Pergamon

Tetrahedron Letters, Vol. 37, No. 51, pp. 9237-9240, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02193-4

Reversal of Stereoselection in Diastereodivergence of *Meso*-Dicarboxylic Anhydrides

Noriaki Hashimoto, Shoko Kawamura, Tadao Ishizuka and Takehisa Kunieda*

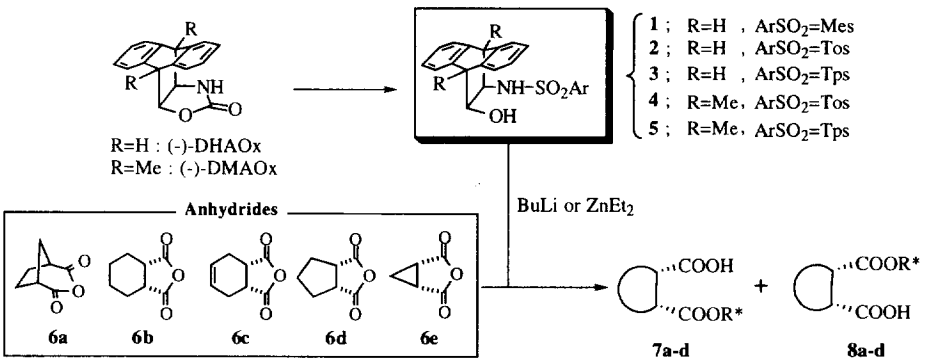
Faculty of Pharmaceutical Sciences, Kumamoto University

5-1 Oe-honmachi, Kumamoto 862, Japan

Abstract : Diastereoselective ring-openings of *meso*-dicarboxylic anhydrides with the Li- and Zn-complexes generated *in situ* from sterically congested chiral *N*-sulfonylaminoalcohols proceed with a reversal of high stereoselection.

Asymmetrization of σ-symmetric compounds is a versatile, synthetic technique which permits the generation of multiple stereogenic centers with correct stereochemistry in a single step.[1] A number of strategies for the enantiodivergence of *meso*-dicarboxylic acid derivatives have been developed through stoichiometric and catalytic processes including the use of enzymes and biocatalysts.[2]

Highly efficient differentiation between the enantiotopic carbonyl groups of *meso*-1,2-dicarboxylic anhydrides including bicyclo[2.2.2] and bicyclo[2.2.1] ring skeletons has been achieved in the presence of hexamethylphosphoric triamide (HMPA) with the lithium salts of sterically hindered chiral *N*-arenesulfonyl-2-aminoalcohols such as **3**-**5**.[3] Our continuing study on the 'mesotrick method' has now revealed that the enantiotopic stereoselection of *meso*-anhydrides by such *N*-sulfonylaminoalcohols is dependent on the organometals employed as bases and that a striking reversal of the diastereoselection is observed when $ZnEt_2$ is substituted for BuLi in such reactions.



Scheme 1

This paper describes such a reversal in diastereoselection for the ring-opening of simple σ-symmetric dicarboxylic anhydrides (**6a-e**) by the Li- and Zn-salts generated *in situ* from sterically constrained *N*-sulfonylaminoalcohols. In this study we have explored a series of aminoalcohol reagents (**1-5**)[3-4] with *N*-mesyl, *N*-tosyl and *N*-2, 4, 6-triisopropylbenzensulfonyl (Tps) groups, which are readily obtained by hydrolytic cleavage of the corresponding *N*-sulfonyl-2-oxazolidinones derived from the 2-oxazolidinone chiral auxiliaries, DHAOx[5a] and DMAOx[5b].

	BuLi / LiCl / THF	28	:	1
Scheme 2	$ZnEt_2$ / CH_2Cl_2	1	:	38

Treatment of *meso*-1, 3-dicarboxylic anhydride (**6a**)[6] with the dilithium salts derived from *N*-tosylaminoalcohol (**2**) and BuLi (2 equiv) in THF at -78 °C resulted in highly diastereoselective ring-opening to give the (*R*)-monoester (**7a**)[7] above 93 % de in 81 % yield under the optimum conditions using LiCl (2 equiv) as an effective additive. Among the *N*-sulfonylaminoalcohols examined, the *N*-tosyl compound (**2**) proved to be the reagent of choice, giving the highest diastereoselectivity and yield. The more sterically congested **3-5** were less effective, in contrast to the promising findings previously pointed out.[3] Metal salts such as $LaCl_3$, LiBr and $LiClO_4$ functioned equally well as effective additives for the enhancement of the diastereoselectivity, while the addition of HMPA and 15-crown ether was not nearly as effective.

On the other hand, the zinc-complexes, generated *in situ* from an equimolar mixture of *N*-tosyl-aminoalcohol (**2**) and $ZnEt_2$ in CH_2Cl_2, underwent an unexpected cleavage to the (*S*)-monoester (**8a**)[7] of the opposite configuration with 91 % de,[8] although the reaction proceeded sluggishly and required the prolonged treatment (24 hr) even at 25 °C, compared to the smooth ring-opening with the lithium salts. The *N*-tosyl agent **2** was the reagent of choice in this reaction as well.[9] Reactions using THF, ether and toluene as solvents resulted in lower diastereoselectivity below 62 %, 70 % and 74 % de, respectively. In this case, additives such as LiCl, $ZnCl_2$ and HMPA were ineffective in enhancing selectivity.

Such a reversal in stereochemisry was also observed for the enantiotopic monoesterification of 1, 2-dicarboxylic anhydrides **6b-e**. The anhydrides **6b** and **c** were previously reported to be smoothly converted in the presence of HMPA to the (*R*)-esters (**7b** and **c**) with nearly complete diastereoselectivity above 500 : 1, on treatment with the Li-salts of sterically hindered **3-5**,[3] while treatment of **7b** and **c** with the zinc-complexes generated *in situ* from **2** and $ZnEt_2$ in CH_2Cl_2 resulted in the preferential formation of the (*S*)-esters (**8b** and **c**) with high diastereoselectivity, nearly 90 % de. An enhancement in diastereoselectivity of up to 93 % de was observed by the addition of equimolar amounts of THF.[8] In contrast to ring-opening with lithium salts, the diastereoselective ring-opening of cyclic 1, 2-dicarboxylic anhydrides **6b-e**, mediated by the zinc-compelxes, were considerably affected by the ring-size of the cycloalkane moiety,[10] as shown in **Table 1.**

Similar treatment of 3-*iso*propylglutaric anhydride (**9**)[11] with the dilithium salts derived from **2** in THF at -78 °C resulted in a moderate level of diastereoselection (up to 74 % de[12]), while ring-opening using zinc-salts proceeded only with poor selectivity of reversed stereochemistry (**Scheme 3**).

Table 1. Diastereoselective Ring-openings of *meso*-Anhydrides with Metal Salts of *N*-Sulfonyl aminoalcohols **2** and **5**

Anhydride	Reagents (equiv)	Additive (equiv)	Conditions (equiv)	Yield (%)	**7** : **8** (% de)[a]
6a	**2** / BuLi (2.0)	none	THF, -78 °C, 3 hr	82	8 : 1 (78)
6a	**2** / BuLi (2.0)	LiCl (2.0)	THF, -78 °C, 3 hr	81	28 : 1 (93)
6a	**2** / BuLi (2.0)	$LaCl_3$ (2.0)	THF, -78 °C, 3 hr	77	16 : 1 (88)
6a	**2** / $ZnEt_2$ (1.0)	none	CH_2Cl_2, 25 °C, 24 hr	90	1 : 22 (91) [b]
6b	**5** / BuLi (1.0)	HMPA (5.0),	THF, -78 °C, 2 hr	93	500 : 1 (>99) [c]
6b	**2** / $ZnEt_2$ (1.0)	none	THF (1.0), CH_2Cl_2, reflux, 6 hr	85	1 : 26 (93)
6c	**5** / BuLi (1.0)	HMPA (5.0)	THF, -78 °C, 2 hr	90	500 : 1 (>99) [c]
6c	**2** / $ZnEt_2$ (1.0)	none	CH_2Cl_2, 25 °C, 24 hr	89	1 : 17 (89)
6d	**5** / BuLi (1.0)	HMPA (5.0)	THF, -78 °C, 2 hr	78	500 : 1 (>99)
6d	**2** / $ZnEt_2$ (1.0)	none	CH_2Cl_2, 25 °C, 24 hr	82	1 : 4 (60)
6e	**5** / BuLi (1.0)	HMPA (5.0)	THF, -78 °C, 2 hr	95	500 : 1 (>99)
6e	**2** / $ZnEt_2$ (1.0)	none	CH_2Cl_2, reflux, 24 hr	85	1 : 1.3 (13)

a) Determined by HPLC after conversion to the alcohols (with BH_3) or methyl esters (with CH_2N_2).
b) The use of 2 equimolar amounts of $ZnEt_2$ improved the selectivity up to 95 % de (1 : 38).
c) Taken from ref. 3.

2 (R*OH) **9** **10** **11**

BuLi / LiCl / THF	6.7	:	1
$ZnEt_2$ / CH_2Cl_2	1	:	1.3

Scheme 3

Reversal of the diastereoselection as a function of the metal species may be of interest from the standpoint of reaction mechanism, although the details are not clear at the present.

REFERENCES AND NOTES

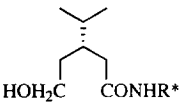
1. For examples, see : a) Ohno, M.; Otsuka, M. *Organic Reactions*; Jone Wiley and Sons *New York*, **1989**, *37*, 1 b) Ward, R. S. *Chem. Soc. Rev.*, 1990, *19*, 1. c) Naemura, K. *J. Synth. Org. Chem. Jpn.*, **1994**, *52*, 49.

2. For recent examples, see : enzymatic method: a) Tamai, S.; Miyauchi, S.; Morizane, C.; Miyagi, K.; Shimizu, H.; Kume, M.; Sano, S.; Shiro, M.; Nagao, Y. *Chem. Lett.*, **1994**, 2381. b) Jones, J. B. *Can. J. Chem.*, **1993**, *71*, 1273. c) Ozegowski, R.; Kunath, A.; Schick, H. *Tetrahedron Asymmetry*, **1993**, *4*, 695. d) Yamamoto, Y.; Iwasa, M.; Sawada, S.; Oda, J. *Agric. Biol. Chem.*, **1990**, *54*, 3269. e) Renold, P.; Tamm, C. *Tetrahedron Asymmetry*, **1993**, *4*, 2295.

   non-enzymatic method: f) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 2395. g) Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.*, **1994**, *42*, 9. h) Maezaki, N.; Soejima, M.; Takeda, M.; Sakamoto, A.; Tanaka, T.; Iwata, C. *J. Chem. Soc. Chem. Commun.*, **1994**, 1345. i) Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett*, **1994**, 611. j) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *J. Chem. Soc. Chem. Commun.*, **1994**, 2699. k) Hodgso, D. M.; Witherington, J.; Moloney, A. *Tetrahedron Asymmetry*, **1994**, *5*, 337. l) Konoike, T.; Araki, Y. *J. Org. Chem.*, **1994**, *59*, 7849. m) Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.*, **1993**, *34*, 1167. n) Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.*, **1991**, *56*, 4120. o) Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jap.*, **1993**, *66*, 2128. p) Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M. *Heterocycles*, **1993**, *36*, 937. q) Hayashi, M.; Kohmura, K.; Oguni, N. *Synlett*, **1991**, 774.
3. Imado, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.*, **1995**, *36*, 931.
4. **1** : mp 178 °C, $[\alpha]_D$ +8.2 ° (*c* 1.0, $CHCl_3$).
5. a) Matsunaga, H.; Kimura, K.; Ishizuka, T.; Haratake, M.; Kunieda, T. *Tetrahedron Lett.*, **1991**, *32*, 7715. b) Kimura, K.; Murata, K.; Otsuka, K.; Ishizuka, T.; Haratake, M.; Kunieda, T. *Tetrahedron Lett.*, **1992**, *33*, 4461.
6. Chenevert, R.; Lavoie, M.; Courchesne, G.; Martin, R. *Chem. Lett.*, **1994**, 93.
7. The stereochemistry of the monoester **7a** was determined by conversion of **7a** into the amide **i** with (*R*)-1-(1-naphthyl) ethylamine (R*-NH_2). See : Jones, J. B.; Hinks, R. S.; Hultin, P. G. *Can. J. Chem.*, **1985**, *63*, 452.

i

8. Typical procedures are as follows : anhydride **6a** (0.4 mmol) was treated with the Li-salts generated *in situ* from **2** (0.4 mmol) and BuLi (0.8 mmol) in THF (4 ml) in the presence of LiCl (0.80 ml) at -78 °C for 3hr. Acidification followed by extraction with Et_2O gave a diastereomeric mixture of **7a** and **8a** which was treated with BH_3·THF (1.20 mmol) in THF (8 ml) for 1 hr to give the alcohols (81 %). The isomer ratio was 28 : 1 based on HPLC analysis (YMC-pack SIL). On the other hand, to a stirred solution of **2** (0.40 mmol) and $ZnEt_2$ (0.40 mmol) in CH_2Cl_2 (16 ml) at room temperature was added **6a** (0.40 mmol) and it was kept for 24 hr. Acidification with 3*N* HCl solution followed by extraction with Et_2O gave the mixed half-esters of **7a** and **8a** (90% yield) which were determined to be in the ratio of 1 : 22 by HPLC analysis (YMC-pack SIL) after the reduction with BH_3·THF. Use of an excess of two equimolar amounts of $ZnEt_2$ increased the diastereomer ratio to 1 : 38.
9. Under the identical conditions, the reagents **1** and **3** gave 79 and 89 % de, respectively.
10. The absolute configurations of the half-esters (**7b-e**) were determined by conversion to the corresponding γ-lactones of known configurations. [2a]
11. Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.*, **1977**, *99*, 556.
12. Stereochemistry of **10** was determined by conversion to the amide **ii** with (*R*)-1-(1-naphthyl) ethylamine (R*-NH_2). See : Yabuta, G.; Mori, K. *Nippon Nogeikagaku Kaisi*, **1982**, *56*, 1121.



ii

(*Received in Japan* 8 *October* 1996; *revised* 31 *October* 1996; *accepted* 5 *November* 1996)