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Memory of Chirality Approach to the Enantiodivergent Synthesis of Chiral Benzo[*d*]sultams

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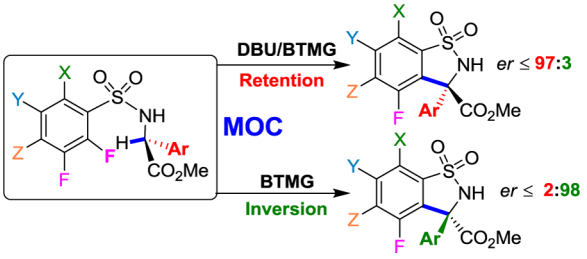
ABSTRACT



The "memory of chirality" stereodivergent synthesis of polyfluorobenzo[*d*]sultams has been developed. The interest of this protocol resides in the possibility of using the chirality of a starting sulfonamide single enantiomer to synthesize the target sultams in both absolute configurations, by using different base systems, under homogeneous conditions.

The "memory of chirality" (MOC) strategy, widely used in asymmetric synthesis, has been extensively applied by Kawabata[1] and other authors[2] to the synthesis of several enantiopure compounds. In particular, Kawabata applied MOC protocols to the enantioselective synthesis of α,α-disubstituted α-amino acids, through intramolecular alkylation,[1g,j,q,r] conjugate addition,[1h,s] carbonyl migration,[1c] and Dieckman condensation[1e] or intermolecular alkylation,[1i,l–n] aldol condensation,[2b] and conjugate addition[2a] of readily available optically active α-amino acid derivatives, without any external source of chirality.[3] The formation of long-lifetime conformers, which derive their

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(3) MOC approach, according to Carlier et al., "... can be defined as a formal substitution at an sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system". Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1–16.

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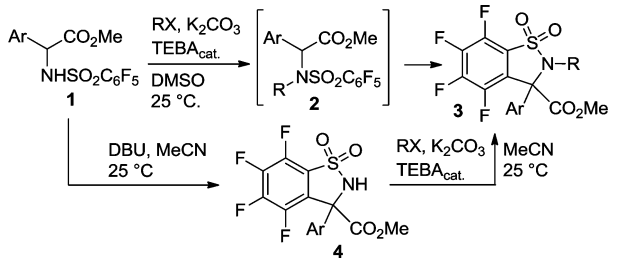
chirality from the presence of a stereogenic element, has been invoked to explain the MOC phenomenon. For instance, enolates of optically pure α-amino acid derivatives bearing two different *N*-substituents may present a stereogenic C−N axis and, therefore, behave as chiral nonracemic compounds. Moreover, in the majority of the literature cases, the configuration of the α-alkylation products of the above enolates is closely related to the absolute configuration of the starting α-amino acids, and the retention products are obtained. Kawabata reported also the enantioselective synthesis of both enantiomers of α-quaternary-α-amino acids, modulated by changing the organometallic bases.[1q] Furthermore, a few examples of "product chirality switching" modulated by the reaction conditions are known,[4] and examples of application of this principle to dendrimers,[5] peptides,[6] and to helical bioorganic systems,[7] such as proteins and DNA's, have recently reported.

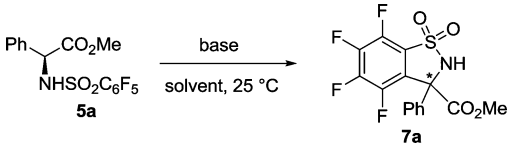
Scheme 1. Synthesis of Racemic Tetrafluorobenzo[*d*]sultams **3**



Here we report the MOC enantiodivergent cyclization of α-arylglycine (polyfluorobenzo)sulfonamides to the corresponding benzo[*d*]sultams, which have been obtained in both their absolute configurations by using different base systems. Sultams, and their fused counterparts, have stimulated vast interest[8] due to their bioactivity and medicinal use as antiviral, anticancer, antimicrobial, antimalarial, antileukemic, etc. and exhibit broad inhibitory properties against a variety of enzymes. Besides, fused sultams have found interesting applications in organic synthesis as protecting groups, chiral auxiliaries, and directed metalation groups (DMGs).[8]

Recently, we have described a novel strategy for the preparation of racemic *N*-substituted 3-aryl-3-carboxytetrafluorobenzo[*d*]sultam **3** (Scheme 1).[9] Starting from the corresponding *N*-sulfonyl-2-amino esters **1**, we proposed two alternative synthetic pathways: (a) a one-pot *N*-alkylation/cyclization, through the intermediate *N*-alkyl amidoester **2**, under phase transfer catalysis (PTC) conditions; (b) a quantitative cyclization to the nonalkylated sultam **4** with 1,8-diazabicycloundec-7-ene (DBU) as a base, under homogeneous conditions, followed by (c) PTC *N*-alkylation of the intermediate **4**. Experiments performed on enantiopure methyl *N*-(pentafluorobenzene)-sulfonyl-L-phenyl-glycinate **5a** under PTC conditions by varying the alkylating agent, the solvent, or PT catalyst gave only minor or no enantioselectivity.[10] On the basis of these results, we turned our attention toward the homogeneous conditions for the cyclization of **5a**. As already reported,[9] when excess DBU was used as a base in acetonitrile (Table 1, entry 1) the NH sultam **7a** was isolated in quantitative yield and in racemic form. Thus, to improve the enantiomeric ratio, both solvent and base effects were investigated (Table 1). A first interesting result (entry 2) was reached by using DME as a solvent at 25 °C and **7a** was isolated with *er* 68:32 in favor of the (−)-enantiomer (the retention *R*-isomer, as demonstrated hereafter); THF gave a minor *er* (entry 3), whereas other common solvents of different polarity (DMSO, DMF, DCM, toluene, chlorobenzene) induced complete racemization. Furthermore, a series of bases similar to DBU regarding structural characteristics and/or basic strength[11] were examined by using DME as a solvent (entries 4−8). Among bicyclic bases, only MTBD (entry 6) was partially effective, giving a *er* comparable to that obtained with DBU, but in longer reaction times. Surprisingly, BTMG (entry 8) completely reversed the enantioselectivity in favor of the (+)-isomer (the inversion *S*-isomer).

Table 1. Synthesis of Sultam **7a** under Homogeneous Conditions[a]



entry	base[b]	solvent	*t* (h)	yield (%)[c]	*er* (%)[d]
1	DBU (24.3)	MeCN	16	98	0
2	DBU	DME	8	98	68:32
3	DBU	THF	8	95	62:38
4	DBN (23.9)	DME	16	94	57:43
5	TBD (25.98)	DME	16	98	52:48
6	MTBD (25.4)	DME	20	56	69:31
7	TMG (23.3)	DME	16	90	52:48
8	BTMG (23.56)	DME	90	95	10:90

[a] Base and Solvent Variation. Reaction conditions. **5a** (1 mmol), base (4 mmol), solvent (4 mL), 25 °C. [b] DBN = 1,5-diazabicyclo(4.3.0)non-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG = 1,1,3,3-tetramethyl-guanidine; BTMG = 2-*tert*-butyl-1,1,3,3-tetramethylguanidine. In parentheses, pk_a value in acetonitrile of the conjugate acid. [c] Isolated yields. [d] Enantiomeric ratio (*R*:*S*) determined by chiral HPLC.

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The ring-closing reaction of methyl ester **5a** was conducted at 25 °C by using molar amounts of DBU in association with catalytic or molar quantities of an additional base, looking forward additive-DBU-substrate interactions capable of inducing the formation of a chiral adduct, which could evolve enantioselectively toward the desired benzosultam. Under the applied reaction conditions, the stereoselectivity of the reaction was not influenced by the presence of any added base, with the substantial exception of BTMG.

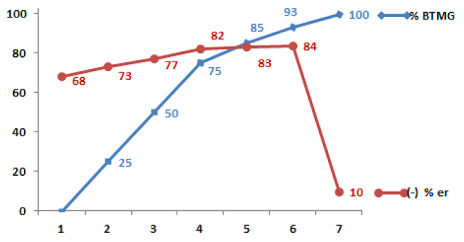


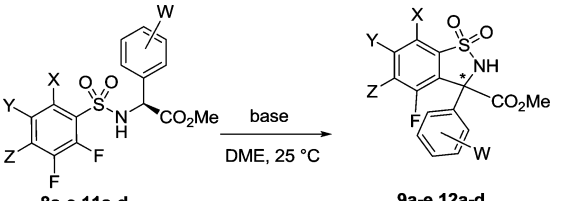
Figure 1. Synthesis of sultam **7a** under homogeneous conditions using the basic system DBU/BTMG (2 mol equiv): influence of the bases ratio on the *er*. Isolated yields are in the range 97 ± 2%.

In fact, the runs carried out by varying the ratio of the basic system DBU/BTMG (Figure 1) evidenced a strong synergistic effect between the two bases on the enantioselectivity, that is, the *er* value increased by increasing the amount of BTMG, up to a maximum (*er* 84:16) with a 7:93 DBU/BTMG molar ratio; as reported, by using only BTMG as a base (Table 1, entry 8), the enantioselectivity is drastically reversed in favor of **(+)-7a** (*er* 10:90, right side of Figure 1).

The influence of the α-proton acidity on the ring-closing stereoselectivity was analyzed by applying both the optimized protocols (methods **R** and **I** in Table 2, note *a*) to the (*S*)-α-aryl (pentafluorobenzene)sulfonamido esters **8a**−**e** series (Table 2). When compounds **8a,b** (entries 3−6), bearing an electronwithdrawing group, were used extensive racemization occurred under both the basic conditions. On the contrary, the presence of an electrondonating group in compounds **8c**−**e** produced good *er*, the stronger the EDG the higher the *er* value (entries 7−12). Both methods were then applied to (*S*)-α-phenyl sulfonamides **11a**−**d** (Table 2), bearing different halogenated sulfonamido-aromatic rings. In all cases, the yields of sultams **12a**−**d** are good; *er* values of the inversion sultams (entries 14, 16, 18, 20) are interesting, whereas the retention products (entries 13, 15, 17, 19) have *er* values somewhat inferior than that found for ***R*-7a**.

As regards the mechanism (Scheme 2) we suppose that the N−H proton, much more acidic than ester α-C−H, is first deprotonated by the sterically demanding base, BTMG, forming the tight ion-pair **A**. The less sterically demanding DBU (path a) favors the enol formation through an intermolecular H-bond from the less crowded side forming the intermediate **B** that, in turn, cyclizes to the retention sultam. In the presence of BTMG

Table 2. Enantiodivergent Cyclization of Substituted α-Aryl (Polyhalobenzene)sulfonamides[a]



8,9, X = Y =Z = F
a, W = 4-NO_2; **b**, W = 2-Cl; **c**, W = 4Ph
d, W = 4-BnO; **e**, W = 4-MeO
11,12, W = H
a, X = Br, Y = F, Z = F; **b**, X = F, Y = F, Z = Br
c, X = F, Y = H, Z = F; **d**, X = Br, Y = H, Z = F

entry		meth[b]	*t* (h)	product[c]	yield (%)	*er* (%)[d]
1	**5a**	**R**	3	*R*-**7a**	97	83:17
2		**I**	96	*S*-**7a**	96	10:90
3	**8a**	**R**	6	**9a**	45	50:50
4		**I**	16	**9a**	47	50:50
5	**8b**	**R**	16	*R*-**9b**	40[e]	53:47
6		**I**	48	*S*-**9b**	33[e]	46:54
7	**8c**	**R**	16	*R*-**9c**	94	78:22
8		**I**	48	*S*-**9c**	88	18:82
9	**8d**	**R**	96	*R*-**9d**	81	97:3
10		**I**	96	*S*-**9d**	35[e]	2:98
11	**8e**	**R**	96	*R*-**9e**	99	89:11
12		**I**	168	*S*-**9e**	70[e]	3:97
13	**11a**	**R**	72	*R*-**12a**	96	76:24
14		**I**	96	*S*-**12a**	93	9:91
15	**11b**	**R**	72	*R*-**12b**	87	74:26
16		**I**	144	*S*-**12b**	92	12:88
17	**11c**	**R**	20	*R*-**12c**	93	74:26
18		**I**	72	*S*-**12c**	94	10:90
19	**11d**	**R**	12	*R*-**12d**	93	74:26
20		**I**	24	*S*-**12d**	89	15:85

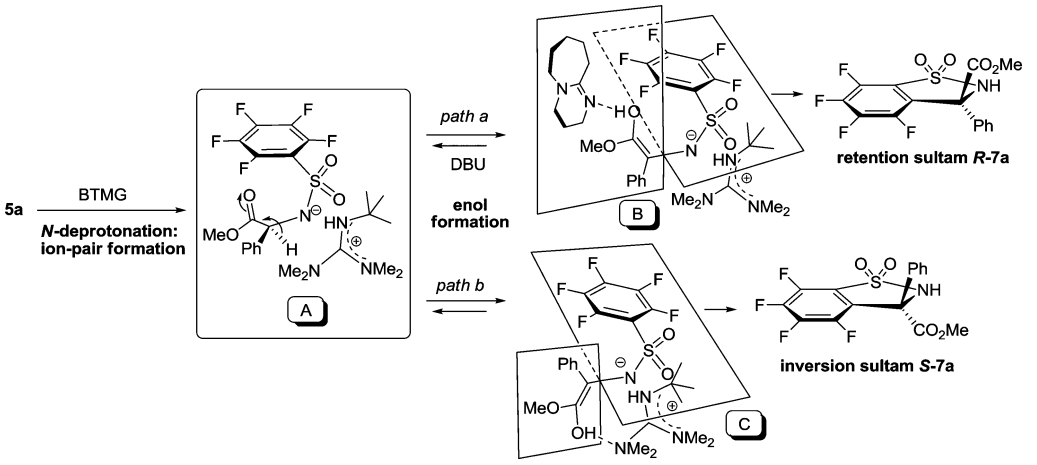
[a] Variation of α-Aryl and Arylsulfonamido Moieties. [b] Reaction conditions. Method **R**: sulfonamide **5a**,**8,11** (1 mmol), BTMG/DBU (2 mol) in 85:15 molar percentage, DME (4 mL), 25 °C. Method **I**: sulfonamide **5a**,**8,12** (1 mmol), BTMG (4 mmol), DME (4 mL). [c] The stereochemical descriptor of the main enantiomer is indicated. [d] The *er* was determined by chiral HPLC. [e] Partial conversion of substrate **8**.

alone (path b), the enol formed from the ion-pair **A**, through an intramolecular H-bond, is forced to the more crowded conformation **C**, which evolves to the inversion sultam.

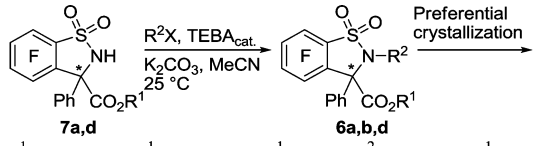
As reported in the literature, MOC conditions are ineffective on symmetrically *N*,*N*-disubstituted substrates, therefore all MOC reactions were carried out using compounds having two different substituents on the nitrogen. To explain the reactivity of our starting NH-sulfonamido esters, we supposed that the very stable tight ion-pair formed by BTMG and the substrate (intermediate **A** in Scheme 2) mimics an unsymmetrically *N*,*N*-disubstituted sulfonamide hence, stabilizing a specific conformation of the formed enol.

To determine the absolute stereochemistry of the main enantiomer, sultams ***R*-7a** and ***S*-7d** (Scheme 3) were *N*-alkylated under SL-PTC conditions to the corresponding compounds **6a**,**b**,**d** that, in turn, were subjected to

Scheme 2. Hypothesized Model that Fits with the Results: Method **R** (path a) and Method **I** (path b)



Scheme 3. PTC Synthesis and Preferential Crystallization of Sultams **6**



7a, R^1 = Me; **7b**, R^1 = *t*Bu; **6a**, R^1 = Me, R^2 = Pr; **6b**, R^1 = Me, R^2 = Allyl; **6d**, R^1 = *t*Bu, R^2 = Me.

preferential crystallization.[11] The Rx analysis[12] of the optically pure enantiomers ***R*-6a**,**b** and ***S*-6d** confirms that method **R** produces mainly the corresponding sultams with retention of the starting configuration, whereas method **I** gives the inversion sultams.[13]

In conclusion, the MOC stereodivergent synthesis here described uses the chirality of a starting sulfonamide single enantiomer to synthesize the target polyfluorobenzo[*d*]-sultams in both absolute configurations by choosing the organic base system, which is the determining factor to direct the cyclization toward either enantiomer. A further feature of this protocol is the use, as starting compound, of an α-amino acid derivative bearing a monosubstituted NH-sulfonamide function, so opening the possibility to study the synthesis under MOC conditions of several amino acid derivatives, without the need of introducing two different *N*-activating groups.

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Supporting Information Available. Full experimental procedures, analyses, and characterization data for all new compounds. X-ray crystallographic data (CIF) for compounds ***R*-6a**,**b** and ***S*-6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) CCDC 920402 (***R*-6a**), CCDC 920404 (***R*-6b**), and CCDC 920403 (***S*-6d**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) The absolute configuration of **9a**–**e** and **12a**–**e** was tentatively assigned by analogy to that of **7a** and **7d**.

The authors declare no competing financial interest.