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Highly Effective Diastereodifferentiation of *Meso*-Dicarboxylic Anhydrides Using Sterically Congested Chiral *N*-Sulfonylaminoalcohols

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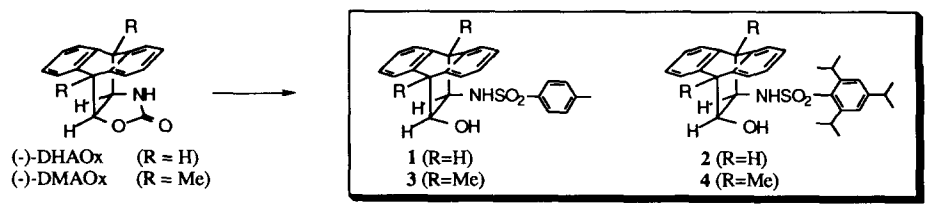
Abstract: The differentiation between enantiotopic carbonyl groups of cyclic *meso*-dicarboxylic anhydrides has been attained with excellent diastereofacial selectivity with an isomer ratio above 99 : 1 by treatment with the lithium salts of sterically hindered chiral *N*-arylsulfonyl-2-aminoalcohols in the presence of hexamethylphosphoric triamide.

Enantiodivergence of σ-symmetric compounds is a useful trick in asymmetric synthesis,[1] since multiple stereogenic centers can be introduced in a single reaction step and the subsequent manipulations lead to the facile synthesis of both enantiomers. This strategy has been successfully substantiated by both enzyme- or microorganism-mediated[2] and non-enzymatic reactions[3] through catalytic or stoichiometric processes. There is, however, still an on-going need for the development of the chemical means of highly versatile use, since the substrate specificity and structure dependence for biological processes have often prevented the general use of this methodology.

Discrimination between enantiotopic carbonyl groups in *meso*-cyclic dicarboxylic acid derivatives such as anhydrides and diesters provides versatile chiral building blocks for the preparation of both medically important enantiomeric compounds such as β-lactams[4] and the family of prostaglandins.[5]

This paper describes a simple and efficient procedure for excellent diastereofacial differentiation of cyclic *meso*-1,2-dicarboxylic anhydrides using the lithium salts of chiral *N*-toluenesulfonyl (Tos) and *N*-2,4,6-tri*iso*propylbenzenesulfonyl (TPS)-2-aminoalcohols (**1**-**4**)[6] which are charactarized by highly steric congestion and conformational rigidity. Such aminoalcohol reagents were readily obtainable by Cs_2CO_3-catalyzed methanolysis[7] or hydrolysis with $Ba(OH)_2$ of the corresponding *N*-arylsulfonyl-2-oxazolidinones derived from recently developed (-)-DHAOx[8a] and (-)-DMAOx[8b] auxiliaries. Symmetrical cyclic anhydrides examined in this study involve *meso*-cyclohexane-1,2-dicarboxylic anhydride (**5a**), bicyclo[2.2.1]heptane- and bicyclo[2.2.2]-octane dicarboxylic anhydrides (**5c** and **e**) and the corresponding unsaturated cycloalkene derivatives (**5b**, **d** and **f**).

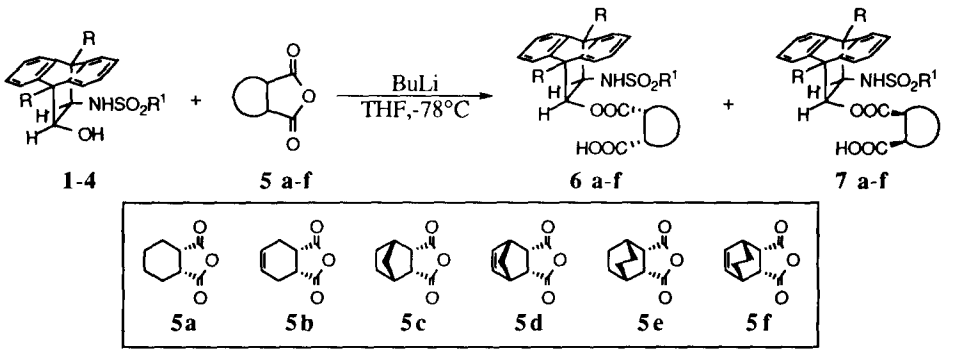


(-)-DHAOx (R = H)
(-)-DMAOx (R = Me)

1 (R=H)
3 (R=Me)

2 (R=H)
4 (R=Me)

Scheme 1



Scheme 2

(The affixes **a-f** refer to anhydrides **5a-f**, respectively)

Enantiotopic mono-esterifications of *meso*-anhydrides (**5**) with the lithium salts derived from *N*-sulfonyl aminoalcohols (**1-4**) and BuLi were extensively explored and the results are summarized in Tables 1 and 2. The efficiency of sterically constrained aminoalcohols (**1-4**) with different bulkiness could be evaluated by a systematic study of the diasterodifferentiation of *meso*-anhydrides (**5a** and **5b**). Thus, treatment of the *meso*-anhydride (**5a**) with an equimolar mixture of (-)-*N*-tosylaminoalcohol (**1**) and BuLi in tetrahydrofuran at -78 °C for 2 h gave a diastereomeric mixture of monoesters (**6a** and **7a**) in 67 % d.e. (88 % yield) (Entry 1). The addition of an excess hexamethylphosphoric triamide (HMPA) (5.0 equiv.) considerably enhanced this diastereoselectivity to 82 % d.e. (Entry 2). The selectivity is highly solvent-dependent and THF appears to be the solvent of choice with or without HMPA.[9]

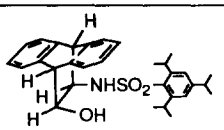
Table 1. Diastereoselective Ring-opening of *meso*-Anhydrides (**5a,b**) with *N*-Sulfonyl-aminoalcohols (**1-4**) and BuLi[a)]

Entry	Aminoalcohol	Anhydride	HMPA (equiv.)	Yield (%)	**6** : **7** (% d.e.)[b)]
1	**1**	**5a**	none	88	5.1 : 1 (67)
2	**1**	**5a**	5.0	94	9.9 : 1 (82)
3	**2**	**5a**	none	87	2.1 : 1 (36)
4	**2**	**5a**	5.0	93	22 : 1 (92)
5	**2**	**5b**	none	89	2.3 : 1 (40)
6	**2**	**5b**	5.0	91	20 : 1 (91)
7	**3**	**5a**	none	63	5.3 :1 (67)
8	**3**	**5a**	5.0	81	32 : 1 (94)
9	**4**	**5a**	none	87	23 : 1 (92)
10	**4**	**5a**	5.0	93	>500 :1 (>99)
11	**4**	**5b**	none	96	31 : 1 (94)
12	**4**	**5b**	5.0	93	>500 : 1 (>99)

a)The reaction was carried out in THF in the presence or absence of HMPA at -78 °C for 2 h.
b) Determined by HPLC after the esterification of the diastereomeric mixture with CH_2N_2.

Steric congestion inherent in the aminoalcohol reagents played a crucial role in the highly diastereodifferentiated ring-opening of the cyclic anhydrides. As seen in Table 1, treatment of **5a** with the monolithium salts derived from the bulky reagents **2** and **3** resulted in excellent discrimination with 92 % d.e. and 94 % d.e., respectively. Perfect differentiation was attained with the highly congested *N*-2,4,6-tri*iso*propylbenzenesulfonylaminoalcohol (**4**) derived from DMAOx. The dilithium salts prepared in situ from **2** equivalents of BuLi and aminoalcohols (**1-4**) were equally effective in attaining high diastereoselectivity. Use of more than two equimolar amounts of HMPA[10] was desirable for producing a high level of discrimination except for the case of reagent **4** which worked well even in the absence of HMPA to give 92-94 % d.e.. The crown-ether and tetramethylethylenediamine (TMEDA) were also effective as coordinating additives for enhancement of the selectivity and yield in place of HMPA.[10]

Table 2. Diastereoselective Esterification of *meso*-Tricyclic Anhydrides (**5c-f**) with the Lithium Salts Derived from Chiral *N*-TPS-Aminoalcohol (**2**)[a)]

Entry	Aminoalcohol	Anhydride	HMPA (equiv.)	Yield (%)	**6** : **7**[b)]
1		**5c**	5.0	99	150 : 1
2		**5d**	5.0	86	99 : 1
3		**5e**	5.0	90	160 : 1
4	**2**	**5f**	5.0	84	140 : 1

a)The reaction was carried out using equimolar amounts of **2** and BuLi in THF at -78 °C for 2 h.
b) Determined by HPLC after the treatment with CH_2N_2.

Even in the reactions with reagent **2** which was rather unsatisfactory for the enantiotopic discrimination of **5a** and **5b**, nearly complete diastereoselectivity was obtained with tricyclic *meso*-1,2- dicarboxylic anhydrides (**5c-f**). All the examined tricyclic *meso*-anhydrides were smoothly ring-opened with diastereomer ratios of 99-160 : 1 under the optimal conditions performed in the presence of an excess HMPA (5.0 equiv.) (Table 2). The absence of HMPA resulted in only poor diastereoselectivity (below 70 % d.e.).

Though the half-esters (**6** and **7**) thus formed were highly sterically congested, the chiral aminoalcohol auxiliaries could be smoothly removed by a reductive or hydrolytic procedure. Thus, preferential ring-openings of the anhydrides **5a-f** to the diastereomers **6a-f** were determined by ready conversion either to the γ-lactones with (*2S, 3R*)-configurations by reductive removal of the chiral auxiliaries with lithium pyrrolidinoborohydride ($LiPyrrBH_3$) complexes[11] followed by lactonizations[12] or to the enantiomeric γ-lactones by reduction with diborane followed by hydrolysis with 2N LiOH solution.

In conclusion, a series of rigid and sterically congested *N*-sulfonylaminoalcohols (**1-4**) serve in combination with BuLi as excellent reagents for the diastereodifferentiation of *meso*-cyclic anhydrides. Thus, compound **4** is the most recommended compound for a versatile use.

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6. Physical data for (*1S, 2R*)-2-aminoalcohols (**1-4**).
   1: mp. 200 °C (from EtOH), $[\alpha]_D$-35.1° ($CHCl_3$). **2**: mp. 213 °C (from EtOH), $[\alpha]_D$-25.4° ($CHCl_3$).
   3: mp. 212 °C (from hexane), $[\alpha]_D$+11.3° ($CHCl_3$) **4**: amorphous solid $[\alpha]_D$+30.0° ($CHCl_3$).
7. *cf.* Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.*, **1987**, *28*, 4185.
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9. The anhydride **5a** was ring-opened by the Li-salts of **1** in Et_2O and toluene in the absence of HMPA with 55 % d.e. (93 % yield) and 49 % d.e. (95 % yield), respectively.
10. In the diastereoselective ring-opening of **5a** with the Li-salts of **2**, the addition of an equimolar and 2-equimolar amounts of HMPA gave 79 % d.e. (86 % yield) and 89 % d.e. (90 % yield), respectively. In place of HMPA, the use of 15-Crown-5 (1.2 equiv.) and TMEDA (5.0 equiv.) gave 67 % d.e. and 62 % d.e., respectively.
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12. Typical procedure: to a solution of the Li-salts derived from **2** (1.01 g, 2.0 mmol) and BuLi (2.0 mmol) in THF (16 ml) was added **5f** (0.37 g, 2.0 mmol) dissolved in THF (4 ml) in the presence of HMPA (1.79 g, 5.0 equiv.) at -78 °C and it was kept for 2 h Acidification followed by extraction with Et_2O gave the mixed half-esters (**6f** and **7f**) (1.16 g, 84 %) which, after treatment with CH_2N_2, gave the **6f / 7f** ratio of 140 : 1 based on HPLC analysis (YMC-Pack SIL).
    To a mixture of **6f** and **7f** (1.16 g, 1.7 mmol) thus obtained, the $LiPyrrBH_3$ complexes (14.9 ml, 8.5 mmol) prepared *in situ* in THF (17 ml) at 0 °C were added. The mixture was stirred at room temperature for 1.5 h and acidified with 3N HCl solution. The usual work-up followed by chromatography on silica gel gave the γ-lactone (0.22 g, 79 %, $[\alpha]_D^{27}$ +90.2° ($CHCl_3$) [*lit.*, $[\alpha]_D^{27}$ +92.0° ($CHCl_3$)[2b] for (*2S, 3R*)-isomer] in addition to the *N*-TPS-aminoalcohol (**2**) (0.84 g, 98 %).

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