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Novel *cis–trans* enantiomeric conglomerates: triage and absolute configurations via anomalous X-ray scattering. A photochemical second order asymmetric transformation

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Abstract—Three tricyclic imides were prepared by a Diels–Alder reaction of 6-arylfulvenes and maleic anhydride, followed by treatment with NH_3. The *exo* isomers were found to exist as conglomerates when the aryl group was either *p*-tolyl or *p*-anisyl (although not phenyl). Triage of the *p*-tolyl racemate, followed by reaction with *p*-toluenesulfonyl chloride in CH_2Cl_2/Et_3N, led to the crystalline enantiopure *N*-tosylimides (these were also conglomerates). X-ray diffraction analysis of the *N*-tosylimides via the anomalous dispersion technique led to assignment of the absolute configurations (as either *E* or *Z*). The original *p*-tolyl imide enantiomers were found to racemize under UV irradiation in $CHCl_3$. Based on this, a possible second order asymmetric transformation under photochemical conditions was attempted, and indeed led to the isolation of crystalline imide with a small ee (~15%).

1. Introduction

We have recently reported a novel case of *cis–trans* enantiomerism in the Diels–Alder cycloadducts **1** (Scheme 1) of several 6-arylfulvenes with maleic anhydride.[1] The resolution of the racemates was accomplished via the formation and separation of diastereomeric imide derivatives with 1(*S*)-(naphth-1-yl)ethylamine. The absolute configurations—as *E* or *Z*—were thus assigned via X-ray diffraction. Anhydrides **1** were also converted to the corresponding imides **2** by reaction with ammonia.

Subsequently, we discovered that two of the imide derivatives, (±)-**2a** and (±)-**2b**, existed as conglomerates[2,3] (as confirmed by triage and X-ray diffraction). In the case of (±)-**2a**, the enantiomers were converted to the crystalline *N*-(4-toluenesulfonyl) derivatives **3a**; racemic **3a** was also found to be a conglomerate, separated via triage, and X-ray analyzed via the anomalous dispersion technique[4,5] to assign the absolute configurations (*E* and *Z*).

Furthermore, we have been interested in racemizing the above *cis–trans* enantiomeric compounds via a possible photochemical isomerization of the stereogenic exocyclic double bond. We have explored the possibility that racemization could be coupled to the preferential crystallization of one of the enantiomers, thereby effecting a novel photochemically mediated second order asymmetric transformation ('SAT')[6,7] (a conglomerate is generally required for an SAT).

Conglomerate behaviour is, of course, a rare occurrence. Rarer still is the spontaneous generation of optical activity under photochemical conditions (apparently unknown, to the best of our knowledge). We herein report in preliminary form on these interesting findings. The practical significance of this work is indicated by the fact that the highly selective rat toxicant 'norbormide' is structurally related to **2**.[8,9] Note also that conglomerates facilitate resolution via the entrainment method.[2,3]

2. Results and discussion

2.1. Preparation, triage and absolute configurations of imides 2a and 2b

The anhydride cycloadducts **1** were prepared and converted to the corresponding imides **2** via treatment with aqueous ammonia (Scheme 1).[1] Pasteur resolution (triage)

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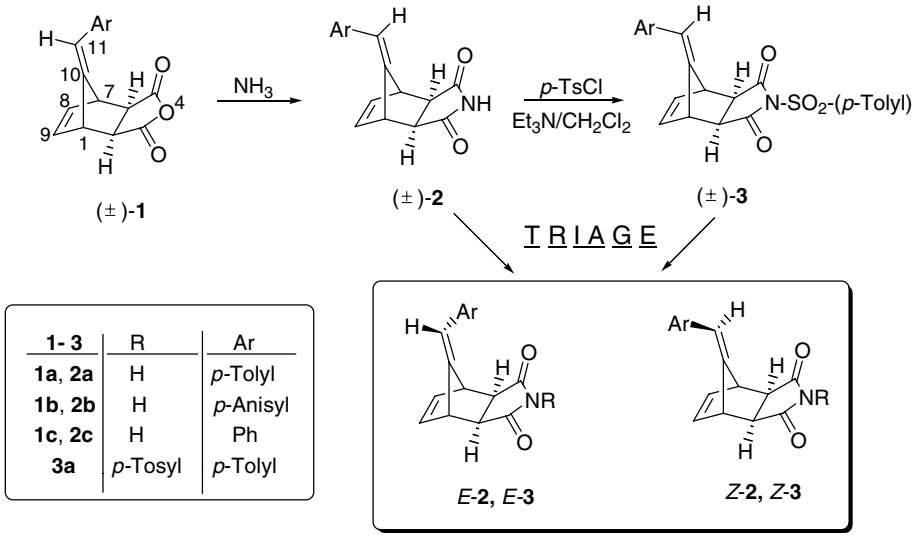

1- 3	R	Ar
1a, 2a	H	*p*-Tolyl
1b, 2b	H	*p*-Anisyl
1c, 2c	H	Ph
3a	*p*-Tosyl	*p*-Tolyl

Scheme 1. Preparation and triage of the conglomerate imides **2** and one of their toluenesulfonyl derivatives **3a**, both the enantiomers of which were studied by the anomalous X-ray dispersion technique (cf. Table 2). The skeletal numbering is indicated in the case of (±)-**1**; 'tolyl' means 'MeC_6H_4' and 'tosyl' means 'tolyl-SO_2'.

of the crystalline racemate of **2** furnished individual crystals, which were separately dissolved in $CHCl_3$ and the resulting solutions studied by polarimetry. The solutions were found to be optically active in the case of *p*-tolyl **2a** and *p*-anisyl **2b** derivatives (but not the phenyl derivative, **2c**). This indicated that the individual crystals in the case of **2a** and **2b** were homochiral, and that the racemates were conglomerates.

This was confirmed by X-ray diffraction analysis, which revealed that the crystal lattices of the *p*-tolyl (+)-**2a** and

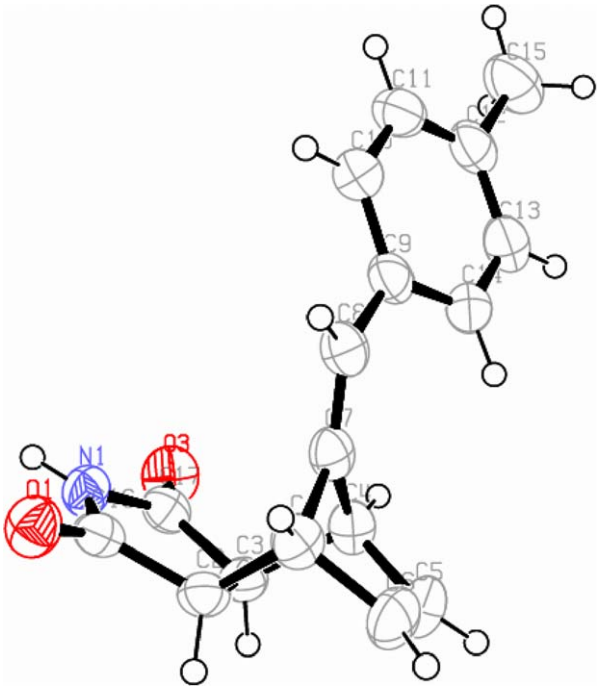

Figure 1. ORTEP diagram of the 11-(*p*-tolyl) tricyclic imide **2a** at 50% ellipsoidal probability as determined by X-ray diffraction (cf. Scheme 1 and Table 1, crystallographic numbering shown above).

p-anisyl **2b** derivatives were composed of non-centrosymmetric unit cells. The unit cell was centrosymmetric in the case of the phenyl derivative **2c**. The results of the X-ray diffraction experiment in the case of (+)-**2a** are shown in Figure 1 (ORTEP diagram) and Table 1 (selected crystallographic data).[10]

We then envisaged that the absolute configurations of (+)- and (−)-**2a** could be determined via the anomalous X-ray dispersion (or scattering) technique. The application of this method to the case of *cis–trans* enantiomerism is practically unknown, to the best of our knowledge. The anomalous dispersion method is based upon the phase change of the scattered X-rays (preferably) induced by a heavy atom, for example, sulfur.[4,5] Hence, the resolved imides (+)-**2a** and (−)-**2a** were converted to the corresponding *N*-(4-toluenesulfonyl) derivatives (+)-**3a** and (−)-**3a**.

Interestingly, the racemic *N*-tosyl derivative (±)-**3a** was also found to be a conglomerate, as was revealed by triage, polarimetry (as described above) and X-ray analysis of both enantiomers via the anomalous dispersion method (cf. Fig. 2 and Table 2). In a separate experiment, (+)-**2a**

Table 1. Selected crystallographic properties of the tolylimide *E*-(+)-**2a** as determined by X-ray diffraction (cf. Scheme 1)[a,b]

Entry	Property	Data
1	Crystal system/space group	Orthorhombic/$P2_12_12_1$
2	No. of molecules in unit cell	4
3	Cell dimensions[c]	$a = 6.5480$ (12) $b = 8.4752$ (16) $c = 24.468$ (5) ($\alpha = \beta = \gamma = 90°$)
4	*R* factor	0.0333

[a] The configuration was assigned via the anomalous dispersion studies described above (cf. Table 2).
[b] See Ref. 10 for full details.
[c] In Å unless otherwise stated, standard deviations in parentheses.

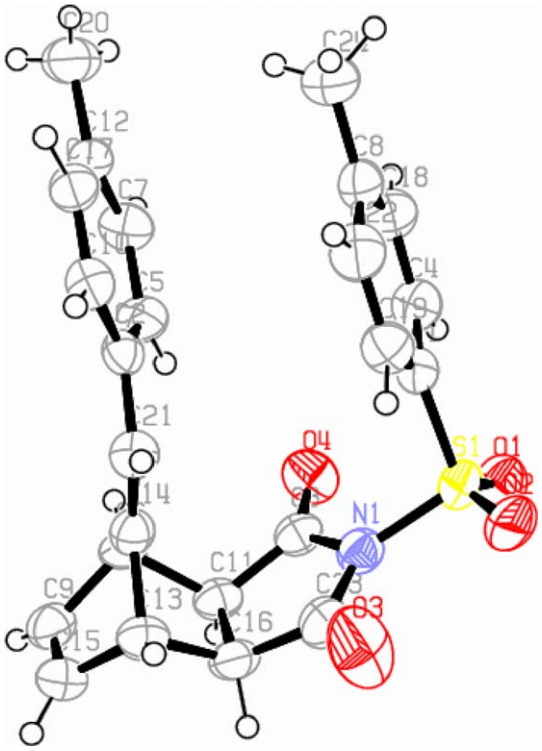

Figure 2. ORTEP diagram of *E*-(+)-11-(*p*-tolyl)-*N*-tosylimide **3a** at 50% ellipsoidal probability from X-ray diffraction, the configuration having been determined by the anomalous dispersion method (cf. Scheme 1 and Table 2, crystallographic numbering shown above).

Table 2. Selected crystallographic properties of the enantiomeric *N*-tosylimides *E*-(+)-**3a** and *Z*-(−)-**3a**, from X-ray diffraction via the anomalous dispersion method[a] (cf. Scheme 1)

Entry	Property		Data	
			E-(+)-**3a**	*Z*-(−)-**3a**
1	Crystal system/space group		Monoclinic/$P2_1$	
2	No. of molecules in unit cell		2	
3	Cell dimensions[b,c]			
		a:	7.9222 (18)	7.932 (3)
		b:	11.653 (3)	11.632 (4)
		c:	10.953 (3)	10.940 (4)
		α:	90.00°	90.00°
		β:	91.45° (4)	91.43° (6)
		γ:	90.00°	90.00°
4	*R* factor		0.0455	0.0528
5	Flack parameter[c]		0.04(8)	0.18(8)

[a] Performed with the SHELXL software provided by WinGX: See Ref. 10 for full details.
[b] In Å unless otherwise stated.
[c] Standard deviations in parentheses.

was converted into *E*-(+)-**3a** via *N*-toluenesulfonylation. These experiments together indicated the following configurational assignments: *E*-(+)-**2a**, *E*-(+)-**3a** and *Z*-(−)-**3a**. The circular dichroism spectra of *E*-(+)-**3a** and *Z*-(−)-**3a** (Fig. 3) also confirmed their enantiomeric interrelationship.

It is noteworthy that the *cis–trans* enantiomeric *exo* imide framework common to both **2** and **3** apparently induces

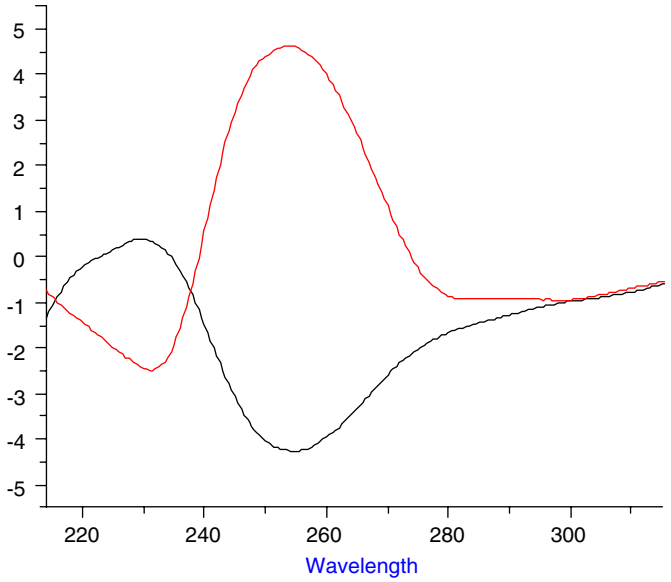

Figure 3. Circular dichroism (CD) spectra of the *cis–trans* enantiomers of the 11-(*p*-tolyl)-*N*-tosylimide **3a** that were resolved by triage (cf. Scheme 1). The *y* axis represents the CD in millidegrees, and the *x* axis the wavelength in nm; the *E*-(+) enantiomer is represented in red and the *Z*-(−) enantiomer in black.

conglomerate behaviour. This is an intriguing and useful correlation, as the structural features that characterize conglomerates (vis-à-vis racemic compounds) are not completely understood at present.

2.2. Photochemical second order asymmetric transformation of (±)-2

A second order asymmetric transformation ('SAT', sometimes termed 'total spontaneous resolution') is a crystallization driven process that can spontaneously generate optical activity.[6,7] It may be observed in the case of a conglomerate the enantiomers of which are rapidly interconverting in solution, when one of them crystallizes out accidentally. Conglomerate behaviour is generally a prerequisite for the success of an SAT, as the enantiomers need to be less soluble than the corresponding racemate form. Although there are several well-documented examples of the process, for example, binaphthyl and tri-*o*-thymotide the interconversion of the enantiomers generally occurs thermally. We are unaware of any case of SAT in which the enantiomer interconversion occurs photochemically.

We envisaged such a process in the case of the *cis–trans* enantiomeric system represented by **1** and **2**, as these enantiomers may (in principle) be interconverted via rotation around the stereogenic C_{10}–C_{11} bond, possibly under ultraviolet irradiation. Preliminary experiments confirmed that the enantiomers of **1** and **2** lost optical activity upon ultraviolet irradiation in solution (i.e., racemized), without undergoing any observable chemical change. The interconversion of alkene geometrical isomers via photochemically induced π–π* transitions is well known.[11] Similar photoisomerization, although involving diastereomers, has been reported in the related norbormide, mentioned above.[9]

As the tolyl imide **2a** is a conglomerate, the possibility of an SAT was investigated with it. When (±)-**2a** was crystallized from a cooled solution of $CHCl_3$ under irradiation with ultraviolet light over several hours, the resulting **2a** was found to be enantiomerically enriched to ~15% in several trials (cf. Table 3). The actual procedure involved alternating cycles of irradiation and cooling at 0–5 °C, for practical reasons; as crystallization is apparently slower than racemization, this procedure is effectively the same as simultaneous irradiation and crystallization. Interestingly, only the laevorotatory form crystallized out in each of the six trials performed.

Table 3. Results of the photochemical second order asymmetric transformation of the imide (±)-**2a**[a]

Trial no.	Total time (h) taken for		Total yield (%)	ee[b] (%)
	Irradiation	Crystallization		
1	8	80	60	16.5 (−)
2	20	96	64	14.9 (−)
3	20	96	44	13.9 (−)

Procedure: Typically, a solution of (±)-tolylimide in 95% EtOH (0.075 M, 2.5 ml) was taken in a 5 ml glass beaker, which was loosely covered with 'parafilm', and irradiated with ultraviolet light from a medium pressure mercury vapour lamp. This was jacketed and cooled by chilled water, thus avoiding excessive heat around it. After 3 h crystals were observed in the reaction mixture, and the beaker was removed and allowed to stand in a refrigerator (0–5 °C) for 8 h. The above process of alternating irradiation and cooling was repeated several times. The crystals were then filtered off, weighed and characterized by mp, IR and ^{1}H NMR spectra, and optical rotation; the ee values were calculated from the observed rotation and the $[\alpha]_D$ (vide supra).

[a] Typical results shown from a total of six trials, procedure as given below.

[b] The sign of the observed rotation is given in brackets, the (−) form predominating in each case.

Although only modest ee levels were obtained by the above process, it has not been optimized; also, the experiment demonstrates the feasibility of a photochemical SAT process. The potential of this process may be appreciated by noting that the thermally induced SAT is limited in practical scope, as it implies that the enantiomers are optically unstable in solution; a photochemically induced process is also 'cleaner' with regards to work-up, etc.

3. Conclusion

In conclusion, we have described the preparation of a novel set of conglomerate racemates based on a *cis–trans* enantiomeric framework, and their characterization via X-ray diffraction and the anomalous scattering technique. In one case, we have also demonstrated the feasibility of a photochemically induced second order asymmetric transformation process.

4. Experimental

4.1. Experimental procedures (general techniques as reported previously[1])

4.1.1. Preparation of racemic imide 2a. A stirred mixture of the tricyclic anhydride (±)-**1a** (0.375 mmol) and 30% aqueous ammonia solution (3 ml) was refluxed for 3 h at 75–80 °C. The mixture was cooled and worked up with CH_2Cl_2 in the normal way to obtain nearly quantitative yields of imide (±)-**2a**, purified by chromatography (SiO_2). Mp 166 °C (EtOH); IR: 3204 (NH), 1766, 1712 (C=O) cm^{-1}; NMR: δ_H 8.00 (1H, br s, N–H), 7.08 (4H, br s, Ar–*H*), 6.51–6.43 (2H, m, endocyclic C=C–*H*), 5.95 (1H, s, exocyclic C=C(Ar)–*H*), 4.14 (1H, d, *J* 2.1 Hz, C=C–C–*H*), 3.55 (1H, d, *J* 2.1 Hz, C=C–C–*H*), 2.88 (2H, s, CO–C–*H*), 2.30 (3H, s, Ar–*Me*); δ_C 177.69 (CO), 177.61 (CO), 147.08 (Ar), 137.62 (Ar), 137.37 (Ar), 136.75 (Ar), 132.81 (C=C), 129.15 (C=C), 127.68 (C=C), 114.04 (C=C), 50.10 (bridgehead), 49.13 (bridge head), 49.02 (CO–*C*), 44.68 (CO–*C*), 21.02 (Ar*Me*); HRMS: Found 288.0995 (calcd for $C_{17}H_{15}NO_2Na$ 288.1000).

4.1.2. Triage of imide (±)-2a. The racemate, prepared as above, was recrystallized from 95% EtOH to obtain colourless plates. These were taken on a watch-glass and sifted with spatula and tweezers, to obtain individual crystals each weighing ~5 mg. These were individually checked for their specific rotation at the polarimeter, and the enantiomers pooled accordingly. In one case, a crystal was spliced into two, one part dissolved in $CHCl_3$ for the rotation and the other mounted on the X-ray diffractometer for analysis (cf. Table 1). (+)-**2a**: mp 184 °C, $[\alpha]_D^{25} = +59.8$ (*c* 1.9, $CHCl_3$); (−)-**2a**: mp 184 °C, $[\alpha]_D^{25} = -57.5$ (*c* 1.9, $CHCl_3$); both were spectrally identical to the racemate reported above, including satisfactory HRMS.

4.1.3. *N*-Toluenesulfonylation of imide 2a. A stirred solution of the (±)-tolylimide in CH_2Cl_2 (0.125 M, 3 ml), at 0 °C/N_2, was treated with Et_3N (1.0 equiv), and *p*-toluenesulfonyl chloride (1.0 equiv) in CH_2Cl_2 (2 ml, dropwise). The mixture was allowed to warm to 25 °C and stirred for a further 24 h. Workup with 1 M HCl etc. afforded the crude sulfonimide, purified by chromatography (SiO_2/EtOAc–hexane) to obtain pure (±)-**3a** (75% yield). Mp 172–174 °C; IR: 1737 (C=O), 1599 (C=C) cm^{-1}; NMR: δ_H 7.77 (2H, d, *J* 8.1 Hz, Ar*H*), 7.01 (2H, d, *J* 8.1 Hz, Ar*H*), 6.88 (2H, d, *J* 8.1 Hz, Ar*H*), 6.75 (2H, d, *J* 8.1 Hz, Ar*H*), 6.48–6.39 (2H, m endocyclic *H*C=C*H*), 5.49 (1H, s, exocyclic C=C(Ar)*H*), 4.13 (1H, dd, J_1 1.5 Hz, J_2 0.6 Hz, bridgehead C=C–C*H*), 3.50 (1H, dd, J_1 1.5 Hz, J_2 0.6 Hz, bridgehead C=C–C*H*), 2.93 (2H, s, –CO–C*H*), 2.33 (3H, s, tosyl Ar*Me*), 2.15 (3H, s, Ar*Me*); δ_C 172.15 (CO), 171.98 (CO), 146.24 (Ar), 145.89 (Ar), 138.21 (Ar), 137.68 (Ar), 136.83 (Ar), 134.21 (Ar), 132.44 (Ar), 129.41 (Ar), 128.98 (C=C), 128.27 (C=C), 127.58 (C=C), 113.75 (C=C), 51.26 (bridgehead), 48.21 (bridgehead), 47.74 (CO–*C*), 45.50 (CO–*C*), 21.58 (tosyl Ar*Me*), 21.12 (tolyl Ar*Me*); LRMS: *m*/*e* 442 ($M^+ + Na$); HRMS: Found 442.1085 (calcd for $C_{24}H_{21}NSO_4Na$ 442.1089).

Similarly, (+)-**2a** was converted to *E*-(+)-**3a**, and (−)-**2a** to *Z*-(−)-**3a**; the configurations of *E*-(+)-**3a** and *Z*-(−)-**3a** were determined by the X-ray anomalous scattering method (cf. Table 2), thus indicating the respective configurations of (+)-**2a** (*E*) and (−)-**2a** (*Z*); *E*-(+)-**3a**: mp 190–192 °C, $[\alpha]_D^{25} = +136.9$ (*c* 1.3, $CHCl_3$); *Z*-(−)-**3a**: mp

190–192 °C, $[\alpha]_D^{25} = -120.0$ (*c* 2.0, $CHCl_3$). [*E*-(+)-**3a** and *Z*-(−)-**3b** were also obtained by triage of (±)-**3a** in the manner reported for (±)-**2a** above.]

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