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Perspective

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Lactam Hydrogen Bonds as Control Elements in Enantioselective Transition-Metal-Catalyzed and Photochemical Reactions

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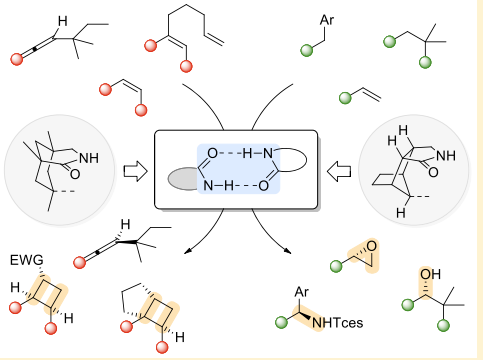
ABSTRACT: In the last two decades, hydrogen bonds have been established as useful interactions to control the selectivity of various chemical transformations. In this Perspective, the contributions by our group to this growing field of research are summarized and analyzed. In the first section, a chiral template is presented which displays a 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton with a lactam binding site and that has been used in superstoichiometric quantities in a variety of photochemical and radical reactions. Chiral catalysts with a related architecture evolved from the template by introducing a suitable chromophore for harvesting photons in the ultraviolet (benzophenone, xanthone) or visible region (thioxanthone). They act mainly by sensitization and allow for a high catalytic turnover in enantioselective [2 + 2] photocycloadditions and in deracemization reactions. Eventually, the concept of lactam hydrogen bonding was transferred to transition-metal catalysis, and catalysts have been developed which combine, in an enzyme-like fashion, a site for substrate binding and a catalytically active site. Substrate binding has been mainly achieved by a V-shaped ligand based on a tricyclic octahydro-1*H*-4,7-methanoisoindol-1-one scaffold with a lactam hydrogen-bonding site. The catalytically active metal (ruthenium, manganese, rhodium) is perfectly positioned to the substrate for a site- and enantioselective transfer of an oxygen atom (oxidation, oxygenation) or a nitrogen-based fragment (aziridination, amination).



INTRODUCTION

Hydrogen bonds belong to the most important noncovalent interactions and have been extensively explored for many decades.[1] Given the vast number of studies on the topic, it is somewhat difficult to introduce the research field of this Perspective without involuntarily omitting many important contributions. This section thus serves exclusively as a personal reflection on how we became interested in the use of chiral lactams for enantioselective transformations but not as a comprehensive survey of work which has been done in the field of hydrogen-bonding catalysis.[2] Our work in the area commenced in the final years of the 20th century and was stimulated by the discovery that several secondary amides and dihydropyridones could be successfully used as olefin components in the Paternò−Büchi reaction.[3] Even sensitive olefins such as *N*-vinyl formamide turned out to be compatible with the irradiation conditions, and this finding raised the question whether hydrogen-bonding interactions might be employed to induce an enantioface differentiation at the olefinic double bond. Encouraging precedence for the fact that even a single hydrogen bond could be a control element to induce facial diastereoselectivity (dr = diastereomeric ratio) came from the early work of Masamune on the intermolecular Diels−Alder reaction of dienophile **1**[4] and from a more recent contribution by Crimmins on the intramolecular intramolecular [2 + 2] photocycloaddition of substrate *rac*-**3**.[5] In both cases, hydrogen bonds were invoked in the respective conformations **1′** and *rac*-**3′** to explain the high diastereoselectivity of the reaction toward products **2** and *rac*-**4** (Scheme 1).

Even more closely related to our olefins were the 2-pyridones which Sieburth and co-workers had employed for photochemical [4 + 4] photocycloaddition reactions.[6] There was evidence that hydrogen bonding was important to control the diastereoselectivity in the intramolecular [4 + 4] photocycloaddition of substrates such as *rac*-**5** (Scheme 2). In the nonpolar solvent benzene, the reaction was proposed to proceed via complex *rac*-**5′** to generate product *rac*-**6**.

As mentioned above, there was extensive additional work which suggested the use of hydrogen bonds as control elements in photochemical reactions. Two reviews which report on noncovalent synthesis using hydrogen bonding and which appeared at the turn of the century may serve to reflect the state of the art at this period in time.[7] The lactam binding motif with which we eventually chose to probe a potential enantioface differentiation in the Paternò−Büchi reaction of achiral olefins rested on the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonane skeleton. The precursor to ester *rac*-**7** could be readily synthesized from Kemp's triacid[8] and related imides had proven to exhibit a U-shaped three-point interaction with various substrates.[9] Still, there was no precedence that a two-point interaction would be sufficient to precoordinate a lactam to a 1,5,7-trimethyl-3-

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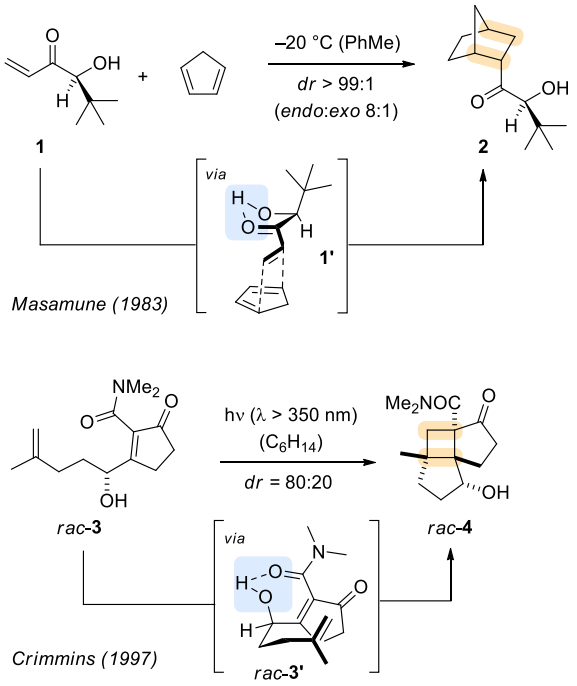
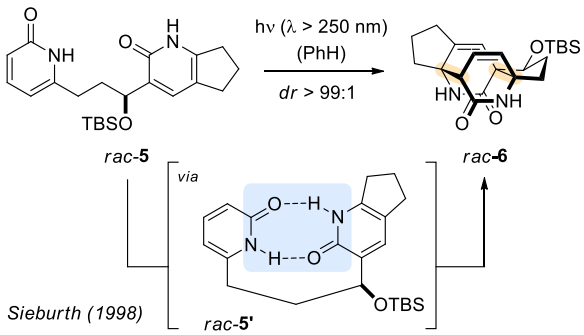
Scheme 1. Seminal Work on Diastereoselective Transformations Mediated by a Single Hydrogen Bond as Control Element



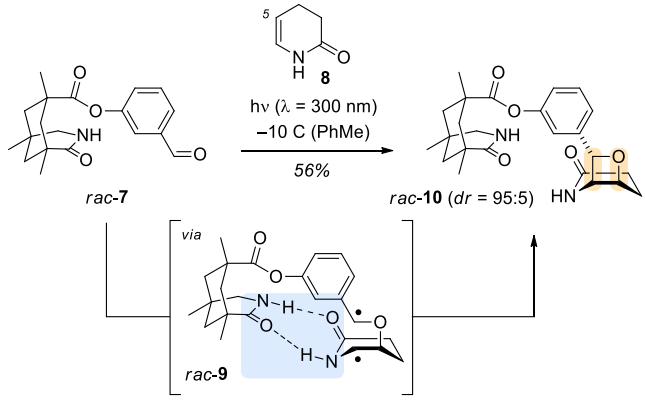
Scheme 2. Intramolecular Two-Point Hydrogen Bonding in the Diastereoselective [4 + 4] Photocycloaddition of Substrate *rac*-5



azabicyclo[3.3.1]nonan-2-one, and we were delighted to find a high diastereomeric excess for oxetane *rac*-**10** (Scheme 3) in the Paternò–Büchi reaction with dihydropyridone **8**. It was assumed that the reaction proceeds via an initial C–O bond formation which occurs almost exclusively at the formal *Re* face of dihydropyridone **8** (relative to carbon atom C-5). 1,4-Diradical intermediate *rac*-**9** gives oxetane *rac*-**10** in which the relative configuration was proven by single-crystal X-ray crystallography.[10]

Encouraged by the promising diastereoselectivity of the Paternò–Büchi reaction, we wondered whether it would be possible to employ a related chiral template (chiral complexing agent) for enantioselective reactions. Such a template would not be involved in the stoichiometry of the individual reaction but would only transfer its chirality to the reaction products by hydrogen bonding. The story of these templates, which are used in stoichiometric quantities or in excess (up to 2.6 equiv), will be told in the next section before continuing with related chiral lactams, which can be employed catalytically.

Scheme 3. Intermolecular Two-Point Hydrogen Bonding in the Diastereoselective Paternò–Büchi Reaction of Aldehyde *rac*-7 and Dihydropyridone 8



CHIRAL COMPLEXING AGENTS

Discovery and Initial Applications. Compound **7** served as a validated starting point to develop a chiral template.[11] The challenge, however, was not only to bind a prochiral substrate by two-point hydrogen bonding but also to provide sufficient enantioface differentiation for an intermolecular approach of a second molecule—as opposed to the intramolecular attack of the aldehyde in the Paternò–Büchi reaction (Scheme 3). It was quickly realized that the flexible ester linkage had to be replaced by a more rigid heterocyclic skeleton and that the potential enantioface differentiating entity had to be extended to a tetrahydronaphthalene unit. The two enantiomeric compounds **11** and *ent*-**11** emerged from our studies and turned out to be readily accessible[12] on large scale in enantiopure form (Figure 1). The absolute configuration of

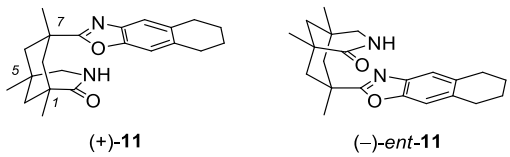


Figure 1. Structure of the dextrorotatory complexing agent **11** and of its levorotatory enantiomer *ent*-**11** with a 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton.

levorotatory compound *ent*-**11** was proven by single-crystal X-ray diffraction (anomalous dispersion), and the compounds were shown to be spectroscopically transparent at a wavelength of $\lambda \geq 300$ nm.[13]

Initial applications of the templates[13a] were performed with 4-alkenyloxyquinolones such as compound **12** which were known[14] to undergo an intramolecular [2 + 2] photocycloaddition. It was found that chiral complexing agents **11** and *ent*-**11** induced a high enantioselectivity in this process. With one equivalent of *ent*-**11**, the reaction already proceeded in 78% enantiomeric excess (ee) at −15 °C, and the enantioselectivity could be further increased at lower temperature employing a superstoichiometric amount of the complexing agent (Scheme 4). Since the recovery of the complexing agent by chromatography is straightforward and recovery yields are close to quantitative, a loading of 2–2.6 equiv has been typically applied in many other enantioselective reactions mediated by compounds **11** and *ent*-**11** (vide infra).

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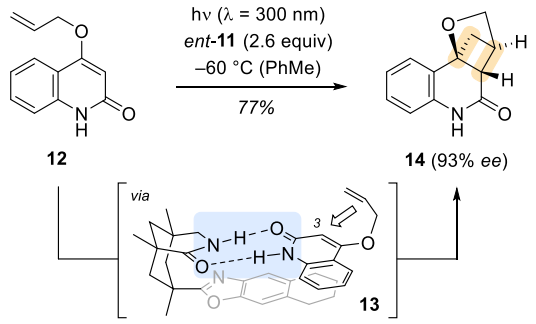
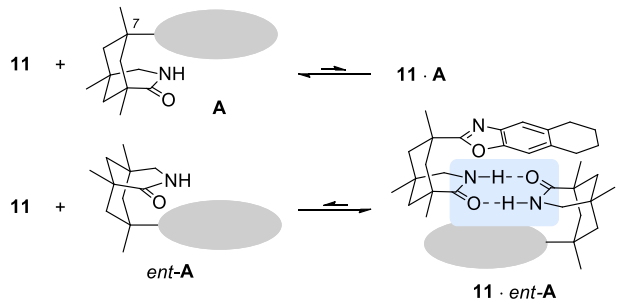
Scheme 4. Enantioselective Intramolecular [2 + 2] Photocycloaddition of 4-Allyloxyquinolone (12) Mediated by Complexing Agent *ent*-11



The absolute configuration of product **14** was in agreement with the assumed complexation of substrate **12** and lactam *ent*-**11** in the hydrogen-bonded complex **13**. The tetrahydronaphthalene unit avoids an intramolecular attack of the olefin from the bottom face but rather the olefin approach to the photoexcited quinolone occurs from the top face (*Si* face relative to carbon atom C-3). The regioselectivity of the reaction is determined by the facile ring closure to a five-membered ring which eventually leads to formation of crossed photocycloaddition products. Indeed, the reaction proceeds on the triplet hypersurface with initial C−C bond formation to a 1,4-diradical and subsequent ring closure.[15]

Binding Properties. The most striking feature of templates **11** and *ent*-**11** is the fact that they operate with only two hydrogen bonds. As any substrate, such as quinolone **12**, can also form two hydrogen bonds by dimerization, it appears to be counterintuitive that lactam substrates would bind exclusively to the template. A closer look at the binding properties of 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-ones serves to resolve this apparent contradiction. Compound **11** does not form a 1:1 complex with another 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one **A** of the same handedness (Scheme 5). There is no dimerization of compound **11**

Scheme 5. Molecular "Handshake" between Two 1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonan-2-ones of Opposite Chirality (11, *ent*-A)

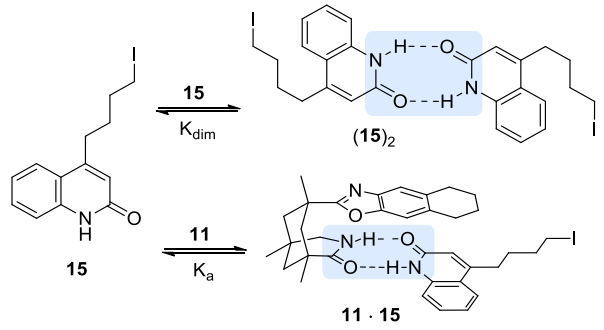


($K_{dim} \cong 0$), and a solution of homochiral template **11** is exclusively composed of the monomeric species.[16] Addition of 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-ones *ent*-**A** with opposite handedness leads to smooth formation of dimers whose existence is apparent by an extensive shift of the NH lactam ^{1}H NMR signal of compounds **11** and *ent*-**A**.[17]

The heterochiral interaction can be extremely useful in assigning the absolute configuration of 7-substituted 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-ones and related compounds.[18] The enantiomer that forms hydrogen bonds with template **11** exhibits an opposite handedness (*ent*-**A**), while enantiomers **A** with the same handedness will not be involved in an association. Unlike a human handshake, the molecular "handshake" of 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-ones requires opposite chirality of the two components. The fact that there are homochiral and heterochiral dimers of compound **11** and its enantiomer *ent*-**11** allowed for an asymmetric amplification in reactions in which the template was not enantiopure. A positive nonlinear effect was observed, i.e., the product ee was higher than the ee of the template.[19]

It is qualitatively clear now why dimerization of lactam substrates in the presence of template **11** is not preferred and why these substrates rather bind to template **11**. The former interaction (dimerization) requires two substrate molecules to form two hydrogen bonds while the latter interaction allows for the total formation of four hydrogen bonds from two substrate molecules. This phenomenon was quantitatively accessed by studying 4-(4-iodobutyl)quinolone (**15**) and template **11** in ^{1}H NMR titration experiments.[19] The dimerization constants were determined in toluene-d_8 at 25 and 0 °C as K_{dim} = 2001 ± 160 M^{-1} and K_{dim} = 5614 ± 706 M^{-1}, respectively. The association constants K_a were in the same ballpark reflecting the fact that the hydrogen bonds are of similar strength. The equilibrium is shifted toward **11·15** because the equilibrium constant for the reaction $(\mathbf{15})_2$ with 2 equiv **11** to form two molecules of dimer **11·15** is $K_a^2 K_{dim}^{-1}$ and roughly equals K_a if K_a and K_{dim} are similar (Scheme 6).

Scheme 6. Representative Example for Binding of a Lactam (Quinolone 15) to Complexing Agent 11



The latter expression reflects quantitatively the qualitative analysis that four hydrogen bonds are preferred over two hydrogen bonds. The data recorded for dimer **11·15** suggest at a typical substrate concentration of c = 10 mM that more than 90% of the substrate is bound to the template at 0 °C. It is conceivable that attractive noncovalent interactions (π stacking) enhance the stability of complexes such as **11·15**, but no attempts have yet been made to quantify this interaction.

Template **11** is very sensitive toward unfavorable steric interactions with its rigid tetrahydronaphthalene unit, and it was shown that enantiomers of chiral lactams (vide infra) bind differently to template **11**. The different binding properties result in different ^{1}H NMR shifts for the lactam protons of the individual enantiomers, and templates **11** and *ent*-**11** can serve as chiral shift reagents.[20]

Applications. Typically, complexing agents **11** and *ent*-**11** have been used to facilitate enantioselective photochemical and

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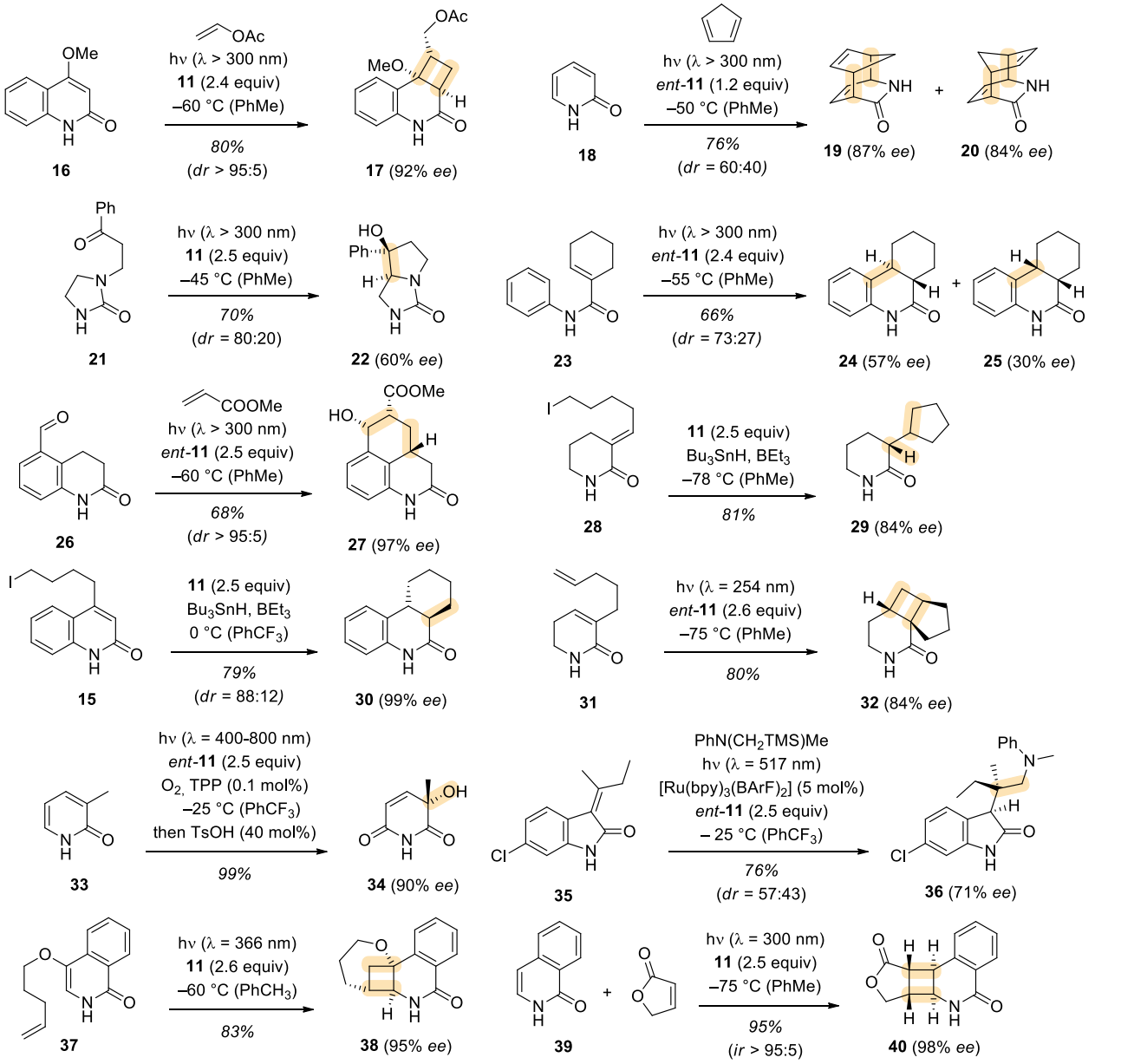
Scheme 7. Enantioselective Photochemical and Radical Reactions Promoted by Chiral Complexing Agents 11 and *ent*-11



radical reactions.[21] A few representative examples for individual reactions are listed in Scheme 7. Several of the early experiments were performed with a mercury high-pressure lamp and a Duran glass filter (λ > 300 nm). More recently, light sources with a narrower emission spectrum have been used, specifically fluorescent lamps or light emitting diodes (LEDs). The [2 + 2] photocycloaddition of vinyl acetate and 4-methoxyquinolone (**16**) to product **17** demonstrates that the above-mentioned intramolecular reactions can be also performed intermolecularly.[13,22] The [4 + 4] photocycloaddition of 2-pyridone (**18**) illustrates the fact that this heterocyclic compound class is also suited for hydrogen bonding to the lactam motif of templates **11** and *ent*-**11**.[23] Even at a relative low loading (1.2 equiv) of template *ent*-**11**, products **19** and **20** were obtained with high enantioselectivity. A first indication that not only the enantiotopic faces of a double bond could be differentiated by hydrogen bonding but also the enantiotopic faces of a prostereogenic carbon radical was realized when studying the Norrish–Yang cyclization of imidazolidin-2-ones such as **21**. Excitation of the ketone carbonyl group leads via hydrogen abstraction to a 1,5-diradical which reacts enantioselectively to alcohol **22**. This study clearly showed the superior properties of templates **11** and *ent*-**11** as compared to 1,5,7-trimethyl-3-azabicyclo[3.3.1]-nonan-2-ones with an ester group in position C-7.[24]

The [6π] photocyclization of amides such as **23**[25] requires the amide bond to be *cis*-configured, which in turn should enable two-point hydrogen bonding to chiral lactam templates. Indeed, it was found that the reaction proceeds enantioselectively to provide a mixture of the two diastereomeric products **24** and **25**.[26] Compound *ent*-**11** served in this reaction not only as a passive template but acted as a chiral Brønsted acid in the protonation of the intermediate zwitterions. When photochemically excited, *ortho*-substituted aromatic aldehydes and ketones undergo an intramolecular hydrogen abstraction and the intermediate (*E*)-dienols (*o*-

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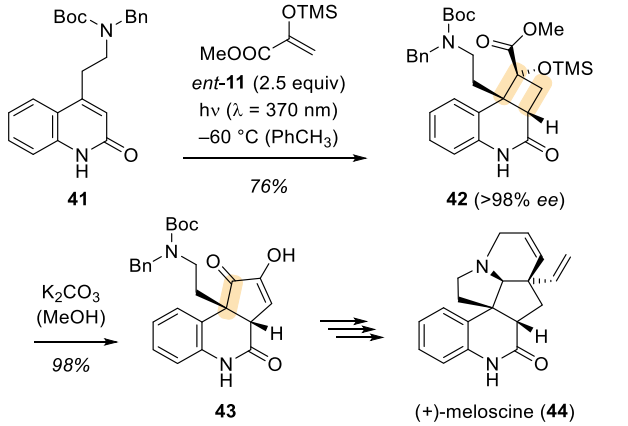
quinodimethanes) are reactive components in a thermal Diels–Alder reaction.[27] This photoenolization/Diels–Alder sequence was first performed with high enantioselectivity for substrates such as aldehyde **26**. In the depicted example, methyl acrylate was employed as the dienophile and product **27** was formed.[28] Apart from photochemical reactions, radical reactions turned out to be particularly suited for an application of chiral complexing agents **11** and *ent*-**11**. Triethylborane was an ideal reagent to initiate radical reactions at low temperature and promoted the reductive cyclization of iodide **28** to product **29**.[29] In this case, the primary 5-*exo*-*trig* cyclization product is a carbon-centered radical, and the attack of the hydrogen atom donor, tributyltin hydride, occurs with high enantioselectivity, presumably because the radical intermediate is bound to template **11**. Templated radical reactions are also enantioselective for substrates which expose a prochiral double bond to a radical.[19,30] Here, the radical addition step is enantioselective, and in some cases, the enantioselectivity is enhanced by hydrogen atom transfer to a second stereogenic center. The radical cyclization of the above-mentioned iodide **15** represents a good example for a 2-fold enantiodifferentiation by chiral template **11**. Even at a relatively high temperature of 0 °C, the formation of *trans*-product **30** remained highly enantioselective. It turned out in the studies on radical reactions that template **11** can also be applied in catalytic amounts (10 mol %) demonstrating its potential for a chirality multiplication.[30a]

In terms of irradiation conditions, the reactions of 5,6-dihydropyridone **31** and 2-pyridone **33** represent rather extreme cases. The former reaction was performed at very short wavelength (λ = 254 nm) because α,β-unsaturated lactams display a blue-shifted absorption as compared to aromatic lactams, such as quinolones and pyridones. Despite the fact that template *ent*-**11** is not transparent for photons of this wavelength, it survived the irradiation conditions sufficiently well to induce a high enantioselectivity in product **32**.[18b] In the latter reaction, the addition of singlet oxygen to 2-pyridones was induced by irradiation at long wavelength with visible light and required a co-catalyst for singlet oxygen formation. Tetraphenylporphyrine (TPP) was used, and the in situ generated singlet oxygen[31] added enantioselectively in a [2 + 4] cycloaddition to 2-pyridones, such as **33**.[32] The primarily formed endoperoxide was not isolated. Instead, it directly underwent an acid-catalyzed Kornblum–DeLaMare rearrangement[33] to tertiary alcohol **34**. Another visible-light-induced reaction required a ruthenium catalyst to generate a radical from an α-silylated amine[34] by single-electron transfer. While the addition reactions to 3-alkylidene indolin-2-ones such as **35** were enantioselective in the presence of template *ent*-**11**, a drawback was the insufficient control of the protonation event which resulted in the formation of two diastereoisomers one of which (**36**) is depicted.[35] In general, photoredox catalytic reactions are frequently incompatible with the requirements of a hydrogen-bonding lactam template. Electron transfer occurs preferentially in polar solvents which preclude coordination of the substrate to the template. Our most recent work with templates **11** and *ent*-**11** was concerned with the intra- and intermolecular [2 + 2] photocycloaddition of isoquinolones. The intramolecular reaction of substrate **37**, for example, was found to proceed to the crossed product **38** with excellent enantioselectivity.[36] Isoquinolone itself (**39**) and some of its substituted derivatives reacted with a wide array of alkenes to afford cyclobutanes such as **40** (ir = isomeric ratio).[37]

Although the isoquinolone [2 + 2] photocycloaddition invites several applications in natural product synthesis,[38] it has not yet been successfully implemented into a complete synthetic sequence toward isoquinoline alkaloids. The enantioselective quinolone [2 + 2] photocycloaddition, however, has proven to be a useful tool in organic synthesis. It is particularly suited to access a 3,4-dihydroquinolin-2(1*H*)-one (3,4-dihydroquinolones) with a high degree of functionalization at carbon atoms C-3 and C-4. Since there are no natural products with a cyclobutane that would be 3,4-annulated to a dihydroquinolone, successive ring opening reactions need to be implemented in the synthesis plan. In the total synthesis of (+)-meloscine (**44**), quinolone **41** was enantioselectively converted into [2 + 2] photocycloaddition product **42** before a retro-benzilic acid rearrangement to **43** was applied that generated the central five-membered ring of the target molecule (Scheme 8).[39]

Scheme 8. Enantioselective [2 + 2] Photocycloaddition Reaction as a Key Step in the Total Synthesis of (+)-Meloscine



The naturally occurring 3,4-dihydroxylated 3,4-dihydroquinolone (−)-pinolinone (**49**) was approached by a combination of a [2 + 2] photocycloaddition and a Baeyer–Villiger type oxidation (Scheme 9).[40] The pivotal photochemical step commenced with quinolone **45** which was enantioselectively converted into cyclobutanes **46** (dr = 71/29). The diastereomeric mixture was *N*-methylated and the acetate was hydrolyzed under mild conditions to deliver free alcohols **47**. Oxidation to lactone **48** erased the stereogenic center at the acetal carbon atom and yielded a single product, the two stereogenic centers of which resulted directly or indirectly from the enantioselective [2 + 2] photocycloaddition step. Reduction to the lactol and a Wittig reaction concluded the total synthesis of (−)-pinolinone (**49**).

Over the years, a few variants of chiral templates **11** and *ent*-**11** have been synthesized for specific purposes. Alcohol **50** (Figure 2) was used to immobilize the lactam template by attaching it either to a Wang resin or to a methoxypolyethylene glycol (MPEG 2000). The transparent MPEG-supported template was soluble in toluene and could be recovered quantitatively by precipitation with ether. In five successive runs of the reaction *rac*-**12** → *rac*-**14** (Scheme 4), there was no deterioration in yield or enantioselectivity when using the recovered MPEG supported template.[41]

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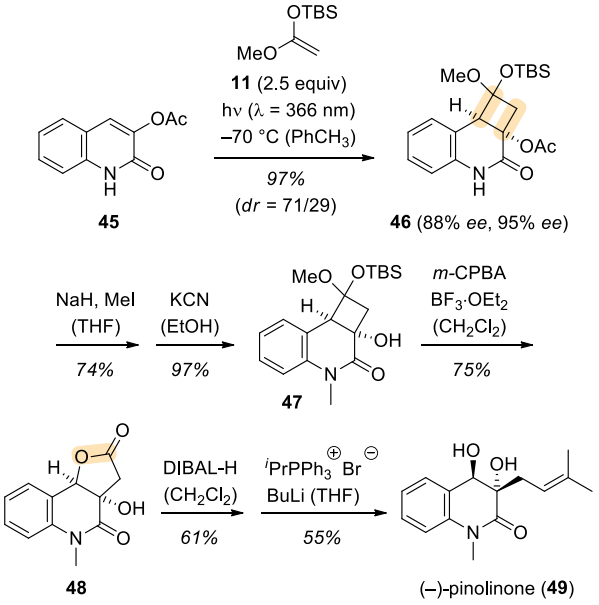
Scheme 9. Enantioselective [2 + 2] Photocycloaddition Reaction as a Key Step in the Total Synthesis of (−)-Pinolinone



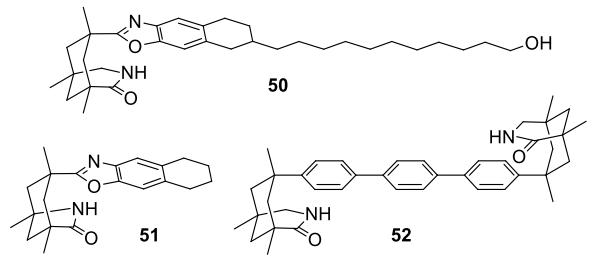


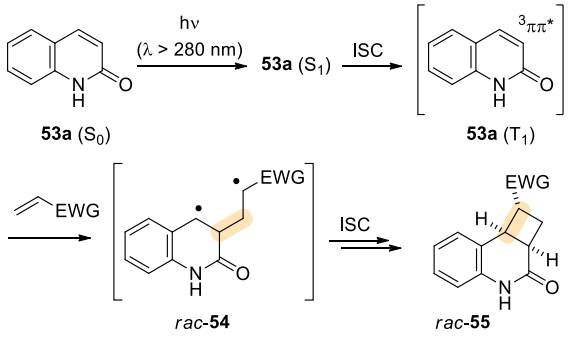
Figure 2. Structure of other complexing agents with a lactam binding site.

The nor-analogue **51** of template **11** was prepared to evaluate its binding properties toward 5,6-dihydropyridone, which in turn underwent an intramolecular [2 + 2] photocycloaddition (e.g., **31**, Scheme 7). There was an improved enantioselectivity but the effect was not very pronounced.[18b] The C_2-symmetric terphenyl template **52** was designed as a complexing agent for dicarboxylic acids. Indeed, it was successfully used to induce a moderate enantioselectivity (up to 55% ee) in the [4 + 4] photodimerization of anthracene-2,6-dicarboxylic acid.[42]

CHIRAL PHOTOCATALYSTS (ELECTRON TRANSFER, SENSITIZATION)

Basic Considerations. Many photochemical reactions do not proceed from the directly accessible, excited singlet state S_1 but from the triplet state T_1. Since relaxation of a molecule from the triplet hypersurface to the ground state (S_0) is spin-forbidden, the lifetime of a molecule in T_1 is long, which in turn allows to utilize its reactivity in intra- and intermolecular reactions. The majority of [2 + 2] photocycloaddition reactions are triplet processes[15] and the triplet state can be populated by intersystem crossing (ISC) from the respective S_1 state. As an example, 2-quinolone (**53a**) can be involved in an intermolecular [2 + 2] photocycloaddition reaction if excited within its typical absorption wavelength range that reaches up to $\lambda \cong 360$ nm (Scheme 10).[14a,43] Irradiation with a high-pressure mercury lamp in Pyrex glass ($\lambda > 280$ nm) promotes

Scheme 10. Reaction Pathway for the Intermolecular [2 + 2] Photocycloaddition of 2-Quinolone (53a) and an Electron-Deficient Olefin[a]



[a]EWG = electron-withdrawing group.

the molecule into its singlet state from which ISC occurs within less than 1 ns. ISC rates are governed by symmetry rules (El-Sayed rules[44]) and ISC from states of nπ* to states of ππ* character is rapid. The long-lived triplet T_1 is quenched by olefins and the initial addition step is decisive for the enantioselectivity of the reaction. In the absence of any chiral information, the intermediate 1,4-diradical is racemic (*rac*-**54**). The regioselectivity of the addition is governed by the stability of the respective 1,4-diradical. The simple diastereoselectivity of the reaction is determined by the constraints within the cyclobutane ring and by the fact that the substituent, in this case an electron-withdrawing group, will be positioned in the least hindered position of product *rac*-**55**, i.e., *trans* to the benzo group.

The relevance of the triplet state to catalytic enantioselective photochemical reactions stems from the fact that it is not only directly accessible via S_1 but also via an indirect excitation, known as triplet energy transfer or sensitization. A typical triplet sensitizer (Sens) that can catalyze a photochemical reaction exhibits a long-wavelength absorption beyond the absorption of the substrate (bathochromic). In other words, its S_1 state must be lower in energy than the S_1 state of the substrate. To be applicable to 2-quinolone (**53a**), an appropriate sensitizer should therefore exhibit a significant absorption at $\lambda > 360$ nm. The sensitizer must have a high ISC rate to populate efficiently its T_1 state, which in turn should have an energy $E(T_1)$ that allows an energy transfer as depicted in Scheme 11 (left panel). Although it is recognized that the energy transfer should be exothermic,[45] a moderately endothermic energy transfer is feasible if the T_1 state of the sensitizer is long-lived and if the T_1 state of the substrate is quickly depopulated. The tabulated triplet energy of 2-quinolone (**53a**) is 276 kJ mol^{-1}.[46] The mechanism of the triplet energy transfer bears some analogy to a single electron transfer as it is an electron exchange process[47] (Scheme 11, right panel).

The unpaired electron which resides in the former LUMO of the sensitizer populates the LUMO of the substrate, which for quinolone is its π* orbital. Simultaneously, the indicated electron of the quinolone π orbital with antiparallel spin is transferred to the single occupied orbital (former HOMO) of the sensitizer. There is no change in the overall spin states and

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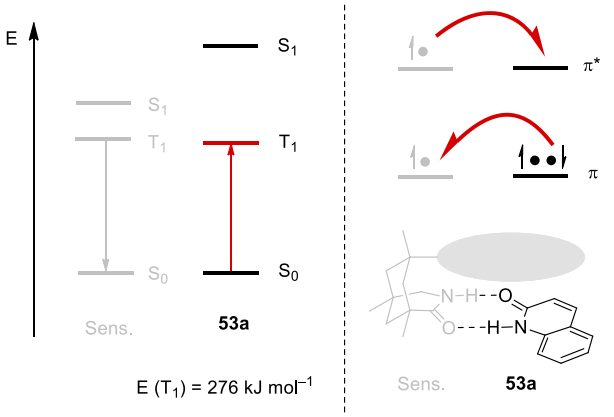
Scheme 11. Important Parameters of Triplet Energy Transfer in Catalytic Photochemical Reactions



the process is rapid, provided that there is a finite orbital overlap. The latter requirement is responsible for the fact that the rate k_{ET} of energy transfer depends—like electron transfer—on the distance between the sensitizer and the substrate. If the molecules are within van der Waals contact, the rate of energy transfer is in the order of $k_0 = 10^{13}$ s^{-1}.[48] The rate falls off exponentially to an increase in distance Δr beyond van der Waals contact, and the rate of energy transfer k_{ET} can be roughly estimated as $k_{ET} = k_0\, e^{-\beta \Delta r}$, with β being typically in a range of 10^{-2} pm^{-1}.[48] The remarkable feature of the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton is the fact that a substituent in the 7-position is spatially extremely close to a bound substrate such as 2-quinolone (**53a**). Molecular models and DFT calculations[26] gave a rough estimate for this distance as being ca. 400 pm. The van der Waals radius of a carbon atom is 170 pm, which seemed for us to indicate that the orbitals of a substrate, such as 2-quinolone (**53a**), and a potential sensitizing entity attached to position C-7 of a 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one are almost in van der Waals contact. If the energy of the sensitizing unit was properly chosen, there was an ideal scenario for efficient sensitization *and* high enantioface differentiation.

The aspect of enantioface differentiation was actually even more important than the energy-transfer criterion since all previous attempts to employ chiral triplet sensitizers for enantioselective photochemical reactions had failed to deliver a high enantioselectivity (>50% ee).[49] Initial experiments by our group to attach the sensitizer to the lactam backbone by an ester bond were equally futile as the respective catalysts did not deliver a high enantioselectivity.[50] Linkage via a rigid oxazole unit turned out to be a superior solution which in turn required that the aromatic ketones are available as *o*-aminophenols or appropriate analogues to allow for the condensation reaction with the carboxylic acid. The first compounds that succeeded in the synthesis were benzophenones **56a** and *ent*-**56a**[18a] (Figure 3) followed by xanthones **56b** and *ent*-**56b**[51] and thioxanthones **56c** and *ent*-**56c**.[52] Since all compounds **56** are preferentially used in a nonpolar solvent to enforce hydrogen bonding, we attempted to measure their triplet energy in a matrix which mimics this environment. Triplet energies were obtained from phosphorescence spectra at 77 K and were found to be (solvent matrix in brackets) 291 kJ mol^{-1} (pentane/isopentane) for **56a**,[53] 316 kJ mol^{-1} (pentane/isopentane) for **56b**,[53] and 263 kJ mol^{-1} (trifluorotoluene) for **56c**.[54]

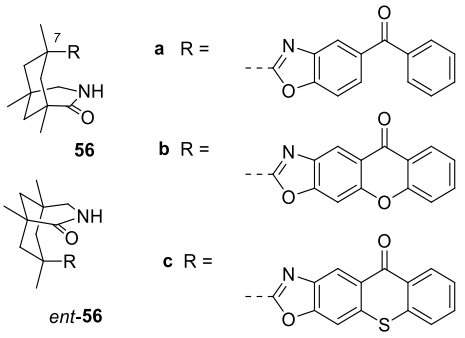
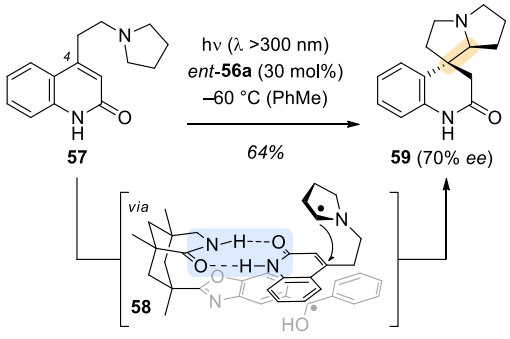


Figure 3. Structure of the chiral photocatalysts **56** and *ent*-**56** with a 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one backbone.

Applications in C–C Bond-Forming Photochemical Reactions. In preliminary [2 + 2] photocycloaddition experiments with benzophenone **56a** as the catalytic triplet sensitizer,[55] the enantioselectivity remained relatively low (39% ee).[51] An explanation for this disappointing outcome rested on an insufficient association due to the nonplanarity of benzophenones. Their aryl groups are twisted out of plane both in the ground state and in the excited state.[56] For example, a twist angle of 44° was calculated for the phenyl planes in the T_1 state of parent benzophenone.[57] It was hoped that a radical process via a ketyl radical[58] intermediate might provide improved results, and 2-quinolone **57** was synthesized which seemed amenable to single electron transfer to a photoexcited benzophenone.[59] To our delight, the respective product **59** was obtained in 70% ee, and the enantioface differentiation could be explained by addition of an intermediate α-amino radical to carbon atom C-4 of the quinolone in complex **58** (Scheme 12).[18a]

Scheme 12. Enantioselective Formation of Tetracyclic Product 59 from 2-Quinolone 57 by a Radical Cyclization



Despite this initial success, benzophenones **56a** and *ent*-**56a** did not find any additional applications and were not further used for sensitization experiments after xanthones **56b** and *ent*-**56b** became synthetically available. The only disadvantage of the xanthones was found to be their high instability in solvents which are amenable to hydrogen abstraction. The xanthone T_1 state in a nonpolar solvent has nπ^* character[60] which translates into a high electrophilicity of the oxygen atom. When irradiated in toluene solution, xanthones **56b** and *ent*-**56b** decomposed instantaneously. Trifluorotoluene turned out to be a suitable nonpolar solvent in which hydrogen abstraction was minimized and which still has a low melting point of −29 °C. Intramolecular [2 + 2] photocycloaddition reactions of various 4-alkenyloxy-2-quinolones (Scheme 13) established

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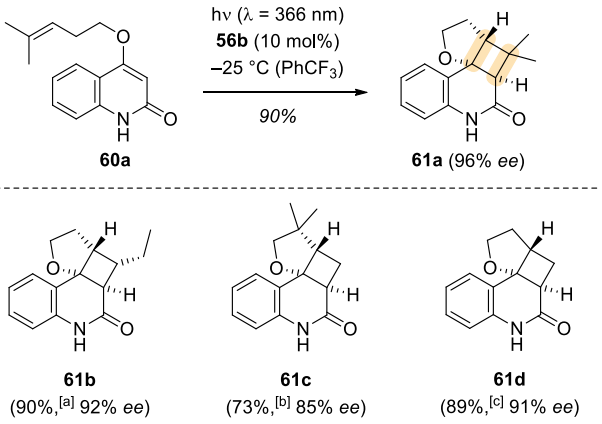
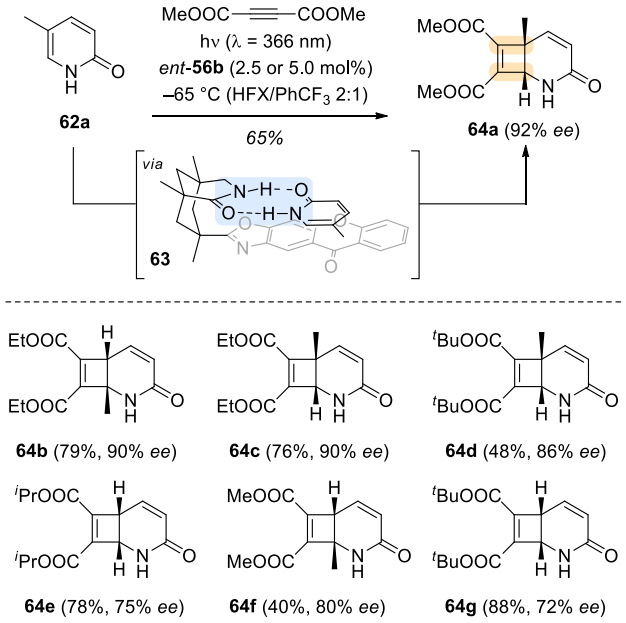
Scheme 13. Enantioselective Triplet-Sensitized [2 + 2] Photocycloaddition Reaction of Various 4-Alkenyloxy-2-quinolones 60 to Cyclobutanes 61[a]



[a]Key: [a] rr = 88:12, [b] rr = 82:18, [c] rr = 77:23.

Scheme 14. Enantioselective Intermolecular [2 + 2] Photocycloaddition of 2-Pyridones 62 and Acetylenedicarboxylates to Cyclobutenes 64



the powerful combination of energy transfer by the sensitizing xanthone unit and high enantioface differentiation due to hydrogen bonding at the lactam motif of catalyst **56b**.[61] Two observations should be mentioned in this context. (a) Xanthone **56b** remained prone to hydrogen abstraction: In addition to product **61d**, its regioisomer was detected after an irradiation time of 1 h (λ = 366 nm, T = −25 °C), and the regioisomeric ratio (rr) was found to be 78/22. After 4 h, the other regioisomer could no longer be detected, and the photocycloaddition yield decreased from 90% to 55%. Simultaneously, a significant decomposition of the xanthone was notable, which indicates that the catalyst deterioration is linked to hydrogen abstraction at the minor regioisomer. (b) The rate of C−C bond formation is important for the enantioselectivity. Although compounds such as **60a** reach their triplet state efficiently by energy transfer when bound to sensitizer **56b** the chirality transfer depends on the rate of initial C−C bond formation relative to the rate of dissociation from catalyst **56b**. The first C−C bond formation (cf. Scheme 10) leads to a 1,4-radical and establishes the first stereogenic center. If dissociation occurs prior to this step, there will be no enantioselectivity. The fact that the 4-alkenyloxy-2-quinolones with a 4-(pent-4-enyl)oxy but not a 4-(but-3-enyl)oxy substituent reacted with low enantioselectivity was ascribed to the fact that their cyclization is slower by 2 orders of magnitude.[61a] The dissociation rate constant of a photoexcited quinolone substrate from **56b** was estimated to be in the order of 10^7 s^{-1}.

Despite the kinetic limitations of an enantioselective photochemical reaction catalyzed by sensitizers **56** and *ent*-**56**, intermolecular processes were discovered which proceed with high enantioselectivity. A notable example is the [2 + 2] photocycloaddition of 2-pyridones such as **62a** with acetylenedicarboxylates, which was performed with low loadings (2.5−5.0 mol %) of catalyst *ent*-**56b** (Scheme 14).[62] The reaction was performed with an excess of the alkyne (50 equiv) in a solvent mixture of hexafluoro-*m*-xylene (HFX) and trifluorotoluene which allowed for irradiation at low temperature (T = −65 °C).[63] Products **64** represent densely functionalized precursors for further reactions at different sites.

Preferable substrates for an application of catalysts **56b** and *ent*-**56b** exhibit a planar π system with prostereogenic carbon atoms. As depicted for complex **63**, the xanthone fulfills nicely its dual task of energy transfer and subsequent enantioface differentiation. Attempts to involve a sp^3-hybridized epoxide in an enantioselective rearrangement to 3-acylindolin-2-ones were met with only limited success (16−33% ee).[64]

Given the large scientific interest in visible light-mediated transformations,[65] thioxanthones **56c** and *ent*-**56c** represent versatile analogues of xanthones **56b** and *ent*-**56b** with the added benefit that they can be excited with long-wavelength light. The absorption maximum is shifted from 350 nm (ε = 9200 M^{-1} cm^{-1}, in $PhCF_3$) for xanthone **56b** to 387 nm (ε = 4540 M^{-1} cm^{-1}, in $PhCF_3$) for thioxanthone **56c**. The thioxanthones are yellow solids and turned out to be extremely useful catalysts. Regarding [2 + 2] photocycloaddition reactions, they initially proved their potential in the reaction of the 4-alkenyl-2-quinolones **65** (Scheme 15).[52] While these substrates do not absorb visible light, they have triplet energies which make their T_1 state accessible by sensitization[66] via thioxanthone **56c**.

Upon binding of substrate **65a**, rapid energy transfer occurs in complex **67** and the intramolecular olefin approaches the prostereogenic double bond in the $\pi\pi^*$-excited quinolone from the bottom face. Products **66** were obtained in good to excellent yields with high enantioselectivity. It was probed whether the reaction can be performed also with sunlight, and an appropriate reactor was designed in which the reaction **65a** → **66a** was performed. In the absence of any cooling device or UV filter, the photocycloaddition reaction proceeded in 90% yield (4 h diffuse sunlight irradiation) and with 80% ee. The enantioselectivity improved when the UV part of the sunlight was removed by an $Fe_2(SO_4)_3$ solution (for the experimental setup, see Scheme 15) and reached 94% ee if additional cooling to −25 °C was applied (92% yield).[67] The UV filter solution serves to avoid direct excitation of substrate **65a** which leads to a racemic [2 + 2] photocycloaddition.

Thioxanthone **56c** also paved the way for the intermolecular [2 + 2] photocycloaddition of 2-quinolones **53**, including the

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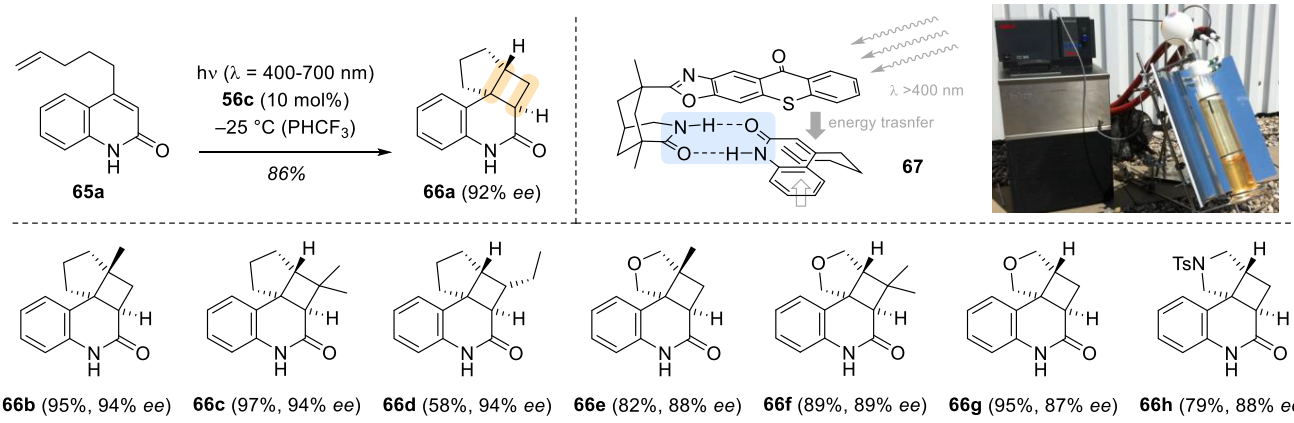
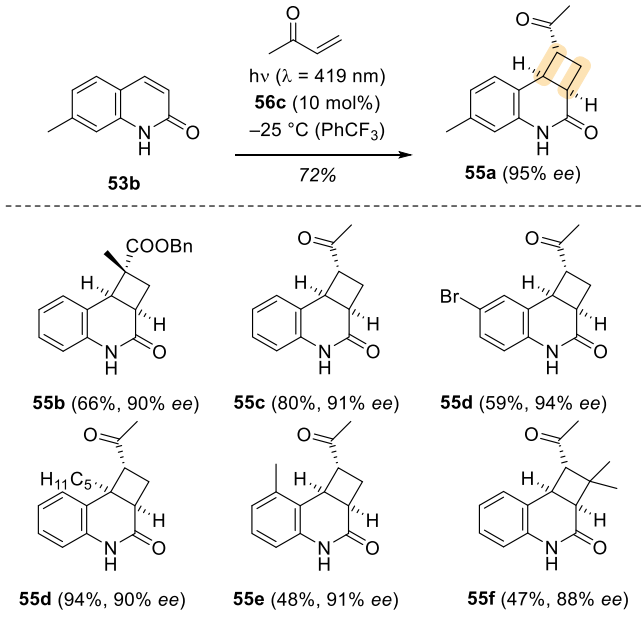
Scheme 15. Enantioselective Visible-Light-Mediated [2 + 2] Photocycloaddition Reaction of Various 4-Alkenyl-2-quinolones 65 to Cyclobutanes 66



parent compound **53a** (cf. Scheme 10), with electron-deficient olefins (Scheme 16).[68]

Scheme 16. Enantioselective Intermolecular [2 + 2] Photocycloaddition of 2-Quinolones 53 and Electron-Deficient Olefins to Cyclobutenes 55



In contrast to xanthone **56b**, thioxanthone **56c** has no spectral overlap with the substrates, and a direct excitation of 2-quinolones can be avoided if the reaction is performed at $\lambda >$ 360 nm. In this specific case, fluorescent lamps were used with an emission maximum at λ = 419 nm. As pointed out previously, an important requirement for intermolecular enantioselective reactions for catalysts **56** to be successful is a high rate constant for the reaction between the sensitized substrate and the intermolecular reaction partner. It was found by competition experiments for the reaction of 2-quinolones that electron-rich olefins (e.g., vinyl acetate) react roughly 1 order of magnitude slower than electron-deficient olefins. As a result, the enantioselectivities in their reaction do not reach the high values obtained with electron-deficient olefins.[68]

Deracemization Reactions. It has been a continuing theme of our research in photochemistry that we wish to access compounds which cannot be formed thermally and that we wish to ideally access them in enantiomerically pure form. In this regard, we were fascinated by an idea that had been formulated for decades but had yet been properly realized: the preparation of enantiopure compounds by a catalytic deracemization reaction with a chiral sensitizer.[49a,69] Transformations of this type would indeed be extremely useful given the fact that racemic chiral compounds are separated on a ton scale to gain access to a single enantiomer[70] and that frequently the other enantiomer is not even needed. A major requisite for this process is—apart from a switchable stereogenic element with a chiral molecule—a more rapid racemization of one enantiomer over the other. Given the previously mentioned ability of 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-ones to distinguish between two enantiomers via hydrogen bonding (vide supra), it was conceivable that one enantiomer would indeed show a higher association constant and a higher reaction rate. The choice for allenes *rac*-**67** turned out to be extremely fortuitous as they underwent from the very start of our experiments an extremely selective deracemization (Scheme 17).[54] Surprisingly, the reaction not only proceeded in the nonpolar solvent trifluorotoluene but also in acetonitrile. The catalyst loading was low (2.5 mol %) and a photostationary state was established in all cases within less than 4 h. A total of 17 allenes were taken into the deracemization reaction several of which bore a functional group. Enantioselectivities were in the range of 89−97% ee, and very often the reactions proceeded in close to quantitative yields.

Although our mechanistic understanding of the deracemization has only started to emerge, it appears that both association constants and sensitization rates are important parameters. The major enantiomer **68a** binds with a lower association constant to the chiral sensitizer *ent*-**56c** than the minor enantiomer *ent*-**68a** (Scheme 18). Sensitization of allenes occurs within complexes **69** and **69′** which induces the racemization process (vide infra). DFT calculations suggest that the distance between the two chromophores in **69′** is in the range of a van der Waals contact. In stark contrast, complex **69** not only forms with a lower association constant but also displays the allene chromophore to the sensitizer at an extended distance with Δr in the range of ca. 150 pm. As a crude estimate, the energy transfer rate k_{ET} within **69** is by a factor of 0.2 ($\cong e^{-1.5}$) smaller than the rate within **69′**.

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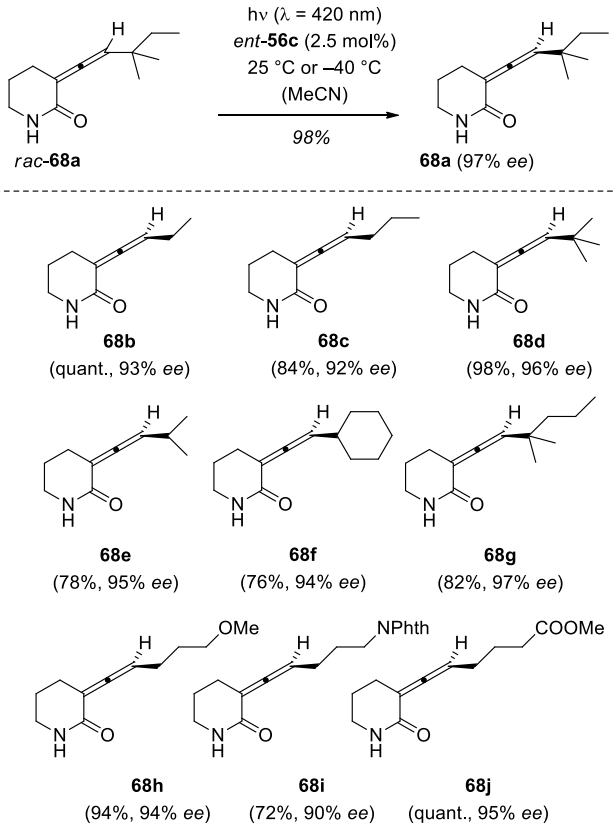
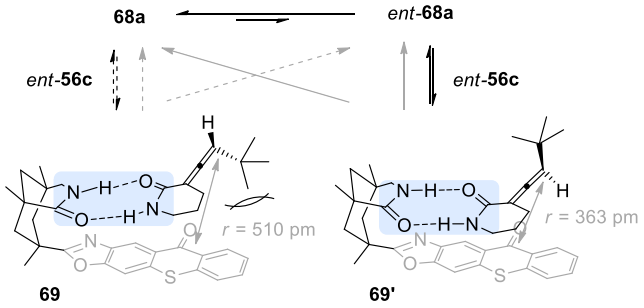
Scheme 17. Catalytic Deracemization of Allenes *rac*-67 by Visible-Light-Mediated Sensitization with Chiral Thioxanthone *ent*-56c



Scheme 18. Key Features of the Enantioselective Deracemization Reaction: Association and Sensitization



So far, the intermediate triplet allene which is responsible for the racemization has not been identified. However, based on analogy to known allene triplets[71] it is assumed to be a planar species **70** (Figure 4) which can rotate in either direction to form allenes **68** or *ent*-**68**.

Indeed, an important key element in any photochemical deracemization reaction is the intermediacy of an achiral intermediate from which the respective enantiomers are to be populated. Accidentally, we came across the putative 1,3-diradicals **71** when studying the di-π-methane rearrangement of 3-alkenyl-2-quinolones **72** (Scheme 19).[72] The substrates

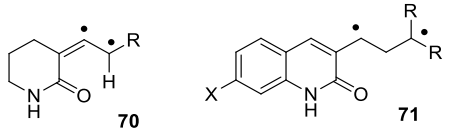
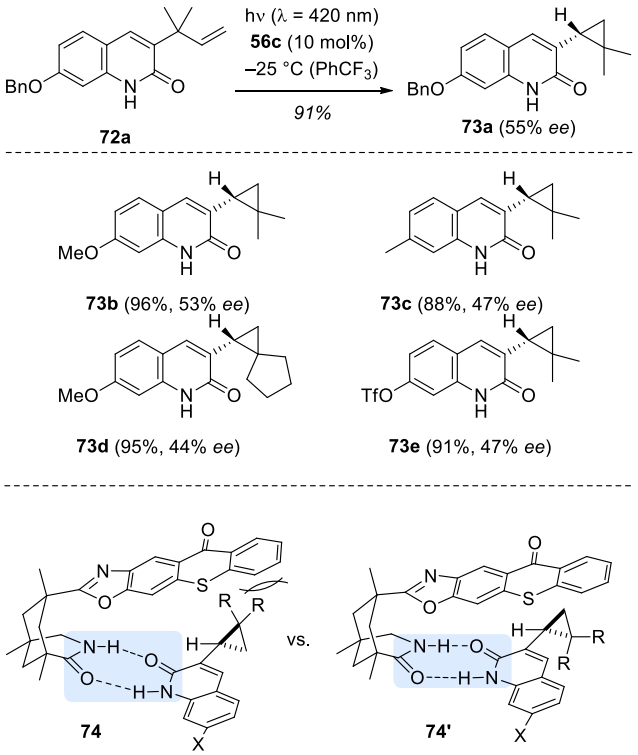


Figure 4. Intermediates **70** and **71** of photochemical deracemization reactions.

Scheme 19. Enantioselective Formation of Cyclopropanes 73 by a Sequence of the Di-π-methane Rearrangement and Deracemization



are related to the 4-alkenyl-2-quinolones **65**, but due to the shorter alkenyl chain, they do not undergo an intramolecular [2 + 2] photocycloaddition but rather form the respective cyclopropanes via a 1,4-diradical intermediate.

It turned out, however, that products **73** are not configurationally stable when irradiated in the presence of an appropriate triplet sensitizer. The enantioselectivity of the reaction was shown to originate from a deracemization reaction but not from a kinetically controlled enantioselective di-π-methane rearrangement. Products **73** were obtained in high yields but with only moderate enantioselectivity. In this case, the most likely intermediates are 1,3-diradicals **71** (Figure 4) which are formed by sensitization within complexes **74** and **74′**. Again, it was shown that the association constants of the two enantiomers are different and that complex **74′** (K_a = 2300 ± 130 M^{-1} in benzene-d_6 at 25 °C) displays a higher association constant than that complex **74** (K_a = 253 ± 14 M^{-1} in benzene-d_6 at 25 °C). Interestingly, preliminary DFT calculation suggest that the distance between the chromophores within **74** and **74′** is less pronounced than in complexes **69** and **69′**. In addition, the short lifetime of 1,3-diradicals **71** might lead to a ring closure within the complex to the sensitizer. Both factors would favor an increased formation of cyclopropanes *ent*-**73** which in turn might explain the lower enantioselectivity of the cyclopropane deracemization as compared to the allene deracemization.

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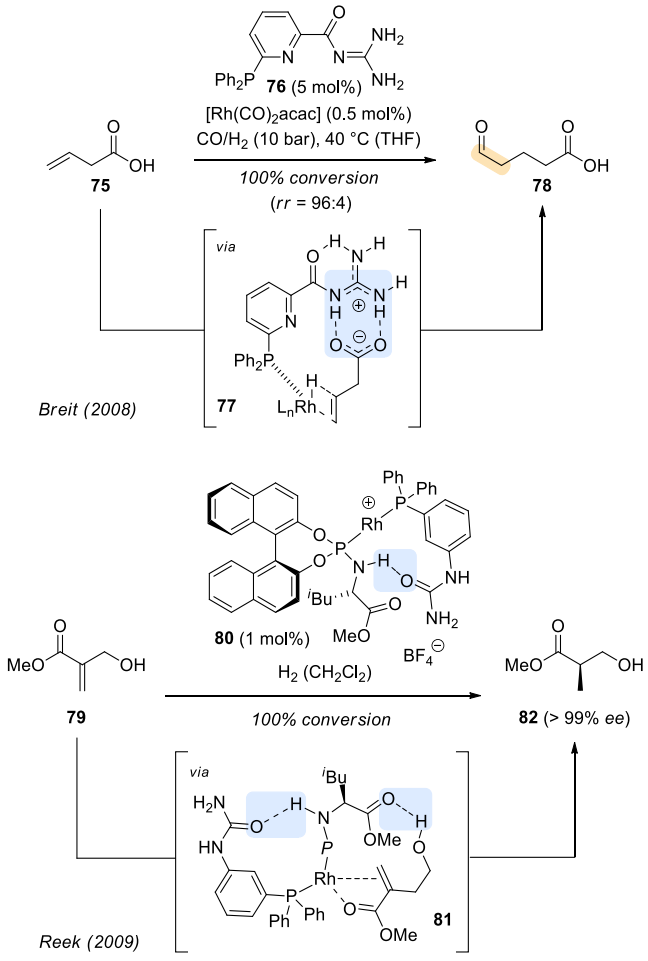
TRANSITION-METAL CATALYSIS

Basic Considerations. Although initially conceived for photochemical reactions, the concept of enantioselectivity control by hydrogen bonding to a lactam binding motif appeared to be also applicable to transition-metal-catalyzed organic transformations. Again, it is beyond the scope of this Perspective to review all previous studies which demonstrated hydrogen bonding in transition-metal catalysis nor is it possible to appropriately give credit to the extensive work on directed functionalization by noncovalent interactions.[73] Two pioneering studies that preceded our own work are mentioned here as they made intentional use of molecular devices which display a two-point or single-point hydrogen-bonding site (Scheme 20).

Scheme 20. Previous Examples on Regioselective and Enantioselective Transition-Metal-Catalyzed Transformations Mediated by Hydrogen Bonding

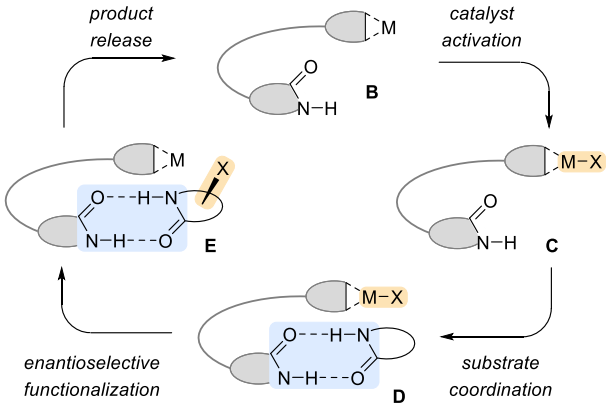


The Breit group achieved a regioselective hydroformylation of vinylacetic acid (**75**) by means of a phosphine ligand **76**, which was modified with a guanidinium-based recognition unit (acac = acetylacetonate). In this specific case, two-point hydrogen bonding between the carboxylic acid and the guanidine in rhodium complex **77** (L = ligand) aligns the olefin in a position that favors almost exclusively formation of the linear product **78**.[74,75]

Notably, if the C−P bond was omitted and a 1:1 mixture of triphenylphosphine and the respective pyridine derivative was applied, there was no considerable regioselectivity (rr = 60:40) and the conversion dropped to 20%, clearly indicating that precoordination of the substrate to the catalytic entity had a rate acceleration effect. While the former system was not designed for any enantioface differentiation, seminal work by the group of Reek[76,77] on hydrogenation reactions impressively showed how a single hydrogen bond can facilitate an enantioselective reaction. The in situ generated rhodium complex **80** (1,4-cyclooctadiene ligand omitted for clarity) was employed in the hydrogenation of alcohol **79** giving access to the enantiomerically pure Roche ester[78] **82** via a hydrogen-bonded intermediate **81** (*P* represents the phosphorus atom and its binol ligand).

Along these lines, we envisioned that the (thio)xanthone moiety from our previously used photocatalysts could be replaced by a catalytically active metal center. Based on what we had learned from catalysts **56** and *ent*-**56**, we expected that a catalyst **B**, once converted into its active form **C** by a stoichiometric reagent, could coordinate to a prochiral lactam to form complex **D**. Enantioface differentiation is now evident, and moreover, only a single reactive site should be exposed to the metal center. It was thus expected that the prefunctionalized metal center M would deliver a functional group X in an enantioselective and site-selective fashion (**E**) whereupon the chiral product would be released and lead to closure of the catalytic cycle. (Scheme 21). Catalyst **B** exhibits a substrate binding site via lactam hydrogen bonding and a reactive metal center which are linked by a U- or V-shaped skeleton.

Scheme 21. Proposed Catalytic Cycle for an Enantioselective Transition Metal-Catalyzed Functionalization Mediated by Hydrogen Bonding



Initially, we attempted to employ the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one scaffold with a potential metal-binding ligand to be attached to position C-7. The bis(oxazoline) ligand **83** (Figure 5) represents a typical ligand of this type which was prepared from the previously reported

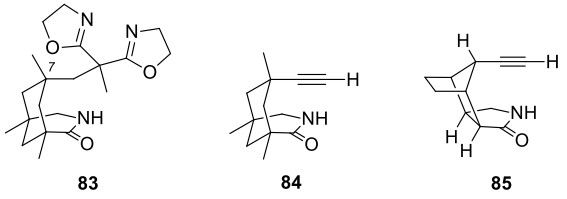


Figure 5. Structure of the bis(oxazoline) ligand **83** and of alkynes **84** and **85**.

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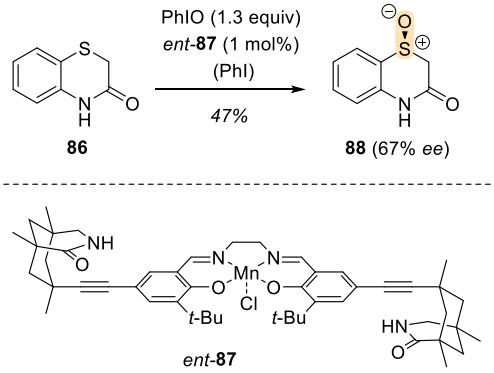
methyl 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-onyl-7-carboxylate.[79] However, it turned out that this approach was tedious and time-consuming as it required to adapt each and every synthesis protocol individually to the ligand. Although bond elongation at C-7 was possible, for example, by an aldol condensation from the corresponding C7-aldehyde or by an S_N2-type reaction from the respective C7-mesylated alcohol, further steps were required to complete the synthesis. A modular strategy seemed desirable which allowed to prepare the hydrogen bonding lactam skeleton separately and to link it—ideally in a single step—to a suitable building block with the preformed ligand. It was therefore fortunate that the previously mentioned C7-aldehyde was easily converted into the terminal alkyne **84**,[18c] whereupon a broad diversification strategy via Sonogashira cross-coupling reactions proved to be successful.

During our initial experiments with ligands derived from alkyne **84** (vide infra), there were indications that the shape of the molecular recognition unit influences the success of the desired transformation (vide infra). Unlike in our photochemical reactions, where the key for achieving high enantioface differentiation was steric shielding induced by close proximity of the substituent at C-7 to the prefunctionalized substrate, transition-metal catalysts demand more spatial flexibility for a functional group to be transferred from the metal center to the prochiral lactam. Accordingly, it appeared that the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one scaffold might not provide sufficient space due to its tight U-shaped nature. Influenced by the work of Deslongschamps,[80] we anticipated that the octahydro-1*H*-4,7-methanoisoindol-1-one skeleton **85** would exhibit a more accessible V-shape geometry and might be the more favorable candidate. The compound was accessible from 6,6-dimethylfulvene and maleic anhydride[81] and served in most future experiments as the lactam component in the synthesis of templated chiral metal complexes.

Oxidation and Oxygenation Reactions. Natural enzymes such as cytochrome P450 possess the unique capability to catalyze highly selective oxidative transformations.[82] Although hydrogen bonds are frequently responsible for high stereocontrol in biological oxidation processes,[83] similar principles have rarely been adopted in modern organic synthesis.[84] Earlier contributions regarding selective oxidative transformations mediated by a noncovalent interplay were made among others[73] by the groups of Breslow[85] and Crabtree.[86] However, the use of hydrogen bonding as a general concept for an enantioselective approach had remained unexplored prior to our work. The well-established oxidation properties of manganese salen complexes[87] in combination with an easily feasible derivatization thereof appeared to be a reasonable starting point for preliminary experiments. The terminal alkyne **84** was linked to a 3-*tert*-butyl-salicylaldehyde via Sonogashira cross-coupling reaction and subsequently the C_2-symmetric manganese salen complex *ent*-**87** was prepared following a literature known procedure.[88] The resulting catalyst was probed in the enantioselective sulfoxidation of commercially available 2*H*-benzo[*e*][1,4]thiazin-2-one (**86**) and of other sulfides with similar structure to deliver the respective sulfoxides such as **88** (Scheme 22).[89] The enantioselectivity was remarkable (up to 71% ee) with respect to the unprecedented mode of action but remained relatively low compared to what we had expected from the results of our photocycloaddition reactions.

Scheme 22. Enantioselective Oxidation of Sulfide 86 to Sulfoxide 88 Mediated by Mn−Salen Complex *ent*-87 with a Remote Hydrogen-Bonding Motif



As previously alluded to, we anticipated that the initial U-shaped 7-ethynyl-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one backbone was less suited for enantioselective transition metal catalysis due to the restricted space available for the substrate at the active site. A subtle structural alteration was required. Besides varying the lactam binding site to the octahydro-1*H*-4,7-methanoisoindol-1-one skeleton , we envisioned that a different choice of the catalytic entity might also be beneficial. In this context, porphyrin ligands seemed to be an excellent choice, not only because of their frequent use in oxidation and oxygenation reactions,[90] but most importantly due to their expansive but planar geometry. At the beginning, we prepared ruthenium complex **89a**,[81b] in which the porphyrin core is flanked by two 2,4,6-trimethylphenyl (Mes) and a phenyl substituent (Figure 6). In a later version

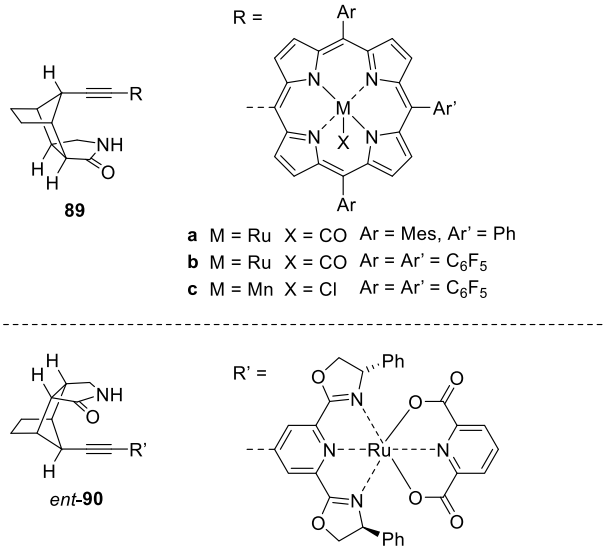


Figure 6. Structure of porphyrins **89** and of pybox complex *ent*-**90** with an octahydro-1*H*-4,7-methanoisoindol-1-one backbone.

of this catalyst (porphyrin **89b**),[91] the substituents were exchanged by three pentafluorophenyl groups with the aim to increase the electrophilicity of the reactive metal-oxo-intermediate by electron withdrawing substituents.[92] Most recently, we synthesized the manganese complex **89c**[93] with a different metal core because the ruthenium insertion step into the porphyrin led to an extensive loss of material in the

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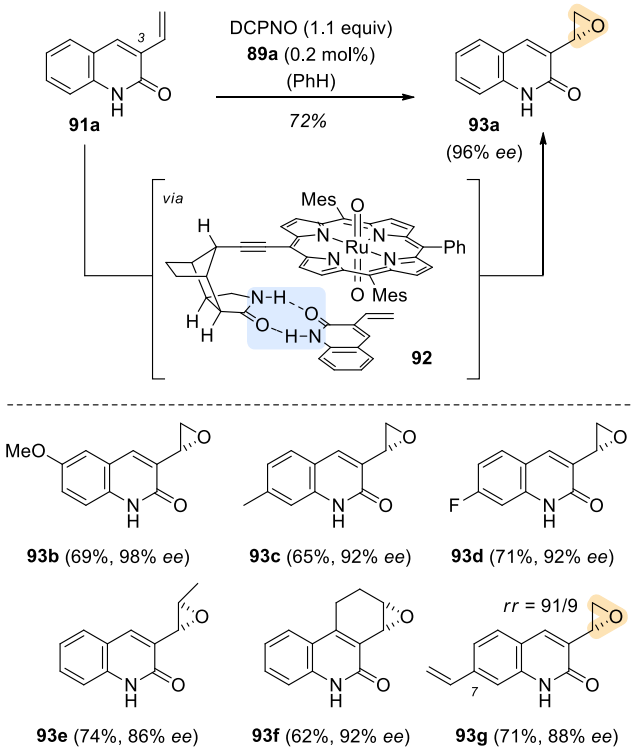
synthesis of **89a** and **89b**. Another promising candidate for the oxidation of sulfides was the pyridine-2,6-bis(oxazoline) (pybox) complex *ent*-**90** in which the ruthenium center is coordinated by an additional equivalent of 2,6-pyridinedicarboxylate.[94]

The first study related to enantioselective C−O bond formation was performed with porphyrin catalyst **89a** and concerned the enantioselective epoxidation of 3-alkenylquinolones, such as compound **91a**, with 2,6-dichloropyridine-*N*-oxide (DCPNO) as the stoichiometric oxidant (Scheme 23).[81b,95] Despite the fact that there is a free rotation around the C−C bond at quinolone carbon atom C-3, the activated ruthenium complex transfers the oxygen atom with almost perfect precision via complex **92** to a single enantiotopic face. DFT calculations support the approach shown and make it likely that a Ru^{VI} oxo complex is the active catalyst but the stereo- and regiochemical consequence would be identical with a Ru^{V} oxo complex as the reactive species. As little as 0.2 mol % of catalyst was needed to furnish the corresponding epoxides **93** in moderate to good yields and with excellent enantioselectivity. The method tolerates substitution in 6- and 7-position of the quinolone substrate (products **93b**−**93d**) as well as 1,2-disubstituted olefins (products **93e**−**93f**). Attack at the C-3 vinyl double bond was favored with high preference (rr = 91/9) over the double bond at position C-7 (product **93g**). The regioselectivity is significantly higher with chiral catalyst **89a** than with an achiral porphyrin catalyst illustrating the importance of the hydrogen bond for substrate precoordination. When the *N*-methylated derivative of substrate **91a** was taken into the reaction, the enantioselecitivity of the epoxidation was negligible (≤5% ee), and the reaction proceeded sluggishly.

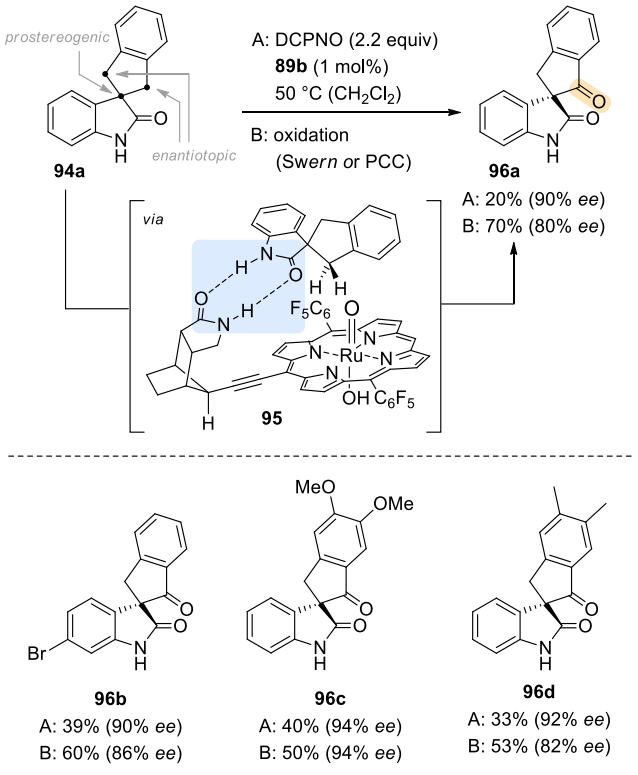
Scheme 23. Enantioselective Epoxidation of Vinylquinolones 91 to Epoxides 93 Catalyzed by a Chiral Ruthenium Porphyrin Complex 89a with a Remote Hydrogen-Bonding Site



The epoxidation conditions shown in Scheme 23 were also applicable to other substrates including 3-alkenylpyridones and primary alkenoic acid amides. In the former case, the epoxidation products were unstable, and the enantiomeric purity (77−87% ee) of the products had to be established after derivatization. In the latter case, the respective products were obtained with lower selectivity (70% and 45% ee) presumably because the alkyl chain lends more flexibility for the approach of the reactive catalyst to the olefinic double bond.

Preliminary attempts to apply catalyst **89a** also to oxygenation reactions at aliphatic C−H bonds were met with limited success. The catalyst seemed to be insufficiently reactive, and conversions remained low. In addition, when methylene groups were successfully oxygenated, overoxidation of the resulting chiral secondary alcohol to an achiral ketone erased the newly created stereogenic center. The reactivity issue could be overcome by attaching more strongly electron-withdrawing groups to the porphyrin ring which in turn make the metal center more electron deficient and, thus, the resulting oxo complex more electrophilic. The selectivity issue was—at least temporarily—resolved by designing C−H activation substrates that would retain a stereogenic center even if the secondary alcohol was further oxidized to a ketone. Along these lines, oxindoles **94** contain a prostereogenic spiro center which carries two enantiotopic methylene groups (Scheme 24).[91] The reaction at one of the methylene groups leads to a secondary alcohol which after further oxidation retains its chirality provided that the oxygenation reaction had selectively occurred at one of the two enantiotopic groups. Starting from

Scheme 24. Enantiotopos-Selective C−H Oxygenation of Spirocyclic Oxindoles 94 to Ketones 96 Catalyzed by the Supramolecular Ru−Porphyrin Complex 89b



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oxindole **94a** and employing DCPNO as the stoichiometric oxidant for the oxygenation reaction, the catalyzed reaction delivered 20% of ketone **96a** and significant quantities of the respective alcohol as the initial reaction product. In order to obtain exclusively a single product, the oxidation of the alcohol to the ketone was performed in a second step by the Swern protocol or with pyridinium chlorochromate (PCC).

The two-step protocol made several chiral ketones **96** accessible in high enantioselectivity. It could be shown that the templated catalyst is likely to operate via the proposed complex **95**, and DFT calculations (Figure 7) provided evidence on the

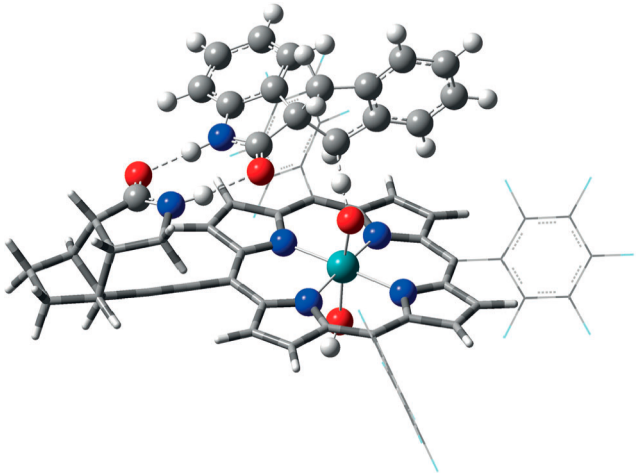
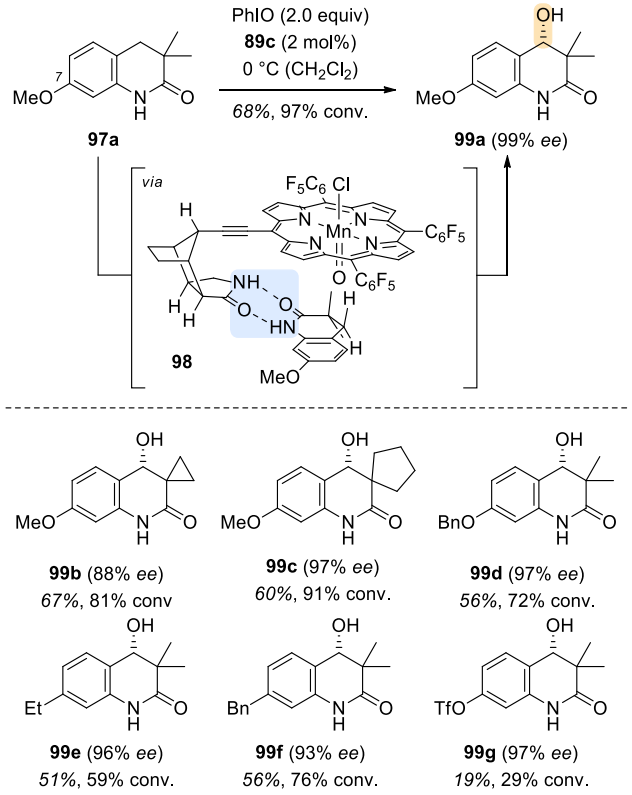


Figure 7. Proposed transition state for the reaction **94a** → **96a** as calculated by DFT methods. Reprinted with permission from ref 91. Copyright 2014 John Wiley and Sons.

selective attack of the Ru^{V} oxo complex at a single C−H bond. The oxygenation was suggested to proceed mechanistically by initial hydrogen abstraction and subsequent rapid rebound of the hydroxy group to the carbon radical center. The calculated primary kinetic isotope effect (k_H/k_D) for the reaction was 6.4, which parallels the experimentally determined value of 6.1. The hydrogen-abstraction step determines the enantioselectivity, and the ligand directs the active site to a specific position within substrate **94a**. The loss of enantioselectivity when comparing the enantiomeric excesses for products **96** before (A) and after alcohol oxidation (B) is likely due to a racemization via a retro-aldol reaction of the secondary alcohol. This hypothesis is in line with the fact that electron-withdrawing substituents at the oxindole showed diminished enantioselectivity.

Given the enormous need for enantioselective oxygenation reactions which allow for a late-stage functionalization of organic compounds, we turned toward manganese porphyrin complexes to achieve a selective oxygenation of secondary alcohols. Literature reports indicated that the propensity for overoxidation with manganese catalysts[96,97] might be lower than with the respective ruthenium porpyhrins. During the preparation of complex **89c**, it was gratifying to note that the catalytically active metal could be introduced into the preformed porpyhrin in the very last step of the synthesis. With ruthenium, all attempts to do so failed due to competitive reduction of the triple bond. 3,4-Dihydroquinolones **97** were selected as the first class of substrates to be tested in the oxygenation reaction (Scheme 25). They exhibit the required lactam binding site and were considered useful due to their

Scheme 25. Enantioselective Hydroxylation of 3,3-Disubstituted 3,4-Dihydroquinolones 97 to their Corresponding Alcohols 99 Catalyzed by the Manganese Porphyrin Complex 89c



known biological activity.[98] Iodosobenzene was found to be a superior oxidant and the reaction was performed with 2 mol % of catalyst **89c** at 0 °C.

For all substrates **97**, the enantioselectivity was high but the conversion depended strongly on the electronic properties of the substrate. Electron-rich 3,4-dihydroquinolones reacted most readily and the reaction was close to completion after a reaction time of 16 h (products **99a**–**99c**). We observed that the more electron-deficient the substituent in position C-7 was, the lower was the conversion (e.g., products **99d**–**99g**). The observed selective formation of product **99a** with (*S*)-configuration correlates with a transition state **98** in which the putative Mn^{V} oxo complex is directed to the substrate by hydrogen bonding. The bent nature of the transition state in Mn-catalyzed oxygenation reaction had been noted earlier and was reflected for the transformation **97a** → **99a** by a relatively low kinetic isotope effect (k_H/k_D = 3.0). The oxygenation is selective for the methylene group at the C-4 site. There was no notable oxygenation at the electronically favored benzylic positions (cf. products **99d** and **99f**).

In the reactions of spiro compounds **94**[91] it was not possible to identify and characterize the secondary alcohol intermediate, but the reaction had triggered our interest in oxidation reactions which would be selective regarding one of the two enantiotopic atoms and simultaneously enantioselective at this very specific atom. Hence, it was a curiosity-driven set of experiments we performed with spirodithiolane-indoles **100**, and we tried to identify which of the four possible stereoisomeric sulfoxides was formed in an enantioselective sulfoxidation protocol.[94] Ruthenium complex *ent*-**90** which was

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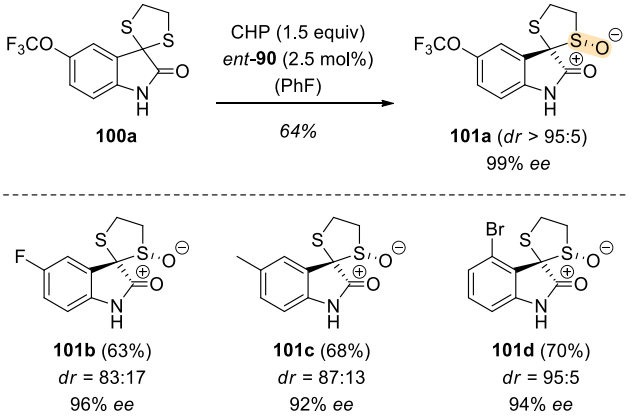
derived from alkyne *ent*-**85** was employed as the oxidation catalyst and cumene hydroperoxide (CHP) as the stoichiometric oxidant (Scheme 26).

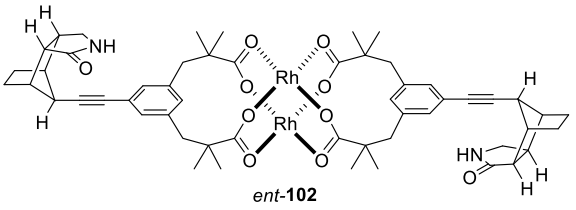
Scheme 26. Enantio- and Diastereoselective Sulfoxidation of Spirodithiolane-Indoles 100 Catalyzed by Ruthenium Complex *ent*-90



Remarkably, a single position was addressed with high preference, and products **101** were obtained with a high degree of stereoselectivity. It was found that the chirality of the pybox ligand at the ruthenium complex has an influence on the stereoselectivity and that the two elements of chirality (ligand and lactam backbone) work synergistically. The observed selectivity is in agreement with a hydrogen bonded substrate which exposes a free electron pair at a defined sulfur atom to the catalytically active ruthenium oxo complex.

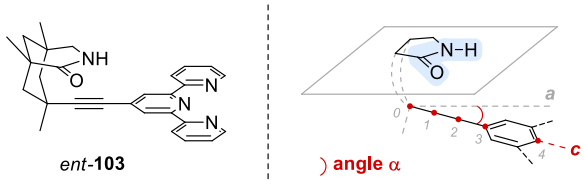
Aziridination and Amination Reactions. Over the past two decades, stereoselective catalytic C−H amination reactions have gained considerable attention[99] owing to the abundant presence of nitrogen atoms in secondary metabolites[100] and nitrogen-containing heterocycles in medicinal chemistry.[101] Among others,[102] seminal studies by the group of Che[103] have shown that metal porphyrin complexes can be effective for the introduction of sulfonamides via nitrene transfer from *N*-sulfonyliminophenyliodinane precursors. Around the same time, Du Bois and co-workers have made fundamental contributions to the field when discovering rhodium-catalyzed intramolecular C−H amination reactions of carbamates and sulfamates[104] and illustrating their application to the total synthesis of complex natural products.[105] The discovery of the dicarboxylate-derived rhodium complex $Rh_2(esp)_2$ was particularly interesting as it provided superior activity in the C−H functionalized process and moreover significantly expanded the scope of this reaction type.[106] Encouraged by this work and inspired by our own interest in diastereoselective amination reactions,[107] we envisioned that a brominated version of the corresponding diethyl $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzoldipropionate (esp ligand) would be easily accessible and thus could be tethered to our previously applied octahydro-1*H*-4,7-methanoisoindol-1-one backbone by Sonogashira cross-coupling. Indeed, the respective diethyl dicarboxylate could be obtained and was readily saponified to the free acid. Rhodium complexation furnished the desired C_2-symmetric catalyst *ent*-**102**, and its structure was unambiguously proven by X-ray crystallography (Figure 8).[108]

Comparison of this structure with the structure of ligand *ent*-**103** that was derived from ethynyl-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one (*ent*-**84**)[109] revealed the anticipated difference in shape (Figure 9). The angle of the ethynyl



ent-**102**

Figure 8. Structure of the C_2-symmetric Rh(II) catalyst *ent*-**102** exhibiting two remote recognition sites for hydrogen-bond-mediated coordination of prochiral quinolones.



ent-**103**

Figure 9. Structure of ligand *ent*-**103** and angle α defining the relative position of a ligand to the lactam plane.

linked substituent to the lactam can be defined as the angle α of the straight line *c* relative to the straight line *a* which in turn is parallel to the lactam plane. The angle α as determined from the mean value for the two lactam units in complex *ent*-**102** ($\alpha \cong 26°$) is significantly different from the angle for *ent*-**103** ($\alpha \cong 16°$). In both cases, the alkyne is not completely parallel to the lactam plane (U-shape) but opens up like the letter V. However, the angle is larger ($\Delta\alpha \cong 10°$) for the octahydro-1*H*-4,7-methanoisoindol-1-one skeleton, thus providing more space for a given ligated transition metal.

Based on our previous epoxidation experiments,[95] we anticipated that the new complex *ent*-**102** would likewise be capable of precoordinating quinolones and thus facilitate a comparable binding mode that would allow for enantioface differentiation. Accordingly, a methylene group in the C-3 position of the heterocyclic carbon skeleton was considered to be an ideal prochiral element, which in turn could further be activated by an electron rich aromatic substituent. We eventually chose quinolone **104** for our preliminary experiments and we were delighted to observe significant enantioselectivity (up to 72% ee) in the rhodium catalyzed amination to sulfonamide **106** (Scheme 27).[108]

The absolute configuration of product **106** was assigned by anomalous X-ray diffraction, confirming the hypothesis that hydrogen bonding is responsible for the differentiation of the two hydrogen atoms in complex **105**. It was observed that the enantioselectivity decreases significantly (30% ee) if the methylene bridge was further extended by an additional carbon atom as the amination proceeded adjacent to the 4-methoxyphenyl moiety. In order to examine whether the amination is both enantio- and site-selective, a second 4-methoxybenzyl substituent was introduced at position C-7 of the quinolone. Notably, a reversal of site-selectivity[110] was observed when *ent*-**102** (rr [C3/C7] = 63/37) was applied instead of the achiral amination catalyst $Rh_2(esp)_2$ (rr [C3/C7] = 39/61).

The application scope of Rh(II) complex *ent*-**102** was further explored regarding a potential catalysis of aziridination reactions.[111] 3-Vinylquinolone derivative **91e** was chosen as

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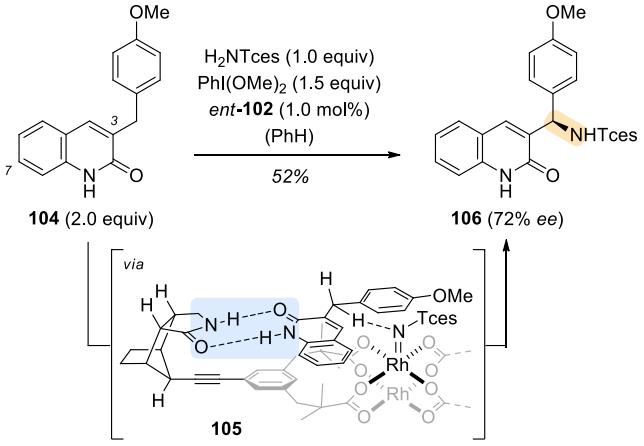
Scheme 27. Enantioselective Amination of 3-(4-Methoxybenzyl)quinolone) 104 to Sulfonamide 106 Catalyzed by the Chiral Rh(II)-esp Catalyst *ent*-102

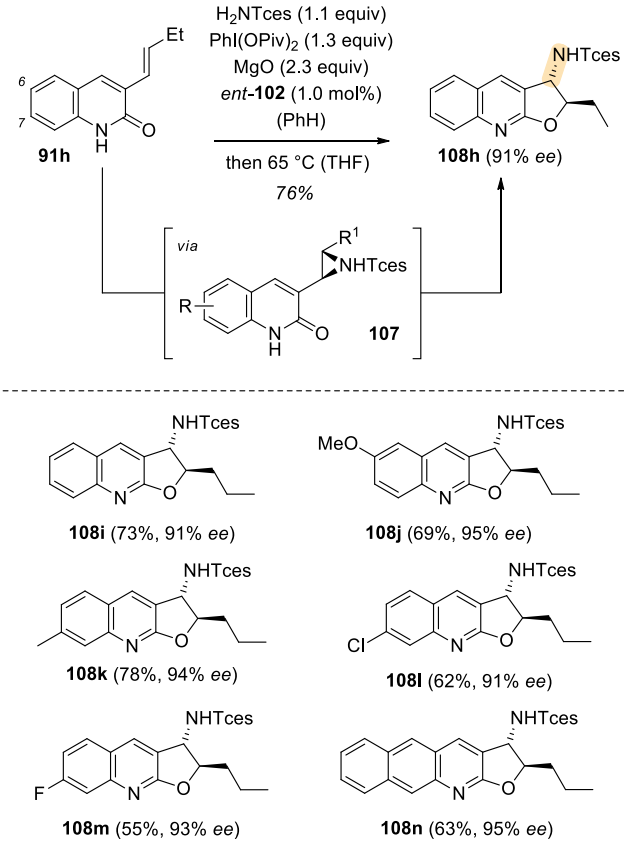


the substrate since it had provided an excellent enantioselectivity in catalytic epoxidation reactions.[81b,95] In preliminary experiments, it was observed that the racemic aziridination with $Rh_2(esp)_2$ gave a clean conversion to the corresponding aziridine *rac*-**107e** (R = H, R^1 = Me) as a single diastereoisomer. However, due to its electron-withdrawing aryloxysulfonyl substituent, the aziridine *rac*-**107e** was sufficiently electrophilic to undergo an intramolecular ring opening reaction. In a cascade reaction the *trans*-substituted heterotricycle *rac*-**108e** formed without isolation of the intermediate aziridine.[112] The asymmetric construction of 2,3-dihydrobenzo[2,3-*b*]quinolines *rac*-**108** had not been investigated prior to our work, and accordingly, we further optimized a new one-pot aziridiniation/ring opening protocol. Polar solvents such as acetonitrile accelerated the cyclization step and 1 mol % of $Rh_2(esp)_2$ was satisfactory to give rise to a large variety of 5-, 6-, and 7-substituted quinolines *rac*-**108** (12 examples, 45−78% yield).

As previously mentioned, nonpolar solvents are beneficial to establish sufficient hydrogen bonding of lactam-based catalysts to prochiral quinolone. It was hence assumed that the developed protocol had to be slightly altered for an enantioselective approach using the chiral complex *ent*-**102**. Indeed, it was found that the use of benzene instead of acetonitrile had a significant impact on the enantioselectivity. In addition, the reaction had to be run under dilute conditions to render the enantioselectivity high (up to 89% ee). At this point, other vinylquinolones **91** were examined (Scheme 28), and it was found that ethyl- or *n*-propylsubstituted olefins delivered superior enantioselectivity (**108h**−**108i**). Moreover, it was found that electron-donating groups (**108j**−**108k**) and electron-withdrawing substituents (**108l**−**108m**) were likewise tolerated in both the 6- and 7-positions of quinolone **91** and that even a benzo[*q*]quinolone delivered the respective tetracyclic ring **108n** in outstanding enantiomeric excess.

The removal of the 2,2,2-trichloroethoxysulfonyl (Tces) group was easily accomplished using zinc in a mixture of methanol and acetic acid without any racemization, and the absolute configuration was assigned by Mosher ester analysis.[113]

Scheme 28. Enantioselective Construction of 2,3-Dihydrobenzo[2,3-*b*]quinolines 108 from 3-Alkenylquinolones 91 Catalyzed by Rhodium Complex *ent*-102



CONCLUSION

The quest for selectivity in chemical transformation can be tackled in various ways, and there is no general solution nor is there one approach which is intrinsically better than the other. A substrate precoordination by hydrogen bonds has been one of the strategies which we have chosen to entail selectivity, and this Perspective describes how different ideas have developed over the years. To this very day, it remains one of the most appealing and scientifically satisfying aspects of this approach that the use of lactam hydrogen bonds can be rationally designed and that their mode of action can be understood at a very fundamental level. It has turned out, however, that there are several complex layers of comprehension beyond the very fundamental two-point interaction which is responsible for substrate binding. As in any scientific endeavor, we learn by success and failure. To our delight, the learning curve in the current project has remained steep over several years, and we hope that this trend continues allowing us to take on even the toughest and most challenging selectivity issues which are imposed on us sometimes by curiosity and sometimes by practical needs.

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Notes

The authors declare no competing financial interest.

Biographies

Finn Burg studied chemistry and biochemistry at the Ludwig-Maximilians-University in Munich, where he was part of the research laboratory of D. Trauner and received his M.Sc. degree in March 2017. During his undergraduate studies he participated in a 3 month internship at Bayer HealthCare, before he conducted his master thesis with A. G. Myers at Harvard University as an Otto-Bayer Fellow. In May 2017, he started his Ph.D. studies in the group of T. Bach concerning hydrogen-bond-mediated enantioselective C−H functionalization reactions catalyzed by metal porphyrin complexes.

Thorsten Bach obtained his education at the University of Heidelberg and at the University of Southern California, where he conducted his Diplom thesis with G. A. Olah. He received his Ph.D. in 1991 from the University of Marburg with M. T. Reetz and did postdoctoral work as a NATO fellow with D. A. Evans at Harvard University. He completed his Habilitation at the University of Münster in 1996, moved to the University of Marburg as an associate professor in 1997, and was appointed to the Chair of Organic Chemistry I at the Technische Universität München (TUM) in 2000. He is an elected member of the German Academy of Sciences (Leopoldina) since 2006 and of the Bavarian Academy of Sciences since 2009.

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■ REFERENCES

(1) (a) *Hydrogen Bonding in Organic Synthesis*; Pikho, P. M., Ed.; Wiley-VCH: Weinheim, 2009. (b) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. Defining the hydrogen bond: An account (IUPAC Technical Report). *Pure Appl. Chem.* **2011**, *83*, 1619−1636. (c) *An Introduction to Hydrogen Bonding*; Jeffrey, G. A., Ed.; Oxford University Press: Oxford, 1997. (d) *Hydrogen Bonding in Biological Structures*; Jeffrey, G. A., Saenger, W., Eds.; Springer: New York, 1991.

(2) Selected reviews: (a) Min, C.; Seidel, D. Asymmetric Brønsted acid catalysis with chiral carboxylic acids. *Chem. Soc. Rev.* **2017**, *46*, 5889−5902. (b) Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277−9306. (c) Yu, X.; Wang, W. Hydrogen-Bond-Mediated Asymmetric Catalysis. *Chem. - Asian J.* **2008**, *3*, 516−532. (d) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107*, 5713−5743. (e) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (f) Schreiner, P. R. Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem. Soc. Rev.* **2003**, *32*, 289−296.

(3) (a) Bach, T. *N*-Acyl Enamines in the Paternò−Büchi Reaction: Stereoselective Preparation of 1,2-Amino Alcohols by C−C Bond Formation. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 884−886. (b) Bach, T.; Bergmann, H.; Brummerhop, H.; Lewis, W.; Harms, K. The [2 + 2]-Photocycloaddition of Aromatic Aldehydes and Ketones to 3,4-Dihydro-2-pyridones: Regioselectivity, Diastereoselectivity, and Reductive Ring Opening of the Product Oxetanes. *Chem. - Eur. J.* **2001**, *7*, 4512−4521.

(4) (a) Choy, W.; Reed, L. A., III; Masamune, S. Asymmetric Diels-Alder Reaction: Design of Chiral Dienophiles. *J. Org. Chem.* **1983**, *48*, 1137−1139. (b) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. Asymmetric Diels-Alder Reactions: Applications of Chiral Dienophiles. *J. Org. Chem.* **1983**, *48*, 4441−4444.

(5) Crimmins, M. T.; Choy, A. L. Solvent Effects on Diastereoselective Intramolecular Photocycloadditions: Reversal of Selectivity through Intramolecular Hydrogen Bonding. *J. Am. Chem. Soc.* **1997**, *119*, 10237−10238.

(6) Sieburth, S. McN.; McGee, K. F., Jr.; Al-Tel, T. H. Fusicoccin Ring System by [4 + 4] Cycloaddition. Control of Diastereoselectivity through Hydrogen Bonding. *J. Am. Chem. Soc.* **1998**, *120*, 587−588.

(7) (a) Prins, J. L.; Reinhoudt, D. N.; Timmerman, P. Noncovalent Synthesis Using Hydrogen Bonding. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382−2426. (b) Archer, E. A.; Gong, H.; Krische, M. J. Hydrogen bonding in noncovalent synthesis: selectivity and the directed organization of molecular strands. *Tetrahedron* **2001**, *57*, 1139−1159.

(8) Kemp, D. S.; Petrakis, K. S. Synthesis and Conformational Analysis of *cis,cis*-1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic Acid. *J. Org. Chem.* **1981**, *46*, 5140−5143.

(9) (a) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. Molecular Recognition: Hydrogen Bonding and Stacking Interactions Stabilize a Model of Nucleic Acid Structure. *J. Am. Chem. Soc.* **1987**, *109*, 5033−5035. (b) Rebek, J., Jr.; Williams, K.; Parris, K.; Ballester, P.; Jeong, K.-S. Molecular Recognition: Stacking Interactions Influence Watson Crick vs. Hoogsteen Base-Pairing in a Model of Adenine Receptors. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1244−1245. (c) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K.-S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. Molecular Recognition with Convergent Functional Groups. 6. Synthetic and Structural Studies with a Model Receptor for Nucleic Acid Components. *J. Am. Chem. Soc.* **1989**, *111*, 1082−1090. (d) Williams,

DOI: 10.1021/acs.joc.9b01299
J. Org. Chem. 2019, 84, 8815−8836

K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K.-S.; Jones, S.; Rebek, Jr. J Molecular Recognition with Convergent Functional Groups. 7. Energetics of Adenine Binding with Model Receptors. *J. Am. Chem. Soc.* **1989**, *111*, 1090−1094. (e) Mori, K.; Murai, O.; Hashimoto, S.; Nakamura, Y. Highly Regio- and Stereoselective Photocycloaddition between Coumarin and Thymine by Molecular Recognition. *Tetrahedron Lett.* **1996**, *37*, 8523−8526. (f) Castellano, R. K.; Gramlich, V.; Diederich, F. Rebek Imides and Their Adenine Complexes: Preference for Hoogsteen Binding in the Solid State and in Solution. *Chem. - Eur. J.* **2002**, *8*, 118−129. (g) Faraoni, R.; Castellano, R. K.; Gramlich, V.; Diederich, F. H-Bonded complexes of adenine with Rebek imide receptors are stabilized by cation−π interactions and destabilized by stacking with perfluoroaromatics. *Chem. Commun.* **2004**, 370−371. (h) Varshney, D. B.; Gao, X.; Friščić, T.; MacGillivray, L. R. Heteroditopic Rebek's Imide Directs the Reactivity of Homoditopic Olefins within Desolvated Quaternary Assemblies in the Solid State. *Angew. Chem., Int. Ed.* **2006**, *45*, 646−650.

(10) Bach, T.; Bergmann, H.; Harms, K. High Facial Diastereoselectivity in the Photocycloaddition of a Chiral Aromatic Aldehyde and an Enamide Induced by Intermolecular Hydrogen Bonding. *J. Am. Chem. Soc.* **1999**, *121*, 10650−10651.

(11) For reviews on templated photochemical reactions, see: (a) Ramamurthy, V.; Sivaguru, J. Supramolecular Photochemistry as a Potential Synthetic Tool: Photocycloaddition. *Chem. Rev.* **2016**, *116*, 9914−9993. (b) Bibal, B.; Mongin, C.; Bassani, D. M. Template effects and supramolecular control of photoreactions in solution. *Chem. Soc. Rev.* **2014**, *43*, 4179−4198. (c) Yang, C.; Inoue, Y. Supramolecular photochirogenesis. *Chem. Soc. Rev.* **2014**, *43*, 4123−4143.

(12) For a related chiral auxiliary, see: Jeong, K.-S.; Parris, K.; Ballester, P.; Rebek, Jr. J. New Chiral Auxiliaries for Enolate Alkylations. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 555−556.

(13) (a) Bach, T.; Bergmann, H.; Harms, K. Enantioselective Intramolecular [2 + 2]-Photocycloaddition Reactions in Solution. *Angew. Chem., Int. Ed.* **2000**, *39*, 2302−2304. (b) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K.; Herdtweck, E. Synthesis of Enantiomerically Pure 1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonan-2-ones as Chiral Host Compounds for Enantioselective Photochemical Reactions in Solution. *Synthesis* **2001**, *2001*, 1395−1405.

(14) (a) Kaneko, C.; Naito, T.; Somei, M. Synthesis of Cyclobuta[c]quinolin-3-ones. Intra- and Inter-molecular Photocycloadditions of 4-Alkoxy-2-quinolone Systems with Olefins. *J. Chem. Soc., Chem. Commun.* **1979**, 804−805. (b) Kaneko, C.; Suzuki, T.; Sato, M.; Naito, T. Cycloaddition in Syntheses. XXXII. Intramolecular Photocycloaddition of 4-(ω-Alkenyloxy)-quinolin-2-(1*H*)-one: Synthesis of 2-Substituted Cyclobuta[*c*]-quinolin-3-(4*H*)-ones. *Chem. Pharm. Bull.* **1987**, *35*, 112−123.

(15) For a review, see: Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions. *Chem. Rev.* **2016**, *116*, 9748−9815.

(16) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. Highly Enantioselective Intra- and Intermolecular [2 + 2]-Photocycloaddition Reactions of 2-Quinolones Mediated by a Chiral Lactam Host: Host−Guest Interactions, Product Configuration, and the Origin of the Stereoselectivity in Solution. *J. Am. Chem. Soc.* **2002**, *124*, 7982−7990.

(17) Bauer, A.; Bach, T. Assignment of the absolute configuration of chiral 7-substituted 3-azabicyclo[3.1.1]nona-2-ones by NMR titration experiments. *Tetrahedron: Asymmetry* **2004**, *15*, 3799−3803.

(18) (a) Bauer, A.; Westkämper, F.; Grimme, S.; Bach, T. Catalytic enantioselective reactions driven by photoinduced electron transfer. *Nature* **2005**, *436*, 1139−1140. (b) Albrecht, D.; Vogt, F.; Bach, T. Diastereo- and Enantioselective Intramolecular [2 + 2] Photocycloaddiiton Reactions of 3-(ω'-Alkenyl)- and 3-(ω'-Alkenyloxy)-Substituted 5,6-Dihydro-1*H*-pyridin-2-ones. *Chem. - Eur. J.* **2010**, *16*, 4284−4296. (c) Voss, F.; Bach, T. An Ethynyl-Substituted 1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonan-2-one as a Versatile Precursor for Chiral Templates and Chiral Photocatalysts. *Synlett* **2010**, *2010*, 1493−1496.

(19) Bakowski, A.; Dressel, M.; Bauer, A.; Bach, T. Enantioselective radical cylisation reactions of 4-substituted quinolones mediated by a chiral template. *Org. Biomol. Chem.* **2011**, *9*, 3516−3529.

(20) Bergmann, H.; Grosch, B.; Sitterberg, S.; Bach, T. An Enantiomerically Pure 1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonan-2-one as ^{1}H NMR Shift Reagent for the *ee* Determination of Chiral Lactams, Quinolones, and Oxazolidinones. *J. Org. Chem.* **2004**, *69*, 970−973.

(21) For previous reviews on the topic, see: (a) Bach, T. The Paternò-Büchi Reaction of *N*-Acyl Enamines and Aldehydes − The Development of a New Synthetic Method and its Application to Total Synthesis and Molecular Recognition Studies. *Synlett* **2000**, 1699−1707. (b) Grosch, B.; Bach, T. Enantioselective Photocycloaddition Reactions in Solution. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M., Lencik, F., Eds.; CRC press: Boca Raton, 2004; Vol. *1*, pp 61.1−14. (c) Grosch, B.; Bach, T. Template Induced Enantioselective Photochemical Reactions in Solution. In *Chiral Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Dekker: New York, 2004; Vol. *11*, pp 315−340. (d) Bach, T. Enantioselective Photochemical Reactions. In *Asymmetric Synthesis − The Essentials*, 2nd ed.; Christmann, M., Bräse, S., Eds.; Wiley-VCH: Weinheim, 2008; pp 166−170. (e) Breitenlechner, S.; Selig, P.; Bach, T. Chiral Organocatalysts for Enantioselective Photochemical Reactions. In *Organocatalysis*; Reetz, M. T., List, B., Jaroch, S., Weinmann, H., Eds.; Springer: Berlin, 2008; Vol. *2*; pp 255−279. (f) Müller, C.; Bach, T. Chirality Control in Photochemical Reactions: Enantioselective Formation of Complex Photoproducts in Solution. *Aust. J. Chem.* **2008**, *61*, 557−564. (g) Austin, K. A. B.; Bach, T. Enantioselective Photoreactions in Solution. In *CRC Handbook of Organic Photochemistry and Photobiology*, 3rd ed.; Griesbeck, A., Oelgemöller, M., Ghetti, F., Eds.; CRC Press: Boca Raton, 2012; Vol. *1*, pp 7.1−23. (h) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. Enantioselective Catalysis of Photochemical Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 3872−3890. (i) Coote, S. C.; Bach, T. Enantioselective Photocatalysis. In *Visible Light Photocatalysis in Organic Chemistry*; Stephenson, C. R. J., Yoon, T. P., MacMillan, D. W. C., Eds.; Wiley-VCH: Weinheim, 2018; pp 335−362.

(22) (a) Bach, T.; Bergmann, H. Enantioselective Intermolecular [2 + 2]-Photocycloaddition Reactions of Alkenes and a 2-Quinolone in Solution. *J. Am. Chem. Soc.* **2000**, *122*, 11525−11526. (b) Brandes, S.; Selig, P.; Bach, T. Stereoselective Intra- and Intermolecular [2 + 2] Photocycloaddition Reactions of 4-(2′-Aminoethyl)quinolones. *Synlett* **2004**, *2004*, 2588−2590. (c) Selig, P.; Bach, T. Photochemistry of 4-(2‘-Aminoethyl)quinolones: Enantioselective Synthesis of Tetracyclic Tetrahydro-1a*H*-pyrido[4‘,3‘:2,3]-cyclobuta[1,2-*c*] Quinoline-2,11(3*H*,8*H*)-diones by Intra- and Intermolecular [2 + 2]-Photocycloaddition Reactions in Solution. *J. Org. Chem.* **2006**, *71*, 5662−5673.

(23) Bach, T.; Bergmann, H.; Harms, K. Enantioselective Photochemical Reactions of 2-Pyridones in Solution. *Org. Lett.* **2001**, *3*, 601−603.

(24) Bach, T.; Aechtner, T.; Neumüller, B. Intermolecular hydrogen binding of a chiral host and a prochiral imidazolidinone: Enantioselective Norrish−Yang cyclisation in solution. *Chem. Commun.* **2001**, 607−608. (b) Bach, T.; Aechtner, T.; Neumüller, B. Enantioselective Norrish−Yang Cyclization Reactions of N-(ω-Oxo-ω-phenylalkyl)-Substituted Imidazolidinones in Solution and in the Solid State. *Chem. - Eur. J.* **2002**, *8*, 2464−2475.

(25) Ninomiya, I.; Yamauchi, S.; Kiguchi, T.; Shinohara, A.; Naito, T. Photocyclisation of Enamides. Part V. Photocyclisation of $\alpha\beta$-Unsaturated Anilides. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1747−1751.

(26) Bach, T.; Grosch, B.; Strassner, T.; Herdtweck, E. Enantioselective [6π]-Photocyclization Reaction of an Acrylanilide Mediated by a Chiral Host. Interplay between Enantioselective Ring Closure and Enantioselective Protonation. *J. Org. Chem.* **2003**, *68*, 1107−1116.

DOI: 10.1021/acs.joc.9b01299
J. Org. Chem. 2019, 84, 8815−8836

(27) Reviews: (a) Cuadros, S.; Melchiorre, P. Organocatalytic Strategies to Stereoselectively Trap Photochemically Generated Hydroxy-*o*-quinodimethanes. *Eur. J. Org. Chem.* **2018**, *2018*, 2884−2891. (b) Segura, J. L.; Martín, N. *o*-Quinodimethanes: Efficient Intermediates in Organic Synthesis. *Chem. Rev.* **1999**, *99*, 3199−3246. (c) Sammes, P. G. Photoenolisation. *Tetrahedron* **1976**, *32*, 405−422.
(28) Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Massa, W.; Bach, T. Highly Enantioselective Diels−Alder Reactions of a Photochemically Generated *o*-Quinodimethane with Olefins. *Angew. Chem., Int. Ed.* **2003**, *42*, 3693−3696. (b) Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Kaneda, M.; Wada, T.; Inoue, Y.; Bach, T. Enantioselective [4 + 2]-Cycloaddition Reaction of a Photochemically Generated *o*-Quinodimethane. Mechanistic Details, Association Studies, and Pressure Effects. *Chem. - Eur. J.* **2004**, *10*, 2179−2189.
(29) (a) Aechtner, T.; Dressel, M.; Bach, T. Hydrogen Bond Mediated Enantioselectivity of Radical Reactions. *Angew. Chem., Int. Ed.* **2004**, *43*, 5849−5851. (b) Dressel, M.; Aechtner, T.; Bach, T. Enantioselectivity and Diastereoselectivity in Reductive Radical Cyclization Reactions of 3-(ω-Iodoalkylidene)-piperidin-2-ones. *Synthesis* **2006**, *2006*, 2206−2214.
(30) (a) Dressel, M.; Bach, T. Chirality Multiplication and Efficient Chirality Transfer in *exo*- and *endo*-Radical Cyclization Reactions of 4-(4'-Iodobutyl)quinolones. *Org. Lett.* **2006**, *8*, 3145−3147. (b) Kapitán, P.; Bach, T. Template-Induced Enantioselectivity in the Reductive Radical Cyclization of 3-(3-Iodopropyloxy)propenoic Acid Derivatives Depending on the Binding Motif. *Synthesis* **2008**, *2008*, 1559−1564.
(31) Reviews: (a) Ghogare, A. A.; Greer, A. Using Singlet Oxygen to Synthesize Natural Products and Drugs. *Chem. Rev.* **2016**, *116*, 9994−10034. (b) Clennan, E. L.; Pace, A. Advances in singlet oxygen chemistry. *Tetrahedron* **2005**, *61*, 6665−6691.
(32) Wiegand, C.; Herdtweck, E.; Bach, T. Enantioselectivity in visible light-induced, singlet oxygen [2 + 4] cycloaddition reactions (type II photooxygenations) of 2-pyridones. *Chem. Commun.* **2012**, *48*, 10195−10197.
(33) Kornblum, N.; DeLaMare, H. E. The Base Catalyzed Decomposition of a Dialkyl Peroxide. *J. Am. Chem. Soc.* **1951**, *73*, 880−881.
(34) Examples: Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. Visible-light-mediated addition of α-aminoalkyl radicals generated from α-silylamines to α,β-unsaturated carbonyl compounds. *Chem. Commun.* **2012**, *48*, 6966−6968. (b) Lenhart, D.; Bach, T. Visible-light-induced, Ir-catalyzed reactions of *N*-methyl-*N*-((trimethylsilyl)-methyl)aniline with cyclic α,β-unsaturated carbonyl compounds. *Beilstein J. Org. Chem.* **2014**, *10*, 890−896. (c) Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. Enantioselective Conjugate Additions of α-Amino Radicals via Cooperative Photoredox and Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 2452−2455.
(35) Lenhart, D.; Bauer, A.; Pöthig, A.; Bach, T. Enantioselective Visible-Light-Induced Radical-Addition Reactions to 3-Alkylidene Indolin-2-ones. *Chem. - Eur. J.* **2016**, *22*, 6519−6523.
(36) Austin, K. A. B.; Herdtweck, E.; Bach, T. Intramolecular [2 + 2] Photocycloaddition of Substituted Isoquinolones: Enantioselectivity and Kinetic Resolution Induced by a Chiral Template. *Angew. Chem., Int. Ed.* **2011**, *50*, 8416−8419.
(37) (a) Coote, S. C.; Bach, T. Enantioselective Intermolecular [2 + 2] Photocycloadditions of Isoquinolone Mediated by a Chiral Hydrogen-Bonding Template. *J. Am. Chem. Soc.* **2013**, *135*, 14948−14951. (b) Coote, S. C.; Pöthig, A.; Bach, T. Enantioselective Template-Directed [2+ 2] Photocycloadditions of Isoquinolones: Scope, Mechanism and Synthetic Applications. *Chem. - Eur. J.* **2015**, *21*, 6906−6912.
(38) (a) Rimböck, K.-H.; Pöthig, A.; Bach, T. Photocycloaddition and Rearrangement Reactions in a Putative Route to the Skeleton of Plicamine-Type Alkaloids. *Synthesis* **2015**, *47*, 2869−2884. (b) Wahl, M. H.; Jandl, C.; Bach, T. A [2 + 2] Photocycloaddition−Fragmentation Approach toward the Carbon Skeleton of *cis*-Fused Lycorine-type Alkaloids. *Org. Lett.* **2018**, *20*, 7674−7678.
(39) (a) Selig, P.; Bach, T. Enantioselective Total Synthesis of the *Melodinus* Alkaloid (+)-Meloscine. *Angew. Chem., Int. Ed.* **2008**, *47*, 5082−5084. (b) Selig, P.; Herdtweck, E.; Bach, T. Total Synthesis of Meloscine by a [2 + 2]-Photocycloaddition/Ring Expansion Route. *Chem. - Eur. J.* **2009**, *15*, 3509−3525.
(40) Mayr, F.; Wiegand, C.; Bach, T. Enantioselective, intermolecular [2 + 2] photocycloaddition reactions of 3-acetoxyquinolone: total synthesis of (−)-pinolinone. *Chem. Commun.* **2014**, *50*, 3353−3355.
(41) Breitenlechner, S.; Bach, T. A Polymer-Bound Chiral Template for Enantioselective Photochemical Reactions. *Angew. Chem., Int. Ed.* **2008**, *47*, 7957−7959.
(42) Maturi, M. M.; Fukuhara, G.; Tanaka, K.; Kawanami, Y.; Mori, T.; Inoue, Y.; Bach, T. Enantioselective [4 + 4] photodimerization of anthracene-2,6-dicarboxylic acid mediated by a C_2-symmetric chiral template. *Chem. Commun.* **2016**, *52*, 1032−1035.
(43) (a) Evanega, G. R.; Fabiny, D. L. The photocycloaddition of carbostyril to olefins. *Tetrahedron Lett.* **1968**, *9*, 2241−2246. (b) Loev, B.; Goodman, M. M.; Snader, K. M. Photochemical cycloaddition reactions involving carbostyrils. *Tetrahedron Lett.* **1968**, *9*, 5401−5404. (c) Evanega, G. R.; Fabiny, D. L. The Photocycloaddition of Carbostyril to Olefins. The Stereochemistry of the Adducts. *J. Org. Chem.* **1970**, *35*, 1757−1761. (d) Buchardt, O.; Christensen, J. J.; Harrit, N. The Photocycloaddition of Cyclohexene to Carbostyrils. *Acta Chem. Scand.* **1976**, *30*, 189−192. (e) Kaneko, C.; Naito, T. Intermolecular Photochemical Cycloaddition of 4-Methoxy-2-quinolone with Olefins: a Regioselective Synthesis of 5-Substituted Cyclobuta[*c*]-2-quinolones. *Chem. Pharm. Bull.* **1979**, *27*, 2254−2256.
(44) (a) El-Sayed, M. A. Spin-Orbit Coupling and the Radiationless Processes in Nitrogen Heterocyclics. *J. Chem. Phys.* **1963**, *38*, 2834−2838. (b) El-Sayed, M. A. Triplet state: Its Radiative and Nonradiative Properties. *Acc. Chem. Res.* **1968**, *1*, 8−16.
(45) (a) Sandros, K. Transfer of Triplet State Energy in Fluid Solutions. *Acta Chem. Scand.* **1964**, *18*, 2355−2374. (b) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy transfer catalysis mediated by visible light: principles, applications, directions. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.
(46) *Handbook of Photochemistry*, 2nd ed.; Murov, S. L., Carmichael, I., Hug, G. L., Eds.; Dekker: New York, 1993.
(47) (a) Dexter, D. L. A. Theory of Sensitized Luminescence in Solids. *J. Chem. Phys.* **1953**, *21*, 836−850.
(48) *Modern Molecular Photochemistry of Organic Molecules*; Turro, N. J., Ramamurthy, V., Scaiano, J., Eds.; University Science Books: Sausalito, 2010.
(49) (a) Ouannès, C.; Beugelmans, R.; Roussi, G. Asymmetric Induction During Transfer of Triplet Energy. *J. Am. Chem. Soc.* **1973**, *95*, 8472−8474. (b) Horner, L.; Klaus, J. Möglichkeiten und Grenzen photochemisch induzierter asymmetrischer Synthesen. *Liebigs Ann. Chem.* **1979**, *1979*, 1232−1257. (c) Demuth, M.; Raghavan, P. R.; Carter, C.; Nakano, K.; Schaffner, K. Photochemical High-yield Preparation of Tricyclo [3.3.0.$0^{2,8}$]octan-3-ones. Potential Synthons for Polycyclopentanoid Terpenes and Prostacyclin Analogs. *Helv. Chim. Acta* **1980**, *63*, 2434−2439. (d) Rau, H.; Hörmann, M. Kinetic resolution of optically active molecules and asymmetric chemistry: asymmetrically sensitized photolysis of *trans*-3,5-diphenylpyrazoline. *J. Photochem.* **1981**, *16*, 231−247. (e) Cauble, D. F.; Lynch, V.; Krische, M. J. Studies on the Enantioselective Catalysis of Photochemically Promoted Transformations: "Sensitizing Receptors" as Chiral Catalysts. *J. Org. Chem.* **2003**, *68*, 15−21.
(50) Sitterberg, S. Chirale Sensibilisatoren für enantioselektive intramolekulare [2 + 2]-Photocycloadditionen. Ph.D. Dissertation, Technische Universität München, 2003.
(51) Müller, C.; Bauer, A.; Bach, T. Light-Driven Enantioselective Organocatalysis. *Angew. Chem., Int. Ed.* **2009**, *48*, 6640−6642.
(52) Alonso, R.; Bach, T. A Chiral Thioxanthone as an Organocatalyst for Enantioselective [2 + 2] Photocycloaddition Reactions Induced by Visible Light. *Angew. Chem., Int. Ed.* **2014**, *53*, 4368−4371.

DOI: 10.1021/acs.joc.9b01299
J. Org. Chem. 2019, 84, 8815−8836

(53) Bauer, A.; Bach, T. Unpublished results, Technische Universität München, 2018.
(54) Hölzl-Hobmeier, A.; Bauer, A.; Silva, A. V.; Huber, S. M.; Bannwarth, C.; Bach, T. Catalytic deracemization of chiral allenes by sensitized excitation with visible light. *Nature* **2018**, *564*, 240−243.
(55) For related work by Wagenknecht and co-workers, see: (a) Gaß, N.; Wagenknecht, H.-A. Synthesis of Benzophenone Nucleosides and Their Photocatalytic Evaluation for [2 + 2] Cycloaddition in Aqueous Media. *Eur. J. Org. Chem.* **2015**, *2015*, 6661−6668. (b) Gaß, N.; Gebhard, J.; Wagenknecht, H.-A. Photocatalysis of a [2 + 2] Cycloaddition in Aqueous Solution Using DNA Three-Way Junctions as Chiral PhotoDNAzymes. *ChemPhotoChem.* **2017**, *1*, 48−50.
(56) (a) Hoffmann, R.; Swenson, J. R. Ground- and Excited-State Geometries of Benzophenone. *J. Phys. Chem.* **1970**, *74*, 415−420. (b) Merz, T.; Wenninger, M.; Weinberger, M.; Riedle, E.; Wagenknecht, H.-A.; Schütz, M. Conformational control of benzophenone-sensitized charge transfer in dinucleotides. *Phys. Chem. Chem. Phys.* **2013**, *15*, 18607−18619.
(57) Sergentu, D.-C.; Maurice, R.; Havenith, R. W. A.; Broer, R.; Roca-Sanjuan, D. Computational determination of the dominant triplet population mechanism in photoexcited benzophenone. *Phys. Chem. Chem. Phys.* **2014**, *16*, 25393−25403.
(58) Kawai, A.; Hirakawa, M.; Abe, T.; Obi, K.; Shibuya, K. Specific Solvent Effects on the Structure and Reaction Dynamics of Benzophenone Ketyl Radical. *J. Phys. Chem. A* **2001**, *105*, 9628−9636.
(59) Bertrand, S.; Hoffmann, N.; Pete, J.-P. Highly Efficient and Stereoselective Radical Addition of Tertiary Amines to Electron-Deficient Alkenes − Application to the Enantioselective Synthesis of Necine Bases. *Eur. J. Org. Chem.* **2000**, *2000*, 2227−2238.
(60) Cavaleri, J. J.; Prater, K.; Bowman, R. M. An investigation of the solvent dependence on the ultrafast intersystem crossing kinetics of xanthone. *Chem. Phys. Lett.* **1996**, *259*, 495−502.
(61) (a) Müller, C.; Bauer, A.; Maturi, M. M.; Cuquerella, M. C.; Miranda, M. A.; Bach, T. Enantioselective Intramolecular [2 + 2]-Photocycloaddition Reactions of 4-Substituted Quinolones Catalyzed by a Chiral Sensitizer with a Hydrogen-Bonding Motif. *J. Am. Chem. Soc.* **2011**, *133*, 16689−16697. (b) Maturi, M. M.; Wenninger, M.; Alonso, R.; Bauer, A.; Pöthig, A.; Riedle, E.; Bach, T. Intramolecular [2 + 2] Photocycloaddition of 3- and 4-(But-3-enyl)oxyquinolones: Influence of the Alkene Substitution Pattern, Photophysical Studies, and Enantioselective Catalysis by a Chiral Sensitizer. *Chem. - Eur. J.* **2013**, *19*, 7461−7472.
(62) Maturi, M. M.; Bach, T. Enantioselective Catalysis of the Intermolecular [2 + 2] Photocycloaddition between 2-Pyridones and Acetylenedicarboxylates. *Angew. Chem., Int. Ed.* **2014**, *53*, 7661−7664.
(63) A related solvent mixture was employed in a study on enantioselective [2 + 2] photocycloaddition reactions mediated by thiourea hydrogen bonds: Vallavoju, N.; Selvakumar, S.; Jockusch, S.; Sibi, M. P.; Sivaguru, J. Enantioselective Organo-Photocatalysis Mediated by Atropisomeric Thiourea Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 5604−5608.
(64) (a) Maturi, M. M.; Pöthig, A.; Bach, T. Enantioselective Photochemical Rearrangements of Spirooxindole Epoxides Catalyzed by a Chiral Bifunctional Xanthone. *Aust. J. Chem.* **2015**, *68*, 1682−1692. (b) Böhm, A.; Bach, T. Synthesis of Supramolecular Iridium Catalysts and Their Use in Enantioselective Visible-Light-Induced Reactions. *Synlett* **2016**, *27*, 1056−1060.
(65) Silvi, M.; Melchiorre, P. Enhancing the potential of enantioselective organocatalysis with light. *Nature* **2018**, *554*, 41−49.
(66) For a related approach, see: Skubi, K. L.; Kidd, J. B.; Jung, H.; Guzei, I. A.; Baik, M.-H.; Yoon, T. P. Enantioselective Excited-State Photoreactions Controlled By A Chiral Hydrogen-Bonding Iridium Sensitizer. *J. Am. Chem. Soc.* **2017**, *139*, 17186−17192.
(67) Alonso, R.; Bauer, A.; Bach, T. Unpublished results, Technische Universität München, 2018.
(68) Tröster, A.; Alonso, R.; Bauer, A.; Bach, T. Enantioselective Intermolecular [2 + 2] Photocycloaddition Reactions of 2(1*H*)-Quinolones Induced by Visible Light Irradiation. *J. Am. Chem. Soc.* **2016**, *138*, 7808−7811.
(69) (a) Hammond, G. S.; Cole, R. S. Asymmetric Induction During Energy Transfer. *J. Am. Chem. Soc.* **1965**, *87*, 3256−3257. (b) Drucker, C. S.; Toscano, V. G.; Weiss, R. G. A General Method for the Determination of Steric Effects during Collisional Energy Transfer. Partial Photoresolution of Penta-2,3-diene. *J. Am. Chem. Soc.* **1973**, *95*, 6482−6484. (c) Balavoine, G.; Jugé, S.; Kagan, H. B. Photoactivation optique du methyl p-tolyl sulfoxyde racemique par emploi d'un sensibilisateur chiral. *Tetrahedron Lett.* **1973**, *14*, 4159−4162.
(70) Lorenz, H.; Seidel-Morgenstern, A. Processes to Separate Enantiomers. *Angew. Chem., Int. Ed.* **2014**, *53*, 1218−1250.
(71) Bucher, G.; Mahajan, A. A.; Schmittel, M. The Photochemical C^2−C^6 Cyclization of Enyne−Allenes: Interception of the Fulvene Diradical with a Radical Clock Ring Opening. *J. Org. Chem.* **2009**, *74*, 5850−5860.
(72) Tröster, A.; Bauer, A.; Jandl, C.; Bach, T. Enantioselective Visible-Light-Mediated Formation of 3-Cyclopropylquinolones by Triplet-Sensitized Deracemization. *Angew. Chem., Int. Ed.* **2019**, *58*, 3538−3541.
(73) Reviews: (a) Mote, N. R.; Chikkali, S. H. Hydrogen-Bonding-Assisted Supramolecular Metal Catalysis. *Chem. - Asian J.* **2018**, *13*, 3623−3646. (b) Davis, H. J.; Phipps, R. J. Harnessing non-covalent interactions to exert control over regioselectivity and site-selectivity in catalytic reactions. *Chem. Sci.* **2017**, *8*, 864−877. (c) Dydio, P.; Reek, J. N. H. Supramolecular control of selectivity in transition-metal catalysis through substrate preorganization. *Chem. Sci.* **2014**, *5*, 2135−2145. (d) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; Van Leeuwen, P. W. N. M. Supramolecular catalysis. Part 1: non-covalent interactions as a tool for building and modifying homogeneous catalysts. *Chem. Soc. Rev.* **2014**, *43*, 1660−1733. (e) Carboni, S.; Gennari, C.; Pignataro, L.; Piarulli, U. Supramolecular ligand−ligand and ligand−substrate interactions for highly selective transition metal catalysis. *Dalton Trans* **2011**, *40*, 4355−4373. (f) Das, S.; Brudvig, G. W.; Crabtree, R. H. Molecular recognition in homogeneous transition metal catalysis: a biomimetic strategy for high selectivity. *Chem. Commun.* **2008**, 413−424.
(74) Šmejkal, T.; Breit, B. A Supramolecular Catalyst for Regioselective Hydroformylation of Unsaturated Carboxylic Acids. *Angew. Chem., Int. Ed.* **2008**, *47*, 311−315.
(75) For additional work by Breit and co-workers on this topic: (a) Šmejkal, T.; Breit, B. A Supramolecular Catalyst for the Decarboxylative Hydroformylation of *α,β*-Unsaturated Carboxylic Acids. *Angew. Chem., Int. Ed.* **2008**, *47*, 3946−3949. (b) Šmejkal, T.; Gribkov, D.; Geier, J.; Keller, M.; Breit, B. Transition-State Stabilization by a Secondary Substrate−Ligand Interaction: A New Design Principle for Highly Efficient Transition-Metal Catalysis. *Chem. - Eur. J.* **2010**, *16*, 2470−2478. (c) Fang, W.; Breit, B. Tandem Regioselective Hydroformylation-Hydrogenation of Internal Alkynes Using a Supramolecular Catalyst. *Angew. Chem., Int. Ed.* **2018**, *57*, 14817−14821.
(76) Breuil, P.-A. R.; Patureau, F. W.; Reek, J. N. H. Singly Hydrogen Bonded Supramolecular Ligands for Highly Selective Rhodium-Catalyzed Hydrogenation Reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 2162−2165.
(77) For additional work by Reek and co-workers on this topic: (a) Dydio, P.; Dzik, W. I.; Lutz, M.; de Bruin, B.; Reek, J. N. H. Remote Supramolecular Control of Catalyst Selectivity in the Hydroformylation of Alkenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 396−400. (b) Dydio, P.; Reek, J. N. H. Supramolecular Control of Selectivity in Hydroformylation of Vinyl Arenes: Easy Access to Valuable *β*-Aldehyde Intermediates. *Angew. Chem., Int. Ed.* **2013**, *52*, 3878−3882. (c) Dydio, P.; Detz, R. J.; de Bruin, B.; Reek, J. N. H. Beyond Classical Reactivity Patterns: Hydroformylation of Vinyl and Allyl Arenes to Valuable *β*- and *γ*-Aldehyde Intermediates Using Supramolecular Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 8418−8429.
(78) For two selected examples in which the Roche ester was used as a key chiral building block in total synthesis, see: (a) Shin, Y.;

DOI: 10.1021/acs.joc.9b01299
J. Org. Chem. 2019, 84, 8815−8836

Fournier, J.-H.; Fukui, Y.; Brückner, A. M.; Curran, D. P. Total Synthesis of (−)-Dictyostatin: Confirmation Of Relative and Absolute Configurations. *Angew. Chem., Int. Ed.* **2004**, *43*, 4634−4637. (b) Smith, A. B., III; Adams, C. M.; Barbosa, S. A. L.; Degnan, A. P. A unified approach to the tedanolides: Total synthesis of (+)-13-deoxytedanolide. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 12042−12047.

(79) Vogt, F. Synthese neuer Liganden und Katalysatoren für einen Wasserstoffbrücken-vermittelten Chiralitätstransfer. Ph.D. Dissertation, Technische Universität München, 2010.

(80) (a) Lonergan, D. G.; Riego, J.; Deslongchamps, G. A Convergent Hydroxyimide Module for Molecular Recognition. *Tetrahedron Lett.* **1996**, *37*, 6109−6112. (b) Lonergan, D. G.; Halse, J.; Deslongchamps, G. Comparative Probe for Stacking Interactions in Simple A:T Base Pair Mimics. *Tetrahedron Lett.* **1998**, *39*, 6865−6868. (c) Lonergan, D. G.; Deslongchamps, G. Tricyclic Scaffolds for the Rapid Assembly of Abiotic Receptors. *Tetrahedron* **1998**, *54*, 14041−14052.

(81) (a) Corwin, L. R.; McDaniel, D. M.; Bushby, R. J.; Berson, J. A. Dimerization and Cycloaddition Reactions of a Trimethylenemethane Derivative, 2-Isopropylidenecyclopenta-1,3-diyl. Mechanistic Separation of Triplet and Singlet Reactions. *J. Am. Chem. Soc.* **1980**, *102*, 276−287. (b) Fackler, P.; Berthold, C.; Voss, F.; Bach, T. Hydrogen-Bond-Mediated Enantio- and Regioselectivity in a Ru-Catalyzed Epoxidation Reaction. *J. Am. Chem. Soc.* **2010**, *132*, 15911−15913.

(82) *Cytochrome P450: Structure, Mechanism, and Biochemistry*, 3rd ed.; Ortiz de Montellano, P. R., Ed.; Kluwer: New York, 2005.

(83) (a) Fasan, R. Tuning P450 Enzymes as Oxidation Catalysts. *ACS Catal.* **2012**, *2*, 647−666. (b) Lewis, J. C.; Coelho, P. S.; Arnold, F. H. Enzymatic functionalization of carbon−hydrogen bonds. *Chem. Soc. Rev.* **2011**, *40*, 2003−2021. (c) Ortiz de Montellano, P. R. Hydrocarbon Hydroxylation by Cytochrome P450 Enzymes. *Chem. Rev.* **2010**, *110*, 932−948.

(84) For reviews on biomimetic oxygenation reactions in organic syntheses, see: (a) Vidal, D.; Olivo, G.; Costas, M. Controlling Selectivity in Aliphatic C−H Oxidation through Supramolecular Recognition. *Chem. - Eur. J.* **2018**, *24*, 5042−5054. (b) Milan, M.; Bietti, M.; Costas, M. Enantioselective aliphatic C−H bond oxidation catalyzed by bioinspired complexes. *Chem. Commun.* **2018**, *54*, 9559−9570.

(85) (a) Breslow, R.; Zhang, X.; Huang, Y. Selective Catalytic Hydroxylation of a Steroid by an Artificial Cytochrome P-450 Enzyme. *J. Am. Chem. Soc.* **1997**, *119*, 4535−4536. (b) Yang, J.; Breslow, R. Selective Hydroxylation of a Steroid at C-9 by an Artificial Cytochrom P-450. *Angew. Chem., Int. Ed.* **2000**, *39*, 2692−2694. (c) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. Catalytic Oxidations of Steroid Substrates by Artificial Cytochrome P-450 Enzymes. *J. Org. Chem.* **2002**, *67*, 5057−5067. (d) Fang, Z.; Breslow, R. Metal Coordination-Directed Hydroxylation of Steroids with a Novel Artificial P-450 Catalyst. *Org. Lett.* **2006**, *8*, 251−254.

(86) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. Molecular Recognition in the Selective Oxygenation of Saturated C-H bonds by a Dimanganese Catalyst. *Science* **2006**, *312*, 1941−1943. (b) Das, S.; Brudvig, G. W.; Crabtree, R. H. High Turnover Remote Catalytic Oxygenation of Alkyl Groups: How Steric Exclusion of Unbound Substrate Contributes to High Molecular Recognition Selectivity. *J. Am. Chem. Soc.* **2008**, *130*, 1628−1637. (c) Hull, J. F.; Sauer, E. L. O.; Incarvito, C. D.; Faller, J. W.; Brudvig, G. W.; Crabtree, R. H. Manganese Catalysts with Molecular Recognition Functionality for Selective Alkene Epoxidation. *Inorg. Chem.* **2009**, *48*, 488−495.

(87) (a) Gupta, K. C.; Sutar, A. K. Catalytic activities of Schiff base transition metal complexes. *Coord. Chem. Rev.* **2008**, *252*, 1420−1450. (b) McGarrigle, E. M.; Gilheany, D. G. Chromium− and Manganese−salen Promoted Epoxidation of Alkenes. *Chem. Rev.* **2005**, *105*, 1563−1602. (c) Venkataramanan, N. S.; Kuppuraj, G.; Rajagopal, S. Metal−salen complexes as efficient catalysts for the oxygenation of heteroatom containing organic compounds−synthetic and mechanistic aspects. *Coord. Chem. Rev.* **2005**, *249*, 1249−1268. (d) Katsuki, T. Catalytic asymmetric oxidations using optically active (salen)manganese(III) complexes as catalysts. *Coord. Chem. Rev.* **1995**, *140*, 189−214.

(88) (a) Larrow, J. F.; Jacobsen, E. N. (*R,R*)-*N,N'*-bis(3,5-Di-*tert*-Butylsalicylidene)-1,2-Cyclohexanediamino Manganese(III) Chloride, A Highly Enantioselective Epoxidation Catalyst. *Org. Synth.* **1998**, *75*, 1−6. (b) Park, J.; Lang, K.; Abboud, K. A.; Hong, S. Self-Assembled Dinuclear Cobalt(II)-Salen Catalyst Through Hydrogen-Bonding and Its Application to Enantioselective Nitro-Aldol (Henry) Reaction. *J. Am. Chem. Soc.* **2008**, *130*, 16484−16485.

(89) Voss, F.; Herdtweck, E.; Bach, T. Hydrogen bond induced enantioselectivity in Mn(salen)-catalysed sulfoxidaton reactions. *Chem. Commun.* **2011**, *47*, 2137−2139.

(90) Reviews: (a) Huang, X.; Groves, J. T. Oxygen Activation and Radical Transformations in Heme Proteins and Metalloporphyrins. *Chem. Rev.* **2018**, *118*, 2491−2553. (b) Baglia, R. A.; Zaragoza, J. P. T.; Goldberg, D. P. Biomimetic Reactivity of Oxygen-Derived Manganese and Iron Porphyrinoid Complexes. *Chem. Rev.* **2017**, *117*, 13320−13352. (c) Senge, M. O. Stirring the porphyrin alphabet soup − functionalization reactions of porphyrins. *Chem. Commun.* **2011**, *47*, 1943−1960. (d) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. Selective functionalisation of saturated C−H bonds with metalloporphyrin catalysts. *Chem. Soc. Rev.* **2011**, *40*, 1950−1975. (e) Costas, M. Selective C−H oxidation catalyzed by metalloporphyrins. *Coord. Chem. Rev.* **2011**, *255*, 2912−2932.

(91) Frost, J. R.; Huber, S. M.; Breitenlechner, S.; Bannwarth, C.; Bach, T. Enantiotopos-Selective C−H Oxygenation Catalyzed by a Supramolecular Ruthenium Complex. *Angew. Chem., Int. Ed.* **2014**, *54*, 691−695.

(92) Chang, C. K.; Ebina, F. NIH Shift in Haemin−Iodosylbenzene-mediated Hydroxylations. *J. Chem. Soc., Chem. Commun.* **1981**, *15*, 778−779.

(93) Burg, F.; Gicquel, M.; Breitenlechner, S.; Pöthig, A.; Bach, T. Site- and Enantioselective C−H Oxygenation Catalyzed by a Chiral Manganese Porphyrin Complex with a Remote Binding Site. *Angew. Chem., Int. Ed.* **2018**, *57*, 2953−2957.

(94) Zhong, F.; Pöthig, A.; Bach, T. Synergistic Stereocontrol in the Enantioselective Ruthenium-Catalyzed Sulfoxidation of Spirodithiolane-Indolones. *Chem. - Eur. J.* **2015**, *21*, 10310−10313.

(95) Fackler, P.; Huber, S. M.; Bach, T. Enantio- and Regioselective Epoxidation of Olefinic Double Bonds in Quinolones, Pyridones, and Amides Catalyzed by a Ruthenium Porphyrin Catalyst with a Hydrogen Bonding Site. *J. Am. Chem. Soc.* **2012**, *134*, 12869−12878.

(96) (a) Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. Highly Enantioselective Benzylic Hydroxylation with Concave Type of (Salen)manganese(III) Complex. *Tetrahedron* **1998**, *54*, 10017−10028. (b) Murahashi, S.-I.; Noji, S.; Komiya, N. Catalytic Enantioselective Oxidation of Alkanes and Alkenes Using (Salen) Manganese Complexes Bearing a Chiral Binaphthyl Strapping Unit. *Adv. Synth. Catal.* **2004**, *346*, 195−198. (c) Srour, H.; Le Maux, P.; Simonneaux, G. Enantioselective Manganese-Porphyrin-Catalyzed Epoxidation and C−H Hydroxylation with Hydrogen Peroxide in Water/Methanol Solutions. *Inorg. Chem.* **2012**, *51*, 5850−5856. (d) Kwong, K. W.; Chen, T.-H.; Luo, W.; Jeddi, H.; Zhang, R. A biomimetic oxidation catalyzed by manganese(III) porphyrins and iodobenzene diacetate: Synthetic and mechanistic investigations. *Inorg. Chim. Acta* **2015**, *430*, 176−183. (e) Milan, M.; Bietti, M.; Costas, M. Highly Enantioselective Oxidation of Nonactivated Aliphatic C−H Bonds with Hydrogen Peroxide Catalyzed by Manganese Complexes. *ACS Cent. Sci.* **2017**, *3*, 196−204. (f) Olivo, G.; Capocasa, G.; Lanzalunga, O.; Di Stefano, S.; Costas, M. Enzyme-like substrate-selectivity in C−H oxidation enabled by recognition. *Chem. Commun.* **2019**, *55*, 917−920.

(97) For Fe-catalyzed C−H oxygenation reactions, see: (a) Groves, J. T.; Viski, P. Asymmetric Hydroxylation by a Chiral Iron Porphyrin. *J. Am. Chem. Soc.* **1989**, *111*, 8537−8538. (b) Groves, J. T.; Viski, P. Asymmetric Hydroxylation, Epoxidation, and Sulfoxidation Catalyzed by Vaulted Binaphthyl Metalloporphyrins. *J. Org. Chem.* **1990**, *55*, 3628−3634. (c) Chen, M. S.; White, M. C. A Predictably Selective

DOI: 10.1021/acs.joc.9b01299
J. Org. Chem. 2019, 84, 8815−8836

Aliphatic C−H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007**, *318*, 783−787. (d) Gómez, L.; Garcia-Bosch, I.; Company, A.; Benet-Buchholz, J.; Polo, A.; Sala, X.; Ribas, X.; Costas, M. Stereospecific C−H Oxidation with H_2O_2 Catalyzed by a Chemically Robust Site-Isolated Iron Catalyst. *Angew. Chem., Int. Ed.* **2009**, *48*, 5720−5723. (e) Chen, M. S.; White, M. C. Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327*, 566−571. (f) Gormisky, P. E.; White, M. C. Catalyst-Controlled Aliphatic C−H Oxidations with a Predictive Model for Site-Selectivity. *J. Am. Chem. Soc.* **2013**, *135*, 14052−14055. (g) Gómez, L.; Canta, M.; Font, D.; Prat, I.; Ribas, X.; Costas, M. Regioselective Oxidation of Nonactivated Alkyl C−H Groups Using Highly Structured Non-Heme Iron Catalysts. *J. Org. Chem.* **2013**, *78*, 1421−1433. (h) Jana, S.; Ghosh, M.; Ambule, M.; Sen Gupta, S. Iron Complex Catalyzed Selective C−H Bond Oxidation with Broad Substrate Scope. *Org. Lett.* **2017**, *19*, 746−749.

(98) (a) Takai, T.; Koike, T.; Nakamura, M.; Kajita, Y.; Yamashita, T.; Taya, N.; Tsukamoto, T.; Watanabe, T.; Murakami, K.; Igari, T.; Kamata, M. Discovery of novel 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine derivatives as γ-secretase modulators. *Bioorg. Med. Chem.* **2016**, *24*, 3192−3206. (b) Susanta, S.; Chandrasekhar, A.; Sanjita, S.; Subramanya, H. Heterocyclic Derivatives as Bromodomain Inhibitors. WO Patent WO 2015/104653, 2015.

(99) For reviews on C−H amination reactions, see: (a) Buendia, J.; Grelier, G.; Dauban, P. Dirhodium(II)-Catalyzed C(sp^3)−H Amination Using Iodine(III) Oxidants. *Adv. Organomet. Chem.* **2015**, *64*, 77−118. (b) Roizen, J. L.; Harvey, M. E.; Du Bois, J. Metal-Catalyzed Nitrogen-Atom Transfer Methods for the Oxidation of Aliphatic C−H Bonds. *Acc. Chem. Res.* **2012**, *45*, 911−922. (c) Collet, F.; Lescot, C.; Dauban, P. Catalytic C−H amination: the stereoselectivity issue. *Chem. Soc. Rev.* **2011**, *40*, 1926−1936. (d) Müller, P.; Fruit, C. Enantioselective Catalytic Aziridinations and Asymmetric Nitrene Insertion into CH bonds. *Chem. Rev.* **2003**, *103*, 2905−2919.

(100) For a comprehensive overview of different type of alkaloid natural products, see: (a) Kobayashi, J.; Kubota, T. The *Daphniphyllum* alkaloids. *Nat. Prod. Rep.* **2009**, *26*, 936−962. (b) Jessen, H. J.; Gademann, K. 4-Hydroxy-2-pyridone alkaloids: Structures and synthetic approaches. *Nat. Prod. Rep.* **2010**, *27*, 1168−1185. (c) Pilli, R. A.; Rosso, G. B.; Ferreira de Oliveira, M. C. The chemistry of *Stemona* alkaloids: An update. *Nat. Prod. Rep.* **2010**, *27*, 1908−1937. (d) Eckermann, R.; Gaich, T. The Akuammiline Alkaloids; Origin and Synthesis. *Synthesis* **2013**, *45*, 2813−2823. (e) Welch, T. R.; Williams, R. M. Epidithiodioxopiperazines. occurrence, synthesis and biogenesis. *Nat. Prod. Rep.* **2014**, *31*, 1376−1404. (f) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. Simple indole alkaloids and those with a non-rearranged monoterpenoid unit. *Nat. Prod. Rep.* **2015**, *32*, 1389−1471. (g) Jin, Z. Muscarine, imidazole, oxazole and thiazole alkaloids. *Nat. Prod. Rep.* **2016**, *33*, 1268−1317.

(101) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(102) (a) Breslow, S.; Gellman, S. H. Tosylamidation of Cyclohexane by a Cytochrome P-450 Model. *J. Chem. Soc., Chem. Commun.* **1982**, 1400−1401. (b) Breslow, R.; Gellman, S. H. Intramolecular Nitrene C−H Insertions Mediated by Transition-Metal Complexes as Nitrogen Analogs of Cytochrome P-450 Reactions. *J. Am. Chem. Soc.* **1983**, *105*, 6728−6729. (c) Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. Allylic amination of alkenes by tosyliminoiodobenzene: manganese porphyrins as suitable catalysts. *Tetrahedron Lett.* **1988**, *29*, 1927−1930.

(103) (a) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M. Asymmetric amidation of saturated C−H bonds catalysed by chiral ruthenium and manganese porphyrins. *Chem. Commun.* **1999**, 2377−2378. (b) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. Amidation of Saturated C-H Bonds Catalyzed by Electron-Deficient Ruthenium and Mangaese Porphyrins. A Hightly Catalytic Nitrogen Atom Transfer Process. *Org. Lett.* **2000**, *2*, 2233−2236. (c) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. Metalloporphyrin-Mediated Asymmetric Nitrogen-Atom Trasnfer to Hydrocarbons: Aziridination of Alkenes and Amidation of Saturated C-H Bonds Catalyzed by Chiral Ruthenium Manganese Porphyrins. *Chem. - Eur. J.* **2002**, *8*, 1563−1572.

(104) (a) Espino, C. G.; Du Bois, J. A Rh-Catalyzed C−H Insertion Reaction for the Oxidative Conversion of Carbamates to Oxazolidinones. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. Synthesis of 1,3-Difunctionalized Amine Derivatives through Selective C-H Bond Oxidation. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (c) Fiori, K. W.; Fleming, J. J.; Du Bois, J. Rh-Catalyzed Amination of Ethereal C^{α}−H Bonds: A Versatile Strategy for the Synthesis of Complex Amines. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349−4352.

(105) (a) Wehn, P. M.; Du Bois, J. Enantioselective Synthesis of the Bromopyrrole Alkaloids Manzacidin A and C by Stereospecific C−H Bond Oxidation. *J. Am. Chem. Soc.* **2002**, *124*, 12950−12951. (b) Hinman, A.; Du Bois, J. A Stereoselective Synthesis of (−)-Tetrodotoxin. *J. Am. Chem. Soc.* **2003**, *125*, 11510−11511.

(106) (a) Roizen, J. L.; Zalatan, D. N.; Du Bois, J. Selective Intermolecular Amination of C−H Bonds at Tertiary Carbon Centers. *Angew. Chem., Int. Ed.* **2013**, *52*, 11343−11346. (b) Zalatan, D. N.; Du Bois, J. Understand the Differential Performance of $Rh_2(esp)_2$ as a Catalyst for C−H Amination. *J. Am. Chem. Soc.* **2009**, *131*, 7558−7559. (c) Fiori, K. W.; Du Bois, J. Calatytic Intermolecular Amination of C−H Bonds: Method Development and Mechanistic Insights. *J. Am. Chem. Soc.* **2007**, *129*, 562−568. (d) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. Expanding the Scope of C−H Amination through Catalyst Design. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379.

(107) Nörder, A.; Warren, S. A.; Herdtweck, E.; Huber, S. M.; Bach, T. Diastereotopos-Differentiation in the Rh-Catalyzed Amination of Benzylic Methylene Groups in α-Position to a Stereogenic Center. *J. Am. Chem. Soc.* **2012**, *134*, 13524−13531.

(108) Höke, T.; Herdtweck, E.; Bach, T. Hydrogen-bond mediated regio- and enantioselectivity in a C−H amination reaction catalysed by a supramolecular Rh(II) complex. *Chem. Commun.* **2013**, *49*, 8009−8011.

(109) Voss, F.; Vogt, F.; Herdtweck, E.; Bach, T. Synthesis of Catalytically Active Ruthenium Complexes with a Remote Chiral Lactam as Hydrogen-Bonding Motif. *Synthesis* **2011**, *2011*, 961−971.

(110) For a recent study, see: Berndt, J.-P.; Radchenko, Y.; Becker, J.; Logemann, C.; Bhandari, D. R.; Hrdina, R.; Schreiner, P. R. Site-selective nitrenoid insertions utilizing postfunctionalized bifunctional rhodium(II) catalysts. *Chem. Sci.* **2019**, *10*, 3324−3329.

(111) Guthikonda, K.; Du Bois, J. A Unique and Highly Efficient Method for Catalytic Olefin Aziridination. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673.

(112) Zhong, F.; Bach, T. Enantioselective Construction of 2,3-Dihydrofuro[2,3-*b*]quinolines through Supramolecular Hydrogen Bonding Interactions. *Chem. - Eur. J.* **2014**, *20*, 13522−13526.

(113) (a) Dale, J. A.; Mosher, H. S. Nuclear Magnetic Resonance Enantiomer Reagents. Configurational Correlations *via* Nuclear Magnetic Resonance Chemical Shifts of Diastereomeric Mandelate, *O*-Methylmandelarate and α-Methoxy-α-trifluoromethylphenylacetate (MTPA) Esters. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher ester analysis for the determination of absolute configuration of stereogenic (chiral) carbinol carbons. *Nat. Protoc.* **2007**, *2*, 2451−2458.

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