Use of Chiral Ionic Liquids as Solvents for the Enantioselective Photoisomerization of Dibenzobicyclo[2.2.2]octatrienes
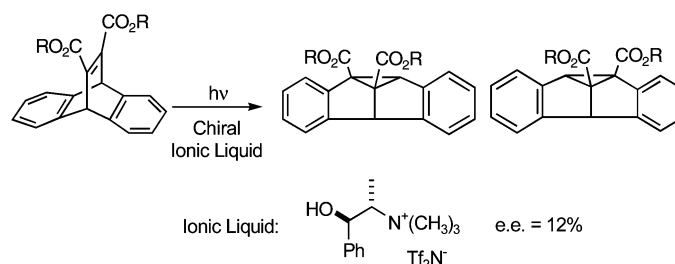
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ABSTRACT

Six chiral ionic liquids were prepared and evaluated as "chiral induction solvents" in which two different dibenzobicyclo[2.2.2]octatrienes were photoisomerized to chiral products. Enantiomeric excesses from 3 to 12% were obtained from the photochemical di-π-methane rearrangement. Results indicate that the chiral induction derives from an ion pairing interaction of the deprotonated diacids with the ionic liquid cation. This is the first report on chiral induction via a chiral IL for an irreversible, unimolecular photochemical isomerization.

The use of chiral solvents as the sole inducer of enantiomeric excess in organic reactions is a strategy that has been investigated previously, and the results have largely pointed out the disadvantages of this approach. Publications in the 1970s reported products of low ee (often <2%), with a single higher value of 9.8% ee.[1] Furthermore, the high cost of optically resolved chiral solvents prevented their wide practical uses.

An attractive alternative to such solvents may be room temperature ionic liquids (ILs). Room temperature ILs are nonvolatile, nonflammable, nonmolecular materials that are widely accepted as alternatives to conventional organic solvents in many areas of organic,[2] organometallic,[2,3] and enzymatic syntheses[3c,4] as well as in analytical applications.[5]

Chiral ionic liquids are particularly attractive due to their potential for chiral discrimination, as in asymmetric synthesis and optical resolution of racemates. Because of their ionic properties, an obvious potential exists for solvent–solute

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interaction that may provide a mechanism for substantial improvement over conventional chiral solvents. Other advantages of using water-immiscible chiral ILs as solvents include the following: (1) the chiral ILs are easily and inexpensively made and can be recycled practically; (2) opposite enantiomers of the ILs can be produced in order to enantioselectively create the desired enantiomer in excess; (3) it is easy to remove the chiral ILs from the final reaction mixture so that no interference is incurred. As a result, the analyses are simple and accurate.

A recent publication has documented the potential utility of chiral ILs as media for inducing enantiomeric excess in the products of a thermal reaction. Using ephedrinium-based ILs, Pégot et al. report[6] up to 44% ee for the Baylis−Hillman coupling of an aldehyde and acrylate.[7] Here, we report the use of chiral ILs for the induction of significant optical activity in the products of an irreversible, unimolecular photochemical isomerization, the di-π-methane rearrangement of dibenzobicyclo[2.2.2]octatrienes (Scheme 1). These

Scheme 1. Photoisomerization of Dibenzobicyclo[2.2.2]octatrienes
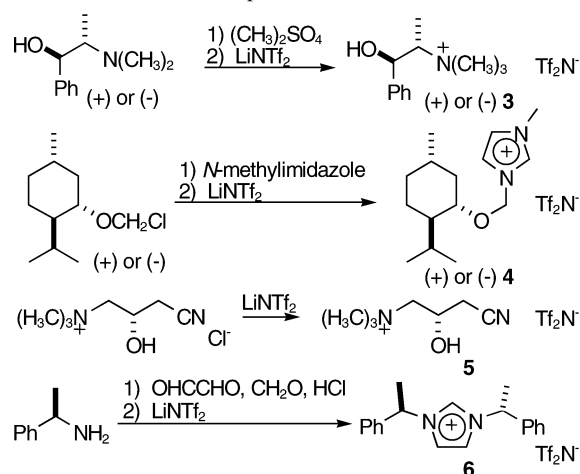
a: R = CH(CH$_3$)$_2$
b: R = CH$_3$
c: R = H
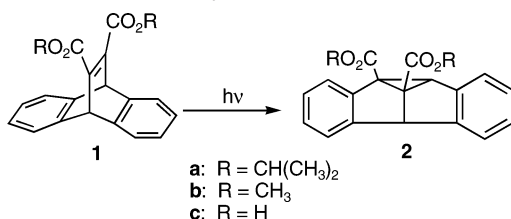
distinctions are worth noting in that the chiral induction is kinetically driven in a reaction that occurs with an activation barrier already known to be low because of its photochemical nature.

The photochemical isomerization of compounds in the dibenzo[2.2.2]bicyclooctene family was first reported by Ciganek in 1966.[8] A remarkable example of chiral induction came twenty years later, when, in 1986, Evans et al. demonstrated the transformation of diester **1a** to **2a** in 100% ee by means of taking advantage of the chiral space group ($P2_12_12_1$) into which **1a** crystallizes and using it as the reaction medium.[9] No ee was obtained using either racemic crystals (space group *Pcba*) or achiral solutions.

The number of reactions that may be carried out in the solid state on a practical basis, however, is limited, compared

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Scheme 2. Preparation of Chiral ILs **3−6**

to solution, and, hence, ionic liquids. Chiral ILs (+)-**3**, (−)-**3**, (+)-**4**, (−)-**4**, **5**, and **6** were derived from commercially available optically resolved materials.[10] Their preparations are shown in Scheme 2.

Initial irradiations of diester **1b** and diacid **1c** in chiral ionic liquids **3−6** led to the formation of racemic photoproduct **2b** for the diester and nonracemic **2c** for the diacid.[11] We interpret this difference in observed ee between products **2b** and **2c** as resulting from the ability of **1c** to form ion pairs with the solvent and thus have a stronger interaction with the chiral discriminator. Since enantioselectivity was only observed for photolysis of **1c**, the later optimization runs focused exclusively on this compound. The results are given in Table 1.[12] Entries 2 and 7 were checked at 8 different conversions ranging from 5% to 100%; the enantioselectivity was constant throughout.

Photolyses in both enantiomers of **3** were carried out at room temperature and 0 °C. Only slightly higher (about 1%) enantioselectivities were observed at the lower temperature. No difference in ee was observed for initial concentrations of **1c** of 1 and 10 mM.

Finally, different bases, both chiral and nonchiral, were explored as additives. Although no ee is achieved on photolysis of **1c** in either enantiomer of **3** alone, modest enantioselectivity was achieved on the addition of any of three basic compounds. Comparison of either entries 2 and 3 or 7 and 8 shows that the greatest part of the chiral discrimination comes from the IL solvent, not the amine base. This is again consistent with the hypothesis that ion pairing is key to the interaction, i.e., that the main effect of the basic additive is to deprotonate the acid and allow ion pairing

(10) ILs **3** have been reported previously. Wasserscheid, P.; Bösmann, A.; Bolm, C. *Chem. Commun.* **2002**, 200−201.

(11) Samples were deoxygenated by flushing with Ar for about 10 min. Irradiation was from broadly emitting low-pressure fluorescent lamps whose output centers at 300 nm (RMR 3000 from Southern New England Ultraviolet). The initial concentration of **1** was 7−10 mM.

(12) All photolyses products were analyzed by HPLC using a Cyclobond AC column with 220 nm UV detection. The mobile phase was 30:70 (v/v) methanol/0.2% TEA + 0.1% H_3PO_4 aqueous solution at a flow rate of 1.0 mL/min.

Table 1. Enantiomeric Excess of **2c** Achieved on Photolysis of **1c** in 2 mL of IL

	IL	additive	time (min), conversion[a] (%)	yield[b] (%)	ee[c] (%)
1	(+)-**3**		60, 60	93	0
2		(+)-*N*-methylephedrine (300 mg)	30, 65	95	−7.0
3		(−)-*N*-methylephedrine (300 mg)	30, 65	91	−7.3
4		*N,N*-dimethylbenzylamine (200 µL)	120, 96	97	−4.2
5		NaOH (2 M) solution (few drops)	60, 100	78	−2.3
6	(−)-**3**		70, 70	93	0
7		(−)-*N*-methylephedrine (300 mg)	15, 30	93	6.9
8		(+)-*N*-methylephedrine (300 mg)	15, 30	87	8.0
9		*N,N*-dimethylbenzylamine (200 µL)	90, 72	94	4.3
10		saturated NaOH[d]	52, 42	93	11.6
11	(+)-**4**		75, 100	77	5.8
12		*N,N*-dimethylbenzylamine (100 µL)	75, 100	67	6.8
13	(−)-**4**		65, 90	68	−6.4
14		*N,N*-dimethylbenzylamine (100 µL)	65, 90	60	−6.5
15	**5**		70, 80	85	0
16		*N,N*-dimethylbenzylamine (100 µL)	120, 62	87	−4.1
17	**6**		65, 95	95	0
18		*N,N*-dimethylbenzylamine (100 µL)	65, 70	86	3.3

[a] Photolysis time is given to indicate relative efficiency. [b] Relative to consumed **1c**. [c] The sign of the ee refers to the sign of the optical rotation at 430 nm. [d] Stirred over a saturated aqueous solution of NaOH before use.

with the IL cation. However, the results also imply that the identity of the additive base is not entirely without conse-

quence and there may be more complex interactions at play. Control experiments were carried out in acetone, benzene, and the achiral IL 1-butyl-3-methylimidazolium chloride. Addition of *N*-methylephedrine to any of these solvents for photolyses of **1c** did not result in observable product enantioselectivity.

One mechanistic hypothesis for the role of the amine bases can be addressed definitively. The fact that ee is achieved with hydroxide as a base in **3** strongly implies that the role of the amine bases—though they are in large excess—is not to act as an electron donor.

Enantioselectivity was observed for photolyses of **1c** in IL **4** without a need for addition of an external base. Addition of *N,N*-dimethylbenzylamine exhibited only a marginal effect. This suggests that, in this IL, the acid is already largely dissociated even in the absence of base. The ILs **5** and **6** both required basic additives to achieve any selectivity.

In summary, several chiral ILs have been successfully used as chiral solvents in the photoisomerization of dibenzobicyclo-[2.2.2]octatriene diacid **1c** to induce enantiomeric excesses. The observed enantioselectivities, though modest in an absolute sense, are among the highest achieved for uni-molecular photochemical reactions by use of a chiral environment. Further optimization of related photochemical reactions and other unimolecular and bimolecular chemistry is underway.

Supporting Information Available: Synthetic details for organic substrates and new ILs, photolytic procedures, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047599I