Enantioselective Photocatalysis

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Enantioselective Catalysis of Photochemical Reactions

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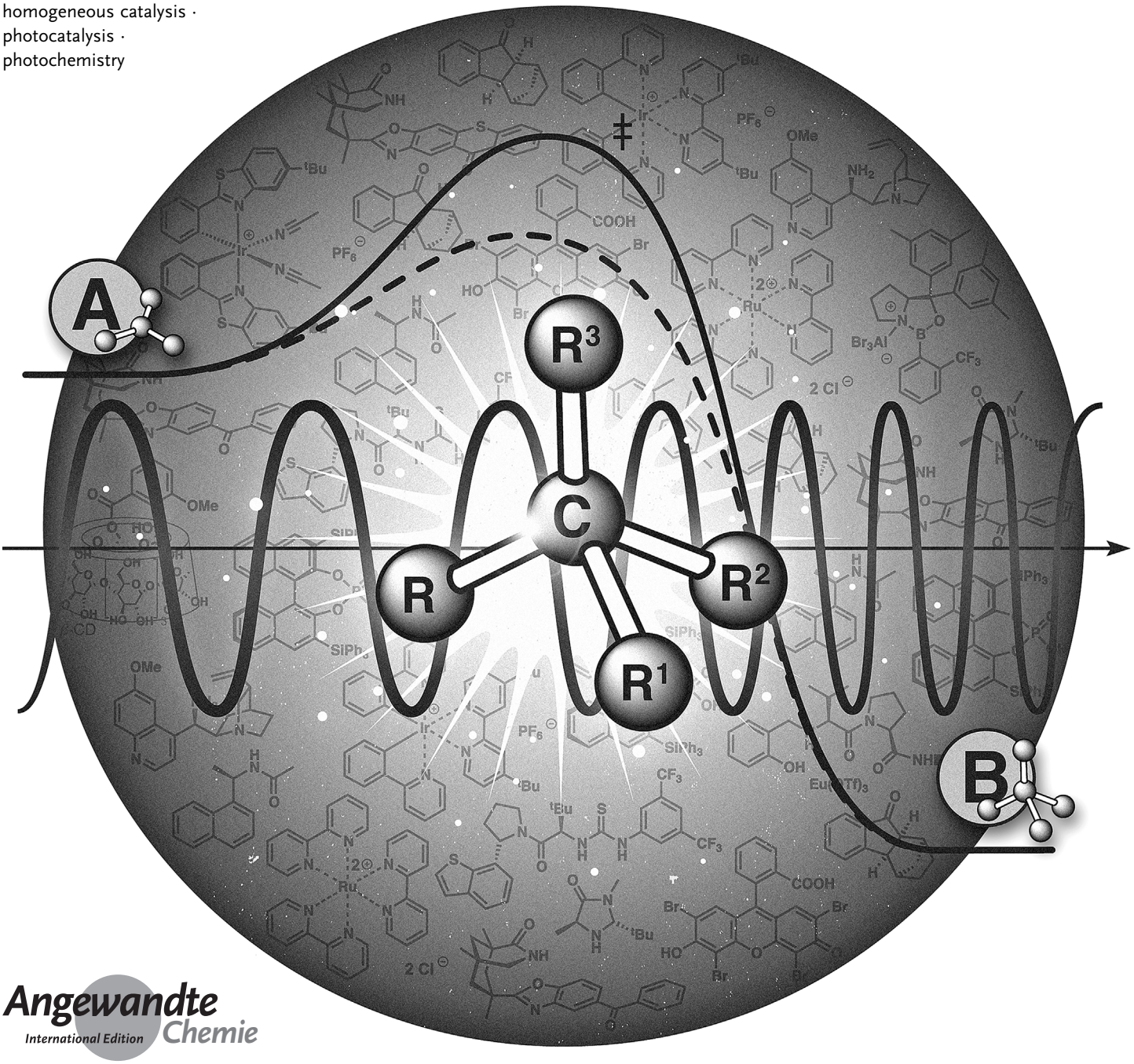

The nature of the excited state renders the development of chiral catalysts for enantioselective photochemical reactions a considerable challenge. The absorption of a 400 nm photon corresponds to an energy uptake of approximately 300 kJ mol^{-1}. Given the large distance to the ground state, innovative concepts are required to open reaction pathways that selectively lead to a single enantiomer of the desired product. This Review outlines the two major concepts of homogenously catalyzed enantioselective processes. The first part deals with chiral photocatalysts, which intervene in the photochemical key step and induce an asymmetric induction in this step. In the second part, reactions are presented in which the photochemical excitation is mediated by an achiral photocatalyst and the transfer of chirality is ensured by a second chiral catalyst (dual catalysis).

From the Contents

1. Introduction

Over the last decades, the enantioselective catalysis[1] of chemical reactions has matured into an independent scientific discipline. Its importance for the selective preparation of enantiomerically pure compounds cannot be overestimated. At the latest when W. S. Knowles, R. Noyori, and K. B. Sharpless were honored with the Nobel Prize for chemistry in 2001 for the "development of catalytic asymmetric synthesis",[2] the significance of this research area became apparent to the general public. Meanwhile, a large variety of methods have been developed for the synthesis of chiral compounds by enantioselective catalytic transformations, and this research field continues to expand vibrantly.[3] Against this background, it seems surprising that until very recently, the enantioselective catalysis of photochemical reactions[4] has—somewhat figuratively speaking—been hidden in the dark. The cause for this shadowy existence does certainly not correlate with the synthetic potential of these reactions, which is tremendous and promises a multitude of applications.[5] Rather, there are intrinsic factors that make it difficult for a chemist to approach the catalysis of a photochemical reaction in a conventional fashion (Figure 1). The fundamental idea behind the design of any catalytic reaction is to decrease its activation barrier by addition of a catalyst. Indeed, owing to their high activation barriers, many reactions can only be performed in the presence of a suitable catalyst. The next step in the design process is to channel the reaction into an enantioselective pathway by means of a chiral catalyst.

In most cases, it is impossible to follow the same approach for developing a catalytic version of a photochemical reaction. Upon excitation by light, the molecule gains sufficient energy[6] to undergo a fast subsequent reaction, which does not require further catalysis. To achieve an enantioselective photochemical reaction, it must consequently be ensured that the substrate molecule already resides in a chiral environment during the excitation step. Different methods and concepts to achieve this goal will be discussed in Section 2, which deals with chiral photocatalysts. An alternative approach is based on the separation of the photochemical reaction and the enantioselective bond formation (dual catalysis). To this end, an achiral photocatalyst is frequently combined with a conventional chiral catalyst. This approach, which is mainly used in redox processes, will be discussed in Section 3.

Reactions that occur in the solid state, in liquid crystals, in enzymes,[7] or in other complex supramolecular units[8] will not be discussed. Similarly, radical chain reactions[9] or reactions in which the catalyst for a thermal reaction is generated by photochemical means[10] are beyond the scope of this Review. As in a previous Review,[5a] a wavelength or wavelength range for the irradiation is given in the Schemes and Figures,[11] provided that this information was reported in the reference material. A temperature is only indicated if the reaction was not performed at room temperature.

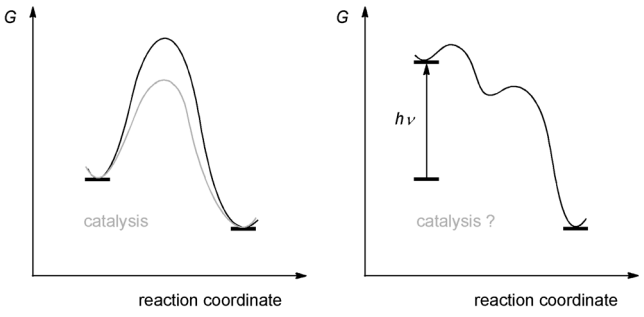

Figure 1. Enthalpy diagrams of a thermal (left) and a photochemical reaction (right).

2. Chiral Photocatalysts

As mentioned above, the photocatalyst does not need to accelerate the photoreaction itself, but it has to interact with the substrate during the excitation step (Figure 1). Different

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modes of action and interaction mechanisms are conceivable, which are schematically shown in Figure 2. The use of a sensitizer lowers the energy that is required to reach the excited state of the substrate (case a). Excitation takes place within the substrate–catalyst complex and can be achieved using light of longer wavelengths compared to the wavelength needed for direct excitation of the substrate. Based on a related mode of action, such a complex can exhibit a bathochromic shift in its absorption, thus enabling the selective irradiation of the complex without exciting the uncomplexed substrate (case b).

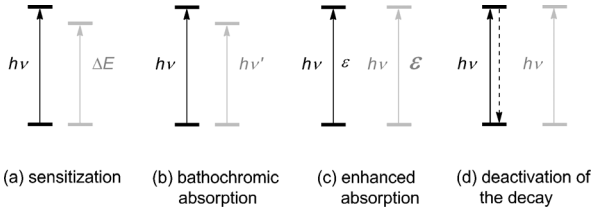

Figure 2. Possible modes of action for chiral photocatalysts.

Selectivity can also be induced at the same excitation wavelength if the substrate–catalyst complex shows a significantly enhanced absorption (higher extinction coefficient ε) than the substrate (case c). A fourth mode of action (case d) applies to photochemical substrates that possess efficient deactivation pathways, such as fluorescence or internal conversion, that slow down the desired photochemical reaction. If the catalyst inhibits the deactivation pathways of the substrate or if it shifts the course of the reaction onto another hypersurface, the reaction can be enantioselectively catalyzed.

2.1. Arenes

From a historical point of view, arenes play an important role as catalysts for enantioselective photoreactions, as naphthalene **1** was the very first chiral photocatalyst (Figure 3). In 1965, Cole and Hammond used this chiral arene for the enantioselective *cis*/*trans* isomerization of 1,2-diphenylcyclopropane (see Scheme 1).[12] Benzoates of chiral alcohols, such as pyromellitate derivatives **2a**[13] and **2b**,[14] binaphthalene and bisanthracene derivatives with axial chirality, such as 1,1′-bis(2,10-dicyanoanthracene) (**3**),[15] and cyclodextrin derivatives of benzoic acid esters, such as β-cyclodextrin **4**,[16] represent further typical arene photocatalysts. In addition, benzoate **5**[17] exhibiting planar chirality and naphthalene dicarboxylates such as **6**[14] play an important role (Figure 3).

Crucial for the success of these catalysts is often their ability to form an excited complex (exciplex)[18] with the substrate, which then undergoes the enantioselective photochemical reaction. Energy transfer from arenes thus occurs predominantly on the singlet hypersurface. Chiral arenes have most frequently been used as sensitizers for isomerization reactions. Upon irradiation, racemic *trans*-1,2-diphe-

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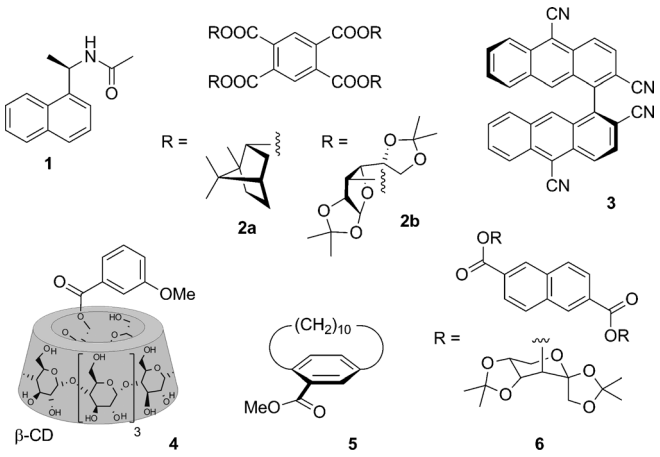
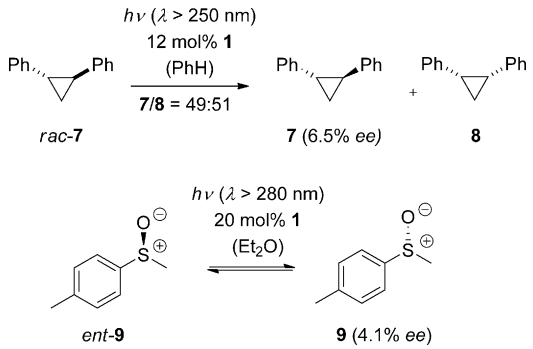


Figure 3. Arenes **1**–**6** as examples of chiral sensitizers for photochemical reactions.

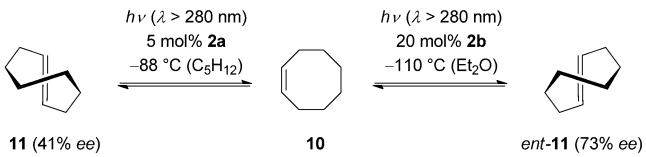
nylcyclopropane (*rac*-**7**)[19] isomerizes and reaches a photostationary state. *Meso* compound **8** is formed with simultaneous accumulation of one of the enantiomers of *rac*-**7** (Scheme 1).



Scheme 1. Enantioselective photoisomerization catalyzed by chiral naphthalene **1** (*ee* = enantiomeric excess).

As already mentioned above, the use of naphthalene **1** led to a preference for enantiomer **7**, resulting in an enantioselective *cis*/*trans* isomerization.[12] In 1973, Kagan and co-workers showed that arene **1** also catalyzed the isomerization of chiral sulfoxide *rac*-**9**.[20] Again, a photochemical equilibrium is established, in which enantiomer **9** is enriched compared to its antipode *ent*-**9**.

One of the most intensively investigated photochemical isomerization reactions is the conversion of (*Z*)-cyclooctene (**10**) into its geometrical isomer (*E*)-cyclooctene (Scheme 2).

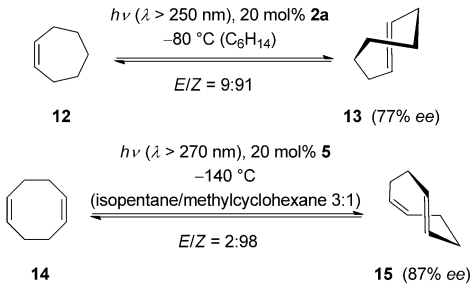


Scheme 2. Enantioselective isomerization of olefin **10** to the *E* isomers **11** and *ent*-**11**.

This reaction strongly depends on external parameters,[21] such as solvent, temperature, and pressure.[22] In 1989, after initial studies on the photoisomerization of (*Z*)-cyclooctene at room temperature,[23] the group of Inoue showed that the enantioselective formation of *E* isomers **11** and *ent*-**11** correlates with the reaction temperature.[13] Depending on the difference in activation enthalpy and activation entropy, there can be an inverse relationship between *ee* value and temperature, that is, the *ee* can increase with an increase in temperature. The preference for the major enantiomer can also change from **11** to *ent*-**11** depending on the reaction temperature. In the course of the above-mentioned study, the highest selectivity was found in favor of **11** at −88 °C in the presence of ester **2a**. In a later series of experiments in which the solvent influence was explored, arene carboxylate **2b** was found to deliver *ent*-**11** with an *ee* of 73 % in diethyl ether as the solvent.[24]

Chiral pyromellitates **2** were also used for the enantioselective photoisomerization of 1,2-diarylcyclopropanes (see Scheme 1) and 2,3-diphenyloxirane. However, the enantiomeric excess that was achieved did not exceed 10 % *ee*.[25] The *E*/*Z* isomerization of (*Z*)-cyclooctene (**10**) was furthermore catalyzed by modified chiral cyclodextrins, as shown by Inoue and co-workers.[26] Cyclodextrin **4** delivered the best result in a mixture of methanol and water as the solvent at −5 °C (46 % *ee* in favor of **11**).[16,26e]

A general drawback of these photoisomerization reactions[27] is the fact that the desired chiral isomer is not necessarily formed in excess compared to the achiral isomer. The yields therefore remain low. This severe issue becomes apparent in the isomerization reactions that are depicted in Scheme 3, which summarizes the best results reported for the respective reactions thus far. (*Z*)-Cycloheptene (**12**) yielded



Scheme 3. Enantioselective *E*/*Z* isomerization of *Z* olefins **12** and **14** catalyzed by various arenes.

E isomer **13** upon irradiation in the presence of aromatic ester **2a**. However, the *E*/*Z* ratio was found to be only 9:91.[28] In a similar fashion, optimization of the reaction conditions for the *E*/*Z* isomerization of (*Z*,*Z*)-1,5,-cyclooctadiene (**14**) in the presence of benzoate **5** led to a high enantiomeric excess in favor of product **15**, but the conversion into the product was very low (*E*/*Z* = 2:98).[17]

The first enantioselective photocycloaddition reaction was realized in 1990. Chiral binaphthalene or bisanthracene derivatives were used as the catalyst in a so called Triplex Diels–Alder reaction.[15] Product **16**, or its enantiomer, was

obtained in 23% *ee*, and yields between 5 and 45% were achieved with anthracene **3** as the catalyst (Figure 4). As implied by the name of this reaction, an intermediary exciplex is formed by β-methylstyrene and the anthracene catalyst, to

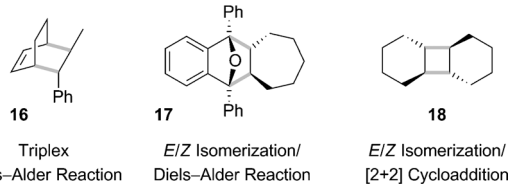
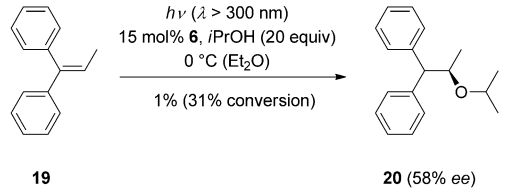


Figure 4. Products **16**–**18** of C–C bond-forming reactions catalyzed by chiral arenes (newly formed bonds marked in gray).

which the diene is coordinated as the third reaction component. Enantioselective C–C bond formation was also observed in the Diels–Alder reaction of photochemically generated (*E*)-cycloheptene (**13**) with diphenylisobenzofuran to product **17** and in the formation of cyclobutane **18** upon photochemical *E*/*Z* isomerization of cyclohexene. However, the enantiomeric excess of **17** was not reported.[28] Cyclobutane derivative **18** was produced with high enantioselectivity (up to 68% *ee*), but in a low yield of 0.2%.[29]

The photochemical generation of arene exciplexes with styrene derivatives can also be favorably employed for an enantioselective addition of nucleophiles to furnish *anti*-Markovnikov products. A first report on this reaction class from the Inoue group dates back to the year 1993.[30] Potential chiral catalysts for this reactions are modified cyclodextrins[31] or naphthalene carboxylates.[14,32] The addition of 2-propanol to 1,1-diphenylpropene (**19**) catalyzed by chiral diester **6** is shown in Scheme 4. A high enantioselectivity was recorded for the addition product **20**, but the yield remained low.[32a]



Scheme 4. Enantioselective anti-Markovnikov addition of 2-propanol to 1,1-diphenylpropene (**19**).

2.2. Ketones

The relatively high triplet energy of ketones and the fact that upon irradiation, they reach the first excited triplet state (T_1) by an efficient intersystem crossing (ISC) with high quantum yields predestines this class of substances for triplet sensitization.[33] The energy of the ketone T_1 is used for direct excitation of a substrate from its ground state (S_0) to its triplet state (Figure 2, case a), which is forbidden by direct excitation of the substrate. During the sensitization process, the ketone relaxes to its ground state. The low energy of the first excited ketone singlet state (S_1) permits the selective excitation of the ketone in the presence of the substrate without exciting the latter. The ideal energy-level distribution of the excited states for sensitization of a given substrate E by a sensitizer S is therefore $T_1(E) < T_1(S) < S_1(S) < S_1(E)$. Mechanistically, the energy transfer results from an exchange of electrons (Dexter mechanism)[34] and strongly depends on the distance between substrate and sensitizer. Owing to the fact that ketones exhibit a high oxidative power in their excited state, they are also capable of inducing a single electron transfer (SET). Some prominent chiral ketones (**21**–**25**) that have been employed in enantioselective photochemical reactions are depicted in Figure 5.

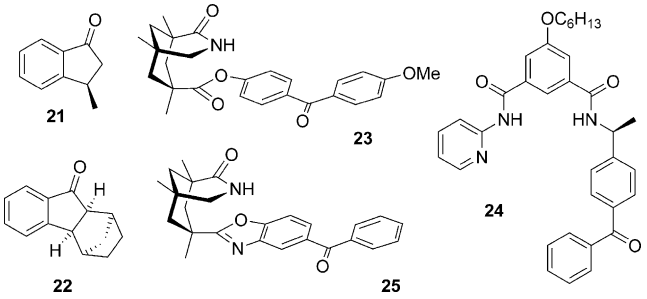
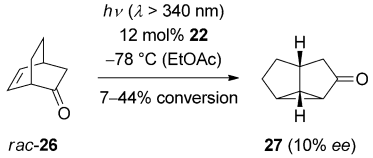


Figure 5. Examples of chiral ketones(**21**–**25**) used as sensitizers for enantioselective photochemical reactions.

Based on the low triplet energy (E_T) of *trans*-1,2-diphenylcyclopropane (*rac*-**7**, Scheme 1), which is approximately 220 kJ mol^{-1}, ketone **21** was used for the enantioselective *E*/*Z* isomerization of *trans*-1,2-diphenylcyclopropane by Ouannès et al. in 1973.[35,36] However, the enantioselectivity was not higher (with a maximum *ee* of 3%) than in the case of singlet sensitization (Scheme 1).

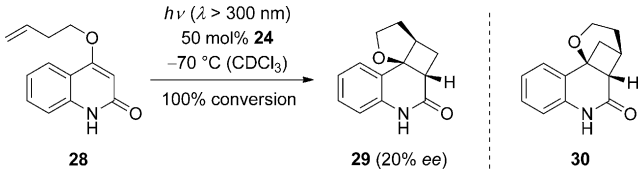
The oxadi-π-methane rearrangement[37] represents a reaction type that is suitable for enantioselective catalysis by triplet sensitization. A commonly used sensitizer for this kind of rearrangement is acetone, which selectively populates the T_1 state of β,γ-unsaturated ketones. After a 1,2-shift, a cyclopropyl ketone is formed as the photoproduct. The prototypical example of this reaction is the rearrangement of bicyclo[2.2.2]oct-5-en-2-one (*rac*-**26**) into tricyclo[3.3.0.0^{2,8}]octan-3-one (*rac*-**27**). However, upon sensitization of *rac*-**26** with chiral ketone **22**, an only marginal selectivity was observed in the attempted kinetic resolution (Scheme 5).[38]

In a similar fashion, again with limited success, the naturally occurring ketones (−)-rotenone and (+)-testosterone were used for the kinetic resolution of 3,5-diphenylpyrazoline. Nitrogen extrusion led to the formation of *trans*-1,2-diphenylcyclopropane (max. 4% *ee*).[39]



Scheme 5. Kinetic resolution in the oxadi-π-methane rearrangement of bicyclo[2.2.2]octenone *rac*-**26**.

Even these few examples illustrate an obvious weakness of triplet sensitization. Although its high efficiency allows for the use of catalytic amounts of chiral ketones, the insufficient orientation of the substrate with respect to the catalyst leads to an unsatisfactory enantioselectivity in the photochemical reaction step. In 1999, our group started with the design of chiral templates that enable an improved enantiotopic face differentiation in photochemical reactions based on a hydrogen-bonding motif. The most efficient templates exhibit a 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton, which can be readily constructed from Kemp's triacid. Preliminary success in diastereoselective Paternò–Büchi reactions[40] was followed by applications of the chiral templates in photocycloaddition and photocyclization reactions.[41] Further attempts to modify these templates for triplet sensitization applications resulted in the synthesis of ketones such as compound **23** during the years 2001 to 2003. Whereas these sensitizers showed the expected catalytic activity, the achieved enantioselectivities remained relatively low ($\leq 25\,\%$ *ee*).[42] At the same time, Krische and co-workers reported their results on the catalytic activity of ketone **24** in the intramolecular [2+2] photocycloaddition of quinolone **28** (Scheme 6). Under optimized reaction conditions, product **29**

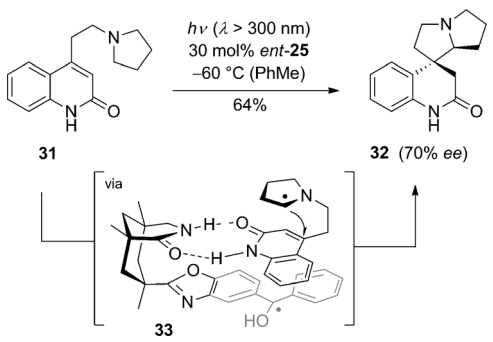


Scheme 6. Enantioselective intramolecular [2+2] photocycloaddition of quinolone **28**.

was obtained in 22 % *ee* using 100 mol % of catalyst **24**, in 20 % *ee* with 50 mol %, and in 19 % *ee* with 25 mol % of the chiral ketone. The reaction time to reach full conversion correlated with the amount of catalyst used.[43] Surprisingly, side product **30**, which was reported by Kaneko et al. in previous work,[44] was not observed.

A major breakthrough in the field of enantioselective photocatalysis was accomplished by the synthesis of ketone **25**. The higher rigidity of the linker allowed for stronger substrate association than with ketones that are connected to the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one backbone by an ester group (e.g., **23**).[45] With ketone **25**, the first enantioselective photoreaction on preparative scale with significant *ee* values and good yields was achieved. Based on the work of Hoffmann and Pete,[46] ketone **25** and its enantiomer *ent*-**25** were used as catalysts for a photoinduced electron transfer (PET) to induce the cyclization of pyrrolidine **31** to spirocyclic compound **32** (Scheme 7). Presumably, the reaction proceeds by an oxidation step and a subsequent proton transfer to generate radical pair **33**. The cyclization occurs enantioselectively before the catalytic cycle is completed by back electron transfer and protonation.

Ketone **25** turned out to be less suitable as a chiral catalyst for traditional triplet sensitization. Its inferior performance might be associated with the fact that a dissociation of the



Scheme 7. Enantioselective PET-catalyzed cyclization of pyrrolidine **31**.

photoexcited molecule from the catalyst is possible at any point of the catalytic cycle and that photoexcited benzophenone is not completely planar,[47] which may facilitate dissociation of the substrate. Furthermore, the electronic changes caused by the annulated oxazole unit might lower the triplet energy of this modified benzophenone.

2.3. Xanthones and Thioxanthones

The structural design of xanthone **34** (Figure 6) took these crucial points into consideration. The compound exhibits a completely flat chromophore, which should favor substrate binding. Furthermore, the tabulated triplet energies[48] for the

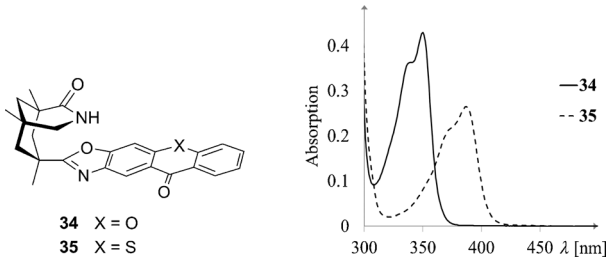


Figure 6. Structures and UV/Vis spectra ($c = 0.5$ mM in trifluorotoluene) of the sensitizers **34** and **35**.

parent compounds xanthone ($E_T = 310$ kJ mol^{-1}) and benzophenone ($E_T = 287$ kJ mol^{-1}) suggest an energetic preference for sensitization by **34** in comparison to **25**. In 2009, our group reported the first application of xanthone **34**,[49] and in 2014, thioxanthone **35** (Figure 6) was introduced,[50] which exhibits a significant absorption at longer wavelengths.

Xanthone **34** catalyzed the previously mentioned intramolecular [2+2] photocycloaddition of quinolone **28** with high enantioselectivity (Scheme 6). Under the optimized conditions ($\lambda = 366$ nm, $c = 5$ mM in $PhCF_3$, $-25\,^{\circ}C$) and using xanthone **34** (10 mol %), the products *ent*-**29** and *ent*-**30** were obtained in 89 % yield after two hours (regioisomeric ratio r.r. = 77:23). Both products were formed with high enantioselectivity (91 % *ee*).[49] As the photoexcited xanthone **34** shows a high tendency for hydrogen abstraction, the reaction was conducted in trifluorotoluene. However, even in this solvent, the catalyst decomposed after prolonged irradi-

ation times. For the reaction of **28**, the simultaneous decomposition of side product *ent*-**30** was observed. Further products **36** resulting from the sensitized enantioselective [2+2] photocycloaddition of quinolones are shown in Figure 7.[51]

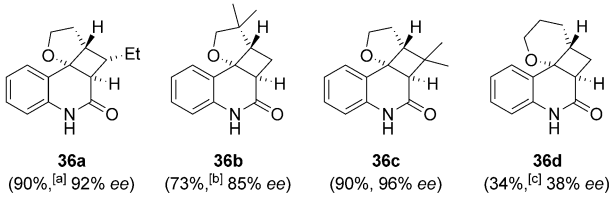
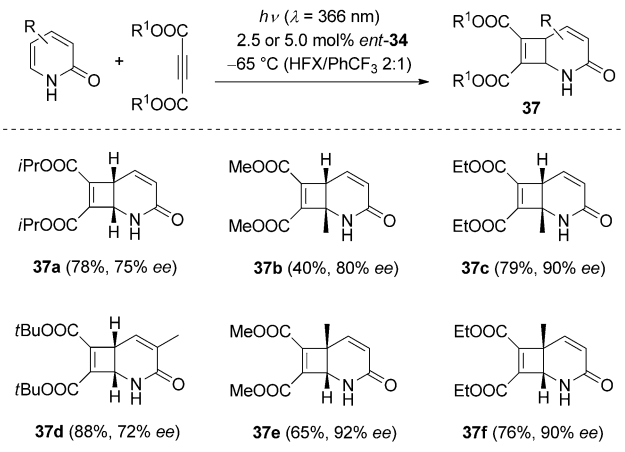


Figure 7. Structures of products **36** formed in an enantioselective [2+2] photocycloaddition catalyzed by xanthone **34** ($\lambda = 366$ nm, $c = 5$ mM in $PhCF_3$, −25 °C). [a] r.r. = 88:12. [b] r.r. = 82:18. [c] r.r. = 78:22.

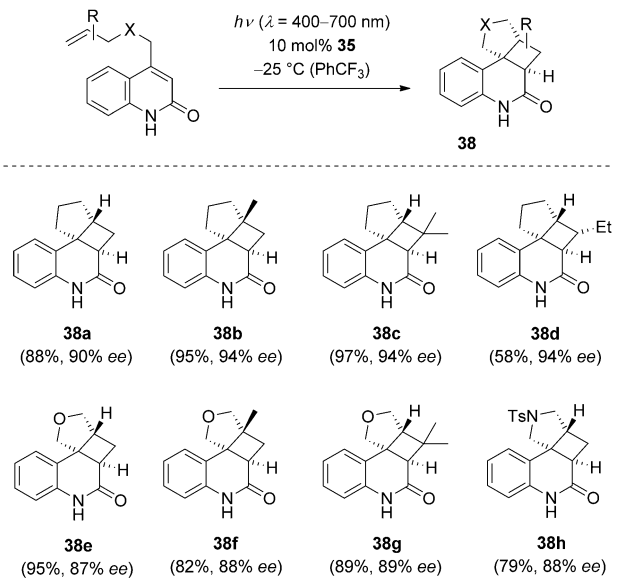
The decrease in enantioselectivity for compound **36d** is notable and explained by the fact that the intramolecular photoreaction occurs more slowly for the six-membered ring than for the corresponding five-membered ring. A significant number of the excited molecules are assumed to dissociate from the catalyst prior to ring formation.[51] It was all the more remarkable that even intermolecular [2+2] photocycloaddition reactions could be conducted enantioselectively using *ent*-**34** (the enantiomer of catalyst **34**). The reactions of pyridones with acetylenedicarboxylates using this catalyst (2.5 or 5 mol%) in a mixture of hexafluoro-*m*-xylene (HFX) and $PhCF_3$ at −65 °C led to the corresponding cyclobutenes in good yields and with high enantioselectivities. Some representative products **37** are depicted in Scheme 8.[52]

The slight bathochromic shift of 4-alkylquinolones in comparison to 4-alkoxyquinolones (Scheme 6 and Figure 7) led to the assumption that these compounds might possess lower triplet energies. Preliminary experiments showed that unsubstituted thioxanthone, with a triplet energy[48] of $E_T = 264\ kJ\,mol^{-1}$, is indeed able to catalyze the intramolecular



Scheme 8. Enantioselective intermolecular [2+2] photocycloaddition reactions of different pyridones with acetylenedicarboxylates catalyzed by xanthone *ent*-**34**.

[2+2] photocycloaddition of 4-(pent-4-enyl)quinolone using visible light. Based on these results, chiral thioxanthone **35** was synthesized and applied to the reaction of substituted 4-(pent-4-enyl)quinolones and their heteroanalogues. The reactions proceeded with outstanding enantioselectivities under visible-light irradiation and delivered the photoproducts **38** (Scheme 9).[50]



Scheme 9. Enantioselective intramolecular [2+2] photocycloadditions of different 4-substituted quinolones catalyzed by thioxanthone **35**.

2.4. Lewis and Brønsted Acids

In 1989, Lewis and Barancyk reported the possibility to catalyze the intermolecular [2+2] photocycloaddition of coumarin and different olefins with Lewis acids (BF_3 or $EtAlCl_2$).[53] This unusual observation is based on the fact that coumarin does not undergo a photocycloaddition in the absence of catalysts as deactivation of the excited state is exceptionally fast.[54] The Lewis acid stabilizes the excited state (Figure 2, case d), which was confirmed by fluorescence measurements, for example. Moreover, Lewis acid coordination leads to an increased ISC rate[55] and to a slight bathochromic shift of the long-wavelength absorption band ($\Delta\lambda =$ 10–20 nm). Although it appears obvious to use this result in the context of enantioselective catalysis, it took until 2010 when in our laboratories, H. Guo identified Lewis acid **39a** in an extensive screening as an appropriate chiral catalyst for an enantioselective photoreaction of coumarins (see Scheme 10).[56] In 2014, the slightly modified Lewis acid **39b**[57] was introduced, and the chiral Brønsted acid **40**[58] was presented in the same year by the group of Sibi and Sivaguru (Figure 8).

To establish the concept of enantioselective Lewis acid catalysis, coumarin **41** was synthesized, which delivered the racemic product *rac*-**42a** in the absence of any chiral information with high regio- and diastereoselectivity. However, this reaction is slow at $\lambda = 366$ nm and probably

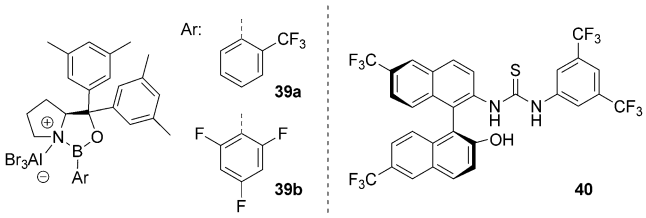
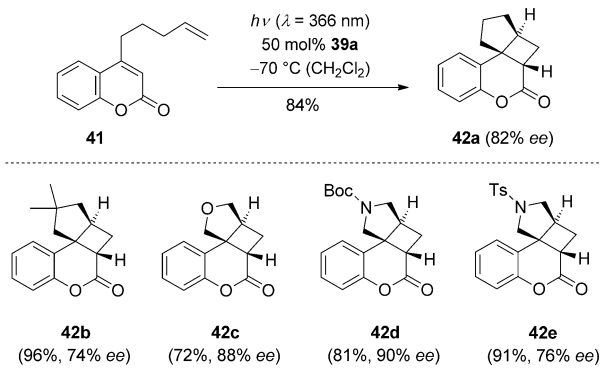


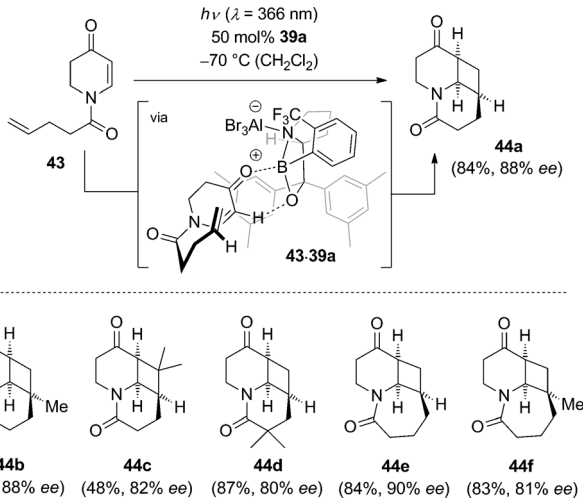
Figure 8. Structures of the chiral Lewis and Brønsted acids **39** and **40** used for enantioselective photocatalysis.

proceeds in the absence of a catalyst on the singlet hypersurface. Oxazaborolidines that are activated by a Lewis acid turned out to be competent catalysts, and compound **39a** was shown to deliver the best selectivities. Under optimized conditions (Scheme 10), product **42a** was isolated with 82% *ee* and in 84% yield. There was evidence that the catalyzed reaction occurs via a triplet intermediate, and further mechanistic studies confirmed that the above-mentioned factors are crucial for the catalytic process.[59] In these studies, the product scope was also extended to lactones **42b–e**, which were formed in good yields and enantioselectivities.



Scheme 10. Enantioselective intramolecular [2+2] photocycloaddition of coumarin **41** to product **42a** and structures of the related products **42b–e**. Boc = *tert*-butoxycarbonyl, Ts = *para*-toluenesulfonyl.

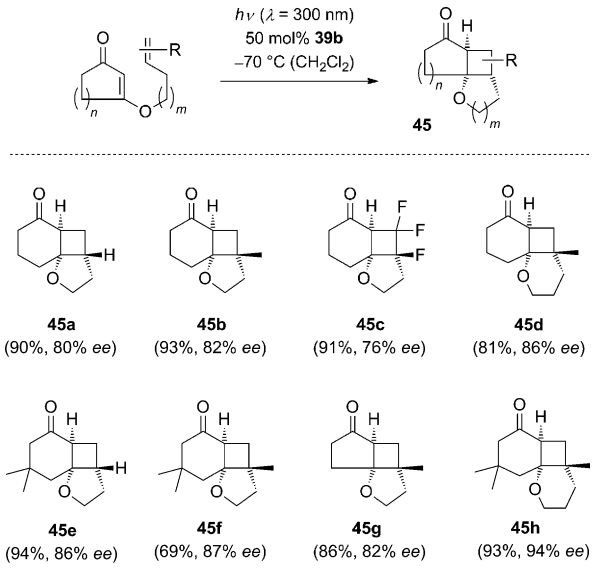
In 2013, it was surprisingly observed in our laboratories that the chiral Lewis acid **39a** also enables the enantioselective intramolecular [2+2] photocycloaddition of a typical enone substrate, namely of dihydropyridone[60] **43**.[61] This was unexpected as the substrate readily reacted in an uncatalyzed [2+2] photocycloaddition at the selected wavelength ($\lambda =$ 366 nm). Indeed, enones are known to undergo a direct [2+2] photocycloaddition owing to a weak long-wavelength n–π* transition, followed by an efficient ISC to the T_1 state.[62] The observed high enantioselectivities can probably be explained by the fact that the complex between substrate and Lewis acid exhibits a very strong absorption ($\varepsilon >$ 10000 $M^{-1}cm^{-1}$) at the irradiation wavelength. It was shown that the coordination of Lewis acids to an enone led to an extensive bathochromic shift of the allowed π–π* transition ($\Delta\lambda = 50$–60 nm). Consequently, it is obvious that light is exclusively absorbed by the complex (Figure 2, case c) and that the reaction to the products **44** proceeds only from this complex (Scheme 11). The face differentiation can be explained by an established model for enantioselective (thermal) reactions of enones catalyzed by oxazaborolidine-based Lewis acids.[63] According to this model, not only the binding of the carbonyl oxygen atom to the Lewis acid center, but also an α-C–H···O hydrogen bond is responsible for the fixation of the substrate (complex **43**·**39a**). The products obtained are interesting in terms of their synthetic potential as they contain a bicyclic framework, which is an integral part of quinolizidine alkaloids. The [2+2] photocycloaddition in combination with the fragmentation of the cyclobutane ring was applied to the total synthesis of (+)-lupinine and to the formal total synthesis of (+)-thermopsine.



Scheme 11. Enantioselective intramolecular [2+2] photocycloaddition of dihydropyridone **43** to product **44a** and structures of the related products **44b–f**.

A further application of the concept of enantioselective Lewis acid catalysis was recently achieved with different 3-alkenyloxy-2-cycloalkenones as the substrates (Scheme 12).[57] In this case, the absorption responsible for the enantioselective reaction is located at about $\lambda \approx 300$ nm, so that an irradiation source with shorter wavelength emission was used. The Lewis acid was modified (**39b**) to achieve the highest enantioselectivity. In this case, the amount of the catalyst could be reduced without a loss of enantioselectivity. However, the reactions were very slow, and 50 mol% of the catalyst were used to achieve complete conversion. Among the products **45**, those bearing a methyl or fluoro substituent at the position where the cyclobutane is connected to the oxygen heterocycle are especially interesting in terms of synthetic applications. These products (**45b–d**, **45f–h**) can undergo ring expansion under acidic conditions and form heterocyclic annelated seven- and eight-membered rings. The enantioselectivities in the [2+2] photocycloaddition reached up to 94% *ee* (product **45h**).

Recently, Sibi, Sivaguru, and co-workers showed that the [2+2] photocycloaddition of coumarin **41** can be enantioselectively catalyzed by thioureas.[58] Under optimized conditions, product *ent*-**42a** was formed with 77% yield and 92% *ee* using only 10 mol% of catalyst **40** (Figure 8). It was demonstrated that the hydroxy group in the naphthalene framework



Scheme 12. Enantioselective intramolecular [2+2] photocycloaddition of 3-alkenyloxy-2-cycloalkenones to yield products **45**.

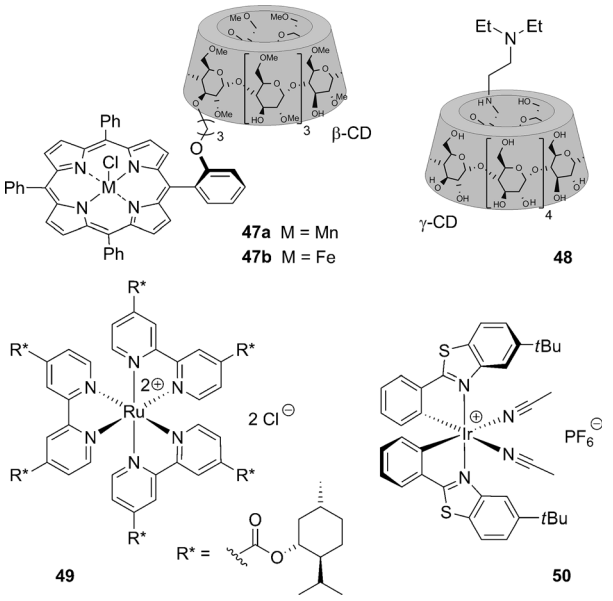


Figure 10. Structures of the chiral ligands and metal complexes **47**–**50**.

of **40** is essential for a successful reaction, as a hydrogen bond is formed to the lactone oxygen atom of the coumarin. The substrate scope was extended to other coumarins, and the corresponding photocycloaddition products **46** were formed with high *ee* values (Figure 9). According to GC or NMR analysis, the reactions proceeded with full conversion, but yields were not given.

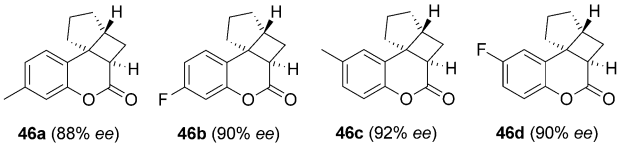
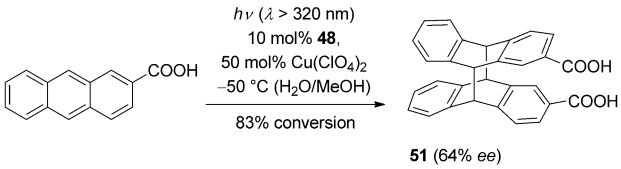


Figure 9. Products **46** formed in an enantioselective [2+2] photocycloaddition catalyzed by Brønsted acid **40** (10 mol%; $\lambda = 350$ nm, $c = 20$ mM in toluene/*m*-xylene (1:1), −78 °C).

2.5. Transition-Metal Complexes

Despite the major importance of transition-metal catalysis for many thermal reactions, there are relatively few examples of enantioselective processes catalyzed by chiral metal complexes in photochemistry. In this context, modified cyclodextrins bearing a ligand for a metal ion, such as compounds **47**[64] and **48**,[65] and the chiral complexes **49**[66] and **50**,[67] are worth mentioning (Figure 10).

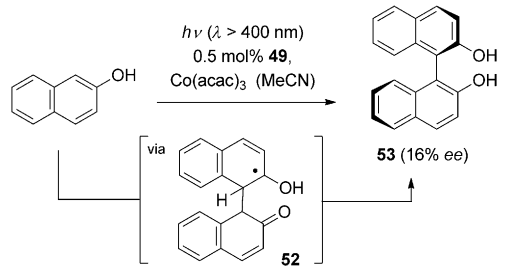
Porphyrin complex **47** was already applied in 1992 by Weber et al. in the kinetic resolution of α-pinene by a photooxygenation process. The reaction was monitored by GC analysis, revealing the formation of several products. The best results (up to 67% *ee* using **47a**) were obtained in the presence of 2-methylpyridine, and the authors assumed that this ligand occupies one face of the complex. Thus, the generated singlet oxygen ($^1O_2$) is guided to the binding pocket in which the substrate is located. The issue as to how to direct the reaction to the binding pocket of a cyclodextrin also plays an important role in the copper(II)-catalyzed [4+4] photodimerization of 2-anthracenecarboxylic acid (Scheme 13).[65]



Scheme 13. Enantioselective [4+4] photodimerization of 2-anthracenecarboxylic acid to chiral product **51**.

It was assumed that the copper atom pre-coordinates both anthracene molecules, and that the reaction occurs only inside cyclodextrin **48**. Outside the chiral cavity, the distances between the reactive centers are too long. The coordination increases the amount of chiral product **51**, which is formed with a relative yield of 51% and with 64% *ee* in a product mixture of four possible dimers at 83% conversion.

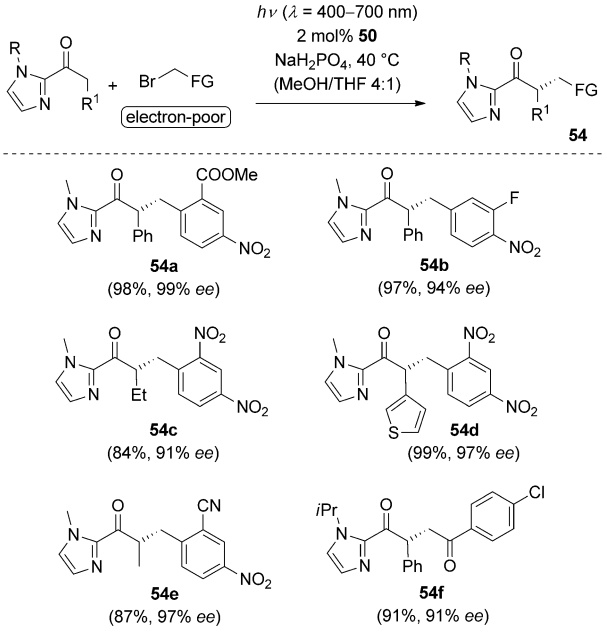
Among the chiral ruthenium complexes[68] described by Ohkubo and co-workers in the 1980s and 1990s, the chiral complex **49**[69] is of considerable interest. Not only was an enantioselective reduction of $[Co(acac)_3]$ to the corresponding Δ-enantiomer (up to 94% *ee*) achieved,[70] but it was also possible to catalyze an oxidative dimerization of 2-naphthol by carbon–carbon bond formation (Scheme 14). In the latter case, the Ru^{II} complex, which can be excited by light of longer wavelengths, is presumably oxidized by $[Co(acac)_3]$, and the resulting Ru^{III} complex acts as a strong oxidant for 2-naphthol. After release of a proton, the resulting radical attacks a second 2-naphthol molecule generating intermediate **52**, which enantioselectively forms 2,2′-binaphthol **53** after



Scheme 14. Enantioselective oxidative dimerization of 2-naphthol to product **53**.

a second oxidation by the photooxidized Ru^{III} complex. The *ee* values were lower with 3-methoxy-2-naphthol (4% *ee*) than with 2-naphthol. Nevertheless, this reaction still represents an important milestone on the road towards enantioselective photocatalysis using visible light.

Recently, iridium complex **50** was synthesized by Meggers and co-workers as a chiral sensitizer for the photochemical alkylation of 2-acylimidazoles.[67a] The proposed catalytic cycle, which includes a single electron transfer from the excited catalyst to the alkyl bromide, resembles the cycle for the dual catalytic process with Ru and Ir complexes that will be discussed in the next Section. Despite this similarity, the design principle is conceptually novel as the metal complex is also responsible for the face differentiation so that the addition of the formed alkyl radicals to the enolate occurs with high enantioselectivity. The low catalyst loading necessary to achieve high yields of products **54** is remarkable (Scheme 15).



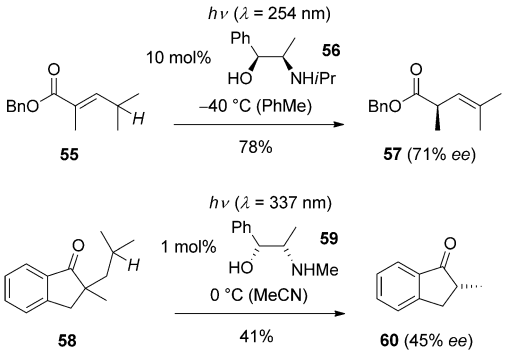
Scheme 15. Enantioselective α-alkylation of 2-acylimidazoles catalyzed by chiral Ir complex **50**.

3. Chiral Catalysts in Photoreactions (Dual Catalysis)

In this Section, photochemical reactions are discussed in which two catalysts are generally involved and usually one of these catalysts is not chiral. In these cases, the light-induced formation of an intermediate occurs in a preceding process; this intermediate then undergoes a successive enantioselective key step under the influence of a chiral catalyst. The first step can simply be light-catalyzed or it can be of higher complexity and involve a reduction or oxidation process. Despite the possibility to divide this Section according to different reaction mechanisms, the concept for Section 2 is retained and the subsections are arranged based on the type of chiral catalyst.

3.1 Amino Alcohols

One of the first enantioselective photoreactions that was extensively investigated in the 1980s and 1990s was the protonation of photochemically generated enols with weak chiral Brønsted acids, mostly β-amino alcohols. In some cases, it was possible to conduct the reaction in a catalytic fashion and to achieve significant enantioselectivities (Scheme 16).



Scheme 16. Photochemically induced enol formation and enantioselective protonation shown exemplarily for substrates **55** und **58**. The abstracted hydrogen (*H*) is drawn in italics.

The photochemical deconjugation of α,β-unsaturated carboxylic acid derivatives was extensively studied in the laboratories of Pete.[71] In these instances, γ-hydrogen abstraction was induced by irradiation leading to the formation of a dienol. In the depicted case with substrate **55**, a photochemical *E*/*Z* isomerization has to occur prior to the abstraction of the hydrogen atom (Scheme 16).[72] Norephedrine derivative **56** turned out to be the best proton source, which led to an enantioselective protonation to product **57**. The reaction is catalytic because the deprotonation of the dienol occurs simultaneously with the enantioselective protonation step. In a similar fashion—albeit probably via a triplet pathway—hydrogen abstraction in ketone **58** induces fragmentation (Norrish type II cleavage)[73] to an enol, which is protonated by (−)-ephedrine (**59**) generating product **60**.[74] Further reactions catalyzed by chiral Brønsted acids can be

found in Section 3.3. However, in these cases, the influence of the chiral counterion is crucial for the chiral induction.

3.2. Amines

The success that chiral amines have had and continue to have in organocatalysis has also extended to the field of enantioselective photochemistry. Many well-known scaffolds are encountered that have already been identified as privileged structures for non-photochemical reactions, such as pyrrolidines **61**,[75] **64**,[76] and **65**,[77] imidazolidinones **62**[78] and **63**,[79] as well as quinine derivatives such as **66**[80] (Figure 11).

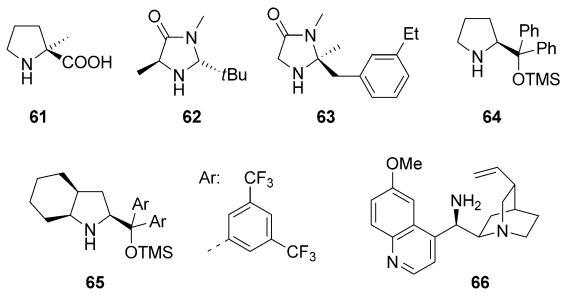
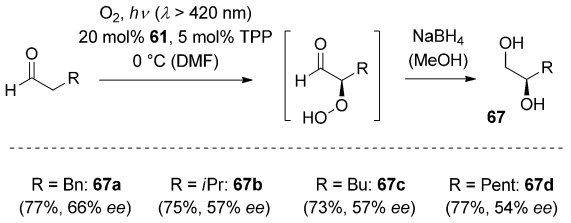


Figure 11. Structures of chiral amines **61**–**66**.

In photochemistry, amines are used almost exclusively for enamine catalysis, that is, carbonyl compounds are temporarily converted into enamines, which exhibit a higher nucleophilicity and are more readily oxidized. In 2004, Córdova et al. reported a first application of enamine catalysis in enantioselective reactions of aldehydes with photochemically generated singlet oxygen ($^1O_2$).[81] In this instance, tetraphenylporphyrin (TPP) was used as a sensitizer, and the generated $^1O_2$ led to the formation of the corresponding hydroperoxide in an ene-type reaction (Scheme 17). Mechanistically, this reaction was suggested to proceed analogously to proline-catalyzed additions of enamines of this type to carbonyl compounds.[82] The intermediary α-hydroperoxy aldehydes were immediately reduced, and the corresponding diols **67** were obtained in good enantioselectivity. In this work, α-methylproline (**61**) was used as the catalyst. In a later study, significantly higher *ee* values were obtained in some cases (up to 98% *ee*) with catalyst **64**.[83] The reaction was also successfully applied to the α-hydroxylation of ketones.[84]



Scheme 17. Enantioselective α-hydroxylation of aldehydes with singlet oxygen catalyzed by amine **61**.

In a publication that was seminal for the further development of this field, Nicewicz and MacMillan showed in 2008,[78] that it is possible to perform enantioselective α-alkylation reactions of aldehydes with visible light. The key finding was that the ruthenium complex $[Ru(bpy)_3]Cl_2$ (**68**),[85] hitherto little used in organic synthesis, could be employed as a PET catalyst (bpy = 2,2′-bipyridine). Instead of the previously used term PET catalysis, the term photoredox catalysis was created. Simultaneously, $[Ru(bpy)_3]Cl_2$ (**68**) was employed by the group of Yoon for a PET-catalyzed, yet racemic reaction with visible light (see Scheme 27).[86] Many other catalysts of this type have been developed since then, and the area of photoredox catalysis is growing rapidly.[87] Several iridium complexes, for example, $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (**69**; ppy = 2-phenylpyridine),[88] are of importance for such enantioselective processes and are therefore depicted in Figure 12 along with eosin Y (**70**)[89] as an example of an organic photoredox catalyst that absorbs in the visible-light region.

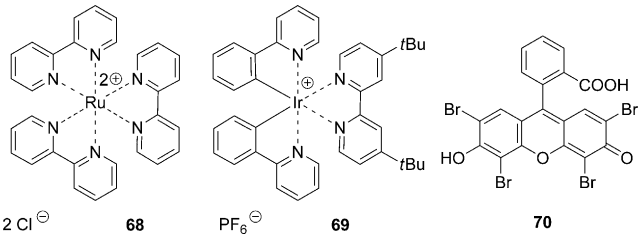
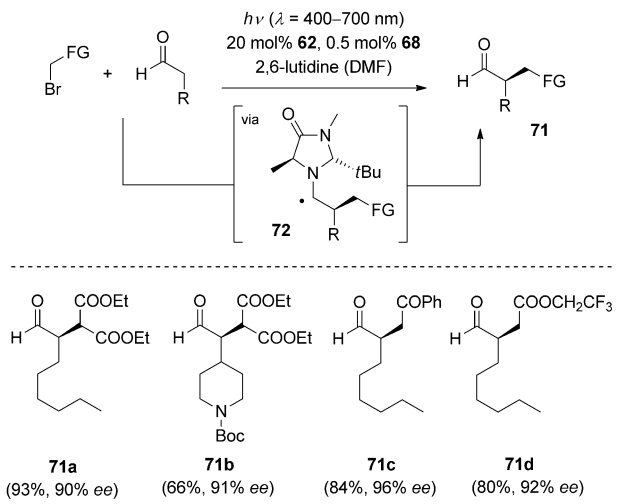


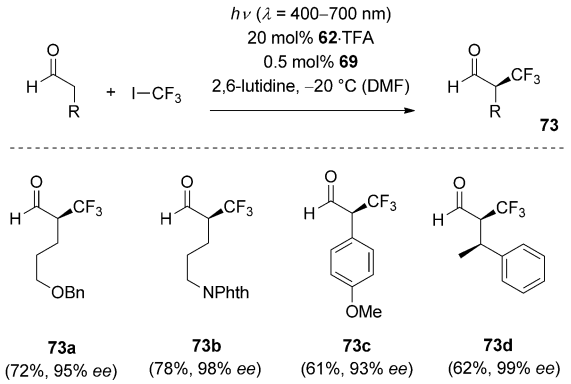
Figure 12. Structures of photoredox catalysts **68**–**70**.

According to the authors, the crucial step in the above-mentioned α-alkylation to products of type **71** is the ability of $[Ru(bpy)_3]Cl_2$ (**68**) to act as a strong oxidant in the excited state.[78] The catalytic cycle is initiated by the oxidation of a small amount of enamine formed from aldehyde and amine. The reduced ruthenium(I) complex is oxidized to $[Ru(bpy)_3]Cl_2$ (**68**) by single-electron transfer to the alkyl bromide, which carries at least one acceptor substituent (FG = functional group). Simultaneously, an electrophilic radical is generated upon bromide cleavage, which adds to the enamine furnishing intermediate **72**. The cycle restarts by oxidation of **72** with photoexcited $[Ru(bpy)_3]Cl_2$ (**68**). The face differentiation as well as the hydrolysis of the enamine follow the established principles of organocatalysis with imidazolidinone **62**.[90] The photoreaction can be conducted with visible light and proceeds much faster upon specific excitation of the MLCT band (MLCT = metal-to-ligand charge transfer) of **68** ($\lambda = 435$ nm) than with commonly used fluorescent lamps. Aside from the examples shown in Scheme 18, compounds bearing nitro or methoxy groups or carrying olefinic double bonds were successfully converted.

Given the importance of organofluorine compounds, the α-trifluoromethylation of aldehydes that was discovered by the MacMillan group in 2009 was a welcome extension of photochemical alkylation methods (Scheme 19).[88] In this study, $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (**69**) was used as the photocatalyst, and the reaction was carried out at −20 °C. Mechanistically, a pathway is assumed to occur that is analogous to



Scheme 18. Enantioselective α-alkylation of aldehydes by dual catalysis with $[Ru(bpy)_3]Cl_2$ (**68**) and amine **62**.

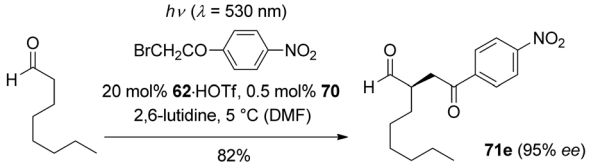


Scheme 19. Enantioselective α-trifluoromethylation of aldehydes by dual catalysis with Ir complex **69** and amine **62**. Phth = phthaloyl, TFA = trifluoroacetic acid.

the above-mentioned reaction course (see Scheme 18). The functional group tolerance as well as the extremely high enantioselectivity are clearly demonstrated by the depicted examples. The diastereoselectivity control by adjacent stereogenic centers is overridden as shown for product **73d**, which was obtained with equally high selectivity as its epimer derived from the enantiomeric alcohol. Apart from iodotrifluoromethane, iododifluoroalkanes can also be used as substrates.

Aldehydes can be α-benzylated in a fashion similar to that depicted in Schemes 18 and 19.[91] Either catalyst **68** or **69** can be used for this purpose, but the uncharged Ir catalyst *fac*-$[Ir(ppy)_3]$ proved to be most versatile. As the fluorescence of the excited complex is not quenched by enamines, the authors postulated a primary reduction of the photoexcited state by the benzylic halide for this transformation; the benzylic radical then enters the cycle described above.

In 2011, a completely metal-free enantioselective alkylation was successfully performed by Zeitler and co-workers using eosin Y (**70**) as the photoredox catalyst.[89] Mechanistically, there is a difference in the primary step because eosin Y undergoes a rapid ISC to the triplet state. However, this triplet state can act as an oxidizing agent in the same way as photoexcited $[Ru(bpy)_3]Cl_2$ (**68**), resulting in a similar mechanism, as indicated in Scheme 18. As an example, the formation of alkylation product **71e** is shown in Scheme 20. Product **71a** (Scheme 18) was obtained in a yield of 85% with



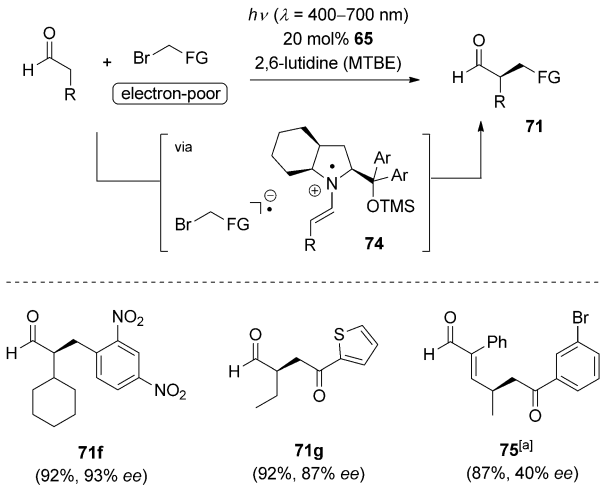
Scheme 20. Enantioselective α-alkylation by dual catalysis with eosin Y (**70**) and amine **62**.

88% *ee* in a process catalyzed by eosin Y (**70**). Monochromatic green light from a light-emitting diode (LED) was used as the light source, resulting in higher reproducibility compared to the use of household lamps. The quantum yield for the eosin Y (**70**) catalyzed photochemical alkylation was reproducibly determined to be 0.06 to 0.09, rendering a radical chain mechanism unlikely.

Aside from eosin Y (**70**), other photocatalysts—some being heterogeneous—were reported that can take on the role of $[Ru(bpy)_3]Cl_2$ (**68**) in enantioselective α-alkylations.[92]

In recent studies, Melchiorre and co-workers showed that in many cases, no second catalyst is necessary for the α-alkylation of aldehydes[77] and ketones.[93] Direct excitation with visible light is sufficient to carry out such alkylations. Nicewicz and MacMillan had already found that the reaction products **71a** and **71c** could be obtained under short-wavelength irradiation ($\lambda = 300$–350 nm) without addition of a photocatalyst.[78] In the laboratories of Melchiorre, phenacyl bromides and electron-deficient benzyl bromides were reacted with various aldehydes in the presence of chiral pyrrolidines, such as **64** and **65**. The occurrence of an absorption band at long wavelengths is noteworthy and was attributed to an electron donor–acceptor (EDA) complex. According to the authors, direct excitation of this complex leads, upon charge separation, to radical pair **74** (Scheme 21). Cleavage of bromide from the radical anion leads to the formation of a radical, which undergoes C–C bond formation within the solvent cage. In this way, products **71f** and **71g** were obtained in an enantioselective fashion. Remarkably, γ-alkylation[94] to products such as **75** is also possible when an α,β-unsaturated aldehyde is used. Mechanistically, the addition of a radical to an enamine was excluded because such an addition would not produce a radical center at the β-position of the enamine, which, however, was substantiated by a radical clock experiment. Of interest is the observation that irradiation of an aliphatic aldehyde (butyric aldehyde) with visible light ($\lambda = 460$ nm) in the presence of phenacyl bromide and a pyrrolidine catalyst (20 mol%) yielded the corresponding product (see product **71c**) even in the absence of a photoredox catalyst (72% yield).

The reaction pathway observed by the Melchiorre group indeed corresponds to a direct photocatalysis as presented in



Scheme 21. Enantioselective α-alkylation of aldehydes by direct excitation and catalysis with pyrrolidine **65**. [a] Pyrrolidine **64** was used as the catalyst for this reaction. MTBE = methyl *tert*-butyl ether.

Section 2, as a red shift of the absorption is induced by the catalyst, which then enables selective excitation (see Figure 2, case b). Some products **76**, which were formed with amine catalyst **66** (20 mol % with 40 mol % trifluoroacetic acid) in an enantioselective α-alkylation, are depicted in Figure 13.

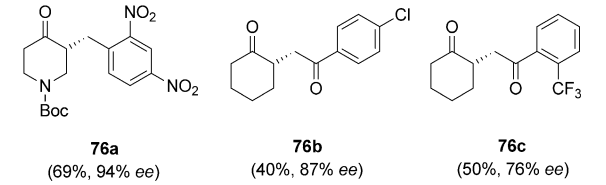
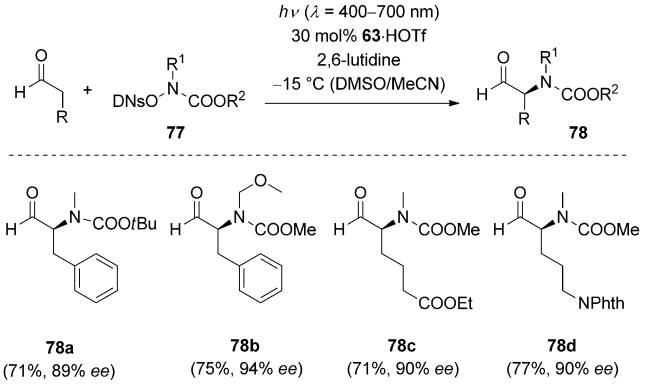


Figure 13. Products **76** obtained in an enantioselective α-alkylation of ketones by direct excitation in the presence of the ammonium salt of amine **66**.

Recently, Luo and co-workers showed that a chiral β-aminoalkylammonium ion allows for the enantioselective alkylation of β-keto esters and 1,3-diketones with α-bromocarbonyl compounds.[95] In a dual catalytic process, $[Ru(bpy)_3]Cl_2$ (**68**) was employed to generate a radical, as described before (Scheme 18), which then attacks the enamine formed from the ketone and the chiral amine. It was assumed that the ammonium ion directs the α-acyl radical to the enamine by a hydrogen bond. An EDA pathway was considered to be less likely in this case.

Aside from an enantioselective C–C bond formation in the α-position of carbonyl compounds, photochemistry has been successfully used for the enantioselective amination and oxamination of this class of compounds. In 2011, the group of Jang reported a photochemical α-oxamination of aldehydes with (2,2,6,6-tetramethylpiperidine-1-yl)oxyl (TEMPO) using TiO_2 and an amine as the catalyst system. The best enantioselectivities (up to 78 % *ee*) were obtained with catalyst **64** or its 3,5-bis(trifluoromethyl)phenyl analogue.[92a] Mechanistically, it remained unclear whether the reaction was induced by photooxidation of TEMPO or the enamine intermediate. In 2013, amination reagent **77** (DNs = 2,4-dinitrophenylsulfonyl) was found to be suitable for SET processes in the MacMillan laboratories.[79] Optimization of the chiral amine led to imidazolidinone **63** as the ideal catalyst (Scheme 22).



Scheme 22. Enantioselective α-amination of aldehydes by direct excitation of reagent **77** and catalysis with imidazolidinone **63**. HOTf = trifluoromethanesulfonic acid.

The authors postulated a mechanism that is related to the α-alkylation mechanism (see Scheme 18). The initial step entails the addition of an amino radical to the enamine to generate a species analogous to **72**. SET from excited **77** generates the iminium ion. Upon hydrolysis, this iminium ion yields products **78** and the radical anion of **77**, which undergoes dinitrophenylsulfonate expulsion to form a new amino radical.

3.3. Anions as Counterions

In recent years, many examples have shown that chiral Brønsted acids induce asymmetric induction via the corresponding counterion.[96] Typical representatives of these compounds, namely **79**[97,98] and **80**[99], which are now also used in photochemistry, are shown in Figure 14.

Rueping and co-workers successfully combined a photochemical *E*/*Z* isomerization with a subsequent organocatalytic reduction. Initial studies in 2013 focused on the enantioselective hydrogenation of benzopyrylium ions that were obtained from *E*-configured chalcones with an *ortho*-hydroxyphenyl group in the β-position of the enone system.[100] In the same year, studies on the reduction of nitrogen analogues, namely *ortho*-amino-substituted chal-

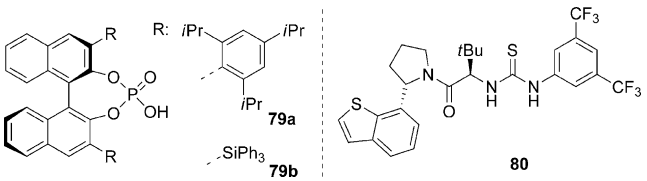
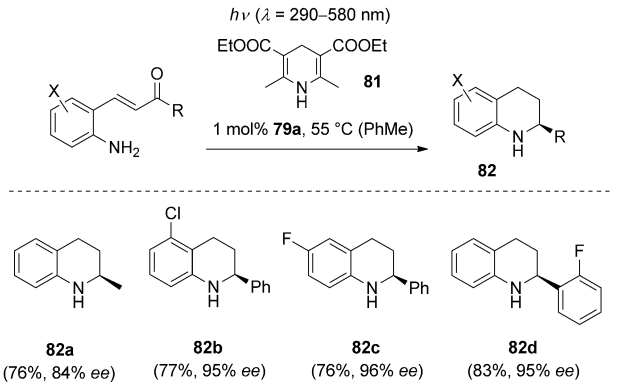


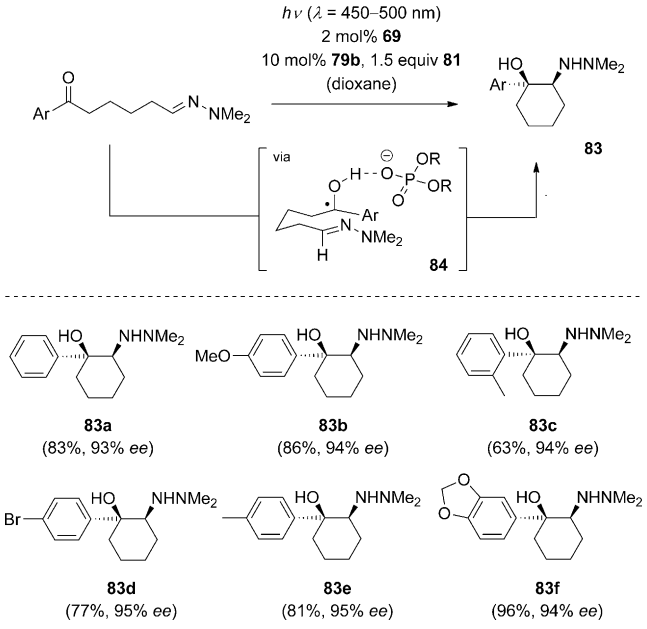
Figure 14. Chiral Brønsted acids **79** and **80** as precursors for chiral anions that are used as counterions.



Scheme 23. Synthesis of 2-substituted 1,2,3,4-tetrahydroquinolines (**82**) by a sequence combining photochemical *E*/*Z* isomerization and enantioselective hydrogenation.

cones (Scheme 23), were performed.[101] A high-pressure mercury lamp was employed to induce the isomerization. The resulting dihydroquinolinium salt is hydrogenated in the presence of chiral phosphoric acid **79a** by Hantzsch ester **81** to produce the corresponding tetrahydroquinolines **82** with high enantioselectivities. This domino reaction can be carried out in a flow reactor, with the best results attained at a substrate concentration of 0.03 M in chloroform as the solvent and at a flow rate of 0.1 mL min^{-1}.[102]

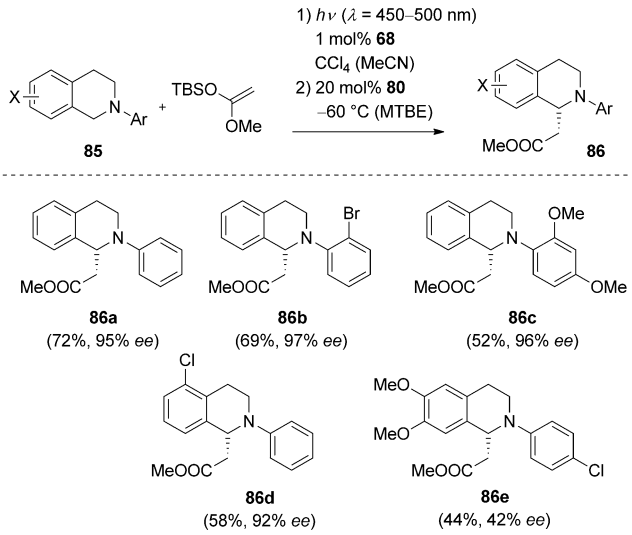
In a novel approach, a photochemical method was used for an asymmetric intramolecular pinacol coupling between a ketone and a hydrazone by the Knowles group in 2013 (Scheme 24).[103] In this study, products **83** were formed with high diastereo- and enantioselectivity. Mechanistically, it was proposed that the reduced iridium(II) complex formed from $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (**69**) induces a proton-coupled electron transfer to the keto group of the substrate. The resulting



Scheme 24. Enantioselective aza-pinacol cyclization by dual catalysis with Ir catalyst **69** and chiral phosphoric acid **79b**.

intermediate is radical **84**, which undergoes cyclization via the conformation shown in Scheme 24. The face differentiation is guaranteed by the chiral counterion derived from phosphoric acid **79b**. As a stoichiometric reductant, Hantzsch ester **81** was used. Blue LED lamps served as the light sources.[11]

In a study reported by the laboratories of Jacobsen and Stephenson in 2014, the photochemical generation of an intermediate was completely separated from the subsequent enantioselective organocatalytic C–C bond formation event (Scheme 25).[99] In the first, photochemical step, the corre-



Scheme 25. Dual catalysis for the preparation of 1-substituted tetrahydroisoquinolines **86** by a sequence combining an oxidation with an enantioselective Mannich reaction.

sponding 1-chlorinated products were generated from 1,2,3,4-tetrahydroisoquinolines (**85**) by photochemical oxidation with carbon tetrachloride as the stoichiometric oxidant. In the second step, a Mannich reaction with a silyl ketene acetal occurred, wherein the chiral counterion **80**-Cl$^-$ was responsible for the asymmetric induction. Aside from the depicted products **86a–d**, there are also examples with significantly lower yields and selectivities, especially for 6,7-dimethoxy-substituted isoquinolines (product **86e**).

A reaction sequence combining photocatalytic oxidation with a semipinacol rearrangement was enantioselectively performed by the group of Xiao employing ruthenium catalyst **68** and a chiral phosphoric acid (one example, 60% *ee*).[104]

3.4. Cations as Counterions

Chiral cations have played a very important role in phase-transfer catalysis for quite some time.[105] In combination with a photooxygenation, ammonium salt **87** was employed for this purpose,[106] whereas amine **88a** and imine **88b** acted as ligands for a cationic metal ion (Figure 15).[107]

In 2012, 1-indanone-derived keto esters were used by Meng, Gao, and co-workers as precursors for enolates, which

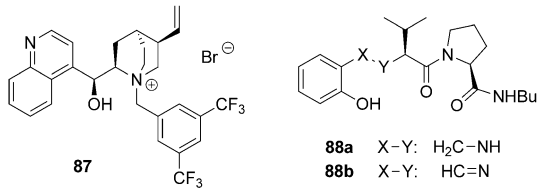
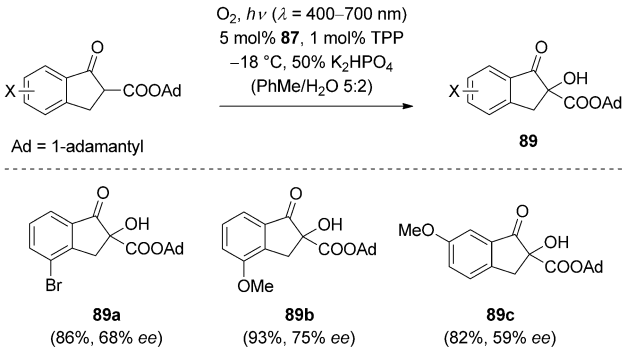


Figure 15. Salt **87** and ligands **88** yield chiral cations.

can react with singlet oxygen in an enantioselective fashion using ammonium salt **87** (Scheme 26).[106] Upon α-oxygenation, products **89** were formed in enantioselectivities of 39–75% *ee*.

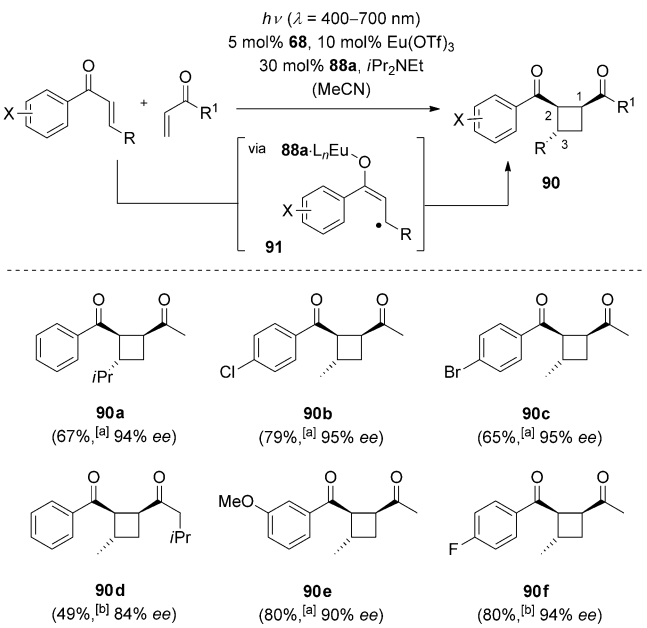


Scheme 26. Enantioselective α-hydroxylation of β-keto esters with singlet oxygen by phase-transfer catalysis with ammonium salt **87**.

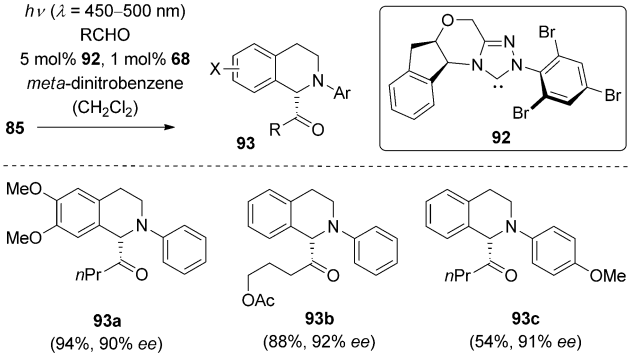
Based on their briefly mentioned pioneering work in photoredox catalysis,[86] the group of Yoon refined the ruthenium-catalyzed [2+2] photocycloaddition to an enantioselective process.[107] The observation that photocatalytic Ru-mediated reduction of the aryl enone component is facilitated by coordination to a Lewis acid was key to successful asymmetric induction. Using $Eu(OTf)_3$ and chiral ligand **88a**, products **90** were formed with high enantioselectivity. The metal salt probably acts as a chiral counterion of radical anion **91** and thus guarantees the face differentiation. Remarkably, the simple diastereoselectivity is highly dependent on the choice of ligand **88**. With amine **88a**, the 1,2-*cis*-2,3-*trans* products (diastereomeric ratio d.r. = 66:34 to 82:18) are preferably formed as shown in Scheme 27. In contrast, imine **88b** as the ligand afforded predominantly the *trans*,-*trans* products while the absolute configuration at the C3 position remained unchanged.

3.5. Miscellaneous

In 2012, Rovis and co-workers reported the formation of iminium ions from 1,2,3,4-tetrahydroisoquinolines (**85**) under oxidative photocatalysis.[108] These iminium ions can be trapped by aldehydes in the presence of nucleophilic carbene **92** (Scheme 28). The chiral catalyst causes an umpolung of the aldehyde so that an acyl anion equivalent adds to the respective iminium ion. In contrast to the reaction discussed



Scheme 27. Dual catalysis of an enantioselective [2+2] photocycloaddition to yield 1,2,3-trisubstituted cyclobutanes **90**. [a] d.r. = 78:22. [b] d.r. = 66:34.



Scheme 28. Enantioselective α-acylation of 1,2,3,4-tetrahydroisoquinolines (**85**) by dual catalysis with $[Ru(bpy)_3]Cl_2$ (**68**) and carbene **92**.

in Scheme 25, the asymmetric induction is determined by the nucleophile, and not by the counterion of the electrophile. The reaction is compatible with a variety of functional groups, which are incorporated as part of the R substituent of products **93**. Aside from the acetoxy group (product **93b**), aldehydes with phenyl, cyclopropyl, vinyl, sulfanyl, and phthalimido groups were successfully reacted.

The oxidative photochemical preparation of 3,4-dihydroisoquinolinium ions has recently been successfully combined with the enantioselective copper-catalyzed addition of alkynes by the group of Li.[109] Among the copper ligands tested (including bisoxazolines[110] and diphosphanes), 1-(2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP) was the most successful. Various 1-alkynylated N-arylated 1,2,3,4-tetrahydroisoquinolines resulted from this reaction with high selectivity (60–97% *ee*). Further single examples in which a photochemically generated dihydroisoquinolinium ion was

reacted enantioselectively with a nucleophile in a dual catalysis approach were described for the Mannich reaction[111] and an aza-Baylis–Hillman reaction.[112]

4. Summary and Outlook

The year 2015 has been proclaimed as the "International Year of Light" by the United Nations. The motto is "Light for Change". No other science can meet this motto better than chemistry as chemistry is the science that is responsible for the change of matter. If one adds the fascinating world of chirality and chiral molecules to the fascinating reagent light, a link to the topic of this Review is readily established. The enantioselective catalysis of photochemical reactions has become an area of chemistry that currently develops quickly and in which the state of knowledge is growing rapidly. In this respect, this Review is only a snapshot[113] that attempts to summarize the developments from several perspectives. The historical perspective begins exactly 50 years ago with the first study on the enantioselective sensitization of 1,2-diphenylcyclopropane. In the last quarter of the twentieth century, the field was led into the 21st century by pioneering work on sensitization on the one hand and on dual catalysis on the other hand. Since the beginning of this century, catalysts that enable photoreactions with both high yields and enantioselectivities have been developed. The mechanistic perspective makes it clear that the dividing line between dual catalysis and classical photocatalysis is not always sharp. Each of the two areas has its advantages and applications, but of course, the charm of photochemistry still lies in the construction of scaffolds and bonds that are not accessible by conventional methods. If visible light, or ideally sunlight,[114] can be used for enantioselective reactions of this kind, innovative, sustainable procedures will be readily developed and widely used. When writing these lines, our thoughts travel almost automatically to G. Ciamician, one of the pioneers of photochemistry, whose visions of photochemical applications[115] have become reality in a way that would certainly leave him amazed.

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