [°C]	t[c] [h]	Yield[d] [%]	ee[e] [%]
1	10	–	10	100	30	1	–[f]	–
2	10	10	10	100	30	1	42	6
3	10	10	10	100	−25	2	42	22
4	10	10	50	100	−25	1	40	42
5	10	10	100	100	−25	1	42	42
6	20	10	100	100	−25	3	61	44
7	20	10	50	33	−65	1	55	48
8	20	5	50	33	−65	4	71	48
9	20	2.5	50	33	−65	4	55[g]	49
10	15	2.5	50	33	−65	4	70	49

[a] All reactions were carried out in a Rayonet RPR-100 reactor with 16 fluorescence lamps (8 W, emission maximum at $\lambda = 366$ nm) as the light source under the given reaction conditions.[9] [b] Trifluorotoluene (TFT) and hexafluoro-*m*-xylene (HFX) were employed as the reaction solvent in the volume ratios given. [c] Irradiation time required for complete conversion. [d] Yield of isolated product. [e] The enantiomeric excess (*ee*) was calculated from the enantiomer ratio, which was determined through HPLC analysis. [f] No conversion. [g] Incomplete conversion.

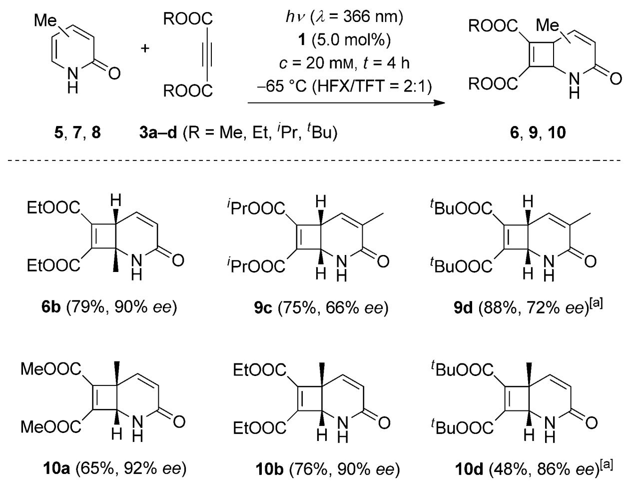
At lower temperatures, the enantioselectivity increased (Table 1, entry 3), and as expected, increasing the amount of alkyne also improved the enantioselectivity (Table 1, entries 4 and 5). Meanwhile, increasing the substrate concentration led to a considerable increase in yield (Table 1, entry 6). Through empirical studies, we found that a 2:1 mixture of hexafluoro-*m*-xylene (HFX) and trifluorotoluene (TFT) has a lower melting point than either of the pure components; using this mixture as the reaction solvent, reactions could be carried out at lower temperatures (up to −65 °C; Table 1, entries 7–9). Under these conditions, the catalyst loading could be lowered to 2.5 mol% without any significant loss in yield and enantioselectivity (Table 1, entry 10). Entries 8 and 10 were identified as the optimal conditions, and these conditions were applied in further reactions.

In a first set of experiments, the size of the ester substituent was investigated, and 2-pyridone (**2**) was reacted with a range of esters **3b–d** (Scheme 2). In comparison with the dimethyl ester product **4a** (Table 1, entry 10, 49% *ee*), the use of the diisopropyl ester variant gave a significant increase in enantioselectivity (product **4c**, 75% *ee*). Since a clear steric influence was not apparent, four acetylenedicarboxylates (R = Me, Et, *i*Pr, *t*Bu) were employed in subsequent experiments, and a full summary of the experiments carried out can be found in the Supporting Information. Diethyl acetylenedicarboxylate (**3b**) emerged as the optimal ester substrate for the reaction of 6-methyl-2-pyridone (**5**), and the corresponding product **6b** was isolated in 53% yield and 88% *ee* (Scheme 2).

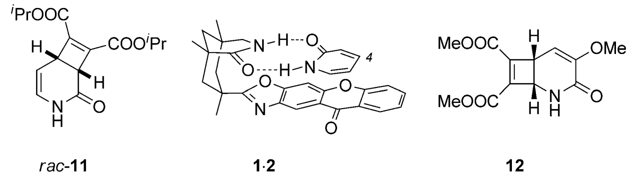


Scheme 2. Enantioselective intermolecular [2+2] photocycloaddition of 2-pyridone (**2**) and 6-methyl-2-pyridone (**5**) with alkynes **3**. All reactions were carried out in a Rayonet RPR-100 reactor with 16 fluorescence lamps (8 W, emission maximum at $\lambda = 366$ nm) as the light source under the given reaction conditions.[9] [a] The *ee* value was determined after acidic hydrolysis (CF_3COOH in CH_2Cl_2) and methylation ($TMSCHN_2$ in PhH/MeOH) through HPLC analysis of the corresponding dimethylester.

For other pyridones, the use of a 2.5 mol% catalyst loading required irradiation times of over four hours in order to reach full conversion. In view of the moderate stability of the sensitizer (which decomposes in the excited state through intermolecular hydrogen atom abstraction)[9,13] an increase in catalyst loading was necessary for such pyridones, and for these cases the conditions described in entry 8 of Table 1 were employed. Under these conditions, the high enantioselectivity



Scheme 3. Enantioselective intermolecular [2+2] photocycloadditions of various methyl-substituted 2-pyridones with alkynes **3** at higher concentration and catalyst loading. All reactions were carried out in a Rayonet RPR-100 reactor with 16 fluorescence lamps (8 W, emission maximum at $\lambda = 366$ nm).[9] [a] The *ee* value was determined after acidic hydrolysis (CF_3COOH in CH_2Cl_2) and methylation ($TMSCHN_2$ in PhH/MeOH) through HPLC analysis of the corresponding dimethyl ester.



Scheme 4. Byproduct *rac*-**11** from the reaction between **2** and **3c** in the presence of benzophenone as the sensitizer; proposed model to account for enantioface differentiation in complex **1·2**; product **12** from the reaction of 3-methoxy-2-pyridone with diester **3a**.

already observed for product **6b** could be further increased to 90% *ee*, and the yield was also increased significantly (79%; Scheme 3). The best yields and selectivities were observed for 3-methyl-2-pyridone (**7**) with the isopropyl and *tert*-butyl acetylenedicarboxylates, furnishing the corresponding products **9c** and **9d** in very good yields (75% and 88%, respectively) and good enantioselectivity (66% *ee* and 72% *ee*, respectively). In terms of enantioselectivity, the best results were obtained using 5-methyl-2-pyridone (**8**): photocycloaddition of **8** with alkyne **3a** gave product **10a** in 92% *ee* (Scheme 3), and high enantioselectivities were also observed using esters **3b** and **3d** (90% *ee* and 86% *ee*, respectively).

As demonstrated in the above examples, in addition to the fact that catalyst **1** is able to effect an unprecedented level of chirality transfer, it is of particular note that the reaction conditions of the catalysis experiments also influence the type and the regioselectivity of the photoreaction. In order to obtain racemic photoproducts for HPLC analysis, the reactions were also carried out using benzophenone as sensitizer. In these reactions, a side reaction involving [2+2] addition to the 3,4 double bond of the pyridone was often observed. Thus, upon photocycloaddition of pyridone **2** and diester **3c**, dihydropyridone *rac*-**11** was obtained as a byproduct in addition to the major product *rac*-**4c** (Scheme 4), in an approximate 1:3 ratio. Such 3,4-addition products (as well as the [4+2] addition products described by Somekawa et al.) were only produced in very small quantities in our catalysis experiments.

The absolute configuration was assigned based on the assumption that the pyridones bind to catalyst **1** as shown for 2-pyridone (**2**) in Scheme 4. Luminescence measurements[14,15] and calculations[16] display a clear preference for the 2-pyridone form over the tautomeric 2-hydroxypyridine form. The binding mode shown (Scheme 4) has already been established for other pyridones and dihydropyridones that bind to templates containing a 1,5,7-trimethyl-3-azabicyclo-[3.3.1]nonane-2-one scaffold, and is consistent with the absolute configuration determined for these substrates.[17] In an analogous fashion, in complex **1·2**[18] an attack from the top face is preferred, resulting in the absolute configuration shown in Table 1 and Schemes 2 and 3. It is likely that the presence of a methyl substituent results in a change in orientation, which is mirrored by a change in the enantioselectivity of the photoreaction. Particularly significant is the introduction of the methyl substituent at the 4-position of the pyridone, since this methyl group points towards the carbonyl group of the xanthone moiety of the catalyst, and is ideally positioned for a hydrogen atom abstraction, resulting in rapid decomposition of the catalyst. Similarly, the catalyzed reaction between 3-methoxy-2-pyridone and dimethyl acetylenedicarboxylate (**3a**) stalls after only low conversion to product **12** (16% yield), which we attribute to decomposition of the catalyst.

In summary, we have shown for the first time that intermolecular [2+2] photocycloadditions can be carried out with high enantioselectivity by using a catalytic amount of a chiral triplet sensitizer. The low catalyst loading is particularly noteworthy; with 2.5 mol% of catalyst, enantioselectivities of up to 88% *ee* were recorded, whilst with 5 mol% of catalyst, products with up to 92% *ee* were obtained. This result is attributed to the interplay between several factors, the most important of which seem to include the effective binding of the substrate to the catalyst through hydrogen bonds, the rapid addition of the alkyne to the excited substrate, and the high enantioface differentiation ensured by the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonane-2-one scaffold. Further study of the mechanistic details should help to clarify the reaction pathway, as well as broaden the application of enantioselective catalysis through triplet sensitization to other substrate classes.

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Keywords: cycloaddition · enantioselectivity · hydrogen bonds · organocatalysis · photochemistry · sensitizers

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