VIP Photochemistry

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Intramolecular [2+2] Photocycloaddition of Substituted Isoquinolones: Enantioselectivity and Kinetic Resolution Induced by a Chiral Template**

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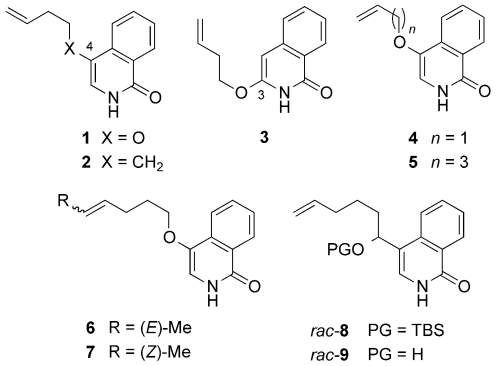
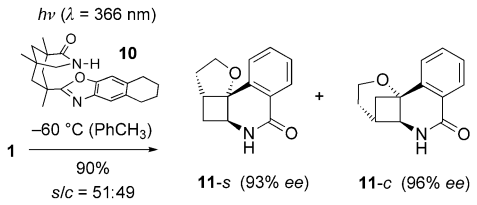
Dedicated to Professor Dieter Hoppe on the occasion of his 70th birthday

Although intermolecular [2+2] photocycloadditions of isoquinolones have been studied for some time,[1] the corresponding intramolecular reactions of this substrate class have received little attention. To date, only isoquinolones that carry the olefin for an intramolecular cycloaddition in an N-tethered chain have been examined.[2] Given the prevalence of isoquinoline-derived natural products,[3] the intramolecular [2+2] photocycloaddition of isoquinolones could potentially be very useful,[4] particularly if these reactions could be performed regio- and enantioselectively. We have now studied the photocycloaddition reactions of a selection of 3- and 4-substituted isoquinolones **1**–**9** (Scheme 1). The various cyclobutane products were formed in high yields and, in the case of 4-substituted isoquinolones, with high enantioselectivities (88–96% *ee*) by employing a chiral template. Moreover, it was shown for the first time that kinetic resolution is possible in template-based organic photochemistry.



Scheme 1. Substrates **1**–**9** employed to probe the selectivity in the intramolecular [2+2] photocycloaddition of isoquinolones. PG = protecting group.

The starting materials for this study were prepared from 4-hydroxyisoquinolone[5] (substrates **1**, **4**–**7**), 4-bromoisoquinolone[6] (substrates **2**, **8**, **9**), and 3-hydroxyisoquinolone[7] (substrate **3**). Further details on the synthesis of these substrates are found in the Supporting Information. Initial reactions were performed with 4-(but-3-enyloxy)isoquinolone (**1**). The optimum wavelength for irradiation was found to be around $\lambda = 366$ nm (fluorescence light tubes), and racemic photocycloaddition products were obtained after 50 min of irradiation at ambient temperature in trifluorotoluene or toluene as the solvent. When performed in the presence of chiral template **10**[8] (2.6 equiv in all experiments), the [2+2] photocycloaddition of isoquinolone **1** ($c = 5$ mM) was found to occur in a highly enantioselective manner (Scheme 2).[9,10] The best results were achieved at low temperature: the straight photoproduct **11**-*s* was obtained



Scheme 2. Typical irradiation conditions for the enantioselective intramolecular [2+2] photocycloaddition of isoquinolones, exemplified in the reaction of substrate **1**.

with 93% *ee* and the crossed photoproduct **11**-*c* with 96% *ee*. The absolute configuration of compound **11**-*s* was proven by conversion into the corresponding *N*-(−)-menthyloxycarbonyl derivative and subsequent X-ray crystal structure analysis (see the Supporting Information).

Based on these results, the mode of action of template **10** is likely effected by hydrogen bonding to substrate **1** and its ability to provide significant enantioface differentiation to the bulky 5,6,7,8-tetrahydronaphtho[2,3-*d*]oxazole substituent ("steric shield").[11] Still, it is surprising that the enantiomeric excess is so high given the fact that the reactive olefinic carbon–carbon bond of the isoquinolone is located on the periphery[12] of the shielding substituent (vide infra).

While the regioselectivity of the intermolecular [2+2] photocycloaddition is significantly influenced by the fact that

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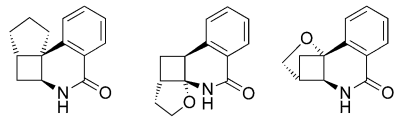
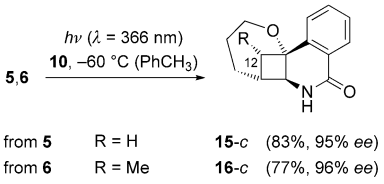
the intermediate (di)radical is stabilized in the benzylic position, that is, at the C4 carbon atom of isoquinolones,[1d] in the intramolecular case the regioselectivity is usually controlled by the operation of the "rule of five".[13] This led us to anticipate that cycloaddition of substrate **1** would result in exclusive formation of **11**-*s*. However, it appears that the stability of the benzylic (di)radical is further enhanced by the 4-alkoxy substituent,[14] resulting in the formation of relatively high amounts of crossed product **11**-*c*. Indeed, for substrates lacking an alkoxy substituent at the C4 carbon atom, only straight photocycloaddition products were observed (Scheme 3). Substrate **2** delivered exclusively tetracyclic product **12**-*s*, and substrate **3** gave product **13**-*s* as a single



Scheme 3. Enantiomerically enriched, diastereomerically pure products **12**–**14** obtained as pure straight (*s*) or crossed (*c*) regioisomers from the [2+2] photocycloaddition of substrates **2**–**4** in the presence of template **10.**

regioisomer. The somewhat lower enantioselectivity in the latter case can be explained by the interference of the substituent at C3 in the binding to template **10**. In all cases, template recovery was high and close to quantitative. Isoquinolone **4** gave the expected crossed product[13] **14**-*c* with high enantiomeric excess.

Given that the enantioselective [2+2] photocycloaddition of 4-(pent-4-enyloxy)quinolone affords exclusively the straight product,[8a,11a] we were quite surprised that 4-(pent-4-enyloxy)isoquinolone (**5**) delivered predominantly—exclusively in the presence of template **10** (Scheme 4)—the crossed



Scheme 4. Highly enantioselective [2+2] photocycloaddition of isoquinolones **5** and **6** to afford the crossed products **15** and **16**.

product **15**-*c*. Again, we believe that this is related to the increased stabilization of the alkoxy-substituted (di)radical, which can be formed only upon ring closure of a seven-membered oxepane in the initial reaction step. The enantioselectivity of the process is very high, which suggests that the photoproduct **15**-*c* has a lower association affinity to template **10** than the starting material.[15]

If the double bond of the tethered olefin is α-substituted ($R \neq H$), an additional stereogenic center is formed at position C12 of the tetracyclic skeleton. The relative configuration of the product was found to be independent of the relative configuration of the starting material (stereoconvergent reaction course). Both *E* isomer **6** or *Z* isomer **7** gave the product *rac*-**16**-*c*, in which the methyl group (R = Me) is *cis*-oriented relative to the oxepane ring. This stereoconvergency is in agreement with a stepwise photocycloaddition, in which the intermediate triplet 1,4-diradical has sufficient time to undergo rotation about the carbon–carbon single bonds.[16] Still, it was not evident to us when we looked at molecular models, why the methyl group would point into a seemingly more congested position. In order to confirm our assignment we obtained a single-crystal X-ray crystal structure of the major photoproduct. The X-ray data[17] support the structure that we had proposed based on analysis of the NMR spectra (Figure 1). When the reaction was performed in the presence of template **10**, product **16**-*c* was obtained as a single isomer in high yield and with close to perfect enantioselectivity (96% *ee*).

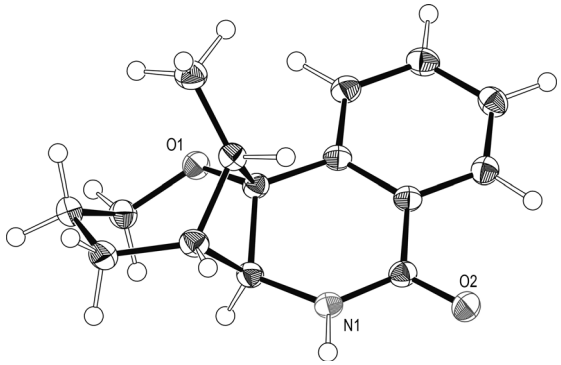
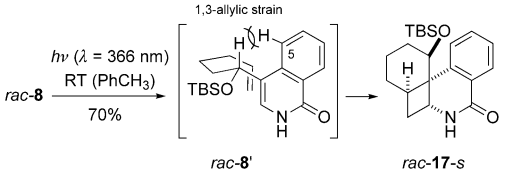


Figure 1. Proof of structure and relative configuration of the crossed product *rac*-**16**-*c* by a single-crystal structure analysis; ellipsoids drawn at the 50% probability level.

Experiments conducted with the racemic starting material *rac*-**8** (TBS = *tert*-butyldimethylsilyl) demonstrated convincingly that a high degree of facial diastereoselectivity can be achieved in the intramolecular [2+2] photocycloaddition of substituted isoquinolones. Even upon irradiation at ambient temperature, the photocycloaddition product *rac*-**17**-*s* was isolated as a single diastereomer. The relative configuration can be explained by assuming conformation *rac*-**8′** to be primarily responsible for the first carbon–carbon bond-forming step in the reaction (Scheme 5). 1,3-Allylic strain[18]



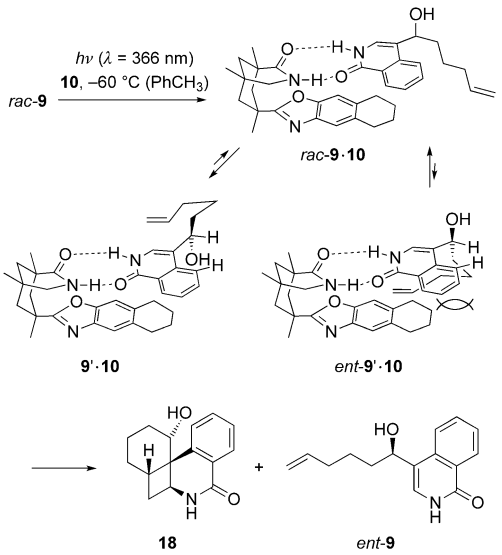
Scheme 5. Perfect facial diastereoselectivity in the intramolecular [2+2] photocycloaddition of isoquinolone *rac*-**8** via conformation *rac*-**8′** leading to product *rac*-**17**-*s*.

between the hydrogen atom at the stereogenic center and the C5 carbon atom of the isoquinolone defines the orientation of the tethered alkene and controls the mode of attack. It also limits the conformational flexibility and, as opposed to alkoxy substrates **5**–**7**, six-membered-ring formation is the exclusive reaction pathway.

The high enantioselectivity of the intramolecular [2+2]-photocycloaddition reactions described at the beginning of this report and the high facial diastereoselectivity observed in the reaction discussed above led us to consider combining both stereochemical aspects to attempt a kinetic resolution[19–21] of a chiral isoquinolone by reaction in the presence of template **10**. Given that the facial diastereoselectivity in the reaction of *rac*-**8** was governed by 1,3-allylic strain, we envisioned that one of the two enantiomorphic transition states of a racemic compound would be severely disfavored if the substrate were bound to template **10**. Indeed, it can be expected, based on previous association data for aromatic six-membered lactams,[22] that the isoquinolone would be bound quantitatively to the template at −60 °C in a nonpolar solvent, if ≥ 2.5 equiv of the template were used. In a situation such as that depicted in Scheme 6, when isoquinolone *rac*-**9** is associated to template **10**, one enantiomer, **9**, is able to adopt the conformation **9′** required for intramolecular ring closure (complex **9′·10**). The relatively small OH group[23] points into the limited space between substrate and template, but should not interfere significantly with the binding event. In the complex of the other enantiomer *ent*-**9**, however, the required conformation *ent*-**9′** cannot be adopted and complex *ent*-**9·10** will not undergo cycloaddition. Indeed, at low conversion we observed formation of only a single enantiomeric [2+2]-photocycloaddition product from substrate *rac*-**9** (> 95 % *ee* at roughly 2 % conversion), to which structure **18** was assigned based on NMR data and on the known face differentiation exerted by template **10**.

As the reaction progressed the enantiomeric excess of the photoproduct decreased but, even when almost all of the starting material had been consumed, it never reached the expected value of 0 % *ee*.[24] On the contrary, the enantiomeric excess was still significant (53 % *ee*) at the end of the reaction. This observation can be explained by the fact that the resolution is accompanied by side reactions (e.g. hydrogen abstraction, dimerization) of enantiomer *ent*-**9**, which in turn are a result of the previously mentioned inaccessibility of conformation *ent*-**9′**. In other words, the disfavored enantiomer *ent*-**9** is not recovered but rather undergoes unspecific photochemical reactions, which lead to its disappearance. Unfortunately, these side reactions complicate the analysis of the product mixture, but it can safely be said that there is also a significant enrichment of the substrate *ent*-**9** (23 % *ee* at about 40 % conversion). Similar experiments performed with racemic compound *rac*-**8** have not been successful. With the bulkier OTBS group, initial results indicate that there is no preference for the respective conformations **8′** and *ent*-**8′** in the presence of template **10**.

In summary, it was shown that intramolecular [2+2]-photocycloaddition reactions of substituted isoquinolones proceed enantioselectively in the presence of chiral template **10**. If the binding of the substrate to the template is favored—as is the case for 4-substituted isoquinolones—high enantioselectivities result. In fact, the association of some isoquinolones to template **10** appears to be so high that the template is able to bias enantiomorphic conformations in a 1:1 assembly of isoquinolone and template. An application of this phenomenon to the kinetic resolution of racemic isoquinolone *rac*-**9** was successfully performed.



Scheme 6. Kinetic resolution in the intramolecular [2+2] photocycloaddition of isoquinolone *rac*-**9**.

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