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COMMUNICATIONS

Use of Chirally Modified Zeolites and Crystals in Photochemical Asymmetric Synthesis

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Received August 31, 2001

Despite recent advances,[1] the field of photochemical asymmetric synthesis is still in its infancy compared to the extremely active and well-developed subject of asymmetric induction in ground-state reactions. It occurred to us that one approach to achieving asymmetric induction in photochemical reactions lay in the use of organized media possessing optically active reaction cavities capable of differentiating enantiomeric transition states. The organized media we chose for these investigations were zeolites and crystals. While crystalline media have proved to be effective in bringing about high asymmetric induction,[2] zeolites represent a more general approach, since even liquid samples can be "caged" close to a chiral inductor in this medium.[3] In this communication we wish to emphasize the complementary nature of the two methods.

The photochemical reaction chosen for investigation was the cis-to-trans photoisomerization of *trans*,*trans*-2,3-diphenyl-1-benzoylcyclopropane (**1a**) and some of its derivatives (Scheme 1). Zimmerman and Flechtner were the first to report the reaction of ketone **1a** in solution (n,π^* triplet, $\Phi = 0.94$), and these authors concluded that the reaction proceeds via rupture of the C_1-C_2 (or C_1-C_3) bond followed by C_2-C_3 bond rotation and closure.[4]

Turning first to the zeolite results, zeolite NaY (300 mg) was doubly loaded with ketone **1a** (2−4 mg) and various chiral inductors (25−30 mg). Eight chiral inductors were tested: (+)- and (−)-pseudoephedrine, (+)- and (−)-ephedrine, (+)- and (−)-norephedrine, and (+)- and (−)-*N*-methylephedrine. Only in the case of pseudoephedrine was any enantiomeric excess (ee) observed. (+)-Pseudoephedrine afforded photoproduct **2a** with an ee of 13% (absolute configuration unknown) and (−)-pseudoephedrine gave rise to its enantiomer with an ee of 16%. We consider these ee's to be identical within the limits of the chiral HPLC analysis. Similar ee's were found in the case of cyclopropane derivative **1b**. Norephedrine was found to be the best chiral inductor for this system, leading to ee's of 20%; pseudoephedrine, diethyl tartrate, phenylalinol, ephedrine, and menthol all gave ee's below 10%. The ability of zeolites to bring about low levels of asymmetric induction on reactions that give racemic products in solution, even in the presence of the chiral inductors,[5] supports the concept that the influence of a chiral inductor can be enhanced within a confined space.

In an effort to improve the level of asymmetric induction, we next turned to the use of intramolecular, covalently attached chiral auxiliaries. Chiral amides **1c**−**1n** were photolyzed in MY-type zeolites in which the cation M is a monovalent alkali cation. The diastereomeric excesses (de's) obtained in these experiments are summarized in Table 1. A striking observation is that, in every case, the compound with the covalent chiral auxiliary in the meta position gives a higher de than its para counterpart. Additionally, NaY and KY zeolites afford the highest de levels. Thus, for example, in zeolite NaY, meta-substituted ketone **1c** photoisomerizes to **2c** with a de of 71%, whereas under the same conditions, the para isomer **1i** gives **2i** in only 11% de.

Scheme 1

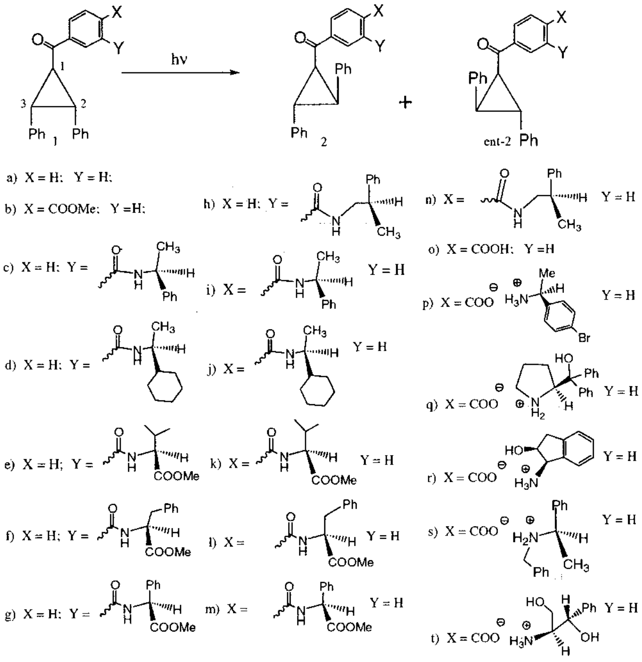

Table 1. Diastereomeric Excesses in MY Zeolites[a]

cmpd	soln	diastereomeric excess (%)				
		LiY	NaY	KY	RbY	CsY
1c	0	8A	71A	14A	5A	3A
1d	1A	18A	30A	14A	11A	3A
1e	0	15B	25B	52B	13B	4B
1f	4A	27A	41A	29A	25A	0
1g	3A	20A	38A	15A	12A	1A
1h	0	1A	11A	14A	5A	8A
1i	2A	0	11A	1A	0	2A
1j	2A	3A	4A	3A	1A	3A
1k	0	1A	1A	11A	1A	0
1l	1A	7A	2A	5A	2A	5A
1m	1A	3A	15A	7A	0	0
1n	0	0	3A	6A	5A	6A

[a] The designations A and B indicate whether the predominant diastereomer eluted from the chiral HPLC column is the first peak (A) or the second (B). The absolute configuration of the photoproducts was not established.

The lower asymmetric induction in the external chiral inductor method compared to the covalent chiral auxiliary approach is due,

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10.1021/ja016989m CCC: $22.00

Table 2. Enantiomeric Excesses in Salt Crystals

salt	conversion (%)	yield (%)[a]	ee (%)[b]	salt	conversion (%)	yield (%)[a]	ee (%)[b]
1p	25	99	99(+)	**1q**	38	85	96(−)
1p	33	95	96(+)	**1r**	33	99	91(+)
1p	50	70	92(+)	**1s**	32	99	76(−)
1q	25	99	99(−)	**1t**	18	99	54(−)

[a] Proportion of **2** and/or ent-**2** in the converted photoproduct mixture. [b] The designations (+) and (−) indicate the sign of rotation of the predominant enantiomer; the absolute configuration was not determined. For each of the salts **1p**−**1t**, irradiation in acetonitrile followed by diazomethane workup led to racemic **2b**.

at least in part, to our inability to control the distribution of chiral inductor and reactant within a zeolite.[6] By permanently attaching the chiral auxiliary to the reactant, one guarantees an asymmetric influence on every reaction. The difference in de between the meta and *para* substituted reactants may simply reflect the fact that, in the meta systems, the chiral auxiliary is closer to the site of reaction and therefore plays a greater role in controlling diastereoselectivity. The importance of proximity is also evident when one compares the de from amide **1c** (71%) with that of its homologue **1h** (11%) in which the chiral center is one methylene unit removed from the reaction site. A final point of discussion concerns the strong de dependence on the zeolite cation. We speculate that a combination of "tightness of fit" and the strength of the binding interaction between cation and reactant play important roles in this dependence.[7] Na^+ and K^+ may represent a happy medium among the alkali metal cations in that they are of an appropriate size to allow a snug fit of the reactant within the zeolite supercage while still possessing binding properties sufficient to maintain strong interactions with the π− and n-electrons of the reactants. Molecular modeling studies designed to test these ideas are planned.

Complementary to the zeolite methods discussed above is the ionic chiral auxiliary approach to asymmetric synthesis, in which reactants and chiral auxiliaries are brought into contact via salt bridges between ions.[2a] Crystalline salts **1p**−**1t** (Scheme 1) were prepared by reacting achiral carboxylic acid **1o** with the appropriate optically pure amine. Salts such as these, in which one of the ions (the ionic chiral auxiliary) is optically pure, are required to crystallize in homochiral space groups, and it is in the optically active reaction cavities of such crystals that asymmetric induction takes place. Pure crystals of salts **1p**−**1t** were photolyzed at room temperature and analyzed as the corresponding methyl esters **1b** and **2b**. The results are summarized in Table 2. As in previous studies of the use of ionic chiral auxiliaries in solid-state asymmetric synthesis,[2a] several of the salts led to near quantitative ee's with a slight diminution in ee as the conversion was increased. We attribute this to the development of defects in the crystal as lattice neighbors are transformed into products; in effect, the reaction cavity becomes more forgiving as the reaction proceeds.

While we cannot rule out the possiblity that topochemical crystal lattice effects play a role, we suspect that conformational factors may be determining enantioselectivity in the case of salts **1p**−**1t** by controlling the direction of initial bond cleavage.[8] With reference to Scheme 1, photoproduct **2** is formed via initial $C_1{-}C_2$ bond cleavage, whereas *ent*-**2** is formed via cleavage of $C_1{-}C_3$. How does conformation determine which bond cleaves preferentially? The answer to this question has been addressed computationally by Sevin and Chaquin, who showed that, for cyclopropyl ketones, the orientation of the carbonyl group with respect to the cyclopropane ring has a profound effect on the relative activation energy for $C_1{-}C_2$ versus $C_1{-}C_3$ cleavage along the $(n,\pi^*)^3$ potential energy surface.[9] The greatest difference in activation energy favoring $C_1{-}C_2$ over $C_1{-}C_3$ cleavage (23 kcal/mol) was calculated for $\theta = 30°$ (Figure 1b), this being the angle at which the p-orbital on the carbonyl carbon is orthogonal to the $C_1{-}C_3$ bond of the cyclopropane ring. Although not included in the calculations of Sevin and Chaquin, logic dictates that a similar large activation energy difference should exist when $\theta = 150°$ (Figure 1a). In this case, $C_1{-}C_3$ cleavage is favored.

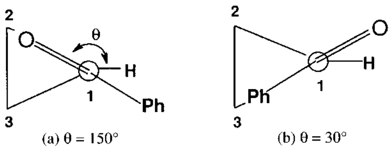

Figure 1. Definition of the angle θ.

To date, salts **1p**−**1t** have resisted attempts to determine their X-ray crystal structures; thus, the value of θ for these systems is unknown. We do have a crystal structure for methyl ester **1b**, however, and in this case $\theta = 164°$.[10] On the basis of the ideas of Sevin and Chaquin, such an angle, if present in crystals of salts **1p**−**1r**, should be more than sufficient to account for the high enantioselectivities observed. As θ approaches 180°, ΔE_a^{diast} should approach zero, and this may be the source of the lower ee's observed in the case of salts **1s**−**1t**.[11] Efforts are ongoing to provide further experimental evidence on the validity of this interesting structure−reactivity relationship.

Acknowledgment. Financial support by the National Science Foundation (CHE-9904187) (V.R.) and the Natural Sciences and Engineering Research Council of Canada (J.R.S.) is gratefully acknowledged. T.S. thanks the Japanese Ministry of Education, Culture, Sports, Science and Technology for a Grant-in-Aid.

Supporting Information Available: Sample preparation, photolysis methods, and analytical techniques used in asymmetric induction studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A density functional theory calculation indicates that $\theta = 176°$ for phenyl cyclopropyl ketone. We thank Frank Saeva, Kodak Research Laboratories, for this calculation.

(11) Support for this picture comes from the crystal structure of the bornyl ester of acid **1o** for which $\theta = 172°$. Irradiation of this material in the solid state leads to cis,trans isomerization with a de of 40% at −10 °C.

JA016989M