Enantioselective Intermolecular [2 + 2]-Photocycloaddition Reactions of Alkenes and a 2-Quinolone in Solution

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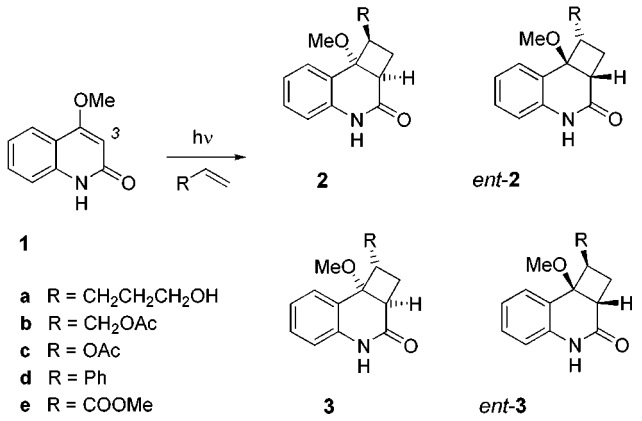
In recent years, there has been tremendous progress in the enantioselective synthesis of strained compounds by *intramolecular* photochemical reactions.[1] Chiral organic[2] and inorganic[3] complexing agents have been employed successfully in solid-state photochemistry. Homochiral crystals of prochiral substrates have been obtained by the "ionic chiral auxiliary" approach[4] or by other methods[5] and yielded enantiomerically enriched products upon irradiation. In the liquid phase, many efforts have centered on the use of circular polarized light to induce an effective differentiation of enantiotopic faces and enantiomeric excesses (ee's) up to 64% have been recorded.[6] Enantioselective photocycloaddition reactions in solution have been achieved using chiral host molecules which bind the substrate by hydrogen bonding.[7]

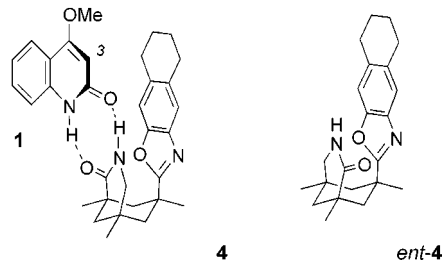
An advantage of the latter approach as compared to the methods employed in the solid state is the fact that it should also be applicable to *intermolecular* photochemical reactions of two different reaction partners. Contrary to the classical auxiliary-based methodology which has been elegantly applied in photocycloaddition chemistry[8,9] the use of a noncovalently bound complexing agent avoids the cleavage of the chiral source.[10] We would now like to report on our preliminary results with regard to enantioselective (81−98% ee) intermolecular [2 + 2]-photocycloadditions in solution.

The quinolone **1** is known to undergo a [2 + 2]-photocycloaddition with different alkene substrates (Scheme 1).[11] Its lactam functionality should be well suited for binding to the lactam-based receptors which we have recently prepared in our laboratory.[7,12] The *endo*- and *exo*-isomers **2** and **3** and their enantiomers *ent*-**2** and *ent*-**3** are obtained as products, the *exo*/*endo* ratio being dependent on the substituent R (vide infra).

Scheme 1



Scheme 2



Binding to a chiral host should facilitate a differentiation of the enantiotopic faces of compound **1**. For the current set of experiments we have employed the chiral amide **4** and its enantiomer *ent*-**4** (Scheme 2). As depicted in Scheme 2 the quinolone **1** was expected to coordinate to the lactam **4** with its NH-group being the hydrogen donor and with the carbonyl group being the hydrogen acceptor. In previous studies it was shown that the association contants of six-membered lactams related to **1** and host molecules related to **4** are high and that the self-association of the host is low.[13] It was consequently expected that the quinolone **1** undergoes a selective photocycloaddition, provided that it binds to the host and provided that the intermolecular reaction occurs at the bound substrate.

The studies were conducted with different alkenes (Scheme 1, Table 1). Only selected experimental data are provided in Table 1, additional data can be found in the Supporting Information. The best results were obtained at low-temperature employing an excess of the host (entries 1, 2, and 3). Either enantiomer of the host **4** or *ent*-**4** was used in these experiments. As expected the product with opposite configuration was obtained upon exchanging the host (entries 4 and 5). In the case of vinyl acetate (R = OAc) both cyclobutane isomers *ent*-**2c** (*endo*) and *ent*-**3c** (*exo*) were isolated. The optical purity of the two diastereoisomers was similar (entry 6). In general, the simple diastereoselectivities (*endo*/*exo* ratios) determined in the presence of the chiral host did not significantly differ from the diastereoselectivities obtained

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Table 1. Enantioselective Photocycloaddition of the 2-Quinolone **1** in the Presence of the Chiral Host Compounds **4** and *ent*-**4**

entry	R[a]	temp [°C]	time [h][b]	host	equiv	dr[c] (**3**/**2**)	yield [%][d]	product	ee [%][e]
1	$CH_2CH_2CH_2OH$	30	2	**4**	1.4	>95/5	75	**3a**	30
2	$CH_2CH_2CH_2OH$	−20	10	**4**	1.3	>95/5	74	**3a**	52
3	$CH_2CH_2CH_2OH$	−60	10	**4**	2.4	>95/5	80	**3a**	81
4	CH_2OAc	−60	10	**4**	2.4	>95/5	80	**3b**	92
5	CH_2OAc	−60	10	*ent*-**4**	2.4	>95/5	81	*ent*-**3b**	91
6	OAc	−60	10	*ent*-**4**	2.4	63/27	89	*ent*-**3c**	93
								ent-**2c**	98
7	Ph	−60	10	**4**	2.4	<5/95	10[f]	**2d**	83
8	$COOCH_3$	−60	10	**4**	2.4	90/10	84	**3e**	82[g]

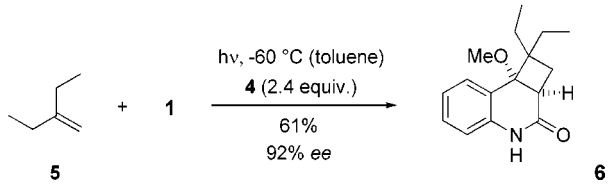
[a] The reaction was conducted in an immersion apparatus (Duran filter; light source: Original Hanau TQ 150). The quinolone concentration was 2×10^{-3} M in toluene as the solvent. The alkene was used in excess (20 equiv). After complete conversion the solvent and the excess alkene was removed in vacuo and the residue was purified by flash chromatography (gradient: *tert*-butyl methyl ether/pentane). [b] Time after which the conversion was complete (except for entry 7). [c] The diastereomeric ratio of cyclobutanes in the crude product was determined by integration of appropriate ^{1}H NMR signals. [d] Yield of isolated product. [e] The enantiomeric excess was determined by chiral HPLC (Chiracel OD; eluent: hexane/*i*-propanol = 92/8). [f] The reaction remained incomplete even upon prolongued irradiation. 65% of the quinolone was recovered. [g] The enantiomeric excess was determined by chiral HPLC after reduction ($LiBH_4$ in THF/EtOH) to the corresponding amino alcohol.

in its absence (see Supporting Information). The enantiomeric excesses achieved at −60 °C were high, and they demonstrate that the enantioface differentiation provided by the bulky tetrahydronaphthalene backbone is very efficient. The host was recovered after separation by flash chromatography (80−95% recovery).

The assignment of the absolute configuration was based on our previous results obtained in the intramolecular reaction of 2-quinolones.[7] A *Re* face attack at the carbon atom C-3 occurs if host **4** is employed. As depicted in Scheme 2, *Re* attack at this position leads to the formation of products **2** (*endo*) or **3** (*exo*). The relative configuration was assigned based on NOESY data and on previous work.[11] The enantioselective photochemical reaction was extended to symmetrical 1,1-disubstituted alkenes. As an example the conversion of 2-ethyl-1-butene (**5**) to the cyclobutane **6** is presented in Scheme 3.

In summary, the host compound **4** and its enantiomer *ent*-**4** have proved to be reliable chiral complexing agents for enantioselective intermolecular [2 + 2]-photocycloaddition reactions of 2-quinolones. Further studies are directed toward additional applications of these hosts in inter- and intramolecular photochemical reactions. These results will be reported in due course.

Scheme 3



5 **6**

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Supporting Information Available: Comprehensive table of the irradiation study including the irradiation results in the absence of the host; NMR data and spectra (^{1}H, ^{13}C) of **2c**, **2d**, **3a**, **3b**, **3c**, **3e**, and **6**; further analytical data and HPLC analyses of **3a**, **3b** (entry 4), **2c** and **3c** (entry 6), **2d** (entry 7), and **6** (Scheme 3) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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