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CRYSTAL ENGINEERING FOR ABSOLUTE ASYMMETRIC SYNTHESIS THROUGH THE USE OF *META*-SUBSTITUTED ARYL GROUPS

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Abstract. A significant tendency towards crystallization in chiral space groups has been found for 4-benzyloxy-2-pyridones whose phenyl groups are *meta*-substituted (*m*-Cl, *m*-Br, *m*-Me and *m*-OMe). Irradiation of single crystals of three of these materials leads to optically active β-lactam derivatives in high chemical and optical yields *via* an allowed disrotatory electrocyclization. © 1997 Elsevier Science Ltd.

Absolute asymmetric synthesis is the term used to describe the formation of enantiomerically enriched products from achiral precursors without the intervention of pre-existing optical activity.[1] Such processes can be brought about through the crystallization of achiral molecules in chiral space groups followed by an enantioselective solid state reaction of one of the enantiomorphs.[2] While very high enantiomeric excesses can be achieved in this way, two difficulties associated with the procedure prevent it from being used as a general method of asymmetric synthesis. The first is that achiral substances seldom crystallize in chiral space groups, preferring instead to adopt centrosymmetric and therefore achiral packing arrangements.[3] Secondly, and probably more importantly, the crystallization of achiral compounds in chiral space groups is unpredictable, and most examples of absolute asymmetric syntheses have been the result of serendipity rather than planning.

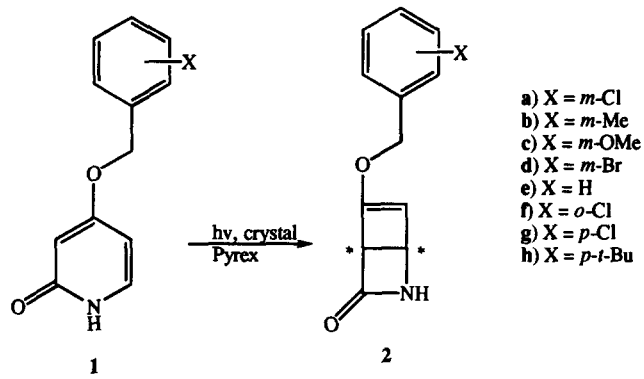
In seeking ways to make absolute asymmetric synthesis more predictable, and therefore useful, we were struck by a paper in which Curtin and Paul pointed out that *meta*-disubstituted benzenes are more likely to crystallize in noncentrosymmetric space groups than are their *ortho* and *para* isomers.[4] Since all chiral space groups are noncentrosymmetric, we reasoned that *meta* substitution might prove to be a structural motif that could be built into a potential reactant in order to increase the chances of crystallization in a chiral space group. Herein we report the successful realization of this concept for the 4-benzyloxy-2-pyridone system (**1**, Scheme 1).

Substituted 2-pyridones have a photochemical history dating back to 1960.[5] Depending on a variety of factors including substituent structure and location as well as reactant concentration, photolysis of 2-pyridones leads either to [4+4] dimerization or to intramolecular electrocyclization. Kaneko *et al.*[6] showed that 4-alkoxy-2-pyridones react preferentially *via* the latter pathway to afford β-lactam derivatives of general structure **2** (Scheme 1), a reaction that provides an ideal test for absolute asymmetric synthesis, since it converts an achiral reactant into a chiral product. Asymmetric electrocyclization reactions employing chiral auxiliaries have in fact been reported for 2-pyridones—one by Sato *et al.*[7] using an enantiomerically pure 4-menthyloxy group and another by Toda and Tanaka[8] in which the chiral auxiliary was an optically active host molecule.

In order to test the ideas presented above, eight variously substituted 4-benzyloxy-2-pyridone derivatives (**1a-h**) were prepared according to the procedure reported for the parent compound **1e**.[9] All eight were sharp-melting crystalline substances whose X-ray crystal and molecular structures were successfully determined.[10] In a

remarkable demonstration of the validity of the *meta* steering effect concept, all four *meta*-substituted derivatives (**1a-d**) were found to be isomorphous, crystallizing in the chiral space group $P2_12_12_1$. In contrast, the unsubstituted (**1e**) and *ortho* and *para*-substituted analogues (**1f-h**) crystallized in centrosymmetric (achiral) space groups. Table 1 summarizes this information along with the melting point of each compound.

Scheme 1



1 2

Irradiation (300 nm, Rayonet Photoreactor) of the 4-benzyloxy-2-pyridones **1a-h** in acetonitrile resulted in the formation of the corresponding racemic β-lactam derivatives **2a-h**. Chemical yields were generally excellent (> 90%), the one exception being *m*-bromo derivative **2d**, which was found to revert thermally to starting material **1d** upon attempted isolation and characterization.[11] The other photoproducts were, however, sufficiently stable to permit isolation in pure form, and they were fully characterized by conventional methods.

Table 1. Space Groups and Melting Points of 4-Benzyloxy-2-pyridones

2-Pyridone	mp (°C)	Space Group	2-Pyridone	mp (°C)	Space Group
1a	165-166	$P2_12_12_1$	**1e**	198-200	$P2_1/n$
1b	163-164	$P2_12_12_1$	**1f**	155-156	$P\bar{1}$
1c	174-175	$P2_12_12_1$	**1g**	194-195	$P\bar{1}$
1d	173-174	$P2_12_12_1$	**1h**	225-226	$P\bar{1}$

We next turned to an investigation of the solid state photochemistry of the *meta*-substituted derivatives **1a-c**. Carefully grown single crystals of these materials were crushed between two Pyrex microscope slides and the resulting "sandwiches" irradiated at room temperature with the output of a 450 W Hanovia medium pressure mercury lamp. The solid state photolyses were carried out for varying lengths of time, conversions being kept below 40% in an effort to minimize complications due to crystal breakdown and photodecomposition of the products. The resulting mixtures were analyzed by capillary gas chromatography (for % conversion) and chiral HPLC (for enantiomeric excess, Chiralcel OD column). The results are compiled in Table 2.

A few comments on the results shown in Table 2 are in order. First of all, for compounds **1b** and **1c**, the crystals to be photolyzed were grown without seeding, and the irradiations were conducted on single crystals selected randomly from the mixture of enantiomorphs so produced. As a result, some photolyses gave an excess of one photoproduct enantiomer, while other photolyses led mainly to the optical antipode. The enantiomeric excesses were similar in both cases, and the *ees* listed in Table 2 represent values averaged without regard to which enantiomer predominated. Recrystallization of the *meta*-chloro compound **1a**, on the other hand, was carried out by seeding the supersaturated solutions with crushed single crystals. This led to crystal batches that were apparently enantiomorphously homogeneous, and photolyses of single crystals selected at random from a given

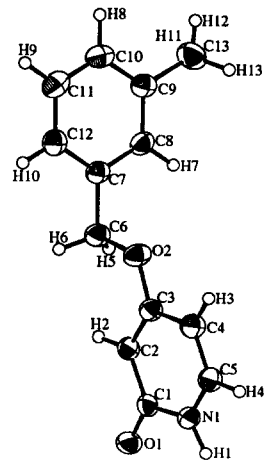
batch afforded the same photoproduct enantiomer each time. In this way, either enantiomer of photoproduct **2a** could be produced as desired. A second point is that the observed enantiomeric excesses in each case decreased with increasing conversion. Similar results have been noted previously,[12] and are what one would expect as the parent crystal lattice becomes disrupted due to the presence of increasing amounts of product. Finally, for reasons that we do not fully understand, compounds **1a-c** reacted at widely different overall rates. Compound **1a** was the slowest, **1b** the fastest, and **1c** intermediate (in solution, there was little difference between the three).

Table 2. Solid State Photolysis Results

Reactant	Irradiation Time (min)	Conversion (%)	Enantiomeric Excess (%)
1a	30	2.5	78
	90	6.9	69
1b	10	8.0	71
	20	16.4	69
	30	37.3	58
1c	15	5.6	~100
	30	10.3	91
	60	20.5	90
	90	27.3	90

There are two plausible *a priori* explanations as to how the observed solid state enantioselectivity is governed by structural factors. First, consider that disrotatory electrocyclization in compounds **1a-c** can occur either from the top or bottom face of the diene system, each possibility leading to a different photoproduct enantiomer. The reactants may adopt conformations in the crystalline state that favor one of the two pathways because orbital overlap and/or intramolecular steric interactions might be more favorable in one direction than the other. Such effects have been identified as controlling enantioselectivity in several solid state di-π-methane photorearrangements.[13] Alternatively, discrimination between the two possible electrocyclization pathways could come about as the result of intermolecular interactions developed between the reactant and the walls of the stationary reaction cavity. Effects of this type have also been well documented in the solid state chemical literature.[14]

The figure at the right shows the molecular conformation of 2-pyridone derivative **1b** as it exists in the chiral crystal lattice; nearly identical conformations are adopted in the solid state by the other *meta*-substituted derivatives. The 2-pyridone ring in these structures is almost perfectly planar, and the ether oxygen (O2) and the benzylic carbon (C6) of the side chain lie in this plane as well. As a result, it seems unlikely that intramolecular orbital overlap and/or steric effects play much of a role in controlling enantioselectivity in the solid state photocyclization of these compounds. Overlap between the orbitals on C2 and C5 is the same on both faces of the 2-pyridone ring, and the benzyloxy group is too remote from the site of reaction to exert a significant intramolecular steric effect on either pathway. We conclude, therefore, that *intermolecular* interactions control solid state reactivity for these compounds. Disrotatory orbital overlap is accompanied by folding of the pyridone ring along the C2-C5 axis, and this could lead to large amplitude motions of the benzyloxy group and/or disruption of intermolecular C=O...H-N hydrogen bonding. We defer a discussion of how such effects might control



enantioselectivity until we have completed absolute configuration correlation studies aimed at determining the facial selectivity of the electrocyclization.

As a final point, we call attention to a recent paper by Hashizume *et al.*[15] which further documents the ability of *meta*-substituted aryl groups to direct crystallization into chiral space groups. Three N,N-diisopropylarylglyoxylamides were prepared in which the aryl groups were *ortho*-Cl, *meta*-Cl and *para*-Cl. Of these, only the *meta*-chloro derivative was found to crystallize in a chiral space group ($P2_12_12_1$); the other two crystallized in the centrosymmetric space groups $P2_1/n$ (*ortho*-Cl) and Pbca (*para*-chloro). We are continuing to explore the generality of the *meta* steering effect.

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10. **1a**: a = 8.203(8), b = 25.99(3), c = 4.996(5) Å; Z = 4, R = 4.4%. **1b**: a = 8.1502(6), b = 25.692(2), c = 5.2180(7) Å; Z = 4, R = 3.5%. **1c**: a = 8.118(1), b = 26.359(2), c = 5.280(2) Å; Z = 4, R = 2.8%. **1d**: a = 8.215(1), b = 26.2972(9), c = 5.057(3) Å; Z = 4, R = 3.4%. **1e**: a = 5.767(5), b = 21.189(12), c = 8.577(7) Å; β = 101.11°; Z = 4, R = 5.7%. **1f**: a = 11.327(1), b = 12.552(1), c = 8.5003(6) Å; α = 101.90(3), β = 110.81(6), γ = 80.04(0)°; Z = 4, R = 4.5%. **1g**: a = 11.2525(8), b = 12.763(1), c = 8.1126(8) Å; α = 108.39(7), β = 99.36(9), γ = 92.76(9)°; Z = 4, R = 3.8%. **1h**: a = 6.071(2), b = 8.649(2), c = 13.970(4) Å; α = 87.46(2), β = 81.29(3), γ = 77.14(3)°; Z = 2, R = 5.3%. Full crystallographic details will be published separately.
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