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Light-Induced Transfer of Molecular Chirality in Solution: Enantiospecific Photocyclization of Molecularly Chiral Acrylanilides

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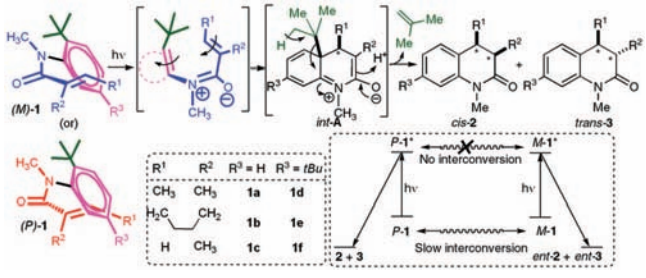
Asymmetric photoreactions have not enjoyed the same level of success as thermal reactions. Conventional chiral inductors employed in thermal reactions alter the relative activation energy in the ground state and therefore are not effective in inducing stereoselection during phototransformations.[1] Chiral discrimination during phototransformation has to occur in the excited state within the short lifetime of the excited molecules, intermediates, and/or transition states.[1,2] Photochemists have successfully employed various organized assemblies[2−4] to carry out asymmetric photoreactions and achieved varying degrees of success. To achieve stereoselection during the phototransformation of prochiral reactants in solution, chiral discrimination of prochiral faces must happen in the substrates. This chiral discrimination is provided by organized assemblies (e.g., crystals, hydrogen-bonded templates),[2−4] leading to noticeable stereoselectivity. Crystals provide a chiral environment if the prochiral substrate(s) crystallizes in one of the chiral space groups (molecular chirality[5]), the process being inherently unpredictable.[6] These molecularly chiral crystals could be transformed to chiral photoproducts with very high stereospecificity.[4,7] It would be ideal to have a similar methodology of transferring molecular chirality in the reactant to point chirality in the product in solution during phototransformations.[8] Our approach is to make use of built-in molecular constraints within a reactant and transform them to chirally enriched photoproducts with high stereospecificity. The constraints make the reactants axially chiral and are based on the well-established concept of rotamer control via restricted bond rotation that has been successfully employed in various transformations.[8a,9,10] These axially chiral chromophores can be synthesized with relative ease using established literature procedures.[9−11]

We chose to investigate 6π-photocyclization of molecularly chiral acrylanilides (Scheme 1) as model system to test our methodology

Scheme 1. Conrotatory 6π-Photocyclization of Axially Chiral Acrylanilides **1**



because (a) the photochemical pathway is well-established in the literature,[12] (b) it is well-known that bulky (*tert*-butyl) ortho substituents in N,N′-disubstituted anilides are molecularly chiral (axially chiral) because of restricted rotation of the N−C(Aryl) bond and fairly stable under ambient conditions, and (c) their synthesis (three steps) and chromatographic separation are well-documented in the literature.[9,10]

We recently established[13] that photocyclization of *o-tert*-butylacrylanilides with *N*-methyl substitution occurs at the ortho carbon bearing the *tert*-butyl group. In this communication, we report a highly enantiospecific photocyclization of the individual atropisomers of *o-tert*-butylacrylanilides (Scheme 1), where the axial chirality in the reactant (**1a**−**f**) is transferred to point chirality in the photoproducts (3,4-dihydroquinolin-2-ones *cis*-**2** and *trans*-**3**) in solution.

We investigated two sets of ortho *tert*-butyl derivatives, namely, 2-*tert*-butyl-substituted derivatives **1a**−**c** and 2,5-di-*tert*-butyl-substituted derivatives **1d**−**f**. As expected,[10] all of the ortho *tert*-butyl derivatives were molecularly chiral atropisomers (*P* and *M* isomers), and they were characterized by NMR spectroscopy, CD spectroscopy, and optical rotation.[13,15] Photoirradiation of optically pure atropisomers (helical isomers) of **1a**−**f** (Scheme 1) in various solvents was performed using a 450 W medium-pressure mercury lamp with a Pyrex cutoff under a constant flow of nitrogen. The conversion in acetone (∼50%) was high compared with that in other solvents (<30%) for the same irradiation time.[13] Use of longer irradiation times to increase the conversion resulted in noticeable amounts of side products. The products were purified by chromatography and characterized by NMR spectroscopy.[15] HPLC analysis of the photolysate on a chiral stationary phase gave enantiomeric excess in the photoproducts (Table 1). Very high enantiomeric excess (∼90%) was observed in the photoproducts from **1a**, **1b**, **1d**, and **1e** in the solvents investigated. The optical antipodes of **1** gave the opposite enantiomers in the photocyclized product, indicating that the system is well-behaved. For example, (−)-**1d** in methanol gave an ee value of 92% in *trans*-**3d**, and the corresponding optical antipode (+)-**1d** in methanol gave the enantiomer of *trans*-**3d** with an ee value of 94% (Figure 1; Table 1, entries 7 and 8).

On the basis of our mechanistic study,[13] we postulated that the photocyclization occurs at the ortho carbon via "*int*-**A**" (Scheme 1), with the eventual loss of the ortho *tert*-butyl substituent. If this holds true, the enantiomeric excess in the photoproducts (*cis*-**2** and *trans*-**3**) must be identical, as the resulting zwitterionic intermediate "*int*-**A**" (Scheme 1) has a defined chiral center at the benzylic position formed from by stereospecific ring closure. The second proton-transfer step (from solvent or intramolecular [1,7]H shift), is nonstereospecific, leading to cis and trans photoproducts with identical ee values. Fortunately, we were successful in separating the enantiomers of both *cis*-**2** and *trans*-**3** in the case of cyclohexyl derivatives **1b** and **1e**. Inspection of Table 1 indicates that similar enantiomeric excess was observed for the *cis*-**2** and *trans*-**3** photoproducts. For example, in the photocyclization of the cyclohexyl derivative **1e**, comparable ee values were observed for the *cis*-**2e** and *trans*-**3e** photoproducts (Table 1, entries 9 and 10). Similarly, in the photocyclization of the cyclohexyl derivative (+)-**1b**, an ee value of 99% was observed for both the *cis*-**2b** and *trans*-**3b** photoproducts (Figure 1).

Inspection of Table 1 reveals that the β-substituent in the alkene is crucial for achieving the high enantiomeric excess under direct irradiation conditions. For example, in methanol, the ee value of 94%

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Table 1. Enantiospecific 6π-Photocyclization of **1**[a]

		acetone		MeOH		$CHCl_3$		2:1 C_6H_6/THF	
entry	cmpd	*cis*-**2**	*trans*-**3**	*cis*-**2**	*trans*-**3**	*cis*-**2**	*trans*-**3**	*cis*-**2**	*trans*-**3**
1	(−)-**1a**[b]	−	90(B)	−	87(B)	−	91(B)	−	89(B)
2	(+)-**1a**[b]	−	94(A)	−	84(A)	−	88(A)	−	95(A)
3	(−)-**1b**[c]	92 (*R*,*S*)	−	85 (*R*,*S*)	−	92 (*R*,*S*)	−	80 (*R*,*S*)	−
4	(+)-**1b**[c]	92 (*S*,*R*)	88 (*S*,*S*)	99 (*S*,*R*)	99 (*S*,*S*)	90 (*S*,*R*)	95 (*S*,*S*)	93 (*S*,*R*)	94 (*S*,*S*)
5	(−)-**1c**[d]	−		0		0		0	
6	(+)-**1c**[d]	−		0		0		0	
7	(−)-**1d**[b]	−	94(B)	−	92(B)	−	85(B)	−	91(B)
8	(+)-**1d**[b]	−	91(A)	−	94(A)	−	99(A)	−	88(A)
9	(−)-**1e**	90(A)	91(A)	99(A)	99(A)	98(A)	99(A)	91(A)	93(A)
10	(+)-**1e**	87(B)	90(B)	99(B)	99(B)	91(B)	95(B)	90(B)	99(B)
11	(−)-**1f**[d]	−		0		0		0	
12	(+)-**1f**[d]	−		0		0		0	

[a] A and B refer to the first and second peaks that elute from the HPLC column for a given pair of enantiomers. Values are averages of 3 runs with ±5% error. The reaction temperature was 0−3 °C. For **1a**−**c**, (+) and (−) represent the signs of their CD signals at 240 nm in methanol. Similarly, for **1d**−**f**, (+) and (−) represent the signs of optical rotation in $CHCl_3$.The *cis*-**2**/*trans*-**3** ratios are provided in the ref 13 and in the Supporting Information. [b] The *cis*-**2** enantiomers were not separable on a chiral stationary phase. [c] Chromatographic separation was necessary prior to HPLC analysis, as the HPLC retention time of *trans*-**3c** overlaps with that of the reactant **1c**. Absolute configurations were assigned on the basis of comparison to optical rotation values from the literature (ref 14). See the Supporting Information for details. [d] Cis and trans isomers are not possible in the case of **1c** and **1f**.

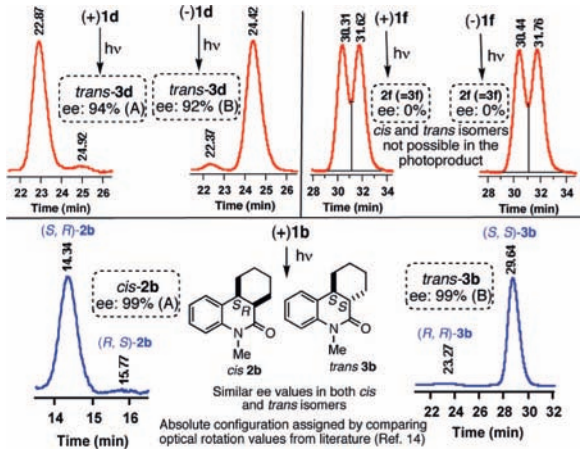

Figure 1. HPLC traces of the photoproducts from the photocyclizations of **1d**, **1f**, and **1b**.

was observed for (+)-**1d** with a β-CH_3 substituent, whereas 0% ee was observed for the corresponding methacryloyl derivative (+)-**1f** with a β-H substituent (Table 1, entries 8 and 12; Figure 1). A closer look at the zwitterionic intermediate "*int*-**A**" reveals that presence of the β-substituent in the reactant is critical in transferring the axial chirality in the reactant to point chirality at the benzylic position in the photoproduct. In the absence of β-substituents in the reactant (as in **1c** and **1f**), photocyclization leads to the zwitterionic intermediate "*int*-**A**" bearing an achiral benzylic carbon ($-CH_2-$) followed by a nonstereospecific hydrogen migration (step 2), resulting in racemic photoproducts. Thus, the intermediate "*int*-**A**" bearing a β-substituent acts as a "mechanistic bridge" for transfer of the axial chirality in the reactant to point chirality in the product.

Our investigation has opened up the possibility of achieving very high enantiomeric excess in phototransformations in solution, which traditionally has been a difficult task. Our methodology of employing molecularly chiral chromophores that equilibrate very slowly in the ground state, leading to very high enantioselectivity in the photoproducts, draws inspiration from Havinga's non-equilibrating excited rotamers (NEER) principle, where conformer-based product control is well-documented.[16] A thorough understanding of how molecular chirality in the reactant is transformed into point chirality in the photoproduct is crucial for developing this methodology. We are currently investigating this methodology for various phototransformations in solution.

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Supporting Information Available: Experimental procedures for photoreactions, synthesis, characterization, and analysis conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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