Spontaneous symmetry breaking during interrupted crystallization of an axially chiral amino acid derivative†

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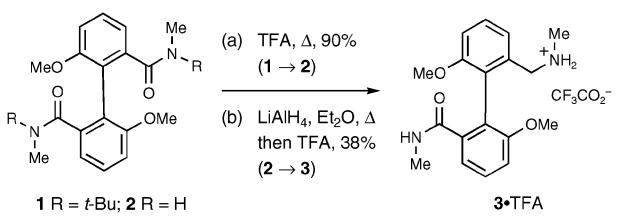
High net enantiomeric excess was observed for crystal collections obtained by crystallization of the TFA salt of a configurationally stable yet racemic axially chiral amidoamine in EtOH solution with or without stirring (up to >99% ee at ≤15% crystallization).

A majority of racemic materials form crystals that belong to centrosymmetric space groups and are correctly categorized as true "racemic compounds" in which each single crystal is composed of a 1 : 1 mixture of enantiomorphs in an ordered arrangement.[1] A second class of crystalline racemate, that of a "conglomerate," is also possible in which individual crystals are homochiral in their composition but such that the bulk solid is a net racemate overall. Formation of conglomerates is comparatively rare (occurring for less than 10% of crystalline racemates),[2] but when encountered this phenomenon allows for direct resolution by a triage process involving: mechanical separation of crystallites, identification of optical series for each, then pooling together of all like individuals. Resolution by crystal triage was most famously employed by Pasteur for the separation of racemic sodium ammonium tartrate into its *d*- and *l*-isomers.[3] A more practical resolution technique that also exploits conglomerate formation is effected by seeding of a racemic mother liquor solution with a single enantiopure crystal. This process, known as resolution by entrainment,[1a] constitutes the most cost effective method for achieving enantiomer separations on an industrial scale. Although often described as such, it is debatable whether either of the resolution processes described above are truly "spontaneous" given that an extraneous source of chiral information is typically required to obtain aggregated scalemic material in each case.

The generation of a meaningful enantiomeric excess in a bulk phase from a racemic or achiral starting state, *without* the intervention of a chiral entity (such as the human operator in crystal triage, or the seed used for entrainment), constitutes a spontaneous symmetry breaking event.[4] Reports of resolution purporting to come about by spontaneous symmetry breaking are rare and present a challenge to orthodox theory.[5] Pertinent to the work detailed herein, Pincock and Wilson observed that net optically active crystalline 1,1′-binaphthyl deposited from a supercooled *melt* at 150 °C.[6] Liquid 1,1′-binaphthyl is *configurationally labile* at this elevated temperature; thus, the Pincock process is a spontaneous resolution under racemizing conditions and it is capable of yielding >50% of enantiopure material. Later, Kondepudi *et al.* reproduced the Gaussian-like distribution of ee (centered at 0% ee) found by Pincock and Wilson and discovered that stirring of the 1,1′-binaphthyl melt resulted in a large net ee developing from almost every crystallization.[7] When stirring was employed, the distribution of product ee was bimodal with mean absolute value of 70% and a random occurrence of *d*- or *l*-isomer predominance. In this communication, we document our findings concerning the spontaneous resolution of a novel biaryl molecule from *solution* and under conditions for which the compound possesses complete *configurational stability*. Significantly, the molecular system in question also manifests organocatalytic activity for the aldol reaction.

In search of new bifunctional templates for enantioselective organocatalysis, we recognized that biaryls in which both a 2° amino moiety and a hydrogen-bond donor flank the chiral axis would likely promote aldol processes.[8] An efficient synthetic entry to one such molecule presented itself when it was found that deprotection and $LiAlH_4$ reduction of bisamide **1** (derived in three steps from *m*-anisic acid) generated an amidoamine **3** rather than the expected symmetrical bisamine (Scheme 1). The racemic samples of **3** (isolated as its crystalline TFA salt) first prepared showed modest catalytic activity for the aldol reaction, presumably *via* the usual enamine mechanism,[9] and we next sought to access this compound in scalemic form to ascertain the level of enantioselectivity. Numerous potentially viable methods to obtain enantiopure amidoamine **3** were evaluated, including classical resolution approaches, but none of the tactics initially surveyed met with a wholly satisfactory outcome. During the course of these studies, X-ray diffraction analyses were performed on single crystals of **3**·TFA‡ (Fig. 1) and its uncharged precursor **1**.§ It was so revealed that both compounds form conglomerate crystals, thus affording us an opportunity to explore "spontaneous" resolution strategies.



1 R = *t*-Bu; **2** R = H **3**•TFA

Scheme 1 Conversion of bisamide **1** to amidoamine salt **3**·TFA.

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† Electronic supplementary information (ESI) available: All synthetic procedures (including three step preparation of **1** from *m*-anisic acid) and chracterization data for prepared compounds, details for crystallization of **3**·TFA, X-ray diffraction data (CIF) for **1** and **3**·TFA, NMR spectra for all compounds, HPLC analysis methods. CCDC 748439 and 748440. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b922028c

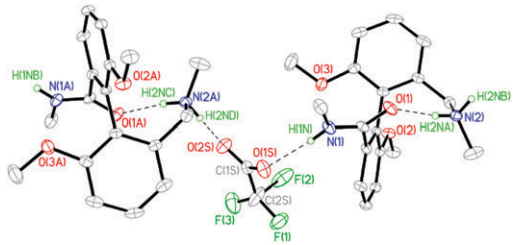


Fig. 1 ORTEP diagram for **3**·TFA conglomerate showing a bridging trifluoroacetate anion between two homochiral biaryl cation units. 50% probability ellipsoids are plotted for non-hydrogen atoms.

The prospects for a practical crystal triage approach for the direct resolution of amidoamine salt **3**·TFA were hampered by the fact that only small needles low in mass ($\leq$1 mg) could be grown from the EtOH mother liquor. By contrast, individual crystals that were monolithic in outward appearance and of over 100 mg in mass were easily grown from EtOAc solutions of bisamide **1**. Regrettably, a wide variation in the magnitude of optical rotation was noted for crystals of **1** that were large enough to be useful (*e.g.*, Chart 1) suggesting that the isolated crystallites were aggregates. Prismatic crystals with volumes in the order of 1 cm^3 were reliably obtained from *dl*-**1** using an historically noteworthy entrainment protocol,[10] but optical purity remained variable. The largest crystal of **1** obtained by entrainment amounted to 1.26 g in mass and this prism gave a polarimeter reading reflecting a net 70% ee when dissolved in MeOH: $[\alpha]_D^{22} = -79.6$ ($c = 1.26$). The levorotatory scalemic material (*l*-**1**) was further converted as before (Scheme 1), but the amidoamine obtained (*l*-**3**·TFA) exhibited low ee (<15%) indicating that partial racemization had occurred during the two step sequence.[11]

With the possibility of converting scalemic bisamide **1** into usefully enantioenriched samples of amidoamine **3** precluded, focus returned to a direct resolution approach. Upon renewed scrutiny, a rare symmetry breaking phenomenon was observed to operate during crystallization of *dl*-**3**·TFA from EtOH and a truly spontaneous resolution was achievable if crystals were harvested during the early phase of deposition. Interruption of crystallization at $\leq$15% yield led to attainment of a significant net ee from most experiments with a random predominance of *d*- or *l*-isomers in up to a >99% ee. By way of illustration, optical rotation data for crystal collections obtained from a series of ten crystallization experiments conducted without stirring of the mother liquor are given in Chart 2 (experiments 1–10). It is emphasized that crystal crops obtained from such experiments consisted of many hundreds of tiny needles, collected *en masse* by filtration and without any attempt to effect an enantiomer differentiating mechanical triage. In an effort to improve on the frequency with which superlative ee would likely be realized, otherwise identical experiments were

crystal #	1	2	3	4	5	6	7	8
mass (mg)	5	7	14	29	72	98	146	182
$[\alpha]_D^{22}$	+91*	–85	–109	+21	+1	–81	–76	+30

* HPLC analysis (with Daicel OD column) indicated 79% ee.

Chart 1 Mass and optical rotation data (in MeOH) for 8 individual crystals collected after non-seeded crystallization of *dl*-**1** from EtOAc.

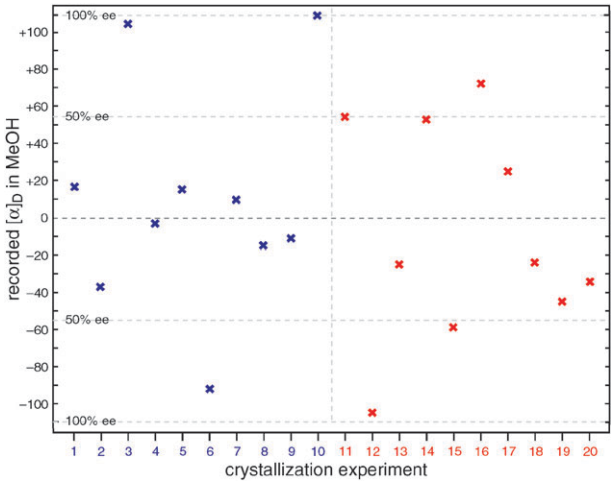


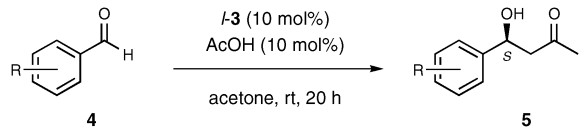
Chart 2 Scattergraph of optical rotation data (in MeOH) recorded from collections of crystals obtained by crystallization of *dl*-**3**·TFA from EtOH solution at rt. Mother liquor unstirred for experiments 1–10, and stirred at 400 rpm for experiments 11–20. Assay of crystal collection #3 by derivatization/HPLC analysis indicated a 97% ee (see ESI†).

evaluated with stirring of the mother liquor (Chart 2, experiments 11–20). The appearance of a significant quantity of solid now occurred rapidly (10–45 min *vs.* 3–24 h without stirring) and individual crystals were minute and virtually indistinguishable to the naked eye. Maximal ee values were not encountered more frequently than before; however, a significantly higher median ee was observed with stirring as compared to without it (44% *vs.* 14%, respectively). The kind of spontaneous resolution encountered herein is probably best rationalized according to Kondepudi's model,[7a] *i.e.*, the result of an atypical autocatalytic secondary nucleation process that satisfies the classical Frank condition[12] by suppressing further primary nucleation.

With a useful and conceptually interesting solution to the resolution problem thus identified, use of the enantioenriched amidoamine **3** as an aldolization catalyst was investigated. As its freebase, the amine was a comparatively poor promoter of the aldol reaction between acetone and benzaldehydes (*e.g.*, <10% yield with *p*-nitrobenzaldehyde). Superior results were obtained by employing **3** in conjunction with modestly acidic additives, particularly acetic acid (Table 1); however, salts of **3** formed from strong acids lacked all catalytic activity (*e.g.*, **3**·TFA and **3**·TfOH). Good conversion was noted for highly electrophilic benzaldehydes, but non-activated and electron rich substrates failed to react appreciably. Stereoinduction from the catalyst was of limited efficacy as revealed by the barely discernable level of enantioselectivity encountered.

In conclusion, the earlier work of Pincock and Wilson[6] and Kondepudi *et al.*[7] had demonstrated that true spontaneous resolution of a biaryl compound was possible under specialized conditions wherein the axially chiral substrate was configurationally labile as it crystallized from a melt. The observations documented herein establish that a symmetry breaking resolution may also occur in the more general and likely to be encountered scenario in which the biaryl maintains stable enantiomeric atropisomers[13] throughout crystallization of its conglomerate from a solution phase. True spontaneous

Table 1 Catalysis of aldol reactions with amidoamine *l*-**3** (of 82% ee)



4 **5**

#	Aldehyde **4** R	Product distribution (mol%)[a] AL : DAL : AC : SM	Aldol adduct **5** Yield[b] (%)	ee[c] (%)
1	4-NO_2	69 : 28 : 3 : 0	34	3
2	4-CF_3	70 : 14 : 9 : 7	41	1
3	4-Cl	23 : 6 : 10 : 61	13	1
4	3-Cl	53 : 8 : 4 : 35	24	<1
5	2,6-Cl_2	79 : 11 : 10 : 0	58	1
6	H	14 : 2 : 17 : 67	6	2
7	4-Me	5 : 2 : 10 : 83	2	nd
8	4-MeO	<1 : <1 : 2 : 97	0	—

[a] Determined by ^{1}H NMR analysis of crude product mixture: AL = aldol (**8**), DAL = α,α′-acetone double aldol, AC = aldol condensation, SM = starting aldehyde. [b] Isolated yield of purified aldol adduct. [c] By HPLC.

resolution of configurationally stable metal coordination complexes is quite well known;[14] however, examples of related symmetry breaking resolution phenomena concerning purely organic molecules, such as that discovered for amidoamine salt **3**·TFA, are dominated by systems which either lack configurational stability[15] or else are achiral[16] in the liquid state. The unanticipated behavior of **3**·TFA is likely linked to its ionic character and the ability of bridging achiral trifluoroacetate anions to communicate spatially pervasive non-covalent interactions.[2,17] Finally, of further significance is the fact that amidoamine **3** exhibits some catalytic activity for the direct acetone aldol reaction. While enantioselectivity in this particular process is low, the observation is supportive of one plausible mechanism by which homochirality could arise in a given prebiotic environment; *i.e.*, spontaneous resolution of an active catalyst component thence propagation of this chiral information *via* enantioselective transformation of some other prochiral substance.[18,19]

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Notes and references

‡ Crystal data for **3**·CF_3CO_2H: $C_{20}H_{23}F_3N_2O_5$, M_r = 428.40, T = 173(2) K, λ = 0.71073 Å (MoKα), 0.35 × 0.15 × 0.10 mm, orthorhombic, $P2_12_12_1$, a = 8.5061(6), b = 12.7978(9), c = 19.4743(14) Å, V = 2120.0(3) Å^3, Z = 4, D_c = 1.342 g cm^{-3}, μ = 0.113 mm^{-1}, $F(000)$ = 896, $2\theta_{max}$ = 50.0°, 20 323 reflections, 3731 unique (R_{int} = 0.0269), 349 parameters, R_1 = 0.0468, wR_2 = 0.1273 [$I > 2\sigma(I)$], GOF = 1.055, max/min residual electron density +0.684/−0.446 e Å^{-3}. CCDC 748440.

§ Crystal data for **1**: $C_{26}H_{36}N_2O_4$, M_r = 440.57, T = 173(2) K, λ = 0.71073 Å (MoKα), 0.35 × 0.24 × 0.17 mm, monoclinic, $P2_1$, a = 10.5558(7), b = 10.4979(7), c = 11.4257(8) Å, β = 103.691(1)°, V = 1230.15(14) Å^3, Z = 2, D_c = 1.189 g cm^{-3}, μ = 0.080 mm^{-1}, $F(000)$ = 476, $2\theta_{max}$ = 55.0°, 8028 reflections, 5304 unique (R_{int} = 0.0121), 433 parameters, R_1 = 0.0329, wR_2 = 0.0844 [$I > 2\sigma(I)$], GOF = 1.017, max/min residual electron density +0.217/−0.151 e Å^{-3}. CCDC 748439.

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