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DOCTORATE SCHOOL OF CHEMICAL SCIENCES AND TECHNOLOGIES
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Doctorate in Industrial Chemistry
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Memory of Chirality: Synthesis of enantiopure sultams derived from α-amino acids

VOICHITA MIHALI
MATR. R08784

Advisor: Prof. Domenico Albanese

Co-advisor: Dr. Michele Penso

Coordinator: Prof. Dominique Roberto

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Dedication

To my parents

"Enigmatici si cuminţi
Terminîndu-şi rostul lor
Lîngă noi se sting şi mor
Dragii noştri, dragi părinţi.
Cheamă-i Doamne, înapoi
Că şi-aşa au dus-o prost
Şi fă-i tineri cum au fost
Fă-i mai tineri decît noi.

Pentru cei ce ne-au făcut
Dă un ordin, dă ceva
Sa-i mai poţi întîrzia
Să o ia de la-nceput.
Au plătit cu viaţa lor
Ale fiilor erori
Doamne, fă-i nemuritori
Pe părinţii care mor.

Ia priviţi-i cum se duc
Ia priviţi-i cum se sting
Lumînări în cuib de cuc
Parcă tac şi parcă ning.
Plini de boli şi suferinţi
Ne întoarcem în pămînt
Cît mai sîntem, cît mai sînt,
Mîngîiaţi-i pe părinţi.

E pămantul tot mai greu,
Despărţirea-i tot mai grea,
Sărut-mana, tatăl meu,
Sărut-mana, mama mea."

A. Păunescu, *Ruga pentru părinţi*

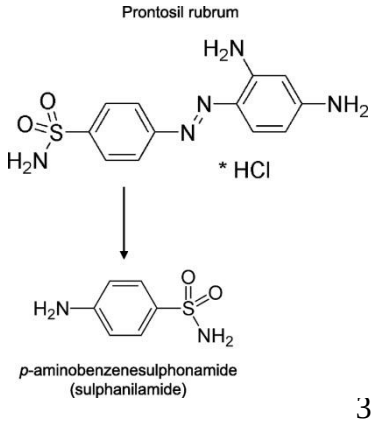
1 Introduction

Sulfonamides are very important compounds due to their wide range of biological activities, being also the first synthetic compounds to have had utility in human therapy as antimicrobial drugs, thus opening the route for the antibiotic revolution in medicine.

Prontosil was the first sulfonamide drug synthesized and tested as antimicrobial by Gerhard Domagk (in the picture), who then received the 1939 Nobel Prize in Medicine.

The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented. Experiments with Prontosil began in 1932 in the laboratories of Bayer AG and showed that it was the first medicine ever discovered that could effectively treat a range of bacterial infections. Prontosil had a strong protective action against streptococcal infections, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other *cocci*. Few people today would deny that 1936 was the turning point in the history of puerperal infection, one of the most common cause of death during childbirth, and that the arrival of Prontosil brought about the change.

In 1935 Tréfouël and his colleagues at the Pasteur Institute observed that Prontosil had no effect at all in the test tube, exerting its antibacterial action only in live animals; they soon surprised the scientific world by the suggestion that the red dye was probably a prodrug and that was metabolized into two pieces inside the body,



to a much simpler compound, *p*-aminobenzene sulfonamide. The discovery helped to establish the concept of "bioactivation".

The active sulfanilamide had been known for many years being synthesized in 1906 and was widely used in the dye-making industry. These findings naturally led to a change-over in human therapy from red Prontosil to the simpler and cheaper compound which we soon came to know by the name Sulfanilide, the first of the ‘‘sulfa drugs’’.

Furthermore, among the numerous other applications, the ability to serve as amide surrogates have made sulfonamide an ideal functional group for the development of novel peptidomimetics.[1,2]

Recently, enormous interest has also been directed to bioactive sultams,[3,4] cyclic analogues of the open-chain sulfonamides, which have shown promising activities as antiviral, anticancer, antimicrobial, antimalarial, antileukemic, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulatory properties, with potential for treating disorders of the brain, novel serine inhibitors, zinc enzyme carbonic anhydrase inhibitors, etc.[5,6]

In particular, a number of fused sultams have recently been reported to exhibit broad inhibitory properties against a variety of enzymes including COX-2,4 HIV integrase,[7] lipoxygenase,[8] Calpain I,[9] and MMP-2.[10]

Fused sultams have found many important applications in organic synthesis including use as protecting groups, chiral auxiliaries, and directed metalation groups (DMGs). For example, Oppolzer’s sultam **1**[11] (Figure 1) are relevant in asymmetric synthesis as chiral auxiliaries in many stereoselective transformations.

1 Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem. Int. Ed.* **1994**, *33*, 2067.
2 Carson, K. G.; Schwender, C. F.; Gallant, D. L.; Briskin, M. *J. Bioorg. Med. Chem. Lett.* **1997**, *7*, 711.
3 Zhuang, L.; Wai, J. S.; Embrey, M.; Fisher, T. E.; Michelson, S. R.; Young, S. S. *J. Med. Chem.* **2003**, *46*, 453.
4 Inagaki, M.; Tsuri, T.; Kakudo, S.; Koizumi, K.; Suzuki, R.; Kato, M.; Kawai, S.; Matsumoto, S. *J. Med. Chem.* **2000**, *43*, 2040.
5 Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925.
6 Supuran, C. T. *Nature Rev. Drug Discovery* **2008**, 7, 168.
7 Brzozowski, F.; Saczewski, F.; Neamati, N. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 5298.
8 Misu, Y.; Togo, H. *Org. Biomol. Chem*. **2003**, 1, 1342.
9 Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R. *J. Med. Chem*. **2001**, *44*, 3488.
10 Cherney, R. J.; Mo, R.; Meyer, D. T.; Hardman, K. D.; Liu, R. Q.; Covington, M. B.; Qian, M.; Wasserman, Z. R.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P. *J. Med. Chem*. **2004**, *47*, 2981.
11 Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Kiran, M. U. *J. Org. Chem*. **2006**, *71*, 337.

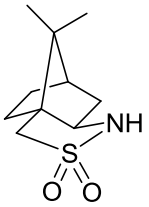
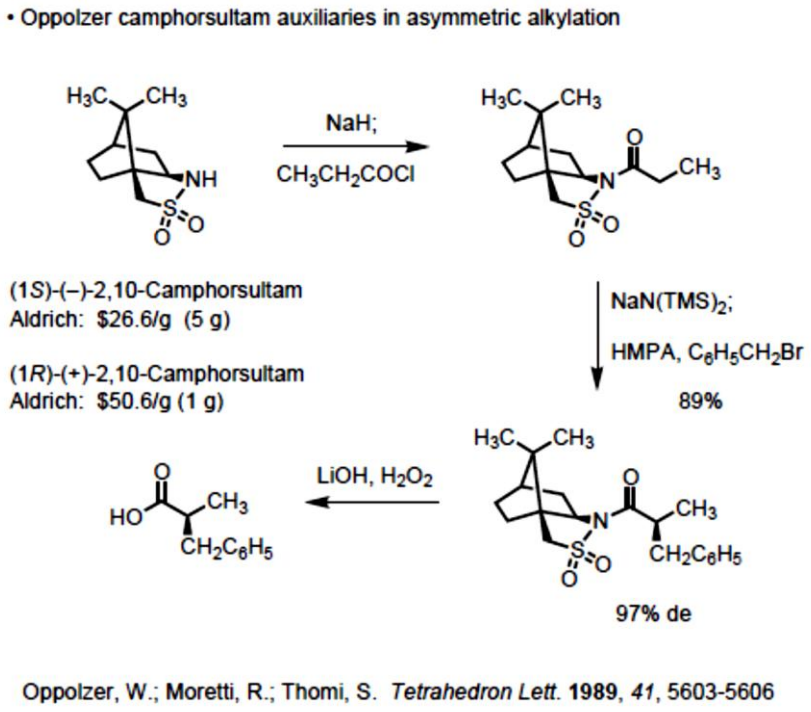


Figure 1. Oppolzer's camphorsultam used as chiral auxiliary in asymmetric synthesis.

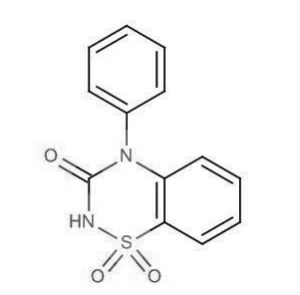
Many protocols have been developed for the synthesis of sultams, e.g., Pictet-Spengler reactions,[12] Friedel-Crafts reactions,[13,14] sulfonamide dianion alkylation,[15] cyclization of aminosulfonyl chlorides,[16] [3+2]-cycloadditions,[17] Diels_Alder reactions,[18] and a number of transition-metal catalyzed cyclizations.[19,20] Some review articles highlighting their biological activities, synthesis, and important uses have also appeared.[21,22]

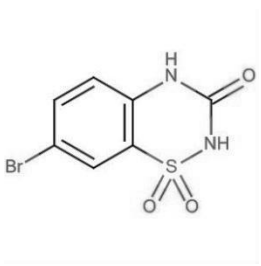


12 Silvestri, R.; Marfe, G.; Artico, M.; La Regina, G.; Ciriolo, M. R.; Russo, M. A.; Cirilli, R.. *J. Med. Chem.* **2006**, *49*, 5840.
13 Bravo, R. D.; Canepa, A. S. *Synth. Commun.* **2002**, *32*, 3675.
14 Katritzky, A. R.; Wu, J.; Rachwal, S.; Rachwal, B.; Macomber, D. W.; Smith, T. P. *Org. Prep. Proced. Int.* **1992**, *24*, 463.
15 Lee, J.; Zhong, Y. L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, *5*, 4175.
16 Enders, D.; Moll, A.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, *5*, 1271.
17 Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Piperno, A.; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425.
18 Plietker, B.; Seng, D.; Frohlich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873.
19 Zajac, M.; Peters, R. *Chem.—Eur. J.* **2009**, *15*, 8204.
20 Vasudevan, A.; Tseng, P.-S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591.
21 (a) Majumdar, K. C.; Mondal, S. *Chem. Rev.* **2011**, *111*, 7749-7773. (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239.
22 Liu, Z.; Takeuchi, Y. *Heterocycles* **2009**, *78*, 1387.

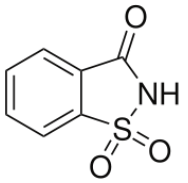
2 Benzosultams

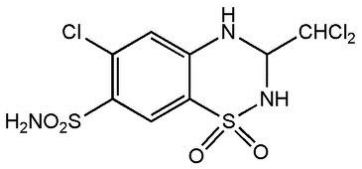
The powerful biological activities found for several categories of benzosultams make these compunds important targets for drug discovery. For example, benzothiadiazin-3-one-1,1-dioxides and their derivatives have shown promising activities as hypoglycemic,[23] anti-HIV,[24] etc.





1,2-Benzisothiazoline 1,1-dioxide (saccharin) is the most famous member of this family, but other benzosultam have a high impact on contemporary life because are widely used drugs, such as trichloromethiazide, a benzothiazine diuretic.[25]

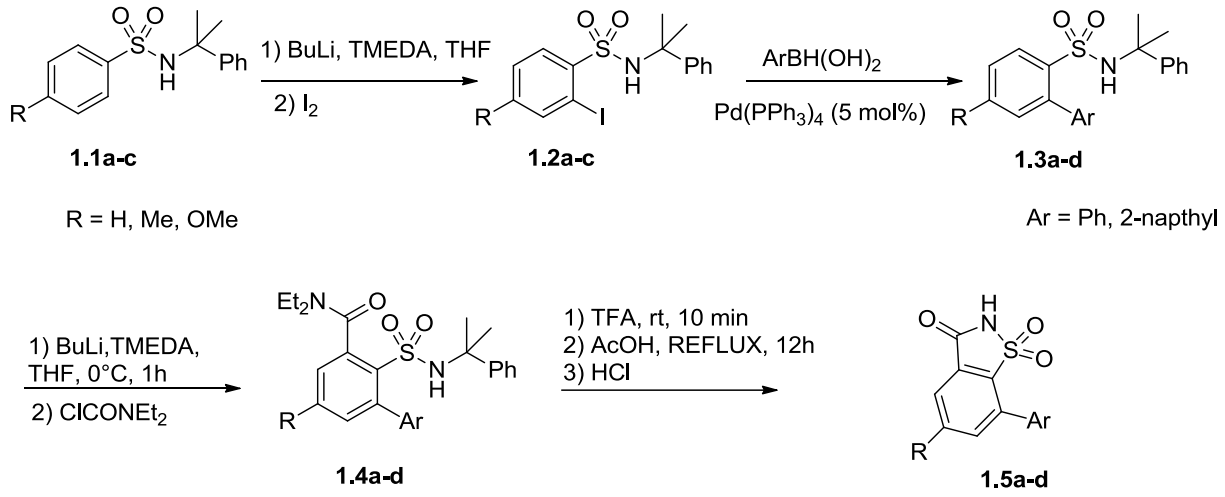




Other benzosultams significantly inhibit carbonic anhydrases (CAs). The newly found binding modes of these diuretics may be exploited for designing better CA II inhibitors as well as compounds with selectivity/affinity for various isoforms with medicinal applications. Because of the important biological activities of benzisothiazoline 1,1-dioxides, much efforts have been devoted to develop novel methods for the sythesis of analogues of the saccharin derivatives.[26] Recently, Snieckus and co-workers developed[27] the synthesis of 7- and 4,7-substituted saccharins

23 Wales, J. K.; Krees, S. V.; Grant, A. M.; Vikroa, J. K.; Wolff, F.W. *J. Pharm. Exp. Ther*. **1968**, *164*, 421.
24 Arranz, E. M.; Diaz, J. A.; Ingate, S. T.; Balzarini, J.; Clercq, E. D.; Vega, S. *Bioorg. Med. Chem*. **1999**, *7*, 2811.
25 Temperini, C.; Cecchi, A.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem.* **2009**, *17*, 1214.
26 Liu, Z.; Takeuchi, Y. *Heterocycles* **2009**, *78*, 1387.
27 Blanchet, J.; Macklin, T.; Ang, P.; Metallinos, C.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 3199.

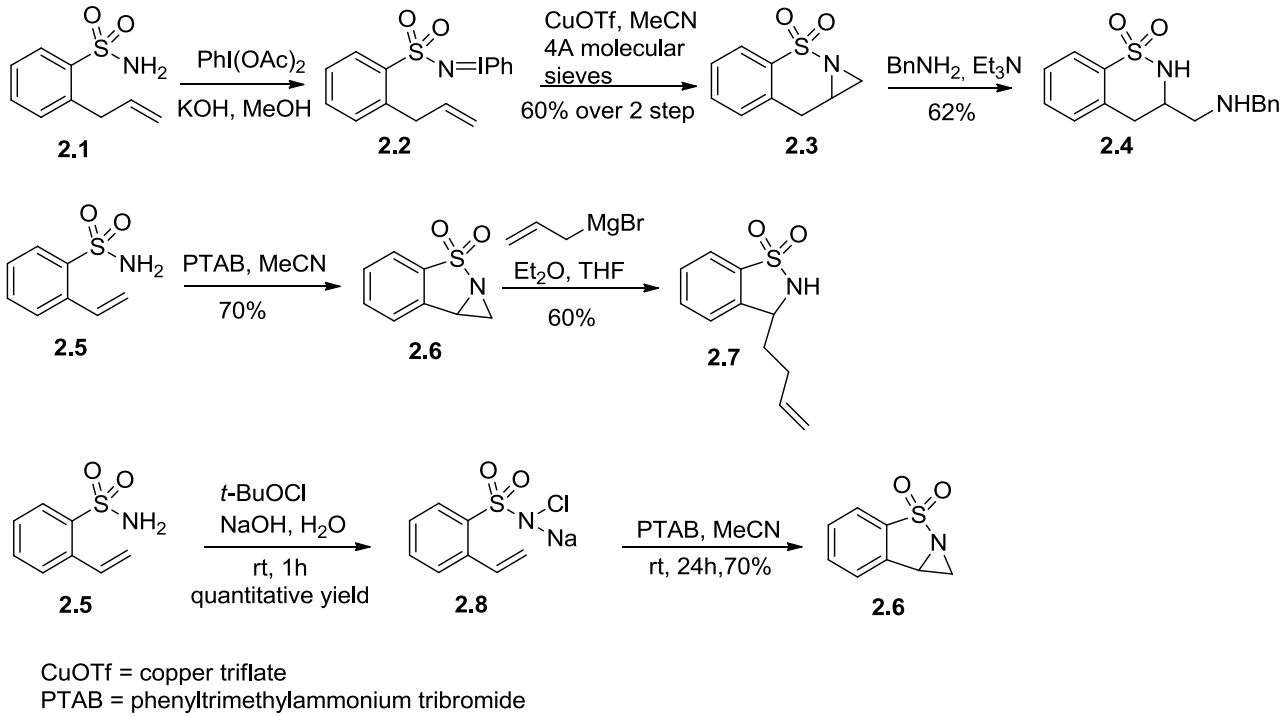
from *N*-cumyl arylsulfonamides by combining directed *ortho*-metalation (DoM) and Suzuki cross-coupling reactions (Scheme 1). Treatment of sulfonamide **1.1** with BuLi in the presence of TMEDA, followed by reaction with iodine, gave the 2-iodo derivatives **1.2** in good yields. Suzuki cross-coupling of the 2-iodo arylsulfonamides **1.2** led to the formation of biaryl *N*-cumylsulfonamides **1.3**. BuLi/TMEDA *ortho*-metalation of **1.3**, followed by quenching with *N*,*N*-diethylcarbamoyl chloride gave the amido-sulfonamides **1.4**. The *N*-cumyl function was removed from these latter compounds with TFA and the resulting sulfonamide was cyclized *in situ* to the 7-arylated saccharins **1.5**.



Scheme 1. Synthesis of 7-arylated saccharins

In 2000, Dauban and Dodd (Scheme 2) described a new methodology for the preparation of benzosultams based on copper- or bromine-catalyzed aziridination.[28] Olefinic primary sulfonamide **2.1** was treated with iodobenzene diacetate and potassium hydroxide in methanol to give the intermediate iminoiodinane **2.2**, which was immediately treated with a catalytic amount of copper triflate to give the aziridine **2.3**. Moreover, application of the bromine-catalyzed aziridination procedure[29] to **2.5** led to the formation of aziridine **2.6**. Aziridines **2.3** and **2.6** were then opened by various nucleophiles to give the corresponding sultams (**2.4** and **2.7**).

28 Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327.
29 Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. J. *Am. Chem. Soc.* **1998**, *120*, 6844.



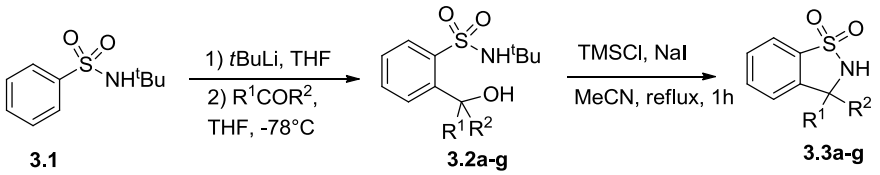
Scheme 2. Synthesis of benzosultams via aziridine formation

In a subsequent report,[30] sulfonamide **2.5** was treated with *tert*-butyl hypochlorite and aqueous sodium hydroxide to give the corresponding *N*-chloramine salt **2.8**, which was reacted with a catalytic amount of phenyltrimethylammonium tribromide (PTAB) to afford the aziridine **2.6**.

Che[31] reported the alternative dirhodium-complexes-catalyzed asymmetric intramolecular aziridation of unsaturated sulfonamides.

In another paper,[32] is described the synthesis of 3,3-disubstituted benzosultams **3.3** by *ortho*-lithiation of *N*-*tert*-butylbenzenesulfonamide **3.1** and subsequent reaction with ketones followed by TMSCl-NaI mediated cyclization (Scheme 3).

30 Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2001**, *42*, 1037.
31 Liang, J. L.; Yuan, S. X.; Chan, P. W. H.; Che, C. M. *Tetrahedron Lett.* **2003**, *44*, 5917.
32 Liu, Z.; Shibata, N.; Takeuchi, Y. J. *Chem. Soc., Perkin Trans. 1* **2002**, *3*, 302.

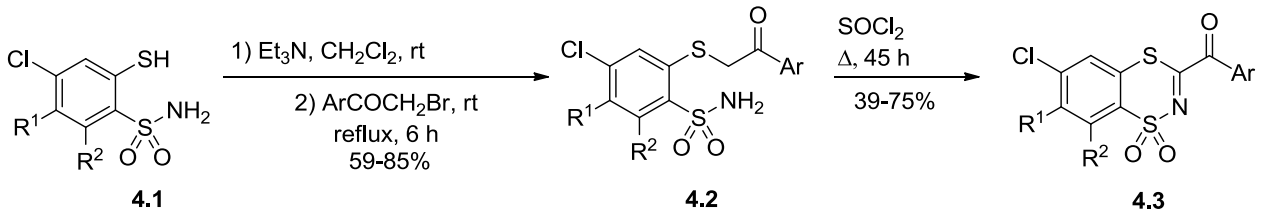


3.1 **3.2a-g** **3.3a-g**

Entry	R^1	R^2	Yield (%) **3.2a-g**	Yield (%) **3.3a-g**
a	Me	Me	85	95
b	Me	Ph	86	99
c	Me	4-MeC_6H_4	84	92
d	Me	1-Naphthyl	55	98
e		-$(CH_2)_4$-	76	96
f		-$(CH_2)_5$-	70	92
g			83	96

Scheme 3. synthesis of benzosultams mediated by TMSCl–NaI–MeCN reagent

Saczewski[33] demonstrated that 1,4,2-benzodithiazines constitute a novel class of nontoxic HIV-1 integrase (IN) inhibitors. Benzodithiazines **4.3** were synthesized by cyclization of derivatives **4.2**, which were obtained from the reactions of 4-chloro-2-mercaptobenzenesulfonamides **4.1** with bromomethyl ketones (Scheme 4).

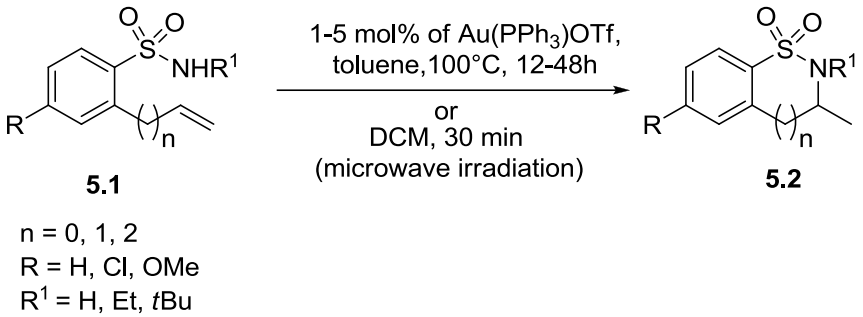


4.1 **4.2** **4.3**

Scheme 4. Synthesis of benzodithiazines

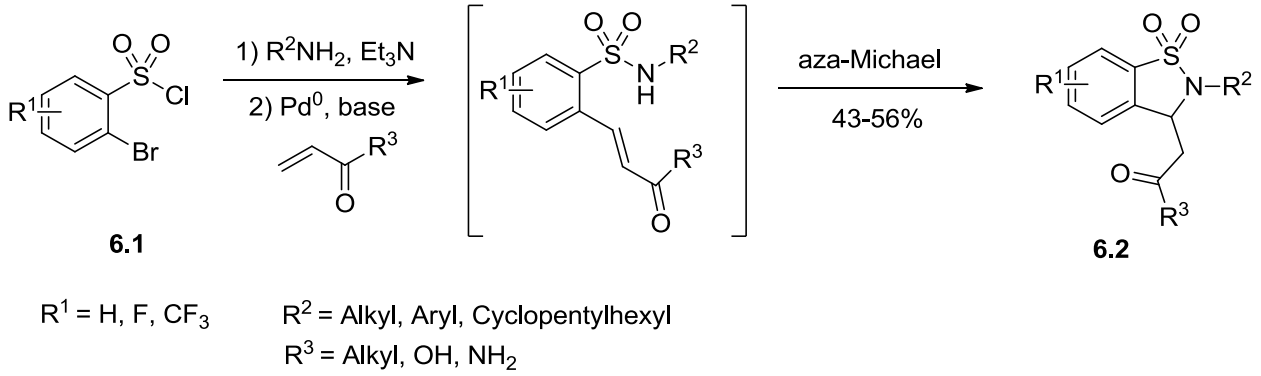
Au(PPh_3)OTf catalyzed cycloisomerization of terminal alkenes **5.1**, under microwave irradiation, gives benzosultams **5.2** in nearly quantitative yields (Scheme 5).[34]

33 Brzozowski, Z.; Saczewski, F.; Sanchez, T.; Kuo, C. L.; Gdaniec, M.; Neamati, N. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 3663.
34 Liu, X. Y.; Li, C. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 2707.



Scheme 5. Synthesis of benzosultams by phosphine gold(I)-catalyzed intramolecular hydroamination

Hanson and co-workers reported[35] a new route to benzosultams **6.2** (Scheme 6) by a one-pot Heck–azaMichael domino process, for a sequential three-component reaction of *α*-bromobenzenesulfonyl chlorides **6.1**, amines, and Michael acceptors.

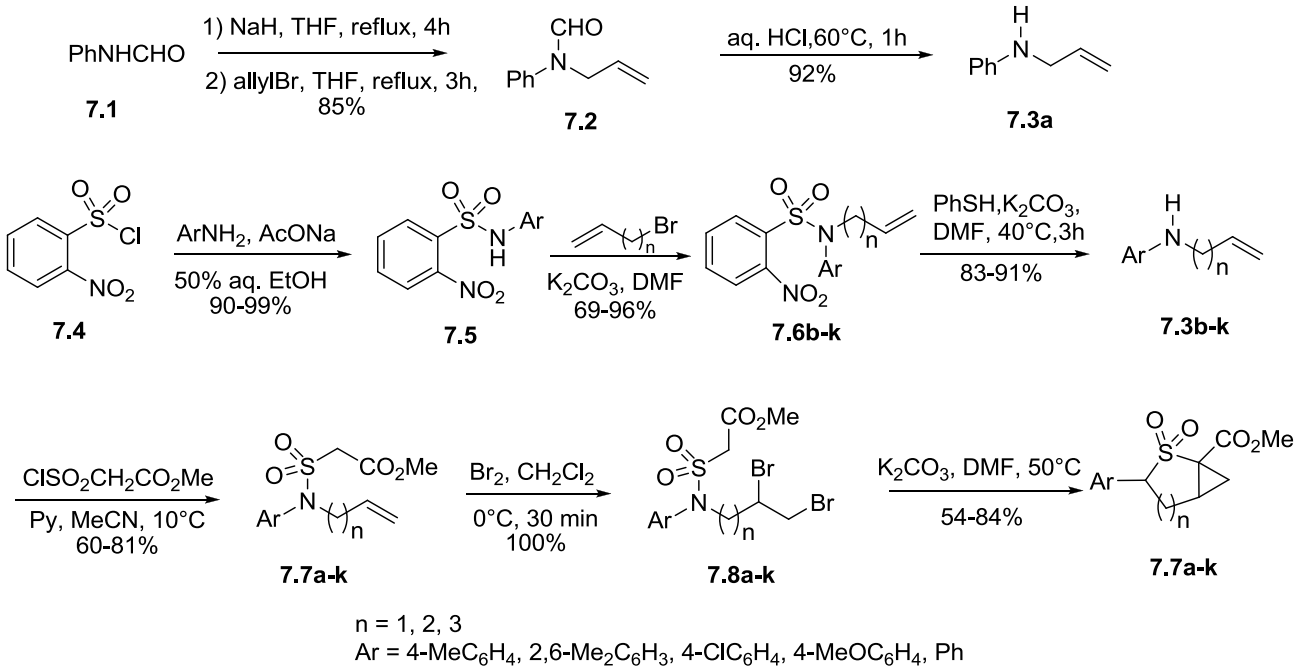


Scheme 6. Synthesis of benzosultams by domino Heck–azaMichael reactions

Recent studies have demonstrated the facile formation of bicyclic sultams by an intramolecular cyclodialkylation reaction (Scheme7).[36] The *N*-alkenylanilines **7.3a-k** reacted smoothly with methyl (chlorosulfonyl)acetate to give the corresponding sulfonamides **7.7** in good yields. Addition of bromine to the C=C double bonds in sulfonamides **7.7** occurred quantitatively to give the corresponding dibromoalkyl derivatives **7.8**. Upon treatment with potassium carbonate in DMF, the (dibromoalkyl)- sulfonamides **7.8** under went intramolecular cyclodialkylation at their C,H-acidic positions to yield the bicyclic sultams **7.9** (n = 1 and 2). Under the established

35 Rolfe, A.; Young, K.; Hanson, P. R. Eur. *J. Org. Chem*. **2008**, *31*, 5254.
36 Rassadin, V. A.; Tomashevskiy, A. A.; Sokolov, V. V.; Ringe, A.; Magull, J.; de Meijere, A. *Eur. J. Org. Chem*. **2009**, *16*, 2635.

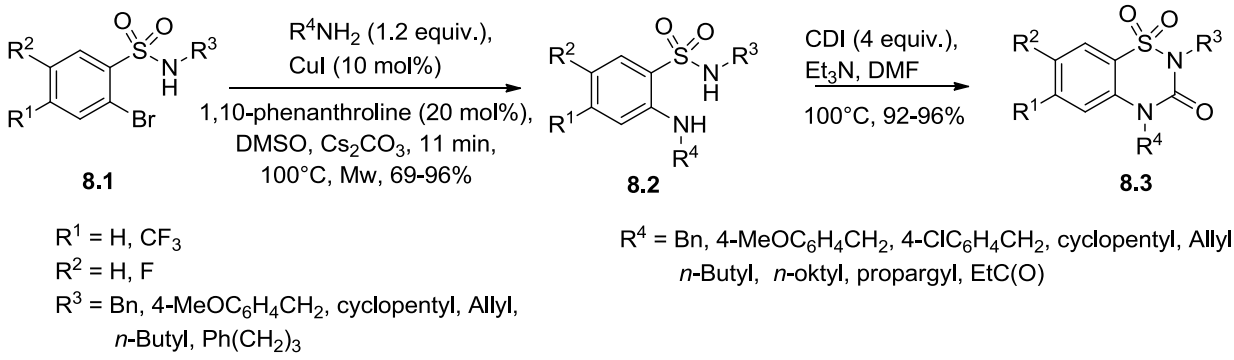
conditions, the dibromoalkyl derivative **7.8** with n = 3 gave an inseparable complex mixture.



Scheme 7. Synthesis of benzosultams by intramolecular cyclodialkylation

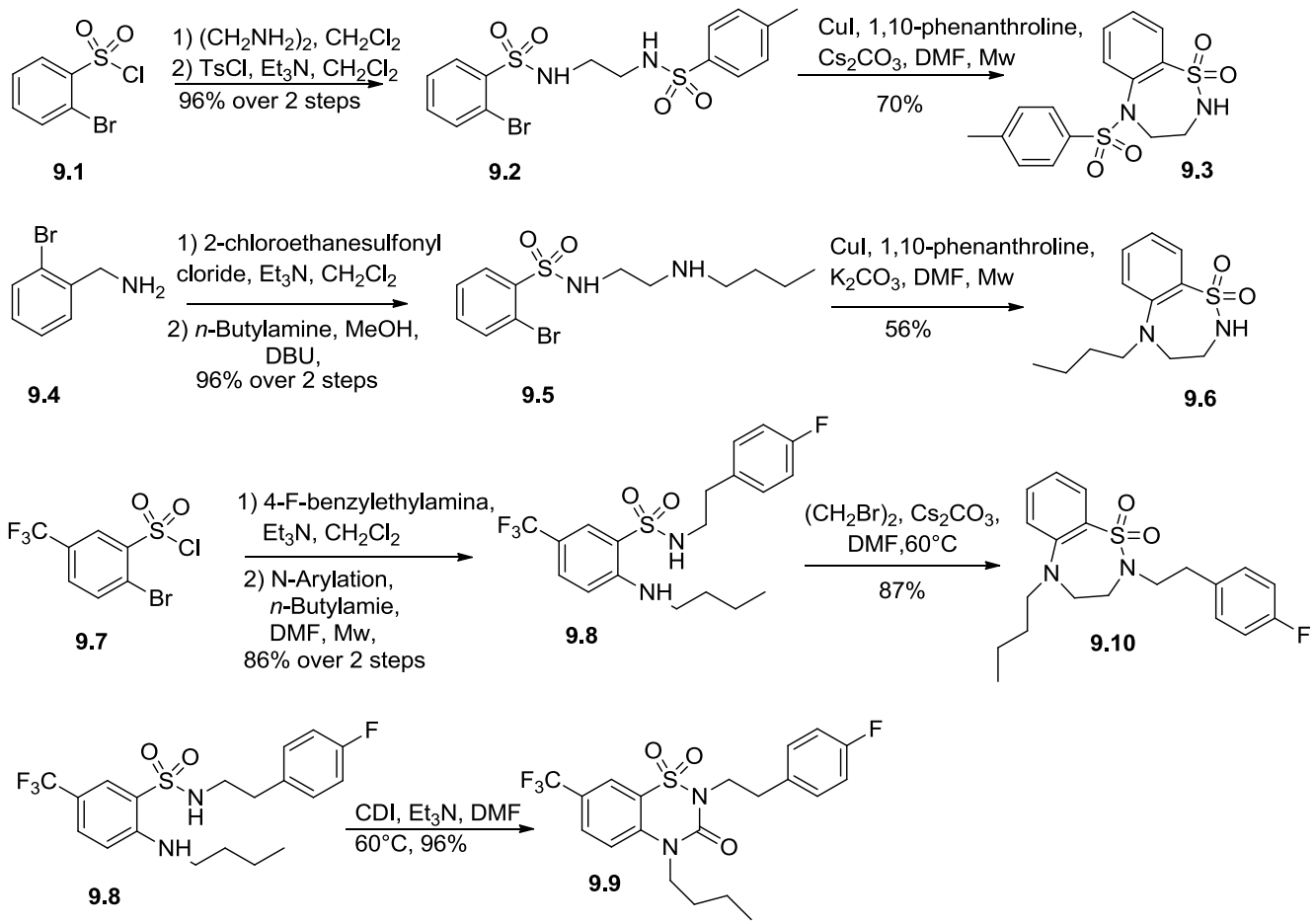
A two-step, one-pot protocol was developed by Hanson for the synthesis of benzosultams (Scheme 8).[37] The first step is a copper-catalyzed *N*-arylation of (2-bromobenzene)sulfonamides **8.1** with different amines to generate the corresponding (2-aminobenzene)sulfonamides **8.2**, which then undergo cyclization to the desired sultams **8.3** upon treatment with carbonyldiimidazole (CDI).

37 Rolfe, A.; Hanson, P. R. *Tetrahedron Lett*. **2009**, *50*, 6935.



Scheme 8. Sequential one-pot synthesis of benzothiadiazin-3-one-1,1-dioxides

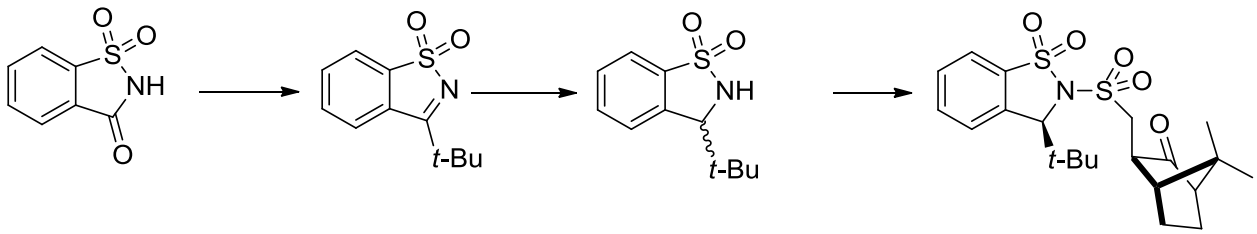
Hanson[38] reported a reagent-based, 'diversity-oriented synthetic' (DOS) strategy termed "Click, Click, Cyclize" en route to structurally diverse sultams **9.3**, **9.6**, **9.9**, and **9.10** from the common sulfonamides **9.2**, **9.5**, and **9.8** (Scheme 9). The yield (96%) reported in the conversion of **9.1** to **9.2** over two steps is notable.



Scheme 9. Synthesis of benzosultams by "Click, Click, Cyclize" protocol

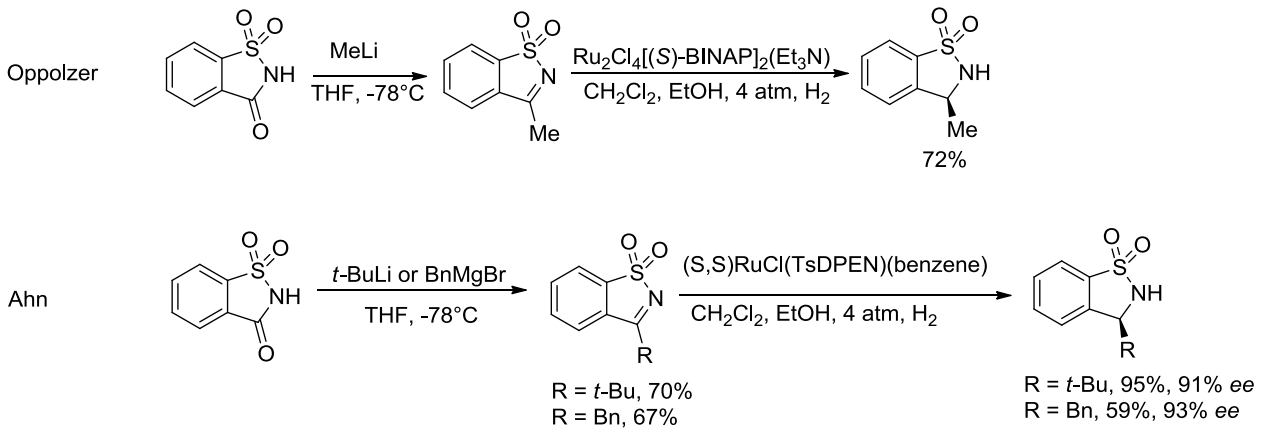
38 Rolfe, A.; Lushington, G. H.; Hanson, P. R. *Org. Biomol. Chem.* **2010**, *8*, 2198.

The 3-substituted γ-benzo[*d*]sultams have received much attention because of their excellent stereofacial discrimination when used as chiral auxiliaries: however, their usefulness has not been explored fully, probably owing to its tedious preparation involving, for example for the 3-*tert*-butyl substituted sultam, a necessary chemical resolution of the racemic mixture via *N*-(*S*)-camphorsulfonylated compound (Scheme 10).



Scheme 10

The 3-alkyl γ-benzo[*d*]sultams became more accessible in 90's, because of the development of a more efficient synthesis via the asymmetric hydrogenation of the sulfonylimine (a synthetic route just exploited by Oppolzer for R = Me, Scheme 11); anyway the requirement of an asymmetric reduction step made with an expansive and hazardous catalyst like Ru-BINAP, make the whole approach not much achievable especially for a large-scale synthesis.



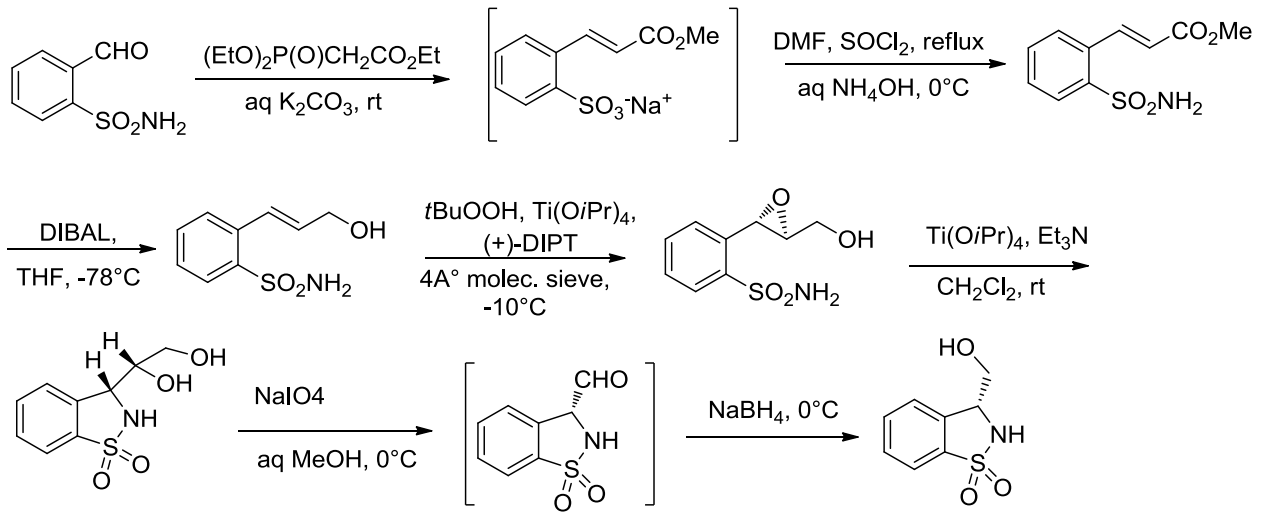
Scheme 11

The most important work appeared in 2000 and described for the first time the attempt of the synthesis of 3-carboxy γ-benzo[d]sultam;[39] although the direct nucleophilic addition approaches

39 Ahn, K. H.; Baek, H-H; Lee, S. J.; Cho, C-W. J. Org. Chem. **2000**, Vol. 65, No. 22, 7690-7696.

are useful for the synthesis of 3-alkyl- or 3-arylsubstituted derivatives, all the attempt to introduce directly a functional moiety such as cyano group were unsuccessful. To synthesize 3-carboxy analogues Ahn has studied both an asymmetric approach and a racemic synthesis followed by chemical resolution.

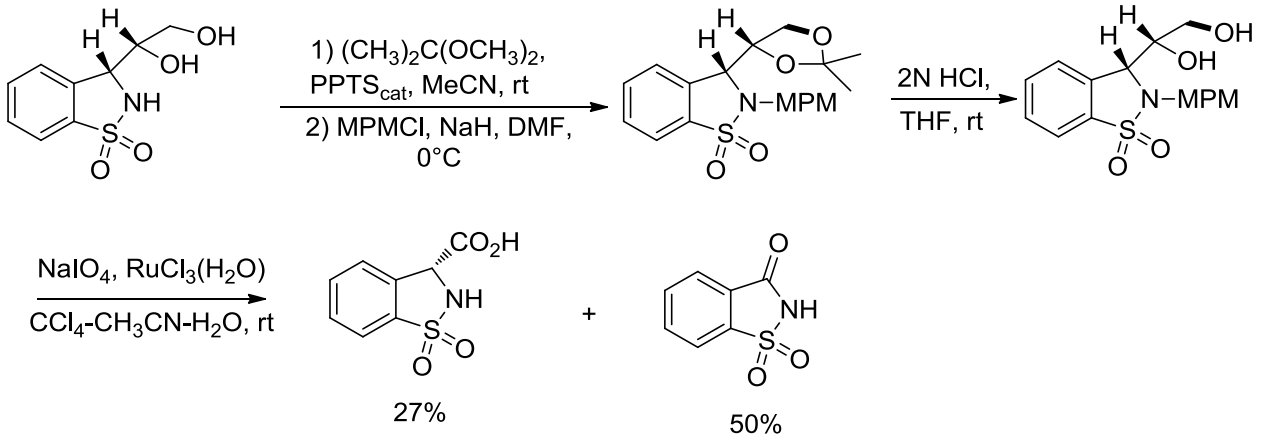
The asymmetric route uses (Scheme 12), as starting material, sodium *o*-formylbenzenesulfonate and pass through an aqueous Wittig-Horner-Emmons reaction followed by the conversion of the resulting cinnamate derivative into a sulfonamide. Reduction of the ester group leads to the *o*-(aminosulfonyl)-trans-cinnamyl alcohol employed in the key steps, the Sharpless asymmetric epoxidation and a subsequent intramolecular epoxide opening by the sulfonamido group. The final step, an oxidative conversion of the diol functionality into the carboxy group, was found to be difficult due to the instability of the reaction intermediate.



Scheme 12

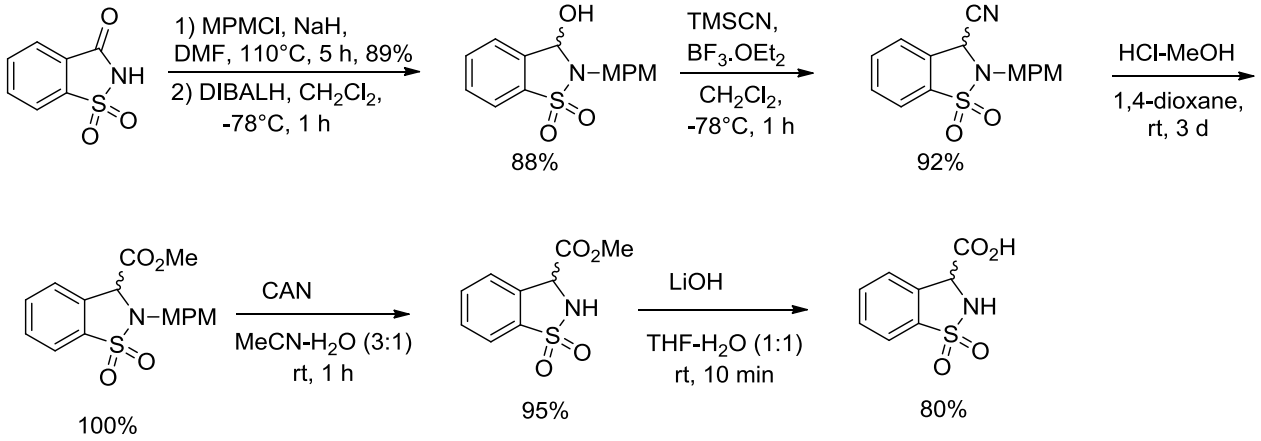
Treatment of diol with sodium periodate produced the corresponding aldehyde, and subsequent in situ oxidation with potassium permanganate produced decomposed products instead of the desired 3-carboxysultam. Treatment with sodium periodate followed by sodium borohydride leads to the corresponding alcohol, compound impossible to oxidize with PDC, $KMnO_4$, or Ru(IV) reagents.

Again when *N*-protected diol was subjected to the $RuCl_3$-$NaIO_4$ oxidation (Scheme 13), the major product was not the desired carboxylic acid but saccharine: these results indicate that 3-formylsultam and its *N*-protected derivatives have limited stability and may undergo deformylation and pushes the authors to turn their attention to a racemic route.



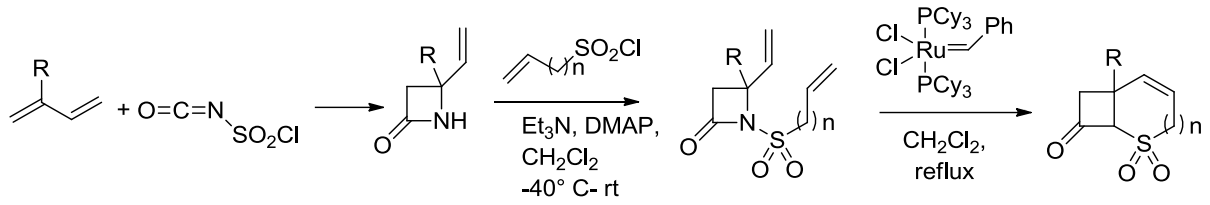
Scheme 13

This one starts from the *N*-protected saccharin, and proceed through conversion to the semi aminal by treatement with DIBALH and subsequent conversion of the hydroxy group into the cyano group with TMSCN in the presence of $BF_3.OEt_2$; after hydrolyzation to the corresponding methyl ester, deprotection of the MPM group and hydrolysis of the ester group, racemic 3-carboxysultam was obtained (Scheme 14) and the two single enantiomers were prepared by coupling with (*S*)-(-)-α-methylbenzylamine and chromatographic separation of the mixture of diastereomeric amide.



Scheme 14

In the past years were reported a range of nonconventionally fused β-lactams. Metz[40] developed β-lactams fused to a sultam from low cost, commercially available starting materials, always using ring closing metathesis as the key operation. Lactams were synthesized by cycloaddition of chlorosulfonyl isocyanate with 1,3-butadiene or isoprene and the resulting compounds were converted to N-sulfonyl derivatives with olefinic sulfonyl chlorides, readily derived from commercially available 2-chloroethanesulfonyl chloride or from the corresponding olefinic bromides; finally RCM strategy allowed the formation of unsaturated sultams with different ring size (from 5 to 8 members, Scheme 15).



Scheme 15

Even β-sultams themselves can be seen as a building blocks for the synthesis of new synthetic drugs, for example corresponding to β-lactam antibiotics In general, β-sultams can be synthesized by [2+2] cycloaddition of sulfene intermediates with imines,[41] of alkenes with *N*-sulfonylamines[42] or by intramolecular cyclization[43].

Kataoka et al., for example, described the diastereoselective [2+2] cycloaddition using mesyl chloride and chiral imines.[44] However, the adaptable substrates are not only restricted in the choice of substituents, the cycloaddition also yields unsatisfactory stereoselectivities. Another access to enantiomerically pure β-sultams is the synthesis starting from natural amino acids.

Initially Otto et al. utilized cysteine derivatives[45] as precursors, but recently also embarked on other amino acids followed by introduction of the sulfur moiety.[46]

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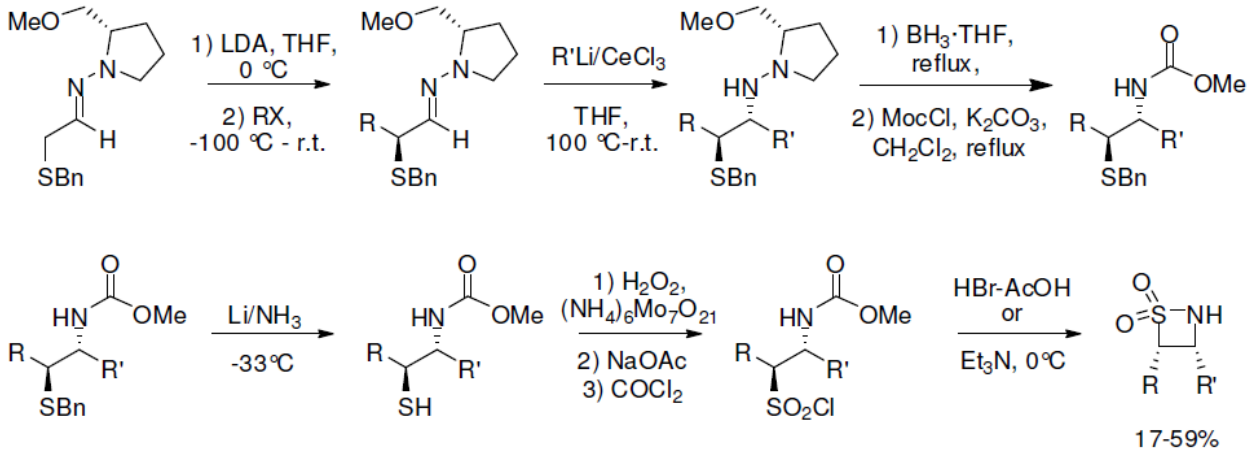
40 Freitag, D.; Schwab, P.; Metz, P. *Tetrahedron Lett*. **2004**, *45*, 3589-3592.
41 (a) Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett*. **1989**, *30*, 2869. (b) Grunder, E.; Leclerc, G. *Synthesis*, **1989**, 135. (c) Grunder-Klotz, E.; Ehrhardt, J.-D. *Tetrahedron Lett*. **1990**, *32*, 751. (d) Gordeev, M. F.; Gordon, E. M.; Patel, D. V. *J. Org. Chem.* **1997**, **62**, 8177.
42 (a) Atkins, G. M. Jr.; Burgess, E. M. *J. Am. Chem. Soc*. **1967**, *89*, 2502. (b) Burgess, E. M.; Williams, W. M. *J. Am. Chem. Soc*. **1972**, *94*, 4386. (c) Atkins, G. M. Jr.; Burgess, E. M. *J. Am. Chem. Soc*. **1972**, *94*, 6135.
43 (a) Schwenkkraus, P.; Otto, H.-H. *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 519. (b) Schwenkkraus, P.; Otto, H.-H. *Liebigs Ann. Chem.* **1994**, 251.
44 Iwama, T.; Kataoka, T.; Muraoka, O.; Tanabe, G. *J. Org. Chem*. **1998**, *63*, 8355.
45 Schwenkkraus, P.; Merkle, S.; Otto, H.-H. *Liebigs Ann./ Recl.* **1997**, 1261.
46 Meinzer, A.; Breckel, A.; Thaler, B. A.; Manicone, N.; Otto, H.-H. *Helv. Chim. Acta*, **2004**, *87*,90.

Among all these protocols, quite interesting is the asymmetric synthesis of *cis*-3,4-disubstituted β-sultams reported by Enders and Moll[47]. The protocol is based on the initial synthesis of the *anti*-1,2-benzylsulfanyl amines previously reported by the same author[48]: key steps are the diastereoselective α-alkylation of α-sulfanylated acetaldehyde-SAMP-hydrazone, reaction conducted with various electrophiles and subsequent nucleophilic 1,2-addition of organocerium compounds to the hydrazone C=N double bond. The resulting hydrazines were converted to the corresponding protected amines by reductive N–N bond cleavage-oxidation of 1,2-aminothiols with H_2O_2 and ammonium heptamolybdate. The obtained *anti*-1,2-benzylsulfanyl amines has been cleaved to the deprotected thiol and sequently oxidized; chlorination of the resulting β-amino sulfonic acids was achieved with phosgene and the β-aminosulfonyl chlorides obtained were cyclized to the title compounds under basic conditions without epimerisation and good overall yields (Scheme 16).



Scheme 16

47 Enders, D.; Moll, A. *Synthesis* **2005**, *No. 11*, 1807-1816.
48 Enders, D.; Moll, A.; Schaadt, A.; Runsink, J.; Raabe, G. *Eur. J. Org. Chem*. **2003**, 3923.

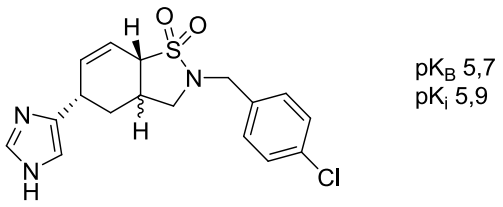
3 Chiral and Enantiomerically Pure Sultams

Chiral sultams have been widely exploited as chiral auxiliaries in asymmetric synthesis. For example, the application of the Oppolzer's sultam for carbon-carbon bond formation has been well documented.[49,50]

The chiral bicyclic sultams can be subdivided into the following categories: (*i*) simply chiral (which can be racemic) and (*ii*) enantiopure sultams.

3.1 Chiral Sultams

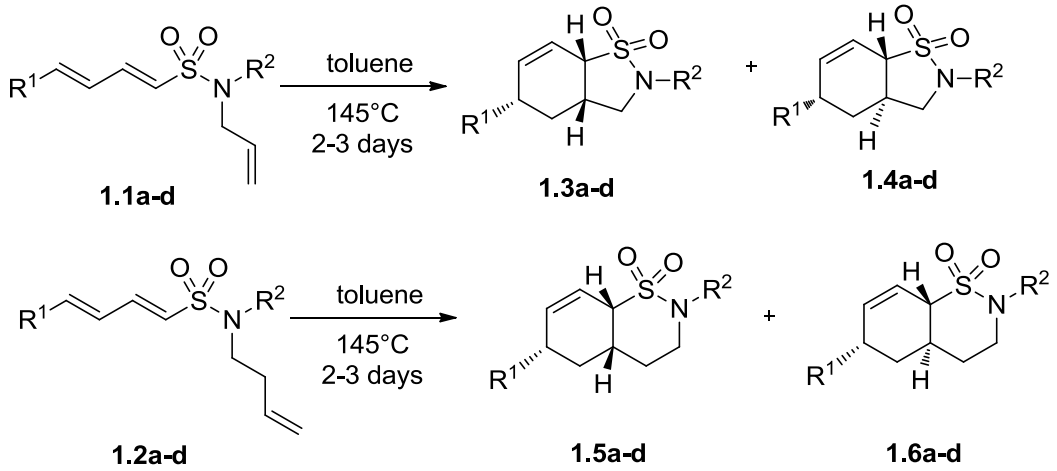
In 2000, Tozer[51] synthesized chiral bicyclic sultams by intramolecular Diels-Alder reactions of suitable trienes. The intramolecular Diels-Alder reactions of compounds **1.1** and **1.2** were carried out at 145 °C in toluene, in a sealed screw-cap vessel under argon. Under these conditions, racemic mixtures of the diastereomeric [4.3.0]-bicyclic products **1.3** and **1.4** and the [4.4.0]-bicyclic products **1.5** and **1.6** were obtained in good yields (Scheme 1). Notably, the sultams **1.3** and **1.4** are closely similar to the compound **1.7** (Figure 1), which is a histamine H3 antagonist.



1.7

Figure 1 Histamine H3 antagonist.

49 Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc*. **1988**, *110*, 1238.
50 Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.
51 Greig, I. R.; Tozer, M. J.; Wright, P. T. *Org. Lett.* **2001**, *3*, 369.



entry	triene	R^1	R^2	product (ratio)	yield (%)
1	**1.1a**	H	4-Cl-$C_6H_4CH_2$	**1.3a**, **1.4a** (6:1)	76
2	**1.1b**	Me	4-Cl-$C_6H_4CH_2$	**1.3b**, **1.4b** (6:1)	71
3	**1.1c**	Ph	4-Cl-$C_6H_4CH_2$	**1.3c**, **1.4c** (3:1)	92
4	**1.1d**	Ph	*n*-Bu	**1.3d**, **1.4d** (3:1)	87
5	**1.2a**	H	4-Cl-$C_6H_4CH_2$	**1.5a**, **1.6a** (5:1)	66
6	**1.2b**	Me	4-Cl-$C_6H_4CH_2$	**1.5b**, **1.6b** (6:1)	74
7	**1.2c**	Ph	4-Cl-$C_6H_4CH_2$	**1.5c**, **1.6c** (4:1)	92
8	**1.2d**	Ph	*n*-Bu	**1.5d**, **1.6d** (4:1)	80

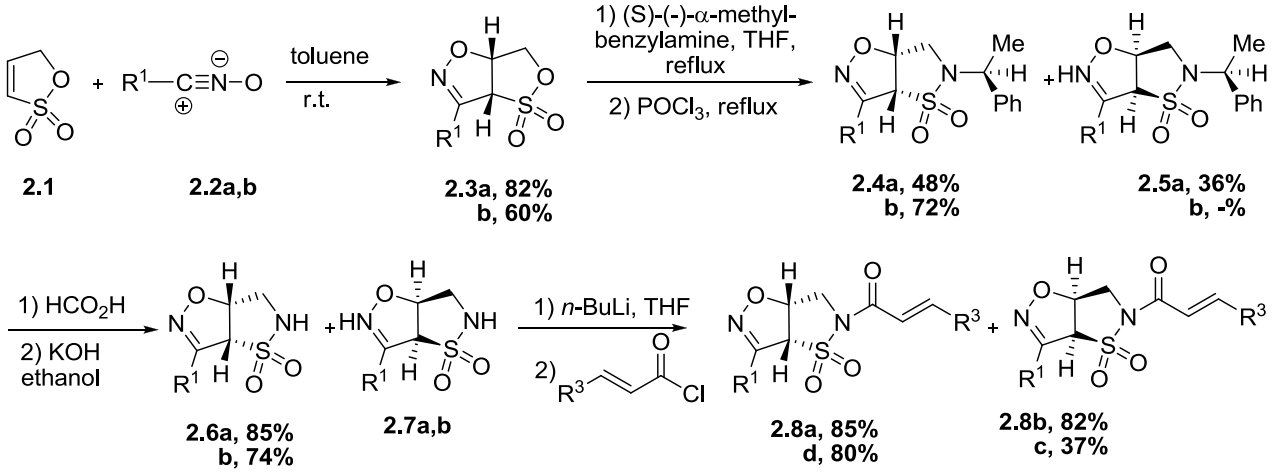
Scheme 1 Synthesis of chiral sultams by intramolecular Diels-Alder reactions

Chan[52] also reported the synthesis of a number of bicyclic chiral sultams for use as chiral auxiliaries in asymmetric Diels-Alder reactions based on 1,3-dipolar cycloadditions of nitrile oxides and nitrones with prop-1-ene-1,3-sultone. Nucleophilic ring-opening of the racemic sultone adducts **2.3a,b** obtained from 1,3-dipolar cycloaddition of **2.1** and nitrile oxides **2.2a,b** with (S)-(-)-α-methylbenzylamine in refluxing THF afforded a mixture of diastereomeric internal ammonium sulfonate salts. $POCl_3$ mediated cyclization of the internal salts gave 1:1 mixtures of the diastereomers **2.4a,b** and **2.5a,b**.

Treatment of **2.4a,b** and **2.5a,b** with concentrated formic acid at 70-80 °C for 5 h followed by subsequent hydrolysis under basic conditions afforded **2.6a,b** and **2.7a,b**, respectively. For the use of these chiral sultams as chiral auxiliaries in asymmetric Diels-Alder reactions, *N*-acylation

52 Zhang, H. K.; Chan, W. H.; Lee, A. W. M.; Wong, W. Y.; Xia, P. F. *Tetrahedron: Asymm.* **2005**, *16*, 761.

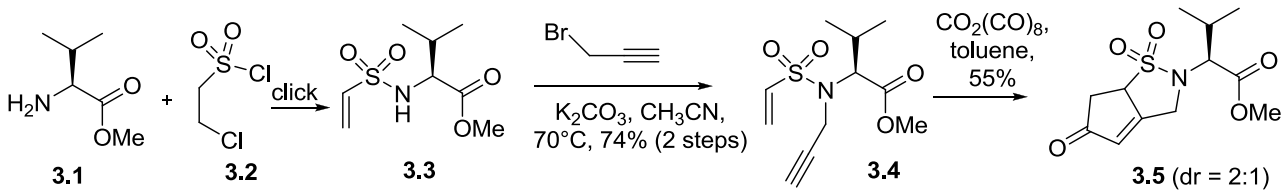
by successive treatment with *n*-butyllithium and acid chlorides were carried out to give the corresponding N-acryloyl sultams **2.8c**, and N-crotonyl sultams **2.8a,b,d** (Scheme 2).



R^1 = Ph, *t*-Bu
R^3 = Me, H

Scheme 2 Preparation of bicyclic chiral sultams based on 1,3-dipolar cycloadditions

Using the "Click, Click, Cyclize" protocol, Hanson and coworkers synthesized a number of chiral sultams from vinyl sulfonamides (Scheme 3).[53] The vinyl sulfonamide **3.3** was prepared from vinyl sulfonylation of valine methyl ester **3.1** with 2-chloro ethanesulfonyl chloride **3.2**. Subsequent alkylation with propargyl bromide followed by intramolecular cyclization afforded sultam **3.5**.

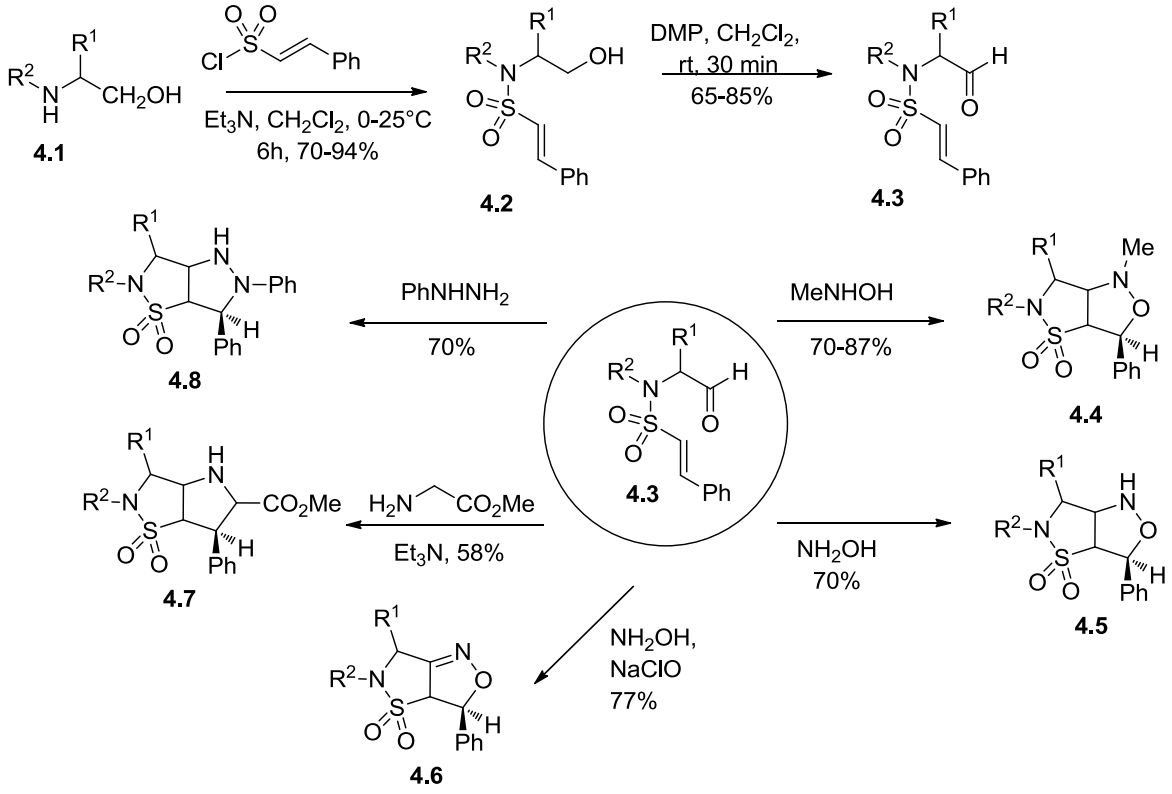


Scheme 3 "Click, Click, Cyclize" protocol for sultams

53 Zhou, A.; Rayabarapu, D.; Hanson, P. R. *Org. Lett*. **2009**, *11*, 531.

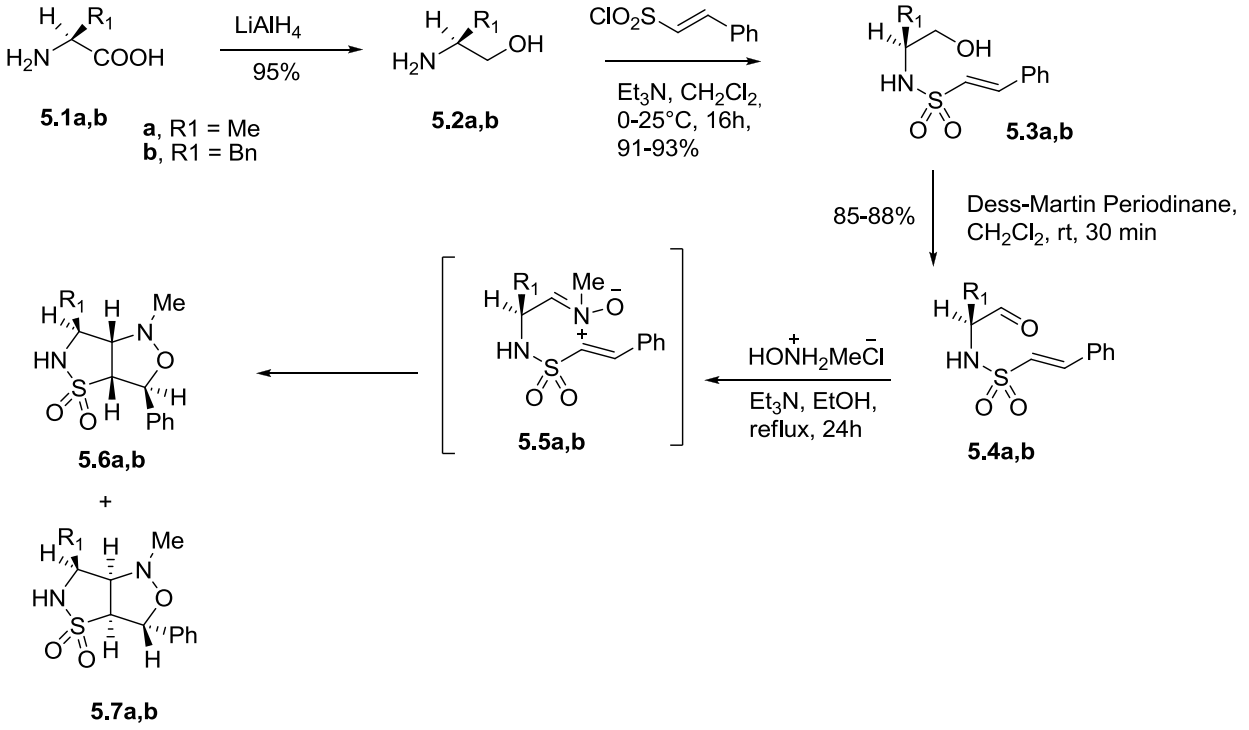
3.2 Enantiopure Sultams

In an effort to synthesize novel enantiopure chiral bicyclic sultams, Chiacchio[45a] exploited the intramolecular 1,3-dipolar cycloaddition of different dipoles, in which the sulfonamide group is located at the α-position with respect to the reactive center. The aminoalcohols **4.1** were treated with trans-2-phenylethenesulfonyl chloride to give the corresponding sulfonamide alcohols **4.2**, which were then converted into the α-sulfonamido aldehydes **4.3** by oxidation with Dess-Martin periodinane (DMP). Subsequent treatment with different nucleophilic reagents followed by intramolecular cycloaddition gave the corresponding sultams **4.4**-**4.8** in enantiomerically pure form and good yields (Scheme 4).



Scheme 4 Stereoselective synthesis of chiral sultams by intramolecular cycloadditions

In a subsequent report,[54b] the work was extended using the same methodology (Scheme 5). The major compounds **5.6a,b** were isolated enantiomerically pure by flash chromatography. Here it is important to note that they have used the chiral bicyclic sultams as chiral auxiliaries in asymmetric conjugate additions of the Grignard reagents.

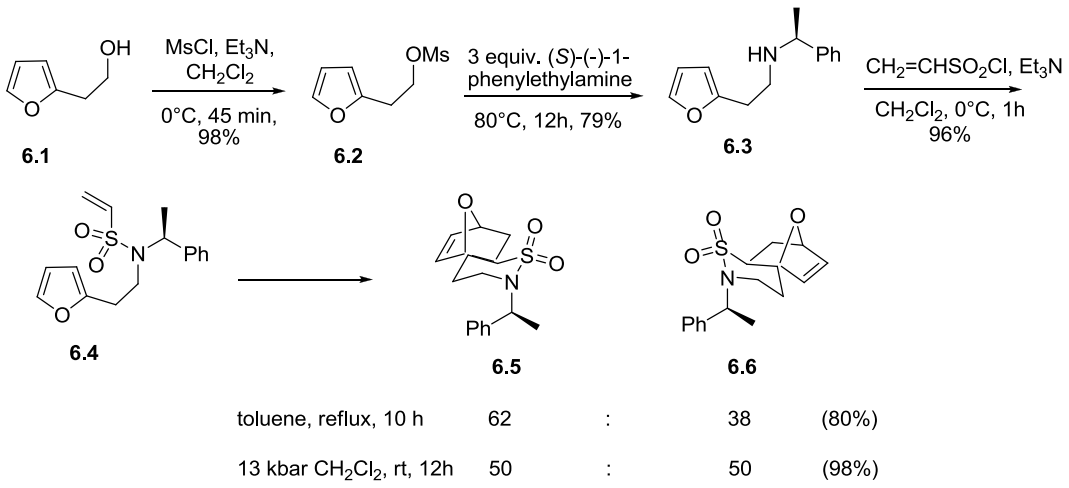


Scheme 5 Synthesis of chiral sultams by intramolecular cycloaddition reactions

Metz[55] described the synthesis of enantiopure bicyclic bridged sultams by intramolecular Diels-Alder (Scheme 6). By refluxing ethenylsulfonamide **6.4** in toluene, sultams **6.5** and **6.6** were formed in 80% yield with diastereomeric ratio 62:38.

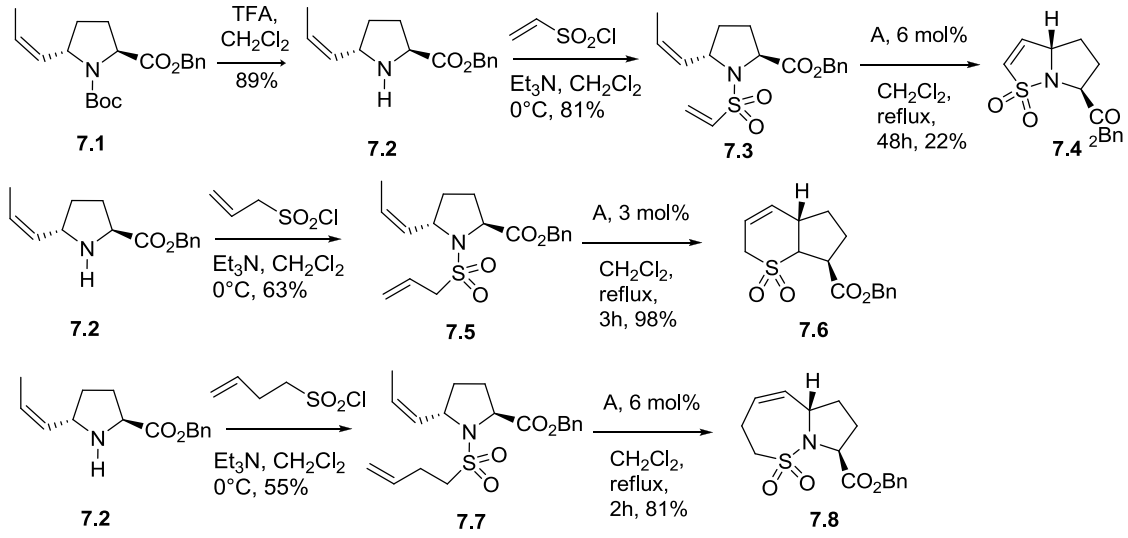
54 (a) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425.(b) Chiacchio, U.; Corsaro, A.; Gambera, G.; Rescifina, A.; Piperno, A.; Romeo, R.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1915.

55 Rogatchov, V. O.; Bernsmann, H.; Schwab, P.; Frohlich, R.; Wibbeling, B.; Metz, P. *Tetrahedron Lett*. **2002**, *43*, 4753.



Scheme 6 Preparation of enantiopure sultams by intramolecular Diels-Alder reaction

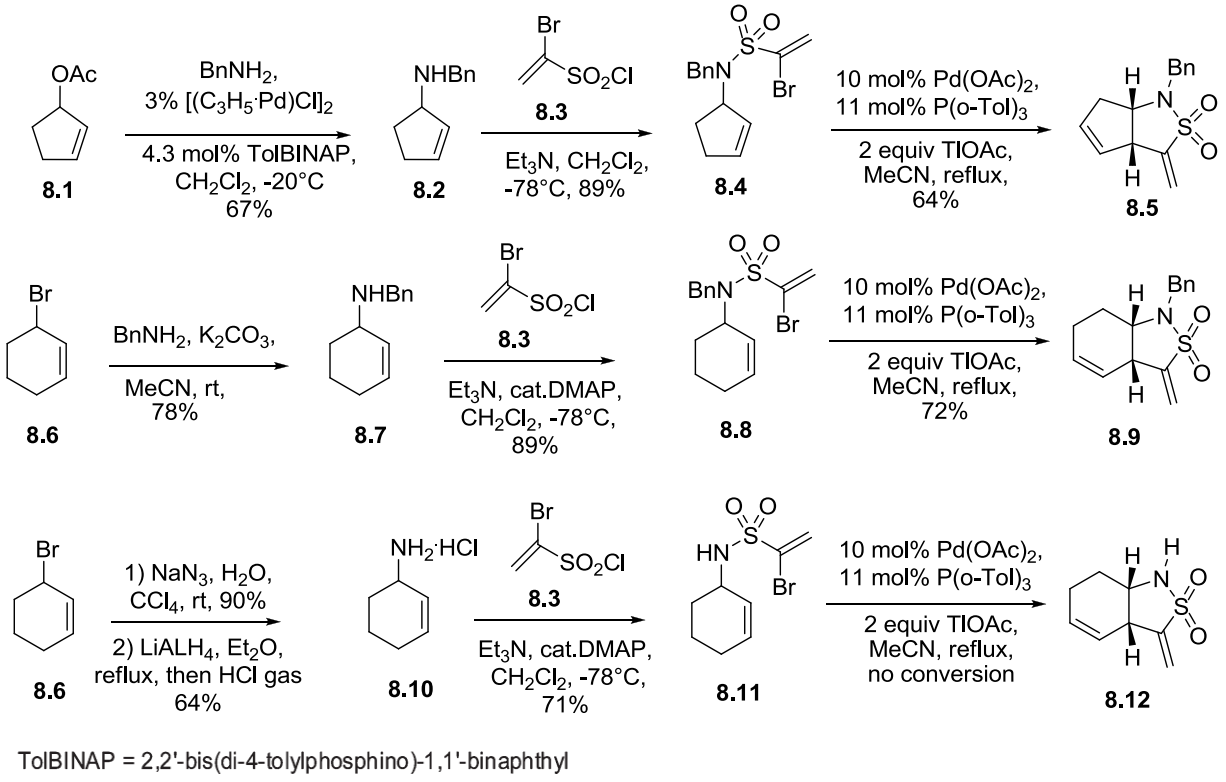
An application of ring-closing metathesis (RCM) in the synthesis of enantiopure bicyclic sultams was reported by Hanessian in 2003.[56] The 4-*cis*-(2-propenyl)-*N*-Boc-L-proline benzyl ester **7.1** was deprotected with trifluoroacetic acid. The product **7.2** was then sulfonated with ethenesulfonyl chloride, to give **7.3** that, by treatment with the Grubbs catalyst **A** and through RCM, produces the bicyclic sulfonamide **7.4** in low yield. Analogously, the *N*-sulfonyl derivatives **7.5** and **7.7** gave the sultams **7.6** and **7.8**, respectively (Scheme 7).



Scheme 7 Synthesis of bicyclic enantiopure sultams by ring-closure metathesis

56 Hanessian, S.; Sailes, H.; Therrien, E. *Tetrahedron*, **2003**, *59*, 7047.

The synthesis of bicyclic sultams by Heck cyclization was described Metz (Scheme 8).[57] The α-bromovinylsulfonamides **8.4**, **8.8**, and **8.11** were prepared in good yields by treatment of 1-bromoethenesulfonyl chloride **8.3** with the amines **8.2**, **8.7**, and **8.10**. The Heck cyclizations of the sulfonamides under established standard conditions afforded the desired sultams **8.5**, **8.9**, and **8.12** along with the undesired products arising from a double-bond migration due to readdition of the hydridopalladium bromide and a complementary regioselectivity of carbopalladation ("6-endo" cyclization instead of the desired "5-exo" cyclization). To avoid these undesired features, silver and thallium additives were used to enhance the selectivity. The optimized conditions for the Heck cyclizations of the precursors **8.4** and **8.8** for the formation of the corresponding sultams **8.5** and **8.9** were 10 mol % $Pd(OAc)_2$, 11 mol%$P(o\text{-}Tol)_3$, 2 equiv TlOAc, MeCN, reflux.

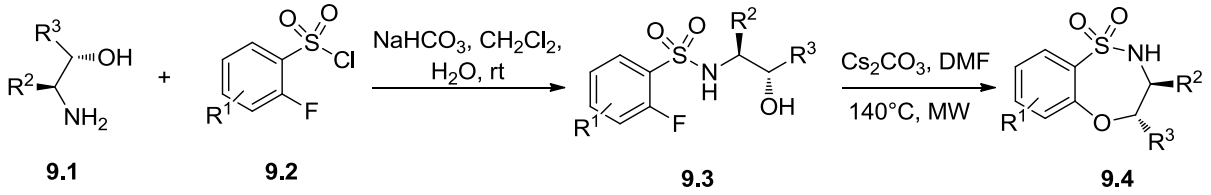


Scheme 8 Synthesis of enantiopure sultams by intramolecular Heck reaction

Recently, Hanson explored the synthesis of chiral benzothiaoxazepine-1,1-dioxides containing a secondary sulfonamide in enantiomerically pure form via an intramolecular S_NAr *ortho*-

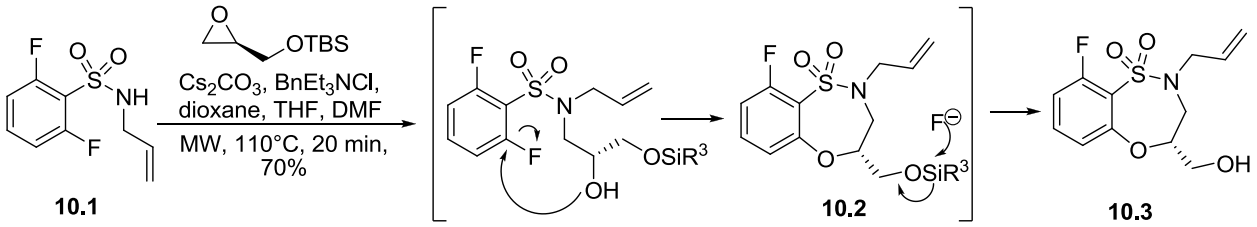
57 Merten, S.; Frohlich, R.; Kataeva, O.; Metz, P. *Adv. Synth. Catal*. **2005**, *347*, 754.

arylation.[58] β-Hydroxy α-fluorobenzene sulfonamides **9.3**, prepared from the corresponding amino alcohols **9.1**, were subjected to microwave irradiation at 140 °C for 30 min in DMF and in the presence of Cs_2CO_3**.** Under these conditions, a variety of chiral benzothiaoxazepine-1,1-dioxides **9.4** were isolated in 83-95% yields (Scheme 9).



Scheme 9 Click-cyclize protocol to diverse benzothiaoxazepine-1,1-dioxides

Hanson also described[59] an alternative route for the synthesis of benzothiaoxazepine-1,1'-dioxides **10.3** through a formal [4+3]-epoxide cascade protocol (Scheme 10).

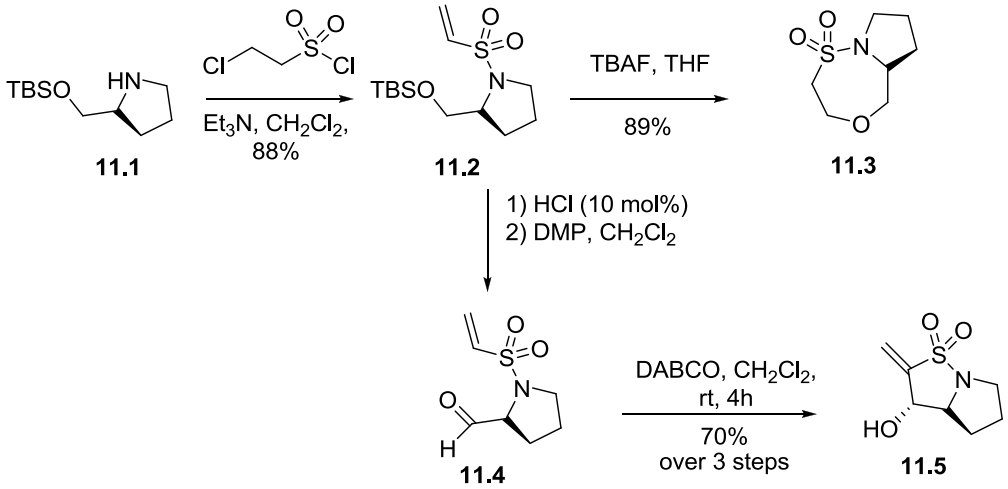


Scheme 10 One-pot epoxide, S_NAr cascade protocol to benzothiaoxazepine-1,1'-dioxides

Zhou and Hanson developed the intramolecular oxa-Michael and Baylis-Hillman approaches for the synthesis of enantiopure sultams (Scheme 11).[60] The *tert*-butyldimethylsilyl protected prolinol-derived vinyl sulfonamide **11.2** was treated with TBAF and the bicyclic sultam **11.3** is produced in excellent yields via an oxa-Michael pathway. In contrast, treatment of **11.2** underr

58 Ullah, F.; Samarakoon, T.; Rolfe, A.; Kurtz, R. D.; Hanson, P. R.; Organ, M. G. *Chem. Eur. J*. **2010**, *16*, 10959.
59 Rolfe, A.; Samarakoon, T. B.; Hanson, P. R. *Org. Lett*. **2010**, *12*, 1216.
60 Zhou, A.; Hanson, P. R. *Org. Lett*. 2008, *10*, 2951.

the orthogonal Baylis-Hillman conditions, involving acidic deprotection, oxidation, and addition of DABCO, gave the bicyclic sultam **11.5** with good yield and excellent diastereoselectivity.



Scheme 11 Oxa-Michael and Baylis-Hillman approaches to sultams

Chen[61] synthesized a number of bicyclic chiral sultams **11.6**, the sultam moiety of which is a part of the compounds **11.7**, novel potent inhibitors of hepatitis C virus (HCV) (Figure 1).

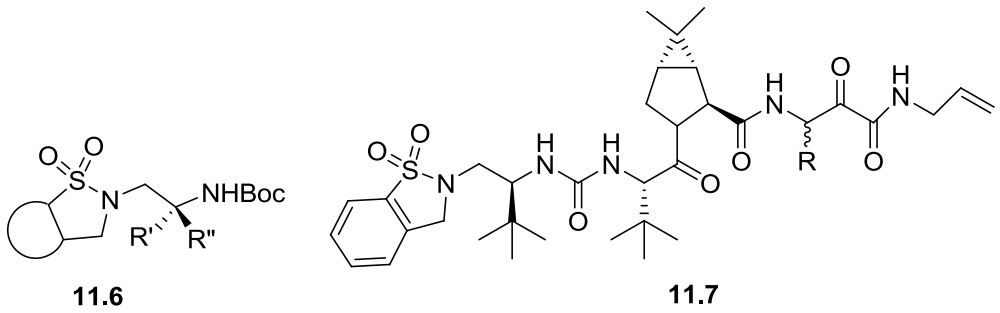


Figure 1 Potent inhibitors of hepatitis C virus

61 Chen, K. X.; Vibulbhan, B.; Yang, W.; Tong, X. Cheng, K. C.; Njoroge, F. G. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1105.

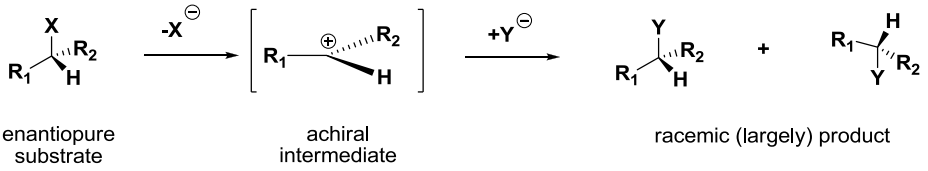
4 Memory of Chirality (MOC)

4.1 Introduction

The term "Memory Of Chirality" (MOC) was coined by Fuji,[62] who was the first to successfully design a reaction to capitalize on this principle. The proposal that MOC could underlay reaction enantioselectivity was actually first offered by Seebach.[63] A MOC reaction "*....can be defined as a formal substitution at a 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*".[64]

4.2 Requirements for Memory of Chirality

Beginning students of organic chemistry learn that if a enantiopure *sp*^{3}-hybridized stereogenic center is trigonalized, any chiral products resulting from that intermediate will be largely racemic (Scheme 1). In some S_N1 reactions a slight preference of retentive substitution is seen, due to shielding of backside attack by the leaving group. However, these low stereoselectivities are not synthetically useful.



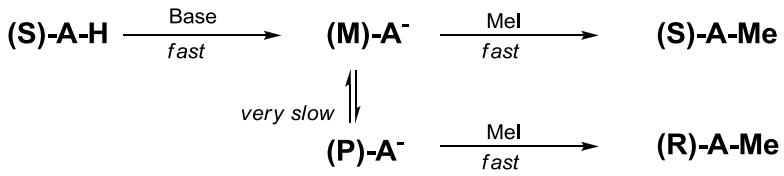
Scheme 1 Racemic products resulting from a planar achiral intermediate

62 Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991,** *113*, 9694.
63 Seebach, D.; Wasmuth, D. *Angew. Chem. Int. Ed.* **1981,** *20*, 971.
64 Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1.

In the absence of any other chiral controllers, a substantially non-racemic outcome would only be possible if the intermediate possesses some form of *conformational* chirality.

By its very nature, this conformational chirality will be short-lived; Fuji and Kawabata have termed this phenomenon "dynamic chirality",[65] since the enantiopurity of this intermediate is dependent on time and temperature.

However, formation of a conformationally chiral intermediate is not a sufficient condition for MOC: this intermediate must be formed *enantioselectively*. The essential requirements for a MOC reaction are illustrated for a hypothetical deprotonation/methylation in Scheme 2.



Scheme 2 Essential requirements for a MOC reaction of hypothetical depronation/methylation

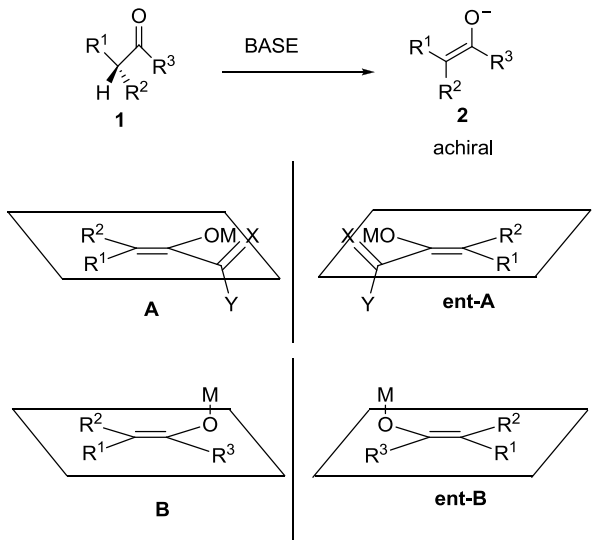
Firstly, deprotonation of the stereogenic center in the enantiopure reactant (*S*)-**A**-H must generate a conformationally chiral reactive intermediate (*M*)-**A** with high enantioselectivity. We use the helical descriptors (*M*)- and (*P*)- to describe the chirality of the intermediates; the choice of (*M*)-helicity in this example is arbitrary. Next, this conformationally chiral intermediate (*M*)-**A** must not readily racemize, at least not on the time scale of the desired subsequent reaction. Finally, the conformationally chiral intermediate must react with MeI with high stereopecificity to produce (*S*)-**A**-Me (again, the choice of (*S*)-configuration is arbitrary). Failure to meet all three of these requirements will result in zero or low enantioselectivity.

Note that both steps of the MOC process involve transfer of chirality: from static, central chirality to transient, conformational chirality (1), and then back again (2). How to ensure efficient chirality transfer in both steps is not immediately clear, and represents the essential challenge of the MOC strategy.

65 Fuji, K.; Kawabata, T. *Chem.-Eur. J.* **1998,** *4*, 373.

4.3 Memory of Chirality in Enolate Chemistry

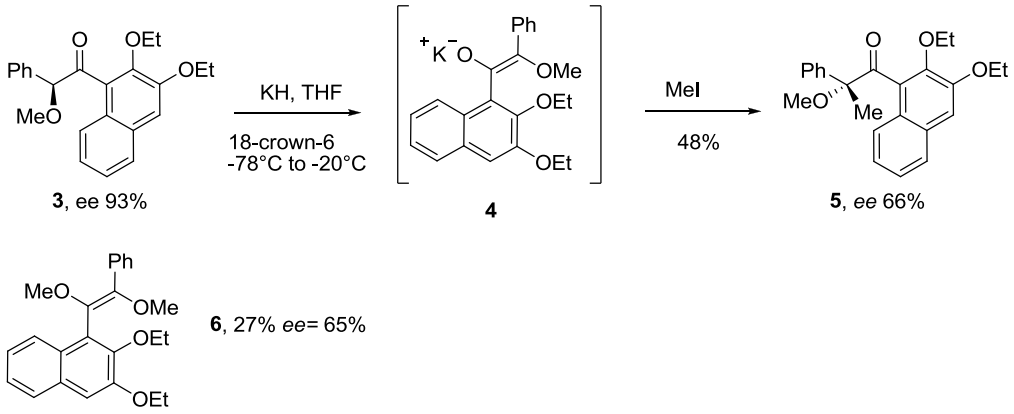
The MOC phenomenon was first demonstrated in the field of enolate chemistry by Fuji,[53] and to date enolates have proven the most fertile ground for the application of the MOC principle. His key insight[53] was that deprotonation of a stereogenic center α to a carbonyl in **1** need not always lead to an achiral enolate intermediate **2** (Scheme 3).



Scheme 3 Intentional design of conformationally chiral enolates

The enantiomeric forms **A** and **ent-A**, and **B** and **ent-B**, under normal conditions are not differentiated because of the rapid equilibrium between them. They may be differentiated from each other at an extremely low temperature or by the introduction of specific structural constraints into the molecule (such as changing 2,2'-dihydroxybiphenyl to the corresponding binaphthalene). Thus, this is a phenomenon in which the information on chirality in the original system is kept in a reactive intermediate for a limited period of time.

Kawabata and Fuji have introduced this concept in 1991[53] in the below mentioned example, the authors showed that treatment of the α-alkoxy naphtyl ketone **3** (93% enantiomeric excess) with potassium hydride and methyl iodide in the presence of 18-crown-6 afforded **5** in 66% enantiomeric excess without any additional chiral source (Scheme 4).



Scheme 4 First MOC reaction

The obtained results suggested the formation of a chiral enolate intermediate in a nonracemic form.

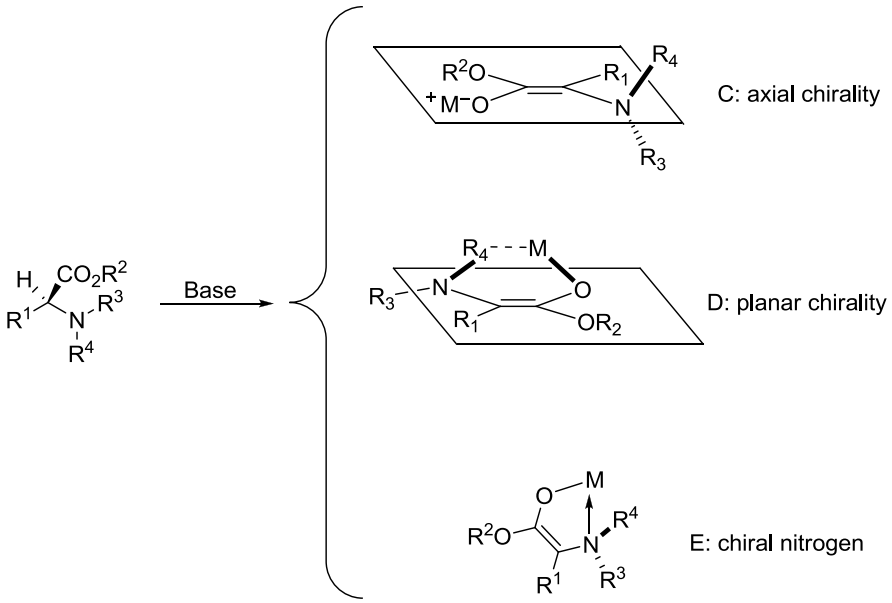
The authors proposed that the reaction occurs via the enolate **4**, whose structure is reminiscent of the atropisomeric 1,1-binaphthyls. In accord with this hypothesis, the *O*-alkylated product **6** was also detected in the reaction mixture with 65% enantiomeric excess. At room temperature, **6** was found to racemize with half-life time of 53 minutes, corresponding to a rotation barrier of 22.6 kcal/mol; the phenyl analogue of **3** subjected to the same reaction conditions, gave the racemic product.

4.4 Enantioselective α-Alkylation of Amino Acid Esters Without External Chiral Sources

In order to extend this strategy, Kawabata studied the α-alkylation of the enolates generated from α-amino acids. In fact, an enolate derived from an optically active amino acid derivative, may not racemize under basic conditions. Here are reported (Scheme 5) three different species of enolates which could furnish an optically active product:

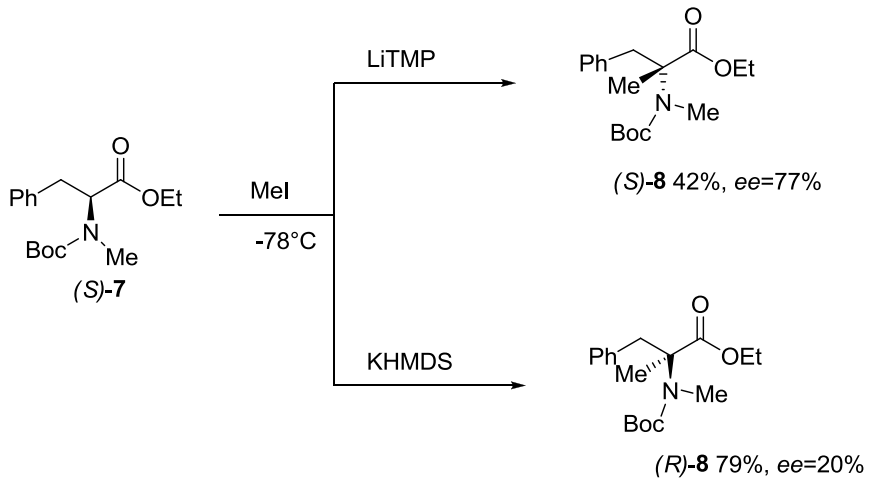
- enolate **C**, which has axial chirality across the carbon- nitrogen bond. This kind of enolates is expected if R^3 is different from R^4;
- enolate **D,** which has planar chirality due to the enolate plane and the metal cation, stabilized by coordination with a substituent on the nitrogen;

- enolate **E** where tight coordination of the nitrogen atom to a metal cation creates a stereogenic nitrogen atom, not allowing the pyramidal inversion.



Scheme 5 Three types of enolate chirality

Kawabata proposed a study on the chirality transfer using as a starting amino acid the *N*-Boc-phenylalanine **6** ethyl ester.[66] Non-racemic products were obtained, the best enantiomeric excess being obtained by using LiTMP as a base. Even more interestingly, KHMDS gave a predominance of the inversion product (20% *ee*), suggesting the existence of two pseudo-enantiomeric transition states (Scheme 6).

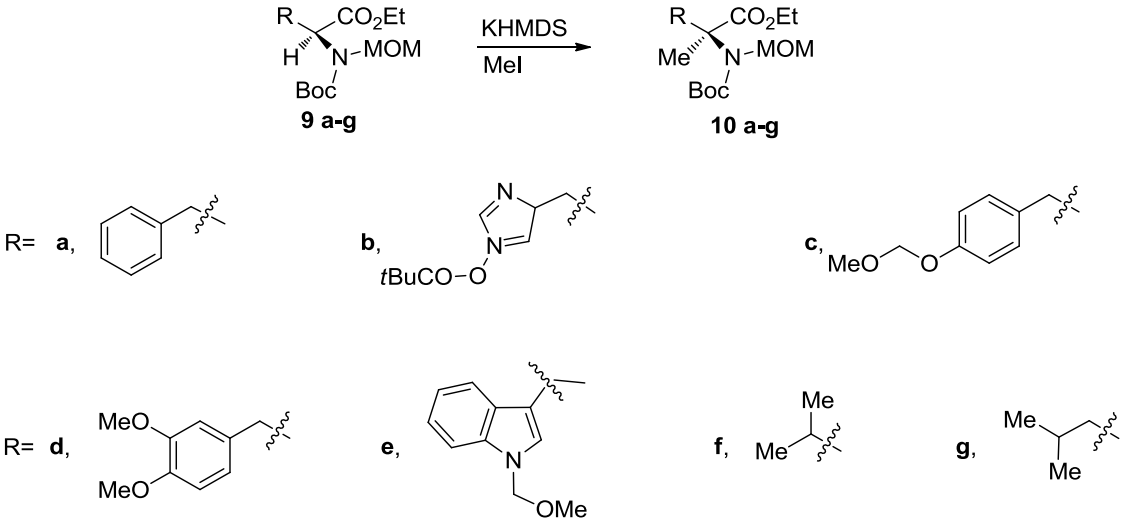


Scheme 6 Asymmetric methylation of (*S*)-**7**

66 Kawabata, T.; Wirth, T.; Yahiro, K.; H. Suzuk; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809-10807;

In order to improve the yields and enantioselectivity of this process, the authors screened a serie of substituents on the nitrogen moiety of phenylalanine derivative **9a**.[67] They found that substrates bearing *tert*-butoxycarbonyl (Boc) and methoxymethyl (MOM) groups gave the best results (Table 1, enrty 1).

Table 1 Asymmetric α-methylation of *N*-MOM-*N*-Boc α-amino acid derivatives



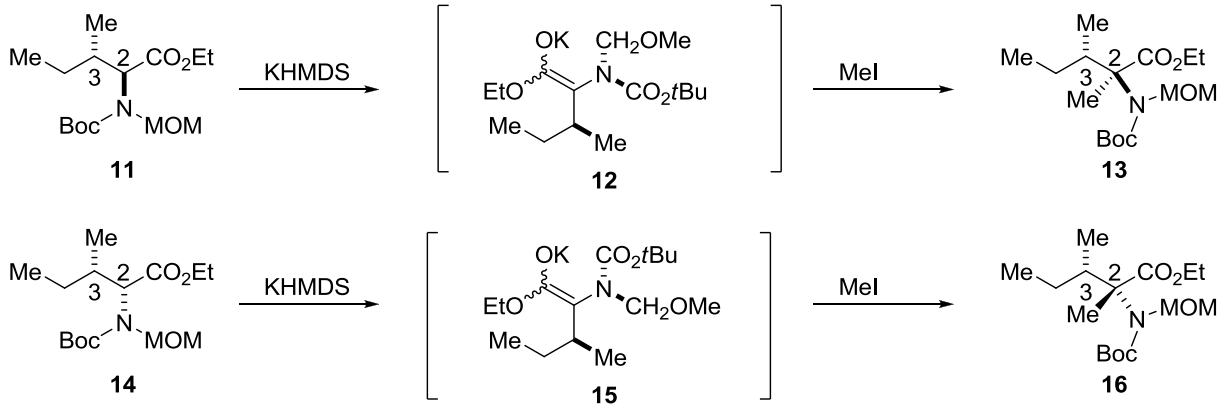
entry	R	yield (%)	*ee* (%)
1	**a**	96	81
2	**b**	83	93
3	**c**	94	79
4	**d**	95	80
5	**e**	88	76
6	**f**	81	87
7	**g**	78	78

Kawabata et al. have also applied the best reaction conditions to amino acid derivatives different from phenylalanine **9** (Table 1). In each case, they obtained quite good yields and enantioselectivity; moreover, differently from the *N*-methyl derivative **8** (Scheme 6), Boc and MOM protective groups are simply removed by treatment with aqueous HCl, affording the corresponding α-methyl-α-amino acids in 51–86% yields. The degree of asymmetric induction in

67 Kawabata, T.; H. Suzuki; Wirth, T.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *12*, 2155- 2158

the α-methylation indicates that MOM and Boc groups on the nitrogen atom have a decisive effect on the stereochemical course of the reaction.

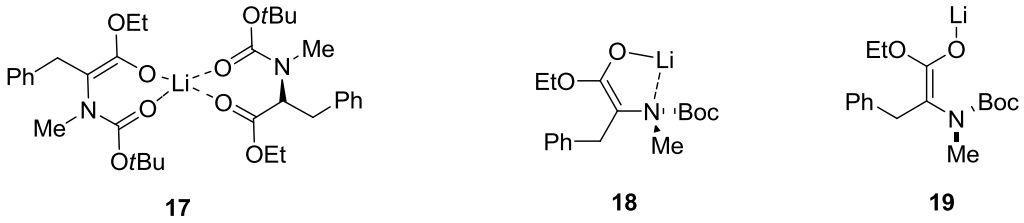
Fuji and Kawabata addressed their study to the α-alkylation of *L*-isoleucine and *D*-allo-isoleucine derivatives **11** and **14** to investigate the influence of an additional chiral center (Scheme 7).[68] Amino esters **11** and **14** have the same absolute configuration at C_3 and opposite configurations at C_2. When the *N*-MOM ethyl esters **11** and the *N*-Boc ethyl esters **14** were subjected to the standard alkylation condition, both the corresponding methylated compounds **13** and **16** were obtained in excellent diastereoselectivities (93% and 86% diastereoisomeric excess respectively). Thus, the stereochemical course of deprotonation/methylation of **11** and **14** appears to be controlled by the chirality at C_2: in fact, if the chiral information at C_2 had been lost during enolate formation, α-methylation would have given products with identical diastereomeric composition via a common enolate intemediate. These results suggest the formation of diastereomeric enolate intermediates such as **12** and **15**.



Scheme 7 MOC α-alkylation of isoleucine derivatives

As regards the reaction mechanism, during the years, Fuji and Kawabata have carried out a number of mechanistic investigations. For the deprotonation/alkylation of *N*-Boc, *N*-Me amino acid esters **16**, the authors considered several mechanistic scenarios (Scheme 8):

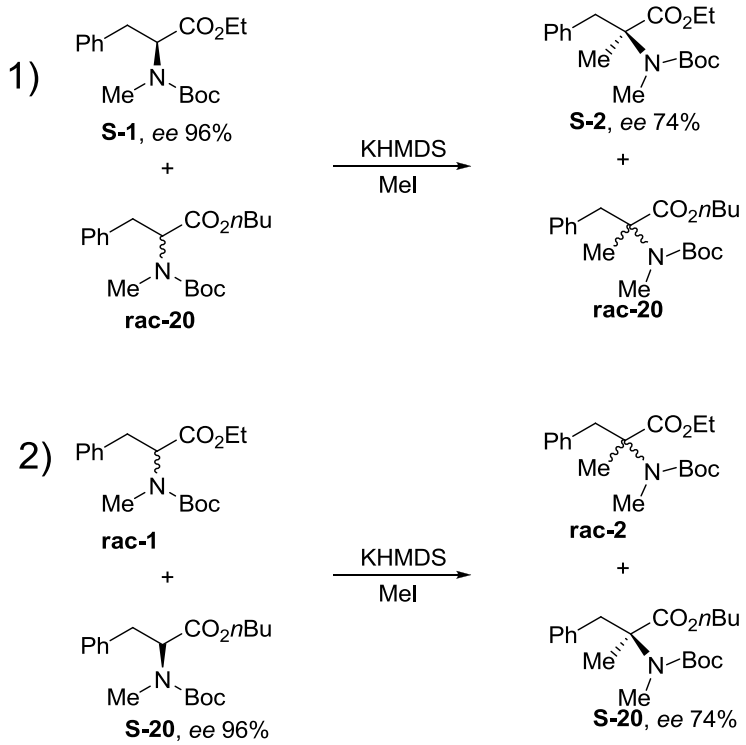
68 Kawabata, T.; H. Suzuki; Wirth, T.; Nagae, Y.; Fuji, K. *Org. Lett.* **2000**, *2*, 3883- 3885



Scheme 8 Three possible intermediates during asymmetric induction

Asymmetric induction could arise from: a chiral enolate/ starting material aggregate **17**; a species **18** with a chiral nitrogen atom; an axially chiral enolate **19**.

To rule out the presence of an aggregate such as **16**, the authors conducted a crossover experiment (Scheme 9).[69]



Scheme 9 Crossover experiment to investigate the origin of chirality

A mixture of optically pure **1** and racemic **20** were subjected to deprotonation with LiTMP at -78 °C followed by addition of methyl iodide, to afford optically active **2** (74% *ee*, 26% yield) and

69 Kawabata, T.; Wirth, T.; Yahiro, K.; H. Suzuk; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809-10807

racemic **20** (30% yield). The same treatment of a 1:1 mixture of racemic **1** and optically active **20** afforded the racemic **2** (17% yield) and optically active **20** (71% *ee*, 24% yield). These observations indicate that **17** (Scheme 8) does not make a significant contribution to the asymmetric induction.

In their opinion, the most suitable intermediate is compound **19** (Scheme 8). As a confirmation, Fuji and Kawabata reported the isolation of the (*Z*)- and (*E*)-TBS ketene acetals **21** (Figure 1).[70]

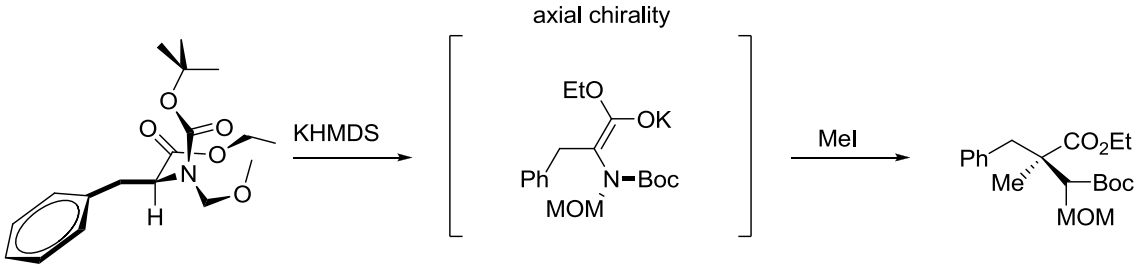
***Z*-21**
major

***E*-21**

Figure 1 (*Z*)- and (*E*)-TBS ketene acetals

The methylene protons of the MOM groups are diastereotopic in both isomers of **21**, indicating restricted rotation of the C_2–N bond. The rotational barrier of the C_2–N bond in the major isomer ***Z*-21** was determined to be 16.8 kcal/mol and it corresponds to a racemization half-life of seven days at -78 °C.

For this reason the authors proposed that deprotonation of **9a** occurs through the most stable conformer **25** (Scheme 10).



9a
most stable conformer

26
non-racemic enolate

10a

Scheme 10 Proposed mechanism of retentive methylation of (*S*)-**9a**

Kawabata found support for the presence of an axially chiral enolate in both deprotonation/alkylation of both substrates **22** and **23** (Figure 2).

70 Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155.

22, R= H
24, R=Me

23, R= H
25, R=Me

Figure 2 Examination of the intermediacy of axially chiral enolate in deprotonation/alkylation

Deprotonation/methylation of enantiopure **22** and enantiopure **23** gave racemic **24** and **25**, because of the formation of an achiral enolate: in fact, the presence of two identical Boc protecting groups in compound **22** rule out the possibility of chirality on the N–C_2 axis. In the case of **23** the five-membered ring prevents the N substituents from rotating out of the enolate plane to attain axial dissymmetry.

In the last few years, Kawabata et al. have also applied the concept of autoinduction of chirality to the synthesis of cyclic amino acids.[71]

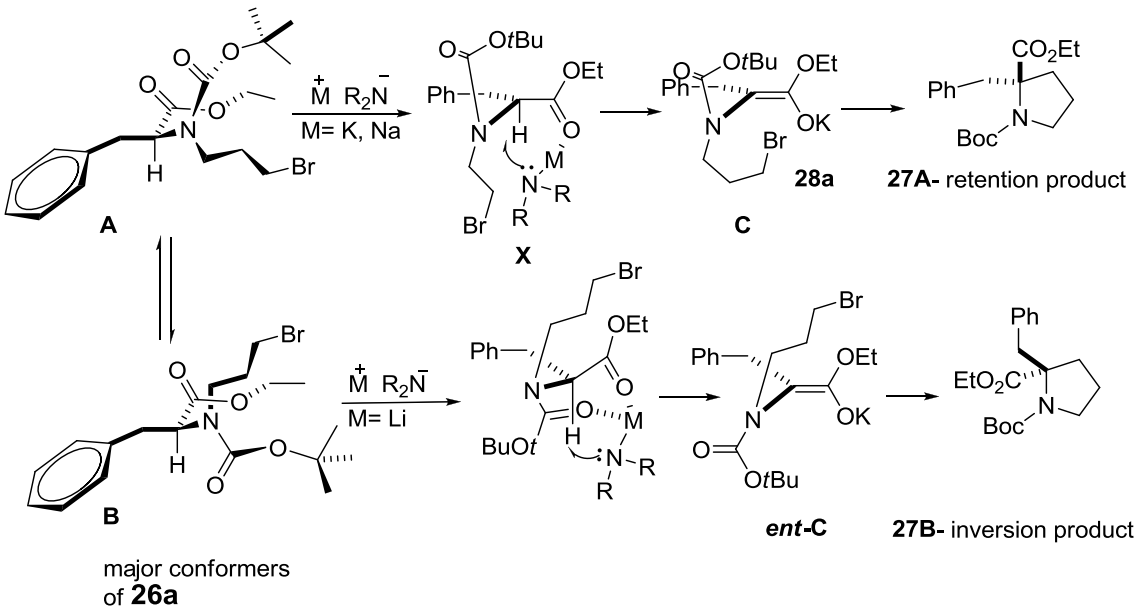
Table 2 Synthesis of cyclic amino acids

26 a-h **27 a-h**

entry		n	R	yield (%)	*ee* (%)
1	**a**	3	Bn	94	98
2	**b**	3	4-EtO(C_6H_4)CH_2	95	97
3	**c**	3	MeSCH_2CH_2	92	97
4	**d**	3	*i*Pr	78	94
5	**e**	3	Me	91	95
6	**f**	2	Bn	61	95
7	**g**	4	Bn	84	97
8	**h**	5	Bn	31	83

71 a) Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012; b) Kawabata, T.; Moriyama, K; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153- 4157

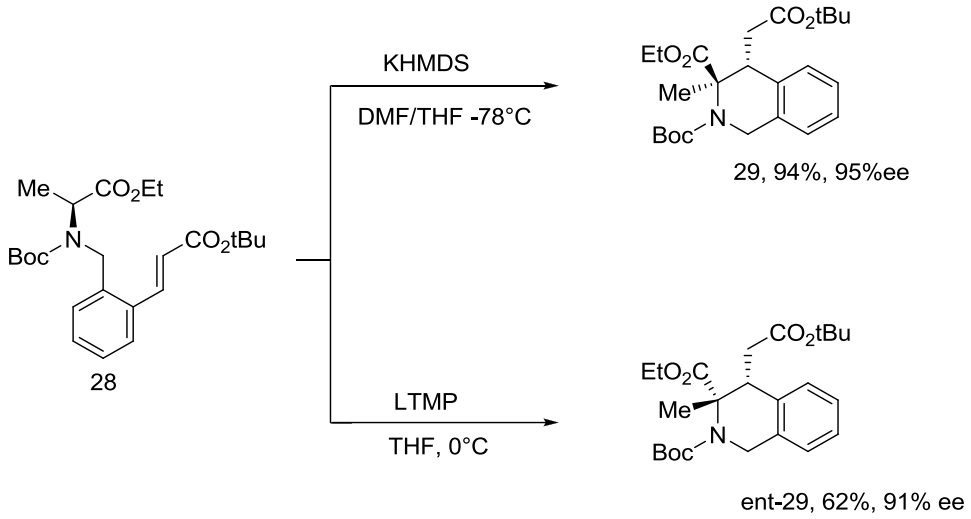
They designed a series of *N*-Boc-*N*-ω-bromoalkyl- α-amino acid derivatives **26a**–**h** for asymmetric intramolecular cyclization (Table 2). Compounds **27** were obtained in quite good enantiomeric excess and fairly yields. The chirality of the starting amino acids **26a-h** was preserved during enolate formation and subsequent cyclization, giving enantiomerically enriched azacyclic quaternary amino acids, with retention of configuration, as found for the acyclic quaternary amino acids. For this reason, Fuji and Kawabata proposed a similar mechanism to that of **9a** (Scheme 10). In this case, a conformational study identified two stable conformers of compound **26a** of similar energy: **A** and **B**. Deprotonation of **B** is disfavored because of a steric interaction between KHMDS and the *N*-Boc group. On the other hand, deprotonation of **A** is favored and gives axially chiral nonracemic enolate **X,** which then cyclizes to give the retention product **27A**. With the aim of shifting the equilibrium, making dominant the transition state **Y**, thus extending this procedure to the synthesis of inversion compounds, the authors investigated the asymmetric cyclization of **26** changing the cation of the employed base.[72] The best result of **27B** (93%, 91% enantiomeric excess) was obtained using as a cation Li^+, which is the smallest metal cation.



Scheme 11 Proposed mechanism of MOC cyclization of (*S*)-**26a**

72 Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D. ; Moriyama, K. *J. Am. Chem. Soc.* **2006**, *128*, 15394.

The protocol for enantio-divergent cyclization was applied to intramolecular conjugate addition of chiral enolates. Treatment of the alanine derivative **28** with KHMDS in DMF-THF (1:1) at -78 °C gave **29** as a single diastereoisomer in 95% *ee* (Scheme 12, (path A). The absolute configuration assignment of **29** was based on the stereochemical course of asymmetric intramolecuar conjugate addition via memory of chirality. Treatment of **28** with LTMP in THF at 0 °C gave ***ent*-29** as a single diastereoisomer in 91% ee.



Scheme 12 Stereochemical diversity in MOC cyclization of **28**

5 Application of MOC to the Synthesis of α-Quaternary α-Amino Acids

Non-natural amino acids have attracted considerable attention in biological and medicinal chemistry,[73] because they are powerful tools for the design of new oligopeptidic fragments, capable of influencing the secondary structure of proteins. In particular, α-quaternary α-amino acids are of great interest for their potential intrinsic bioactivity.[74] In addition, new foldamers are formed by the introduction of quaternary α-amino acids into peptidomimetics. This procedure increases the lipophilicity of the oligomeric chain, and restricts its conformational flexibility, thus making the peptide more resistant to metabolic and chemical degradation.[75]

A number of strategies[56] and, among them, those that adopt the well-known Kawabata's principles of "memory of chirality" (MOC)[43,44] and of "chiral non-racemic enolate"[76] emerge as the most appealing-have been proposed for the stereoselective synthesis of quaternary α-amino acids. In particular, the synthetic methods for quaternary prolines[77] involve the enantioselective functionalization of L-proline derivatives, for example, through self-reproduction of chirality, diastereoselective alkylation, or transfer of stereochemical information via cyclic ammonium ylides.

In the past few decades, a variety of synthetic strategies for such important building blocks have been developed.[78] In the field of carbon-carbon bond formation, synthetic strategies based on sigmatropic rearrangements are one of the most interesting method to obtain α-quaternary prolines.

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73 (a) S. Hunt, *Chemistry and Biochemistry of the Amino Acids*, ed. G. C. Barrett, Chapman and Hall, London, **1985**, p. 55; (b) Y. Ohfune, *Acc. Chem. Res*., **1992**, 25, 360.

74 (a) T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta and T. Fukuyama, *Org. Lett.*, **2008**, 10, 169; (b) S. Pizzarello, *Acc. Chem. Res.*, **2006**, 39, 231; (c) Y. Ohfune and T. Shinada, *Eur. J. Org. Chem.*, **2005**, 5127.

75 (a) M. Tanaka, *Chem. Pharm. Bull.*, **2007**, 55, 349; (b) C. Toniolo, F. Formaggio, Q. B. Broxterman, *Synlett*, **2006**, 1295; (c) S. J. O'Connor and Z. Liu, Synlett, 2003, 2135;

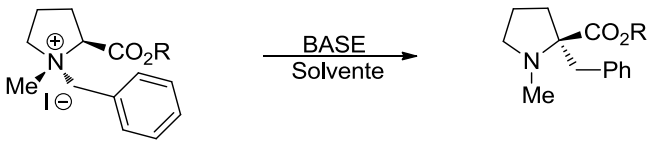
76 a) T. Kawabata, S. Majumdar, K. Tsubaki, D. Monguchi, *Org. Biomol. Chem.* **2005**, 3, 1609 –1611; b) T. Kawabata, S. Kawakami, K. Fuji, *Tetrahedron Lett*. **2002**, 43, 1465 –1467; c) T. Kawabata, H. Suzuki, Y. Nagae, K. Fuji, *Angew. Chem.* **2000**, 112, 2239 –2241; *Angew. Chem. Int. Ed*. **2000**, 39, 2155 –2157.

77 a) M. I. Calaza, C. C. Cativiela, *Eur. J. Org. Chem*. **2008**, 3427 –3448; b) P. Tuzina, P. Somfai, *Org. Lett.* **2009**, 11, 919 – 921; c) C. Caup_ne, G. Chaume, L. Ricard, T. Brigaud, *Org. Lett*. **2009**, 11, 209 –212; d) K. Sakaguchi, M. Yamamoto, Y. Watanabe, Y. Ohfune, *Tetrahedron Lett.* **2007**, 48, 4821 – 4824; e) E. Tayama, H. Kimura, *Angew. Chem.* **2007**, 119, 9025 –9027; *Angew. Chem. Int. Ed*. **2007**, 46, 8869 – 8871; f) E. Tayama, S. Nanbara, T. Nakai, *Chem. Lett*. **2006**, 35, 478 – 479; g) D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc.* **1983**, 105, 5390 –5398.

78 (a) C. Cativiela and M. D. Dìaz-de-Villegas, *Tetrahedron: Asymmetry*, **2007**, 18, 569; (b) C. Cativiela and M. D. Dìaz-de-Villegas, *Tetrahedron: Asymmetry*, **2000**, 11, 645; (c) C. Cativiela and M. D. Dìaz-de-Villegas, *Tetrahedron: Asymmetry*, **1998**, 9, 3517;

West and Glaeske reported a study on chirality transfer in [1,2]-Stevens rearrangement of the diastereomerically pure cyclic ammonium salt methyl ester **1** (Table 1, entry 1).[79] Using tetrahydrofuran as solvent under the action of potassium *tert*-butylate, the quaternary proline ester **2** was isolated with fairly good enantioselectivity.

Table 1



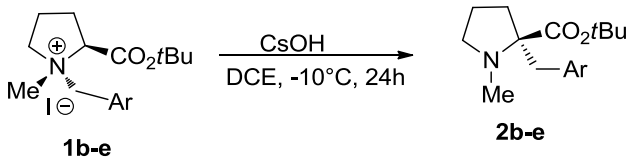
1 **2**

entry	R	base	solvent	T(°C)	t (h)	yield (%)	*ee* (%)
1	Me	*t*BuOK	THF	rt	1.5	73	54
2	*t*Bu	*t*BuOK	DCM	rt	3	80	72
3	*t*Bu	50% KOH	DCM	-10	24	45	86
4	*t*Bu	KOH	DCM	-10	24	52	94
5	*t*Bu	CsOH	DCM	-10	24	88	84
6	*t*Bu	CsOH	DCE	-10	24	73	92

This technique was further improved by Tayama et al. by employing solid-liquid biphasic reaction conditions (entry 2,5); the best yield and enantioselectivity were reached by using caesium hydroxide in dichloroethane (entry 6).[80] It has also been noticed that the level of N-C chirality transfer depends not only on the reaction conditions but also on the *N*-benzyl moiety (Table 2).

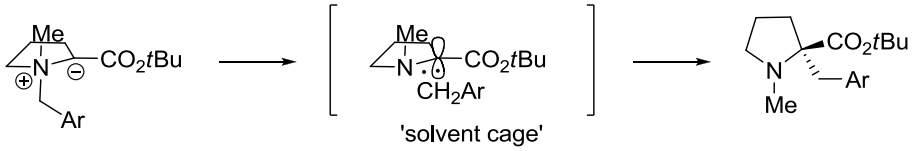
79 Glaeske, K. W.; West, F. G. *Org. Lett*. **1999**, 31-33.
80 Tayama, E.; Orihara, E.; Kimura, H. *Org. Biomol. Chem.* **2008**, 3673-3680.

Table 2



Ar	**2**	yield (%)	*ee* (%)
4-Me-Ph	**2b**	77	84
4-MeO-Ph	**2c**	56	86
4-F-Ph	**2d**	69	90
4-*t*BuOCOPh	**2e**	42	99

This rearrangement is assumed to proceed by a radical cleavage-recombination mechanism. Tayama et al. suggested that the stability of the benzylic radicals involved and the solid–liquid biphasic reaction conditions employed determine the stereochemical course of the reaction (Scheme 1). The recombination of the radical pair initially formed from the *N*-ylide occurs more rapidly in a solvent cage and hence more preferentially in a retentive fashion.

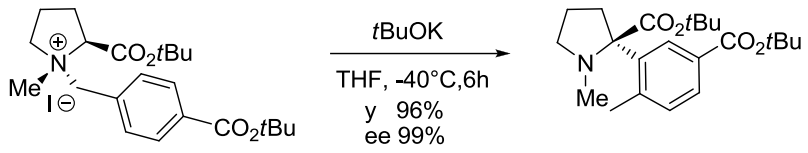


Scheme 1

The main drawback of this methodology is accessing the pure diastereomer of the ammonium salt, which requires stereoselective quaternization with methyl iodide followed by several recrystallizations and ultimately yielding the pure diastereomer in low yields.

Tayama has also observed that, when the rearrangement is performed in THF at -40°C using potassium *tert*-butoxide as a base, the Sommelet–Hauser rearrangement (concerted [2,3]sigmatropic process) proceeded exclusively to give the corresponding α-aryl proline derivative **3** in 96% yield and 99% enantiomeric excess (Scheme 2).[81]

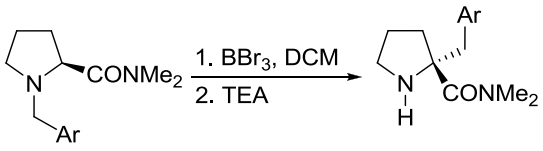
81 Tayama, E.; Kimura, H. *Anghew. Chem.Int. Ed.* **2007**, 8869-8871.



Scheme 2

Another example of Stevens rearrangement was described by Somfai.[82] He performed an asymmetric Lewis acid mediated [1,2]-shift of proline derivatives; he found that complexation of proline amide derivatives **4** with BBr_3, followed by addition of Et_3N, gave the corresponding products **5** in good yield and excellent enantiomeric excess.

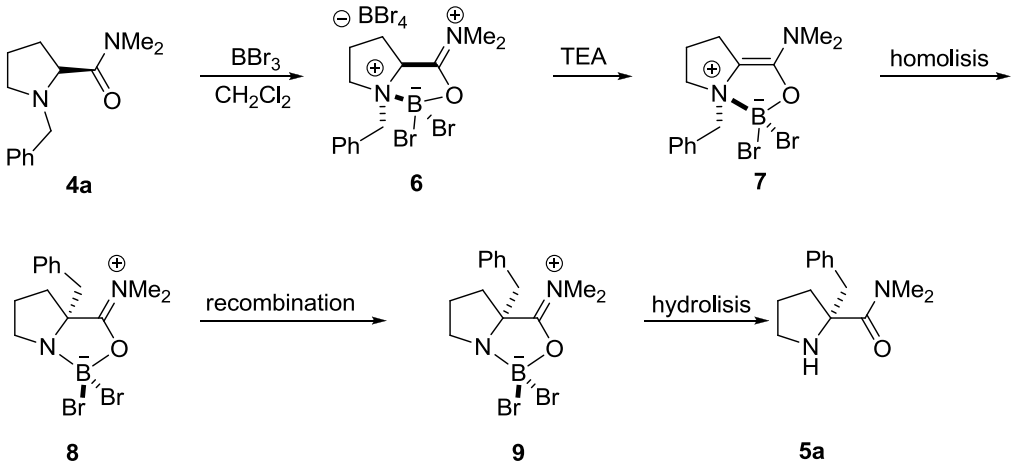
Table 3



entry	4	Ar	t (h)	5	(%)	*ee* (%)
1	**4a**	Ph	1	**5a**	85	96
2	**4b**	4-*t*Bu-Ph	1	**5b**	82	96
3	**4c**	4-Br-Ph	1	**5c**	76	96
4	**4d**	4-CF_3-Ph	1	**5d**	82	96
5	**4e**	2-Me-Ph	2	**5e**	81	96
6	**4f**	2-Tyophene	1	**5f**	79	96

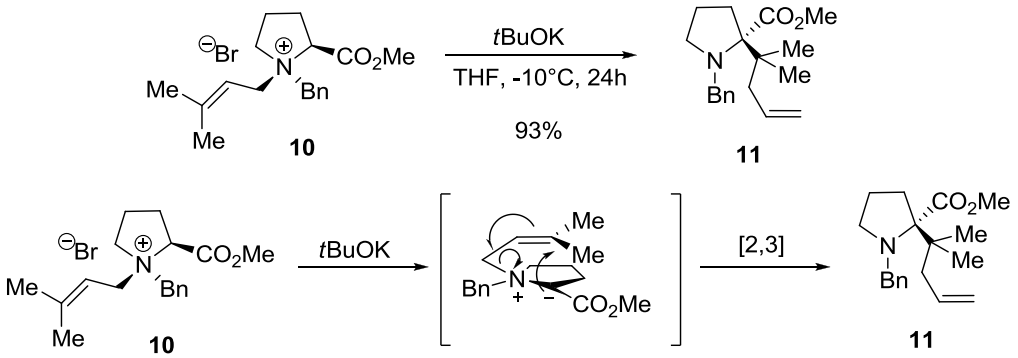
The high enantiomeric excess can be explained by an *in situ* formation of the rigid bicyclic complex **6** (Scheme 3). Treatment of amide **4a** with BBr_3 results in coordination of the Lewis acid *cis* to the amide moiety, which is followed by formation of structure **6**. Subsequent deprotonation of **6** with Et_3N provides ylide **7**, which suffers a homolytic cleavage of the C-N bond (structure **8**) and then a radical recombination to form complex **9**. An efficient N-C chirality transfer is secured by selective migration of the benzyl radical on the Re-face. Finally, hydrolysis of **9** gives **5a**, the absolute stereochemistry of which is identical to the starting material **4a.**

82 Pavel, T.; Somfai, P. *Org. Lett.* **2009**, 919-921.



Scheme 3

An exclusive [2,3]-shifts of a prenyl group for substrate **10** has been reported by Coldham,[83] (Scheme 4). In this case, the rearrangement is stereospecific because the [2,3]-migration is restricted to the same face.



Scheme 4

The ester-enolate Claisen rearrangement is a powerful method for enantioselective C–C bond formation from an original chiral ester. Recently this type of reaction was applied to and α-acyloxy-α-vinylsilane possessing a proline as the acyloxy group (Scheme 5).[84] The enolate generated from **12** underwent the Claisen rearrangement, through a chair-like transition state with a *Z*-enolate in the presence of HMPA, to give the α-substituted proline derivative **13** with transfer of the original chirality of the ester counterpart.

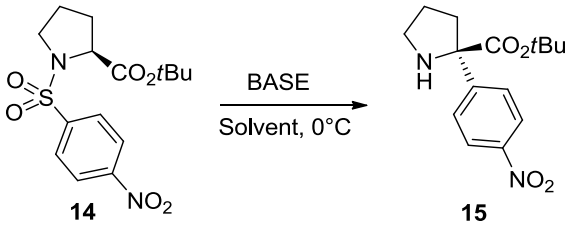
83 Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236–238
84 Sakaguchi, K.; Yamamoto, M.; Watanabe, Y.; Ohfune, Y. *Tetrahedron Lett.* **2007**, *48*, 4821–4824.

12 >95%ee **13** >95%ee

Scheme 5

Recently, our group reported on the enantioselective synthesis of quaternary *N*-alkyl-α-4-nitrophenyl-α-amino *tert*-butyl esters, through *N*-alkylation of the corresponding α-*N*-(4-nitrophenyl)sulfonamido esters, followed by degradative rearrangement, with loss of SO_2 (Table 4)[85]

Table 4

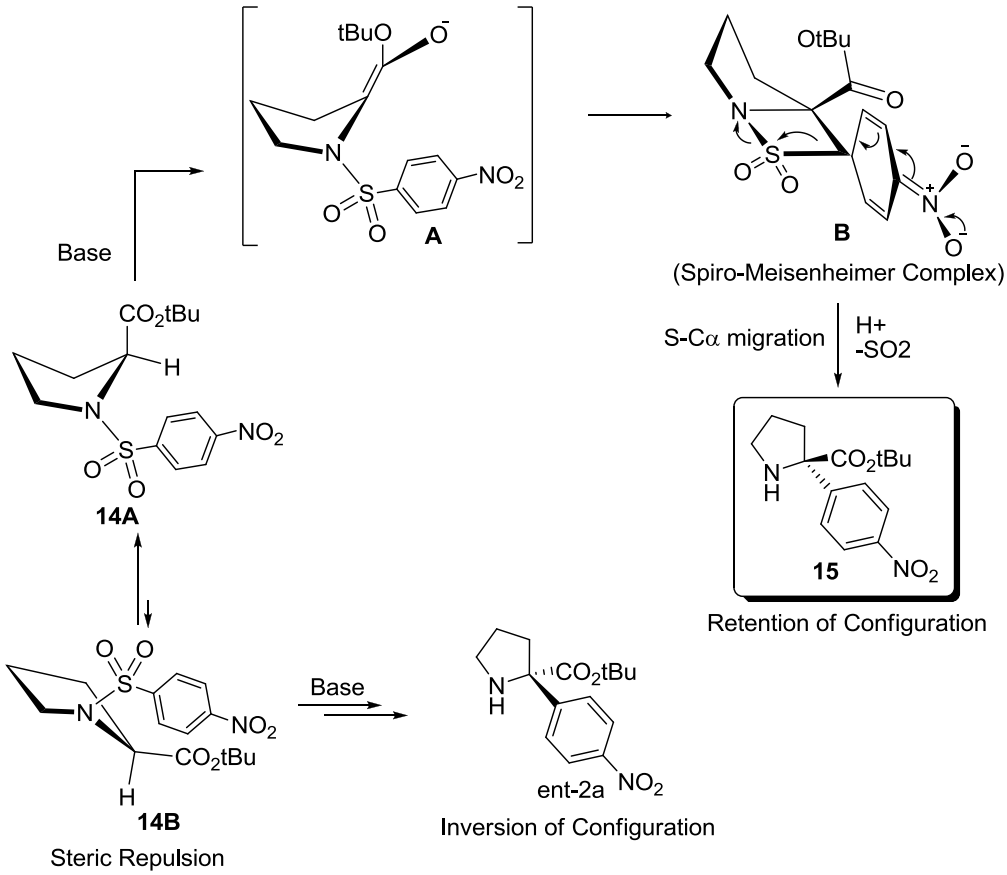


14 **15**

Entry	Base	Solvent	*t* (h)	**15**(%)	*ee* (%)
1	$NaNH_2$	DMA	0.25	90	94
2	$NaNH_2$	DMA	1.5	89	96
3	$NaNH_2$	DMF	1	68	94
4	$NaNH_2$	NMP	24	–	–
5	$NaNH_2$	DMSO	24	–	–
6	$LiNH_2$	DMA	24	–	–
7	LDA	DMA	0.25	–	–
8	LDA	THF	24	–	–
9	LDA	DMF	96	40	77
10	*t*BuOK	DMA	48	15	92
11	DBU	DMA	48	–	–
12	MeONa	DMA	48	–	–
13	NaH	DMA	26	79	94
14	NaH/NH_3	DMA	1	97	94

85 Foschi, F.; Landini, D.; Lupi, V.; Mihali, V. ; Penso, M.; Pilati, T.; Tagliabue A. *Chem. Eur. J*. **2010**, *16*, 10667.

The elevated reaction rates, together with the high yields and ee's, highlight the paramount efficiency of $NaNH_2$: in fact, the reaction is 10^2 times faster than with NaH. Sodium amide was used, because ammonia produced in the process solvates the sodium ion associated to the carbanion derived from **14**, forming a loose ion-pair that is much more reactive than the unsolvated tight ion pair generated by deprotonation with sodium hydride. Deprotonation of the less crowded conformer of the substrate **14A,** in which the arylsulfonyl group is far from the *tert*-butyl ester, gives the non-racemic enolate **A**. This intermediate, through a *Re*-face attack, evolves into a chiral spiro-Meisenheimer complex **B** that, in turn, undergoes the *S*-C_α migration of the aryl group, with an overall configuration retention (Scheme 6).

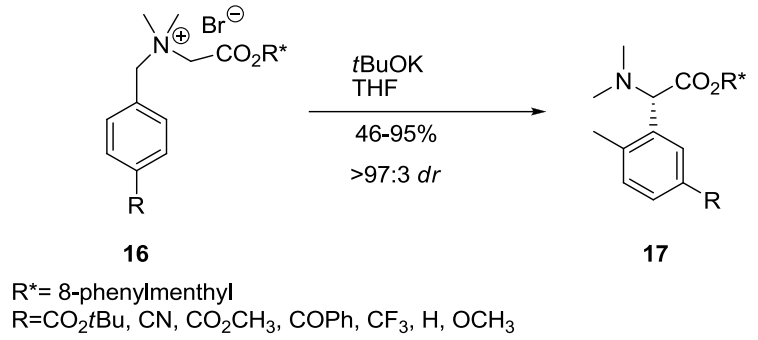


Scheme 6

Tayama et al. recently described the straightforward application of the Stevens and Sommelet–Hauser (S.–H.) rearrangements in the preparation of non-natural amino acid derivatives.[86] In

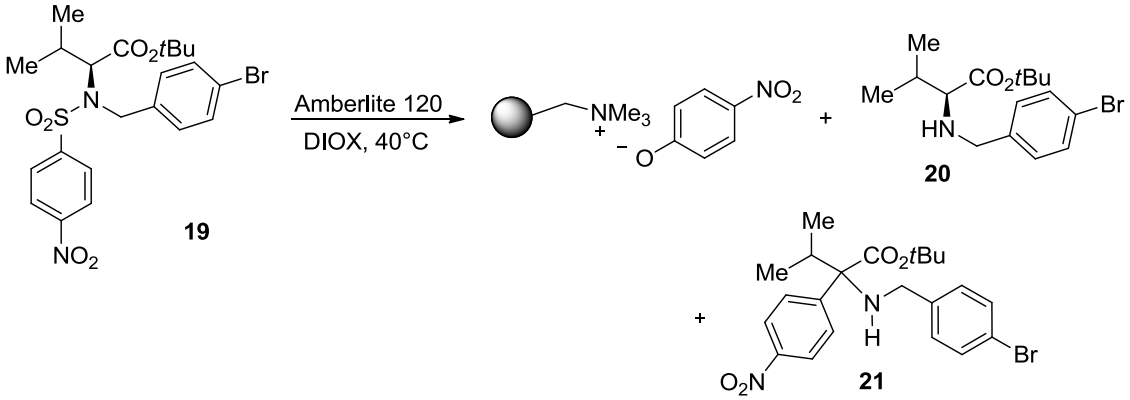
86 (a) E. Tayama, K. Orihara and H. Kimura, *Org. Biomol. Chem.*, **2008**, 6, 3673; (b) E. Tayama, S. Nanbara and T. Nakai, *Chem. Lett.*, **2006**, 35, 478.

particular, the S.–H. rearrangement of *N*-benzylic α-ammonium acid esters gave quaternary α-aryl-α-amino esters, through a [2,3]-sigmatropic shift of an aromatic ring, bearing an electron-withdrawing group. However, in order to display stereoselectivity, this process required the presence of the expensive (-)-8-phenylmenthyl ester that acts as a chiral auxiliary (Scheme 7).



Scheme 7 Diastereoselective Sommelet-Hauser rearrangement

Wilson,[87] with the aim to deprotect a series of optically pure *N*-alkyl-*N*-(nitrobenzenesulfonyl)amino acid *tert*-butyl esters, found that the reaction between the tertiary protected amino acid and the basic ion exchange resin (Amberlite 120) gave a large amount of a by-product. As an example, in the reaction of valine derivative **19** (Scheme 8), the analyses of by-product **21** (^{1}H NMR and Mass spectral analyses) were consistent with the absence of sulfur dioxide.

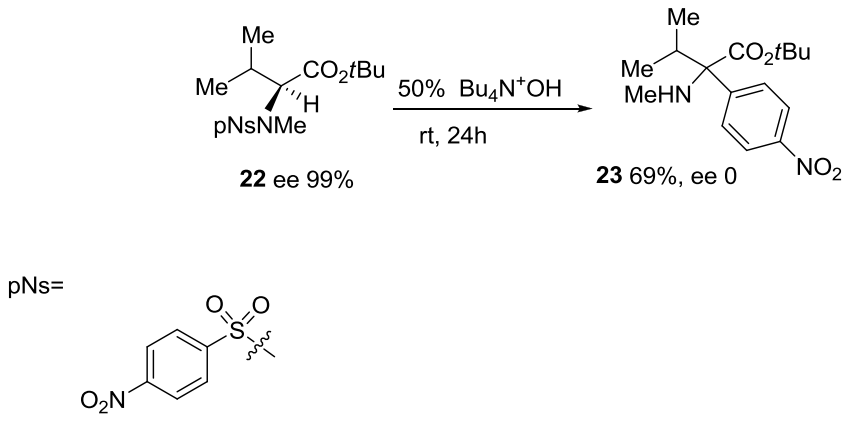


Scheme 8

87 M. W. Wilson, S. E. Ault-Justus, J. C. Hodges and J. R. Rubin, *Tetrahedron* **1999**, *55*, 1647.

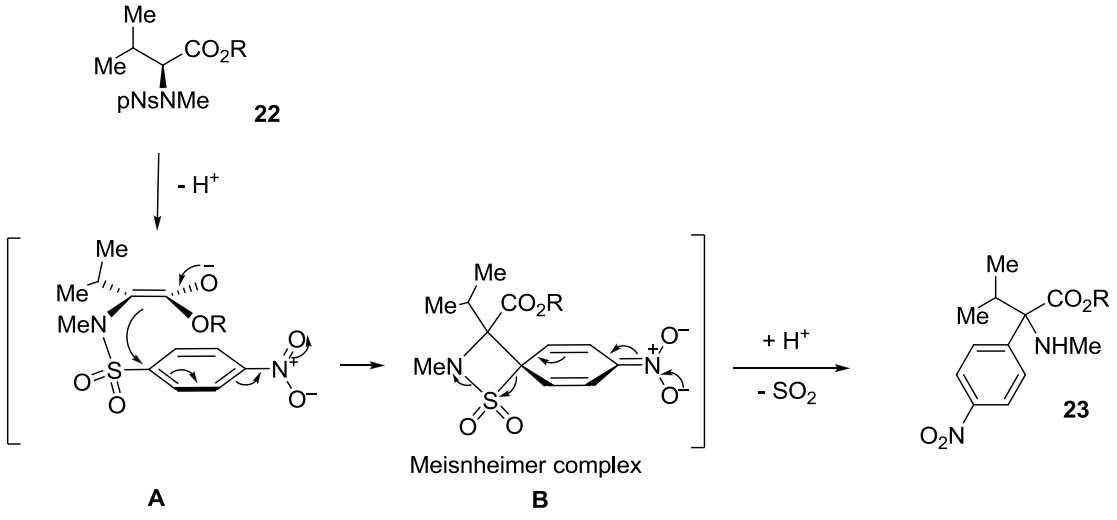
The X-ray crystallographic analysis of the **21** hydrochloride salt confirmed both his structure and racemic nature**.**

Further investigations revealed that quaternary amino ester **23** could be obtained as the main product as a racemic mixture, when 50% aqueous $Bu_4N^+OH^-$ solution was used as a base (Scheme 9).



Scheme 9

The migration of the 4-nitrophenyl moiety is due to the intramolecular nucleophilic attack of the enolate **A** toward the aromatic ring, which affords the Meisenheimer intermediate **B** (Scheme 10).

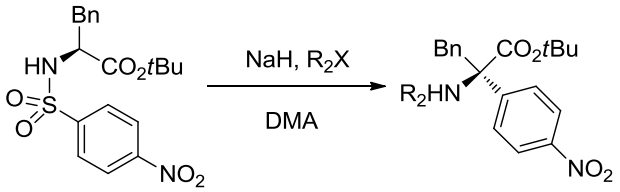


Scheme 10

Subsequent *S*-C_α migration of the *p*-nitrophenyl group is promoted by loss of sulfur dioxide, whom gaseous nature act as a strong driving force shifting the equilibrium toward the product **23**. An analogous rearrangement has been reported for a 9-(*N*-4-nitrobenzenesulfonyl-*N*-methylamino) fluorene system[88] and 2-cyano-(*N*-4-ntirobenzenesulfonyl)- acetamide.[89]

Recently, we have reported[90] on a powerful method for enantioselective C–C bond formation in a synthesis of quaternary α-aryl-α-amino acids, starting from optically pure phenylalanine derivative (Table 7).

Table 7 Rearrangement of sulfonamido *tert*-butyl ester **24a** with several alkylating agents R^2X



24a **25a-h**

entry		R^2X	at 0 °C			at -20 °C		
			t (h)	yield (%)	*ee* (%)	t (h)	ayield(%)	*ee* (%)
1	**a**	AllBr	5	**25a** 87	62	48	**25a** 85	74
2	**b**	MeI	2	**25b** 96	82	24	**25b** 90	91
3	**c**	EtI	7	**25c** 99	57	–	–	–
4	**d**	*n*PrI	16	**25d** 80	57	–	–	–

88 Meng, Q.; Thibblin, A. *J. Am. Chem. Soc.* **1997**, *119*, 1224-1229.

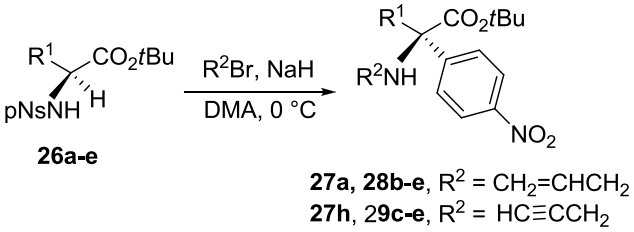
89 Naito, T.; Dohmori, R.; Nagase, O. *J. Pharm. Soc. Japan.* **1954**, *74*, 593-595.

90 Lupi V.; Penso M.; Foschi F.; Gassa F.; Mihali V.; Tagliabue A. *Chem. Commun.*, **2009**, 5012–5014.

5	**e**	*n*BuI	4	**25e** 86	62	–	–	–
6	**f**	$C_8H_{17}I$	16	**25f** 73	61	–	–	–
7	**g**	BnBr	4	**25g** 75	51	48	**25g** 84	61
8	**h**	PrgBr	8	**25h** 88	80	–	–	–

This methodology was extended using allyl bromide and propargyl bromide as alkylating agents to study the reactivity of several representative α-(*p*-nosylamido)acid *tert*-butyl esters (Table 8). Quantitative yields and very high ee's of the corresponding rearranged products (>95%) were reached with strongly hindered valine (**26d**) and isoleucine (**26e**) derivatives (entries 4, 5, 8, 9). The phenylglycine derivative **26b** is very sensitive to basic conditions and reacted with poor enantioselectivity (entry 2). Due to the ready *N*-deallylation, the *N*-allyl derivatives **27a** and **28** are useful intermediates for the preparation of the *N*-unsubstituted α-quaternary α-amino acids.

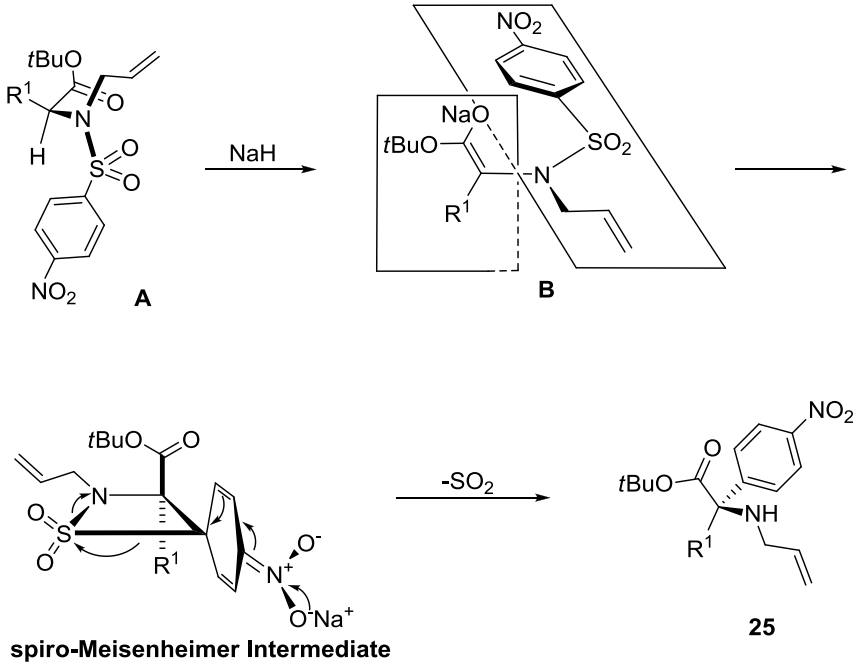
Table 8 Alkylation–rearrangement of *tert*-butyl esters **26a–e** with allyl and propargyl bromide



			N-Allyl Derivative					
Substrate			At 0 °C			At -20 °C		
Entry		R^1	t (h)	Yield (%)	*ee* (%)	t (h)	Yield (%)	*ee* (%)
1	**26a**	$PhCH_2$	5	**27a** 87	62	48	**27a** 85	74
2	**26b**	Ph	28	**28b** 92	50	48	**28b** 65[b]	58
3	**26c**	Me	6	**28c** 89	59	16	**28c** 89	68
4	**26d**	*i*Pr	24	**28d** 99	95	–	–	–
5	**26e**	*s*Bu	26	**28e** 99	96	–	–	–

			N-Propargyl Derivative		
			t (h)	Yield (%)	*ee* (%)
6	**26a**	$PhCH_2$	8	**27h** 88	80
7	**26c**	Me	5	**29c** 93	68
8	**26d**	*i*Pr	20	**29d** 98	96
9	**26e**	*s*Bu	26	**29e** 97	98

Regarding the reaction mechanism, we hypothesized that the stereochemical information is transferred from the *N*-alkylated sulfonamide **24** to the final rearranged product **25** via a non-racemic enolate **B**. This intermediate, through a *Re*-face attack, evolves into a chiral spiro-Meisenheimer complex that, in turn, undergoes the stereoselective *S*-*C*α migration of the aryl group. The enolate **B** is probably formed by deprotonation of the less crowded conformer **A**, in which the arylsulfonyl group is far from the *tert*-butyl ester. (Scheme 11).

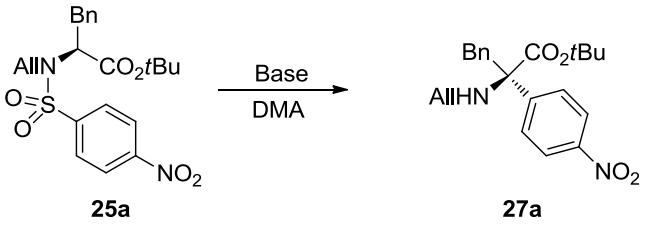


Scheme 11 Proposed mechanism and stereochemical course.

In order to generate a reactive intermediate (enol/enolate) in which the rotation along the C-N bond was minimum, we have chosen the *N*-allyl phenylalaninate **25a** as model compound for an extensive study devoted to find the optimal reaction conditions able to stabilize a chiral non racemic species.

Compound **25a** was reacted in the presence of several basic systems (Table 9). A support for our hypotheses was obtained from the reaction, in the presence of a strong organic base likes DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), under mild homogenous conditions. Using DMA as solvent, at 25 °C, the target compound **27a** was obtained in 95% *ee* (Table 9, entry 2). Also in these cases the retention product was the major enantiomer isolated.

Table 9 Rearrengement of *N*-allyl phenylalanine **25a** with different bases

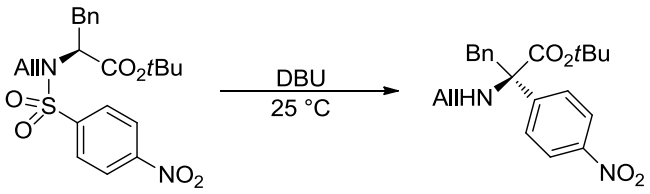


25a **27a**

entry	base	T (°C)	t (h)	**27a** (%)	*ee* (%)
1	NaH	0	1	90	28
2	$NaNH_2$	0	0.5	78	35
3	DBU	25	14	89	95
4	TMG	25	-	-	-
5	BTMG	25	-	-	-

We carried out several experiments using DBU as a base and varying the nature of the solvent (Table 10): in each reaction compound **27a** has been isolated in good yields, and the best ee was obtained using dimethoxyethane (DME) or DMA (Table 10, Entry 1-3). Eventually, our choice fell on DME, because of its higher vapor pressure thus easier removal.

Table 10 Rearrengement of *N*-allyl phenylalanine **25a** with different solvents

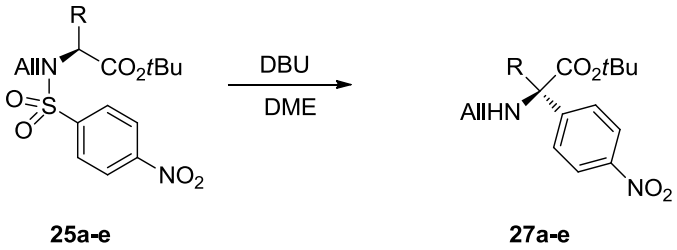


25a **27a**

entry	Solvent	T (°C)	t (h)	yield (%)	*ee* (%)
1	DMA	25	14	89	95
2	DME	25	12	94	95
3	DME/ DMA	25	10	94	94
4	THF	25	12	88	83
5	CH_2Cl_2	25	12	85	81

We have also studied the reactivity of a representative number of α- (*p*-nosylamido)acid *tert*-butyl esters **25** using DBU as organic soluble base and DME as a solvent (Table 11).

Table 11 Rearrengement of *N*-allyl α-amino-acids **25a-e**



25a-e **27a-e**

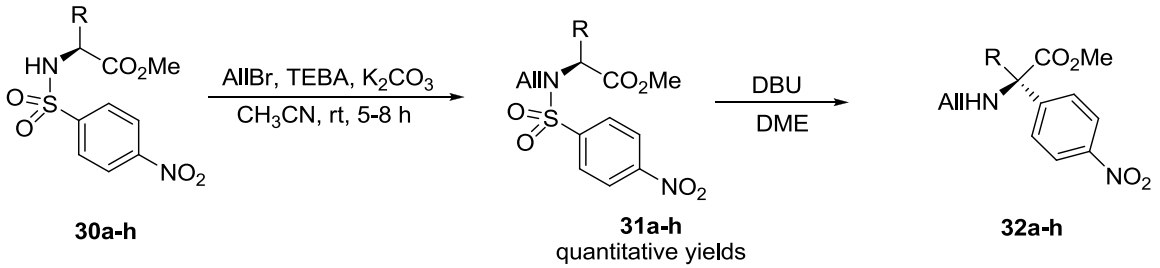
entry	R	T(°C)	t (h)	yield (%)	*ee* (%)
1	Phe	0	36	85	95
2	Phe	25	36	94	91
3	Ala	0	20	92	43
4	Leu	25	60	25	96
5	Val	25	60	30	95

While a low *ee* was detected using alanine (entry 3), very poor yields were obtained with strongly hindered valine and isoleucine derivatives (entries 4,5). The obtained data indicate a strong reactivity dependence on the increasing dimension of the side chain on the amino acid: the smaller the steric hindrance near the reacting centre, the greater the reaction reactivity.

Thus, the steric hindrance was decreased by using the methyl ester instead of *tert*-butyl ester. The methyl *N*-allyl-phenylalaninate **31a** was treated with DBU in DME (Table 12, entry 1).

Besides nearly quantitative yields, a very high *ee* of the corresponding rearranged products **32a, c-g** (entries 1, 4-8) and excellent diastereoselectivities of quaternary derivatives **32h-i** (entries 9-10) were reached.

Table 12 Rearrangement of *N*-allyl α-amino acid methyl esters **30a-h**



30a-h **31a-h** quantitative yields **32a-h**

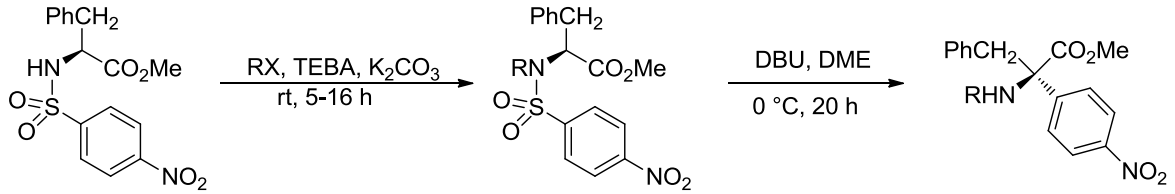
entry		R		T(°C)	t (h)	**32** (%)	*ee* (%)
1	**a**	Bn	Phe	0	14	95	95
2	**b**	Me	Ala	-50	16	90	55
3	**c**	4-$HOC_6H_4CH_2$	Tyr	0	16	88	88
4	**d**		DHPhG	0	48	94	79
5	**e**	*i*Pr	Val	25	48	93	95
6	**f**	$MeSCH_2$	Met	0	8	60	60
7	**g**	Me_2CHCH_2	Leu	25	36	78	90
8	**h**	(2*S*,3*R*)-MeCH(OH)	Thr	25	24	90	99 (*de*)
9	**i**	$MeCH_2CH(Me)$	*i* Leu	25	48	84	99(*de*)

In particular, under homogeneus conditions, we synthesized derivatives **32c,h** bearing a hydroxylic function like threonine or tyrosine (entries 4-9). On the contrary, unsatisfying ee were obtained with the alaninate derivative **32b** (entry 2), even operating at -50 °C (Table 12, entry 3)

Finally, we evaluated the reactivity of a series of alkyl halides RX using the phenylalanine derivative **30a** as model compound (Table 13). The use of SL-PTC for the synthesis of *N*-alkyl derivatives was the best choice because the reaction condition did not interest the stereocentre of the amino acid and the reaction proceeds with quantitative yields under mild condition.

The application of the homogeneus transposition conditions furnished the corresponding *N*-alkylated-α-quaternary esters **32a, i-n** in excellent yields, and *ee*'s major of 90%.

Table 13 Alkylation/Rearrangement of sulfonamide **30a** with several alkylating agents RX

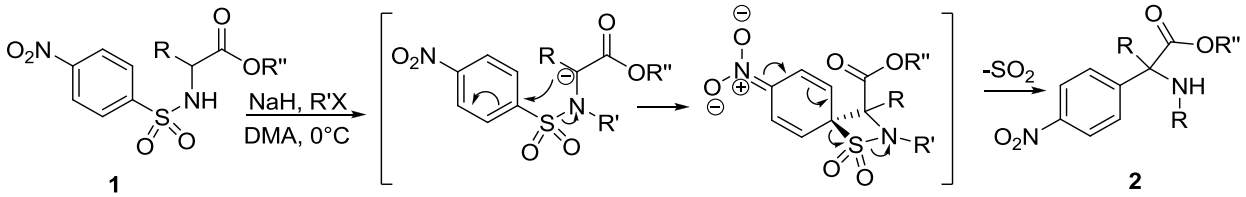


30a **31a, i-m** **32a, i-m**

entry		**R**	yield **31**%	yield **32** (%)	**32** ee (%)
1	**a**	All	98	95	95
2	**i**	Prg	95	84	92
3	**l**	Bn	96	84	90
4	**m**	Me	98	97	93
5	**n**	Bu	94	82	95

6 Results

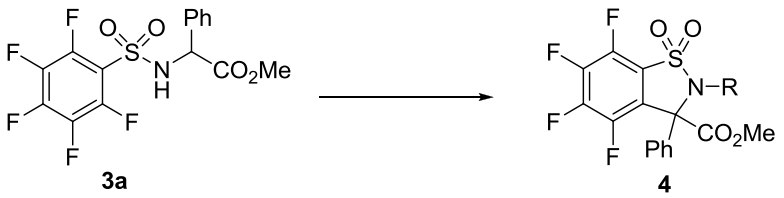
6.1 Synthesis of Racemic Benzosultams



Scheme 1

In the screening of various sulfonamido esters activated to this transposition, we tested the *N*-(pentafluorobenzene)sulfonyl derivative. In fact, we supposed that this compound, bearing the strongly electronegative five fluorine atoms, could easily give the bicyclic Meisenheimer activated structure, through the aromatic intramolecular substitution.

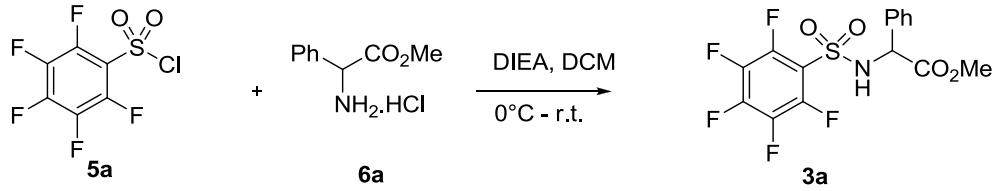
Preliminary tests showed a particularly interesting behavior of **3**: the molecule, after the initial *N*-alkylation with an alkyl halide, cyclizes by displacement of the fluorine atom in the ortho position to the sulfonyl group furnishing the N-alkyl benzo[d]isothiazole-1,1-dioxide 4 (Scheme 2).



Scheme 2

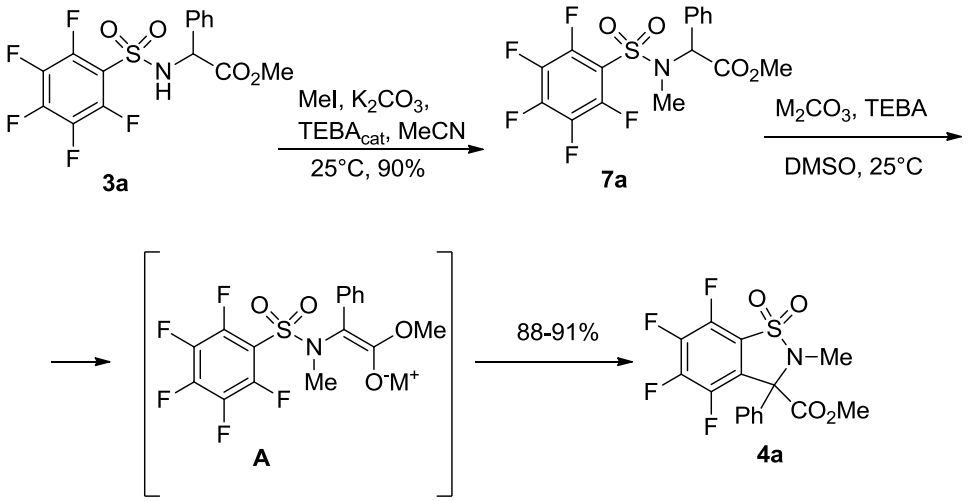
Starting materials are racemic (pentafluorobenzene)sulfonamides **3** prepared, in turn, from the corresponding α-amino esters.

Sulfonamide **3a** has been prepared by condensation of the commercially available (pentafluorobenzene)sulfonyl chloride **5a** and phenylglycine methyl ester hydrochloride **6a**.
The reaction, conducted at 0−25°C, in dichloromethane with di-(*iso*-propyl)ethylamine (DIEA) as a base, to neutralize the hydrogen chloride formed during the condensation, gave the desired product **3a** in good yield after crystallization of the crude (Scheme 3).



Scheme 3

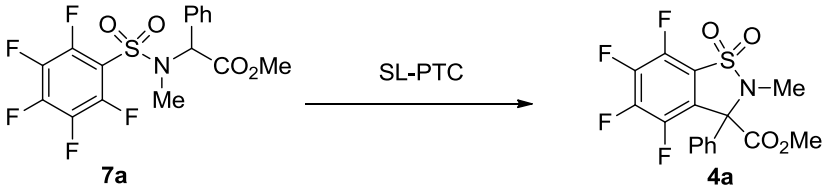
Sulfonamide **3a** was the starting point for an extensive study devoted to find the best reaction conditions for the cyclization. In a preliminary step, we studied the alkylation of **3a** with an activated alkylating agent, such as BnBr, MeI, etc. Analogously to that obtained with (4-nitrobenzene)sulfonamides, we found that solid-liquid phase transfer catalysis (SL-PTC) conditions provide good reactivity. The reaction was carried out in highly polar solvents, at room temperature, using a solid, anhydrous alkaline metal carbonate as a base, and in the presence of a catalytic amount (10% molar) of triethylbenzylammonium chloride (TEBA) as PTC agent. The initial step of the optimized SL-PTC procedure (Scheme 4) was the reaction of sulfonamide **3a** with methyl iodide in MeCN, in the presence of anhydrous K_2CO_3 (0.1 mol equiv.). The resulting *N*-methyl sulfonamide **7a** was transformed into the corresponding *N*-methyl(tetrafluorobenzo)[*d*]sultam **4a** by generating, under SL-PTC in DMSO, the enolate **A**, which rapidly cyclizes through an intramolecular nucleophilic displacement of the aromatic ortho fluorine atom.



Scheme 4

The role of the solvent is particularly crucial for the selectivity of both *N*-alkylation and ring-closing step (Table 1). Actually, rapid cyclization rate of **7a** and high yield of sultam **4a** were reached by operating in pure DMSO (entry 1) or in MeCN containing at least 1 mol equiv. of DMSO as an additive (entry 3). On the contrary, a low **7a** yield was obtained with a catalytic amount of DMSO (entry 4), indicating the formation of an equimolar adduct (**enolate A** : DMSO) as the plausible activated species. In pure MeCN, under analogous conditions, the starting material was recovered unchanged (entry 5), whereas at 50 °C only a minor yield of **4a** was obtained (entry 6).

Table 1

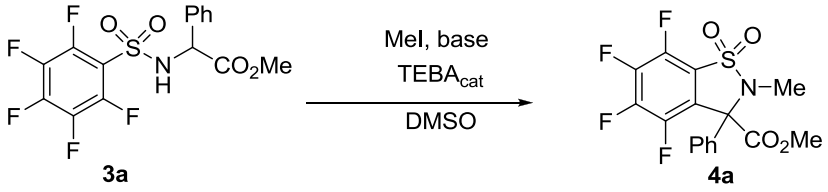


entry	solvent	DMSO (mol equiv.)	t (min)	**4a** (%)
1	DMSO	–	15	91
2	MeCN	5	90	89
3	MeCN	1	90	86
4	MeCN	0.1	90	68
5	MeCN	–	90	–
6	MeCN	–	90	5

In the screening for the best reaction solvent, the use of DMSO resulted in an increased yield of **4a** operating at 25°C in 20 h. As indicated by these preliminary data, DMSO shows the better solvent ability toward the cyclization process. In summary, an excess of potassium carbonate, in DMSO, at room temperature represent the best reaction conditions for the cyclization reaction.

With these results in hand, we focused our attention on the SL-PTC "one-pot" *N*-methylation/cyclization process (Table 2). Several experiments were performed by reacting sulfonamide **3a** with methyl iodide in DMSO, in the presence of different bases. Using anhydrous cesium carbonate, **4a** was isolated after 75 min in 94% yield (entry 1), whereas the reaction with potassium carbonate required longer reaction times (entries 2, 3). All the other tested bases gave lower yields of **4a**, but *n*-BuLi produced only byproducts, derived from nucleophilic substitution of aromatic fluorine atom(s) by *n*-butyl anion. Finally, the non-catalyzed process (i.e. entry 4, without PTC agent) was not complete even after prolonged reaction times and **4a** yield was moderate, thus confirming the effectiveness of the PTC agent.

Table 2

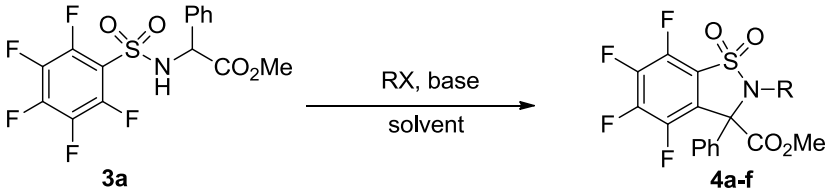


entry	base (mol equiv)	t (h)	**4a** (%)
1	Cs_2CO_3 (2)	1.25	94
2	K_2CO_3 (2)	2	88
3	K_2CO_3 (2)	20	92
4	K_2CO_3 (2)	20	61
5	Na_2CO_3 (2)	48	75
6	$NaHCO_3$ (5)	48	70
7	NaH (2.5)	26	28

The "one-pot" procedure was applied to the synthesis of different sultams, using several alkyl halides (Table 3). Good to acceptable yields of **4** were reached with ethyl, propyl, and butyl iodide, in DMSO at room temperature (entries 2–5). In the reaction with BuI, other non-hydrogen-bonding donor (non-HBD) solvents were tested, but only DMPU (entry 7) and NMP

(entry 8) gave comparable yields. In the reaction with benzyl bromide, an unexpected behavior was observed, both in DMSO and in MeCN. In fact, after a rapid conversion of **3a** to the *N*-benzylsulfonamide **7e**, only minor amounts of **4e** were isolated (entries 10-13). The reaction with allyl bromide gave a similar result (entry 14) indicating, most likely, that the introduction of the benzyl or allyl group increases the steric hindrance of both the intermediate open-chain sulfonamides **7e** and **7f**, reducing the cyclization rate, as confirmed by the scarce efficiency of the PTC ring-closing of *N*-benzyl sulfonamide **7e** (**4e** in 45% yield) prepared, in turn, by *N*-benzylation of **3a** in 88% yield.

Table 3

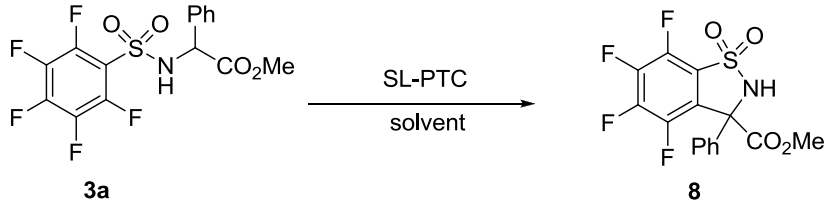


3a **4a-f**

entry	RX	solvent	base (mol equiv)	t (h)	yield (%)
1	MeI	DMSO	Cs_2CO_3 (2)	1.25	**4a** 94
2	EtI	DMSO	K_2CO_3 (2)	20	**4b** 83
3	EtI	DMSO	Cs_2CO_3 (4)	12	**4b** 81
4	*n*-PrI	DMSO	K_2CO_3 (2)	24	**4c** 51
5	*n*-PrI	DMSO	Cs_2CO_3 (4)	16	**4c** 50
6	*n*-BuI	DMSO	K_2CO_3 (4)	48	**4d** 61
7	*n*-BuI	DMPU	K_2CO_3 (2)	48	**4d** 58
8	*n*-BuI	NMP	K_2CO_3 (2)	20	**4d** 62
9	*n*-BuBr	DMSO	K_2CO_3 (2)	48	**4d** 37
10	BnBr	DMSO	Na_2CO_3 (4)	20	**4e** 32
11	BnBr	DMSO	Cs_2CO_3 (4)	12	**4e** 20
12	BnBr	MeCN	Na_2CO_3 (4)	20	**4e** 15
13	BnBr	MeCN	Na_2CO_3 (4)	20	**4e** 12
14	AllylBr	MeCN	Na_2CO_3 (4)	24	**4f** 46

In order to solve this problem, we thought that the ring closure of the sulfonamide **3a** without the alkylating agent, would lead to the non-alkylated sultam **8**, a much more interesting compound. This molecule, in fact, is the single scaffold which could eventually be N-alkylated in a subsequent step, therefore this way represents a valid alternative to the "one-pot" cyclization. A screening of reaction conditions showed that PTC technique failed (Table 4, entry 1) even when drastic conditions were applied (entry 2); a change in the anhydrous alkaline carbonate indicates a decreasing yield along the series Na > K > Cs (entries 2-4), while any attempt to change the reaction solvent (entries 5,6) was unsuccesful.

Table 4

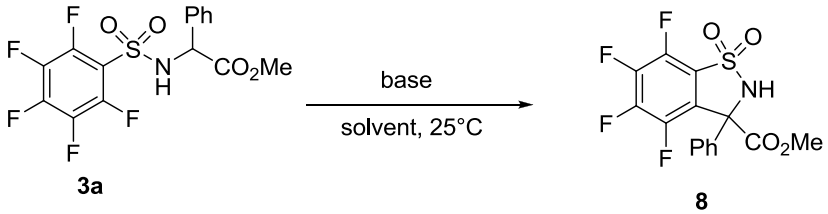


3a **8**

entry	solvent	base	T(°C)	t (h)	Yield **8** (%)
1	DMSO	Na_2CO_3	25	90	-
2	DMSO	Na_2CO_3	80	90	28
3	DMSO	K_2CO_3	50	90	10
4	DMSO	Cs_2CO_3	50	90	8
5	DMF	Na_2CO_3	80	60	-
6	MeCN	Na_2CO_3	80	60	-

After these negative results obtained under PTC conditions, we turned our attention to the cyclization of the *N*-unsubsituted sultams under homogeneous conditions, considering that it is well known that many organic soluble bases are able to enolize carboxylic derivatives. Among the bases employed DBU gave the best yields (Table 5, entries 4,5); 1,4-diazabycyclo[2.2.2]octane (DABCO, entry 3) gave low yields, while tetramethylguanidine (TMG, entry 2) gave good yields but in very long times. Also in this case, the choice of the solvent is important as demonstrated by the different yields obtained passing from DMSO (entry 1) to the less polar DME (entries 4).

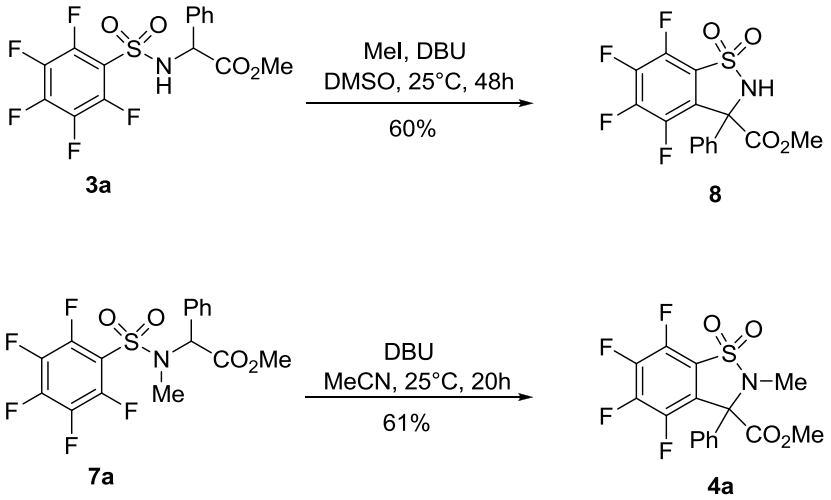
Table 5



3a **8**

entry	solvent	base	t (h)	yield **8** (%)
1	DMSO	DBU	48	62
2	MeCN	TMG	80	96
3	MeCN	DABCO	24	54
4	DME	DBU	16	96
5	MeCN	DBU	20	98

The application of the homogeneous methodology to the "one-pot" synthesis of the *N*-methyl benzosultam **4a** starting from sulfonamide **3a** with excess MeI, gave only low yields of the non-alkylated benzosultam **8**. Analogously, the cyclization of the *N*-methyl sulfonamide **7a** failed, producing the correspondent sultam **4a** only in modest yield (Scheme 5).



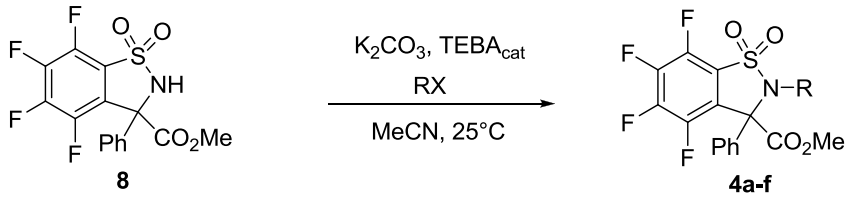
3a **8**

7a **4a**

Scheme 5

To complete the synthetic procedure, the NH sultam **8** has been reacted under SL-PTC conditions with a series of alkyl halides RX (Table 6), and the desired *N*-alkyl tetrafluorobenzo sultams **4a-f** were obtained in very good overall yields (74-90%), starting from sulfonamide **3a**.

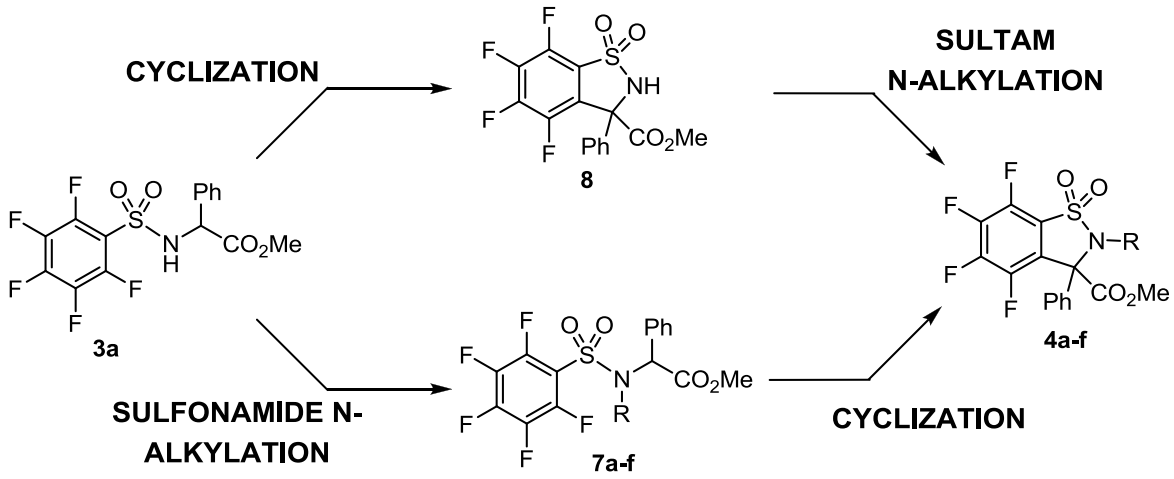
Table 6



entry	RX	t(h)	yield (%)
1	MeI	18	**4a** 99
2	EtI	48	**4b** 95
3	*n*-PrI	48	**4c** 88
4	*n*-BuI	48	**4d** 82
5	BnBr	20	**4e** 85
6	AllBr	20	**4f** 82

These results clearly show that homogeneous cyclization followed by N-alkylation emerges as the best protocol to produce *N*-alkyl benzo[*d*]sultams, and preferred alternative to the "one-pot" cyclization, especially in the case of the bulky benzyl and allyl derivatives **4e** and **4f**.

In summary, sulfonamides **3a** have been cyclized to the corresponding benzo[*d*]sultams through two different and complementary synthetic pathways: *N*-Alkylation of open-chain sulfonamides **3a** with an alkyl halide, then cyclization of the intermediate *N*-alkylsulfonamide **7a-f** under solid-liquid phase transfer catalysis (SL-PTC) conditions, gave the corresponding *N*-alkylbenzosultams **4a-f**. Alternatively, using DBU as organic soluble base under homogeneous conditions, sulfonamides **3a** were transformed into the unsubstituted benzosultams **8** that, in turn, can be *N*-alkylated to sultams **4a-f** (Scheme 6).

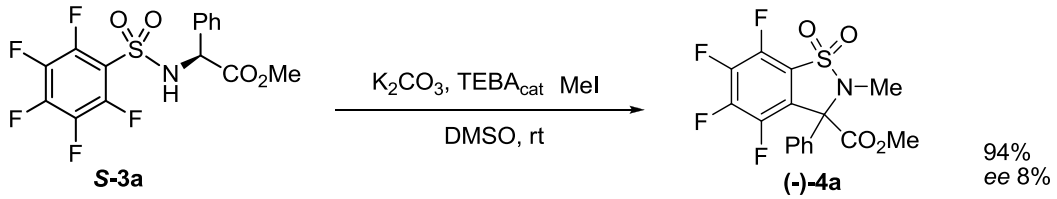


Scheme 6

6.2 Enantiodivergent Synthesis of Chiral Benzo[d]sultams

After having defined the optimal conditions to reach the highest yields for the cyclization step, we turned our attention to the stereoselective synthesis of our sultams: in fact, as we have seen in the previous chapter, the synthesis of optically pure benzo[*d*]sultams is a subject of great interest, even in the light of the very small number of synthetic methods available in literature.

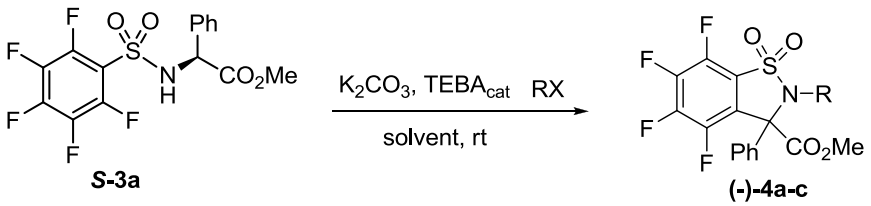
When we performed the SL-PTC "one pot" reaction on the optically pure sulfonamide ***S*-3a**, we found small but encouraging enantiomeric excess of benzosultams (Scheme 7) with the prevalence of the (-) isomer.



Scheme 7

Moreover, the variation of the alkylating agent led to a continuous, even if low, increase of *ee*'s with the increasing dimension of the alkyl chain, along with decreasing yields (Table 7).

Table 7



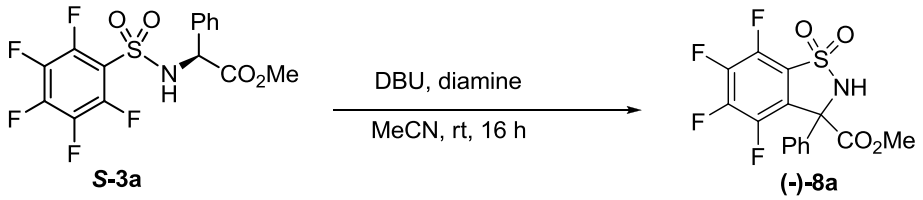
entry	solvent	RX	t (h)	yield (%)	*ee* (%)
1	DMSO	EtI	20	83	16
2	DMSO	*n*-PrI	24	50	25
3	DMF	MeI	48	47	13

The complete absence of an external source of stereochemical information, suggested to investigate the nature of the auto-induced stereoselectivity and the influence of the single reaction parameters of the cyclization process.

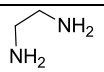
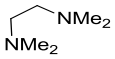
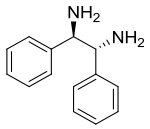
In the light of the very scarce results obtained under heterogeneous conditions, we turned our attention to the cyclization under homogeneous conditions. Since the ring-closing of sulfonamide ***S*-3a** with DBU as a base in CH_3CN, as described before, leads to the racemic benzosultam, we decided to evaluate the use of an additive in the system sulfonamide-DBU, looking for additive-base-substrate interactions capable of inducing the formation of a chiral adduct, which can evolve enantioselectively toward the desired benzosultam.

Preliminary positive results have been obtained by reacting ***S*-3a** with DBU, in acetonitrile at 25°C in the presence of 0.2 molar equivalents of a diamine: the choice fell both on simple diamines (Table 8, entries 1-4) and on more complex chiral diamines (entries 5-8). All these reactions gave an almost quantitative yield of **8a** and the *ee* ranging from 19 to 23%. The results show that the added base induces a general effect, probably due to a modulation of the DBU basic strength, rather than to the formation of a chiral complex.

Table 8

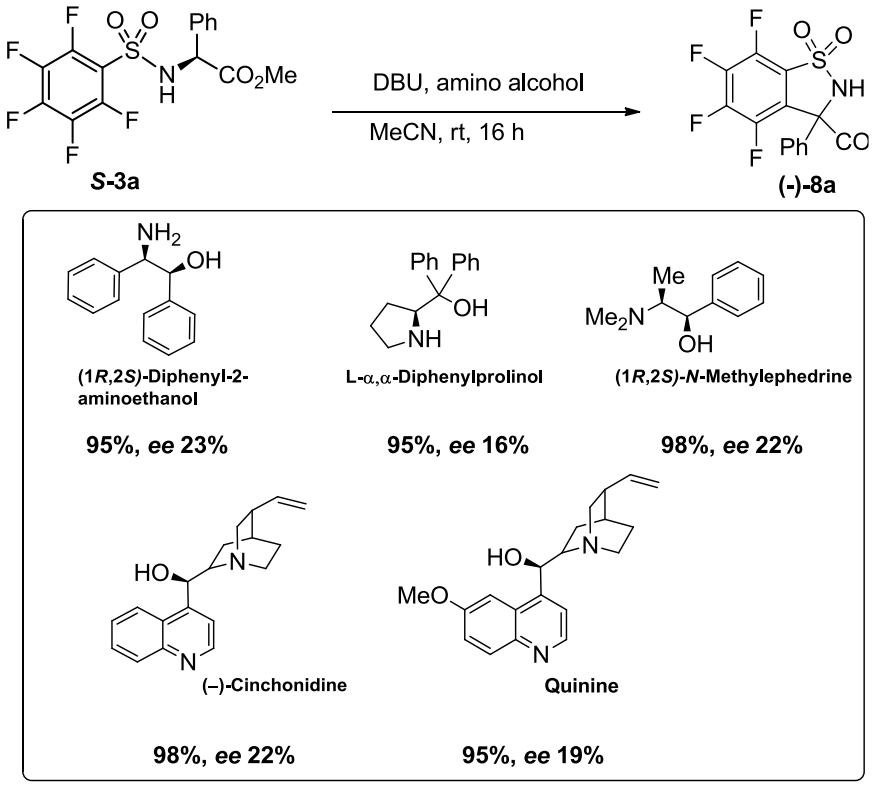


***S*-3a** **(-)-8a**

entry	diamine	yield (%)	*ee* (%)
1		98	21
2		98	20
3		98	19
4		98	23
5		98	21
6	(*RR*)-1,2-diamino cyclohexane	97	23
7	(*SS*)- 1,2-diamino cyclohexane	98	22
8	*rac*-1,2-diamino cyclohexane	98	22

This hypothesis is confirmed by the reaction of the achiral bases (entries 1-4) and by the use of both the enantiomer of 1,2-diaminocyclohexane (entries 6-7), and of their racemic mixture (entry 8). All these reactions, in fact, lead to nearly identical *ee* values, with prevalence of the same enantiomer **(-)-8a**.

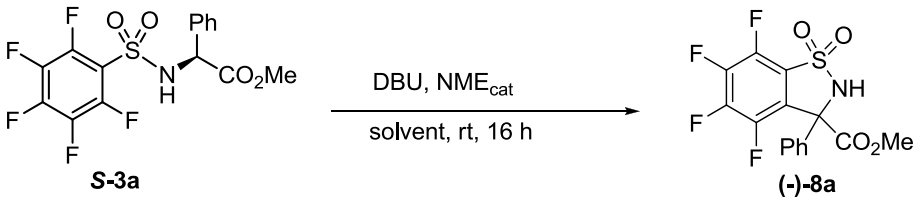
Similar results were obtained by addition of both a chiral amino alcohol (Scheme 8) and cinchona alkaloid derivatives, compounds that are often used in asymmetric synthesis.



Scheme 8

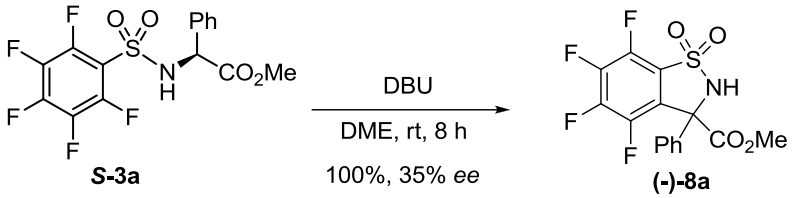
Several experiments were then conducted with (1*R*,2*S*)-*N*-methylephedrine as additive and by varying the solvent (Table 9): the best *ee*'s were obtained in ethereal solvents like THF (entry 2) and DME (entry 3). In DCM (entry 4) both *ee*'s and yields were very low, while in chlorobenzene and toluene quantitative yields and, conversely, poor *ee* values were obtained (entries 5-6).

Table 9



entry	solvent	yield (%)	*ee* (%)
1	MeCN	98	22
2	THF	98	24
3	DME	98	33
4	DCM	85	14
5	PhCl	98	18
6	toluene	95	18

An improved result was reached by using DME as a solvent and DBU alone and **(-)-8a** was isolated in quantitative yield and with 35 % *ee* in favor of the (−) isomer (Scheme 9).



Scheme 9

With the aim of screening the effects of both the strength and the structure of the base/additive, we carried out experiments (Table 10) in DME with a series of bases (Figure 1) similar to DBU regarding structural characteristics and/or basicity.

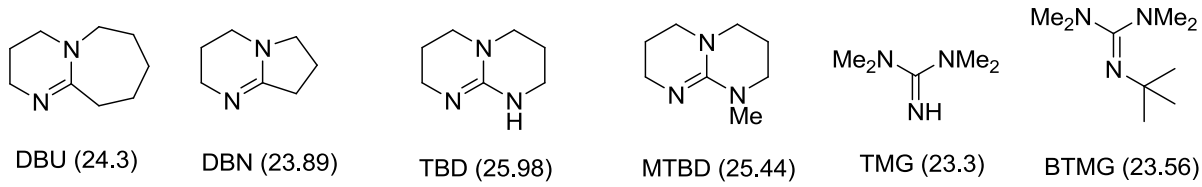
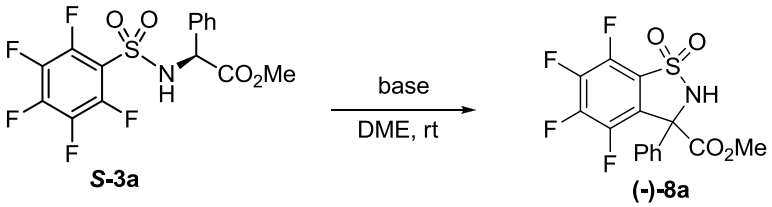


Figure 1. Organic bases used in the sultam **8a** synthesis**.** In parentheses, pk_a value of the conjugate acid in acetonitrile.

Among bicyclic bases, only MTBD (entry 4) was partially effective, giving a *ee* comparable to that obtained with DBU, but in a longer reaction time. Surprisingly, BTMG completely reversed the enantioselectivity in favor of the (+) isomer with the highest *ee* found until now (entry 6).

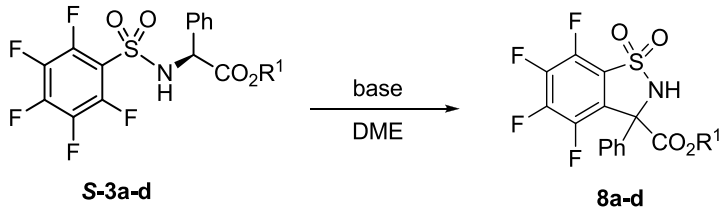
Table 10



entry	base	solvent	t (h)	yield (%)	*ee* (%)
1	DBU	DME	8	98	(-) 35
2	DBN	DME	16	94	(-) 14
3	TBD	DME	16	98	< 5
4	MTBD	DME	20	56	(-) 38
5	TMG	DME	16	90	< 5
6	BTMG	DME	90	95	(+) 80

The influence of the ester group bulkiness was also analyzed (Table 11): as expected, the larger the alkyl group, the higher the *ee*, but the longer the reaction time and, when BTMG was used, only partial conversion was reached (entry 5). By decreasing the reaction temperature to 0 °C better *ee*'s were reached, but the reaction rate drastically dropped, especially in the case of *tert*-butyl ester (entry 6). Considering these results, we decided to conduct the following experiments on methyl ester (***S*-3a**) by operating at 25 °C.

Table 11



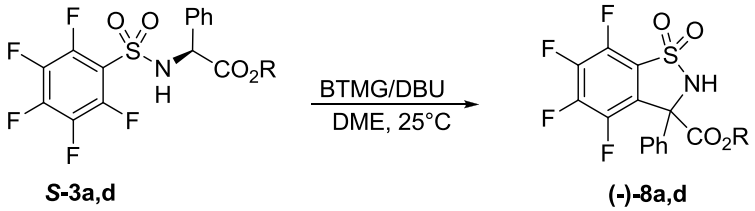
***S*-3a-d** **8a-d**

entry	R^1		base	T (°C)	t (h)	product	yield (%)	*ee* (%)
1	Me	**3a**	DBU	25	8	**8a**	96	(-) 35
2	Et	**3b**	DBU	25	16	**8b**	94	(-) 44
3	*i*Pr	**3c**	DBU	25	20	**8c**	93	(-) 48
4	*t*Bu	**3d**	DBU	25	20	**8d**	91	(-) 52
5	*t*Bu	**3d**	BTMG	25	140	**8d**	37	(+) 88
6	*t*Bu	**3d**	DBU	0	160	**8d**	66	(-) 68

In the light of the possibility to choose between chiral and achiral base/additive, we focused our attention on the good results obtained with BTMG (entry 5).

Interesting results were achieved using the system BTMG/DBU in variable molar ratios (Table 12): the use of a large molar excess of BTMG (entries 1−3) with decreasing quantity of DBU led to prolonged reaction times, but gave good *ee*'s. The best *ee* of the methyl ester **(-)-8a** was obtained using equimolar amount of the two bases (entry 5). A similar behavior was found with the *tert*-butyl ester ***S*-3d**, which gave the desired sultam **(-)-8d** in 54% *ee* in longer reaction times (entry 6).

Table 12

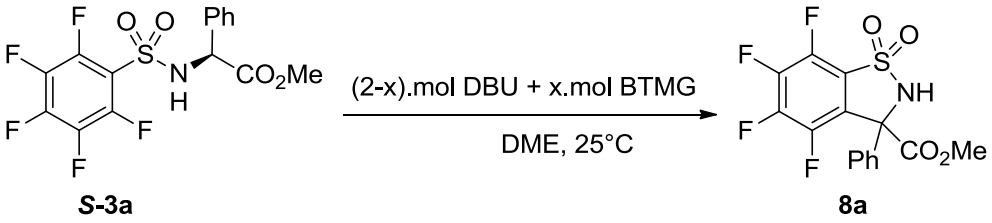


***S*-3a,d** **(-)-8a,d**

entry	R	BTMG (mol)	DBU (mol)	t (h)	product (%)	*ee* (%)
1	Me	4	2	20	**(-)-8a** 96	50
2	Me	4	0.5	20	**(-)-8a** 96	48
3	Me	4	0.25	30	**(-)-8a** 93	47
4	Me	2	1	20	**(-)-8a** 95	48
5	Me	1	1	20	**(-)-8a** 91	53
6	*t*Bu	1	1	144	**(-)-8d** 90	54

To better understand the outcome of the cyclization reaction, it was then conducted by using molar amounts of DBU as a base in association with variable quantities of BTMG. In fact, the runs carried out by varying the ratio of the basic system DBU/BTMG (Figure 3) evidenced a strong synergistic effect between the two bases on the enantioselectivity, i.e. the *ee* value increased in favour of the retention product by increasing the amount of BTMG, up to a maximum (*ee* 67%) with a 7:93 DBU/BTMG molar ratio; as reported before, by using only BTMG as a base (Table 13, entry 7), the enantioselectivity drastically changed in favour of the inverted configuration (Figure 2, right side of the graphic).

Table 13



entry	BTMG (×mol %)	t (h)	yield (%)	*ee* (%)	*er* (%)
1	0	8	98	(-)35	(-)68
2	25	16	95	(-)44	(-)73
3	50	20	96	(-)53	(-)77
4	75	24	95	(-)63	(-)82
5	93	24	94	(-)67	(-)83
6	95	24	97	(-)64	(-)84
7	100	90	95	(+)80	(+)90

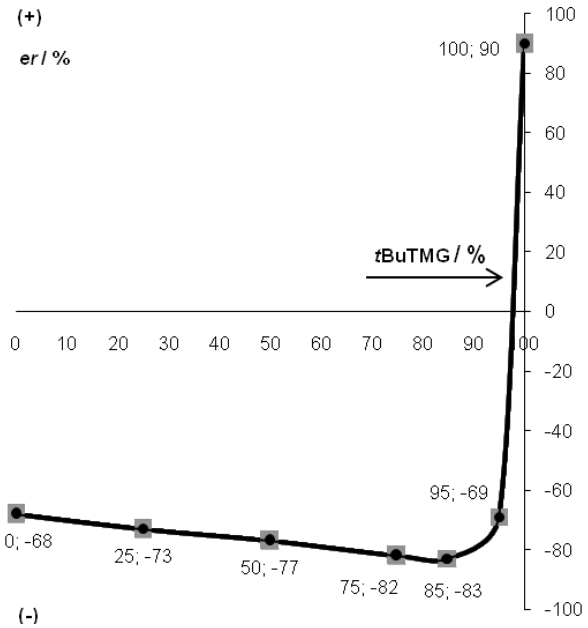
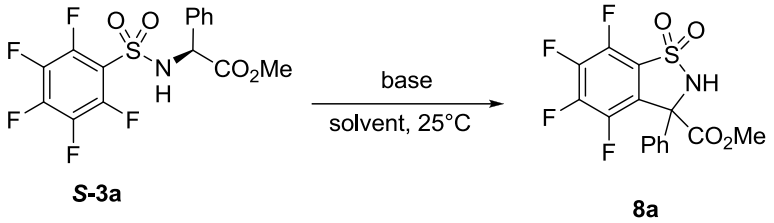


Figure 3. Synthesis of sultam **8a** under homogeneous conditions using the basic system DBU/BTMG (2 mol equiv.): influence of the bases ratio variation on the *er*. On the abscissas is the molar percentage of BTMG; on the ordinates is the percentage of the main enantiomer.

We have also observed that the use of DME as the reaction solvent is essential for the enantiodivergent course of this process. In fact, by operating in more polar solvents (Table 14), such as DMSO or MeCN (entries 3-6), longer reaction times and very low *ee*'s were found.

Table 14

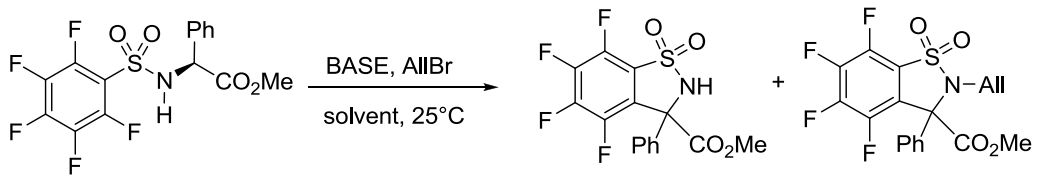


***S*-3a** **8a**

entry	solvent	base	t (h)	yield (%)	*ee* (%)
1	DME	BTMG/DBU	24	**(-)-8a** 94	67
2	DME	BTMG	90	**(+)-8a** 95	80
3	DMSO	BTMG/DBU	1 week	**(+)-8a** 70	< 5
4	DMSO	BTMG	1 week	**(-)-8a** 30	< 5
5	MeCN	BTMG/DBU	48	**(+)-8a** 38	13
6	MeCN	BTMG	48	**(+)-8a** 76	10

Interestingly, the application of the best cyclization conditions (BTMG/DBU basic system or BTMG alone in DME) to ***S*-3a**, in the presence of an alkylating agent such as allyl bromide, gave the non alkylated sultam. On the contrary, by operating in DMSO we isolated the racemic *N*-allylated sultam **4f** (Table 15).

Table 15

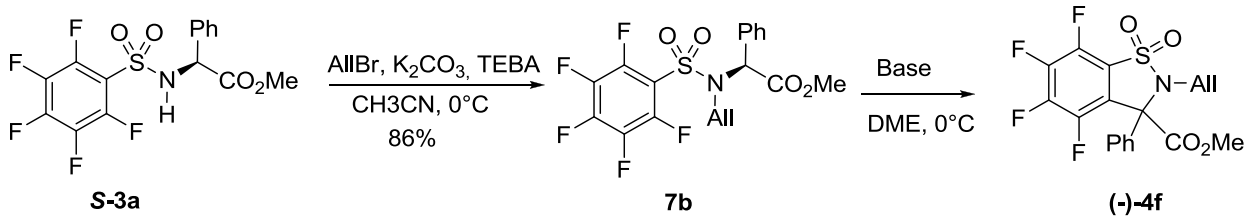


***S*-3a** **8a** **4f**

entry	solvent	base	t (h)	yield (%)	*ee* (%)
1	DME	BTMG/DBU	24	**(-)-8a** 94	67
2	DME	BTMG	90	**(+)-8a** 95	80
3	DMSO	BTMG/DBU	2	**4f** 60	–
4	DMSO	BTMG	2	**4f** 85	–

Furthermore, the optically pure *N*-alkylated tertiary sulfonamide **22**, prepared under SL-PTC conditions, gave in a short reaction time the corresponding *N*-allyl sultam **(-)-4f** in good yields, but with very low *ee*'s, in the presence of both BTMG and DBU/BTMG (Table 16).

Table 16

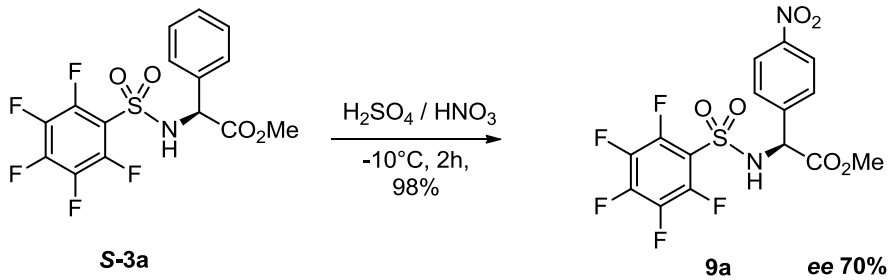


***S*-3a** **7b** **(-)-4f**

entry	base	t (min)	yield (%)	*ee* (%)
1	BTMG/DBU	15	**(-)-4f** 77	8
2	BTMG	20	**(-)-4f** 86	21

In order to analyze the effect of the H_α acidity on the stereoselectivity of the process, we modulated the mesomeric (M) and inductive (I) effects on the aryl moiety of the starting phenylglycine. Several sulfonamides were synthesized: sulfonamide **9a** (Scheme 10) bearing a *para*-nitro group (-M, -I); **9b** having an *orto*-chlorine atom (+M, -I); the *para*-biphenyl (+I) derivative **9c** (Scheme 12); sulfonamides **9d,e** containing strong *para*-$PhCH_2O$ (Scheme 13) and *para*-MeO (Scheme 14) electrondonating groups (+M).

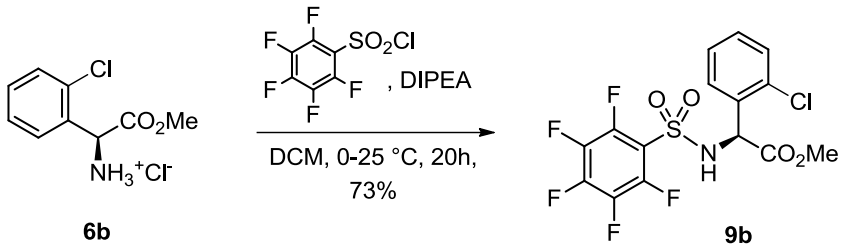
As regards the phenylglicine derivative **9a** bearing the *para*-nitro group position, the direct nitration of the sulfonamide ***S*-3a** was the only synthetic strategy we found to isolate an enantiomerically enriched (*ee* 70%) product (Scheme 10).



***S*-3a** **9a** ***ee* 70%**

Scheme 10

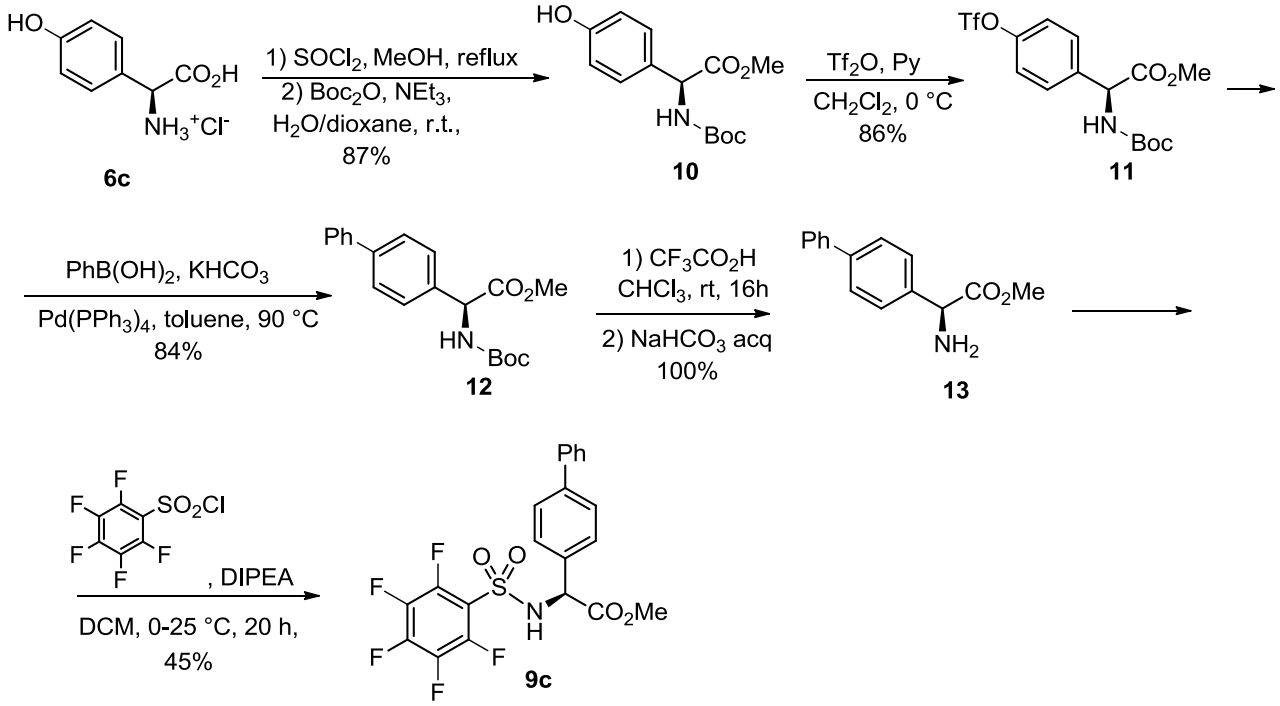
The enantiopure (pentafluorobenzene)sulfonamide **9b** was obtained by *N*-sulfonylation of the corresponding commercially available α-amino ester **6b** (Scheme 11).



6b **9b**

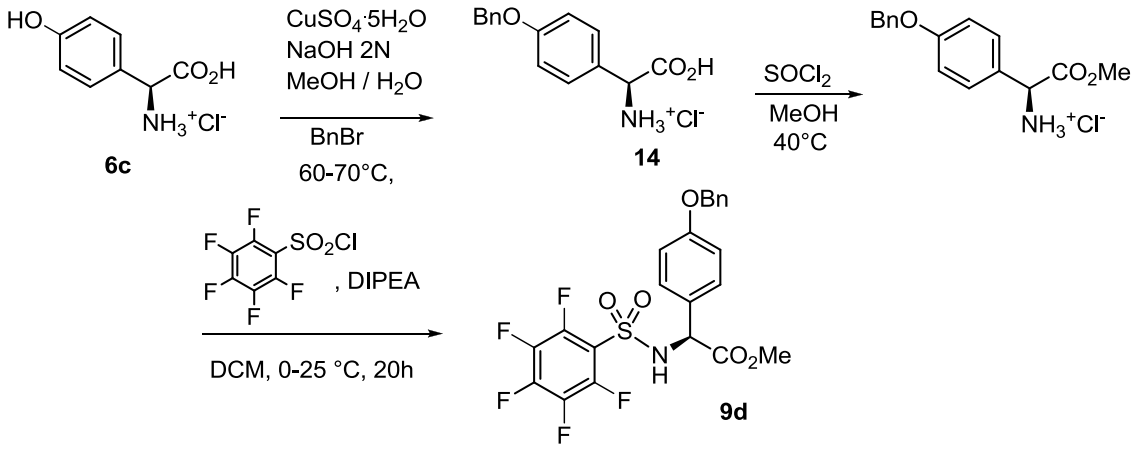
Scheme 11

Commercially available 4-hydroxy-D-phenylglycine **6c** was used as starting material for the synthesis of sulfonamide **9c** (Scheme 12). After esterification of the carboxylic function and protection of the amino group, the intermediate **10** was made to react with (trifluoromethane)sulfonic anhydride, to generate the corresponding triflate **11**, that was isolated in good yield. Suzuki cross-coupling reaction with phenylboronic acid in toluene, using tetrakis(triphenylphosphine)palladium as catalyst, led to the desired N-*tert*-butyloxycarbonyl-4'-biphenylglycine methyl ester **12** in 84% yield. The compound **12** was N-deprotected under acidic conditions to the hydrochloride of **13**, which is obtained as free amino ester by washing with aqueous saturated solution of $NaHCO_3$; **13** was finally sulfonylated as usual to the target compound **9c**.



Scheme 12

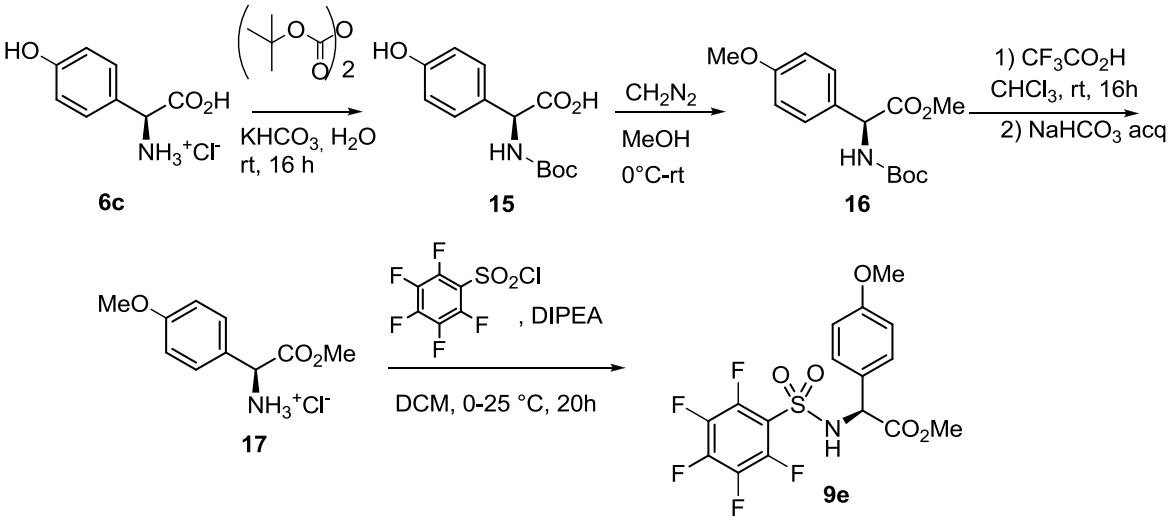
Sulfonamide **9d** (Scheme 13) was obtained from (4-hydroxyphenyl)glycine **6c** by alkylation with benzyl bromide, in the presence of copper(II) sulfate, to the benzyloxy derivative **14** that, in turn, was converted into the target sulfonamide **9d** by first esterification, followed by N-arylsulfonylation as usual.



Scheme 13

The sulfonamide **9e** (Scheme 14) was prepared starting from the *N*-Boc amino acid **15** that is transformed into its methyl ester **16** by reaction with diazomethane. The ester was N-deprotected

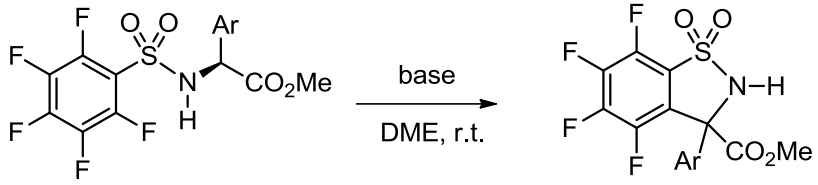
under acidic conditions to the hydrochloride **17**, which is sulfonylated as usual to the target compound **9e**.



Scheme 14

The results obtained in the cyclization reactions confirm that the presence of a substituent in *para* or *ortho* position effectively modulates the sulfonamide reactivity. In particular, the presence of an electron withdrawing group (EWG) on the aromatic ring was detrimental to the overall process, decreasing the reaction enantioselectivity. Actually, practical complete racemization was obtained starting from compounds **9a,b** with both the base systems (Table 17, entries 1-4). On the contrary, the presence of an electron donating group (EDG) in compounds **9c–e** produced good *ee*, the stronger the EDG the higher the *ee* value (entries 5-10). Furthermore, as found for ***S*-3a**, the reactions promoted by BTMG are sensibly slower than those promoted by BTMG/DBU also in the case of substrates **9**.

Table 17



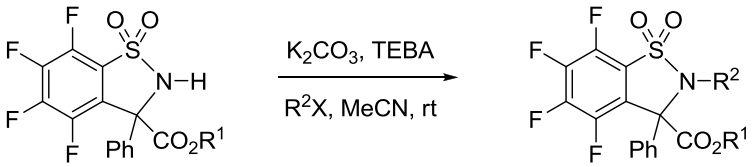
9a-e **18a-e**

base: A = BTMG
B = DBU/BTMG

entry	Ar	sulfonamide	base	product	yield (%)	*ee* (%)
1	4-$NO_2C_6H_4$	**9a**	A	(+)-**18a**	94	<5
2	4-$NO_2C_6H_4$	**9a**	B	(–)-**18a**	97	<5
3	2-ClC_6H_4	**9b**	A	(+)-**18b**	18	5
4	2-ClC_6H_4	**9b**	B	(–)-**18b**	19	15
5	4-PhC_6H_4	**9c**	A	(+)-**18c**	94	56
6	4-PhC_6H_4	**9c**	B	(–)-**18c**	98	64
7	4-$BnOC_6H_4$	**9d**	A	(+)-**18d**	35	96
8	4-$BnOC_6H_4$	**9d**	B	(–)-**18d**	83	94
9	4-$MeOC_6H_4$	**9e**	A	(+)-**18e**	70	94
10	4-$MeOC_6H_4$	**9e**	B	(-)-**18e**	79	95

Finally an important progress toward the obtainment of enantiopure benzosultams, was the *N*-alkylation of the enantio-enriched sultams here before. The non-racemic sultams were reacted under SL-PTC conditions with different alkyl halides and the *N*-alkyl derivatives **4** were isolated in good yields (Table 18).

Table 18

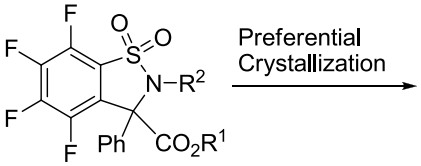


8a,d **4c,f,g**

	R^1	*ee* (%)	R^2X	product	yield (%)	*ee* (%)
(-)-**8a**	Me	68	AllylBr	**4f**	94	68
(-)-**8a**	Me	68	PrI	**4c**	95	68
(+)-**8d**	*t*Bu	87	MeI	**4g**	93	87

The *N*-alkylated benzosultams **4** were then subjected to preferential crystallization (Table 19). By this protocol, the optically pure enantiomers ***R*-4f** and ***S*-4g** were recovered from the mother liquor, after removal of the crystallized racemic mixture by filtration and evaporation of the solvent, whereas ***R*-4c** crystallized in an enantiopure form and the racemic mixture remained in the mother liquor. All these enantiomers were isolated in theoretical yields, i.e. equal to the enantiomeric excess values of the starting compounds.

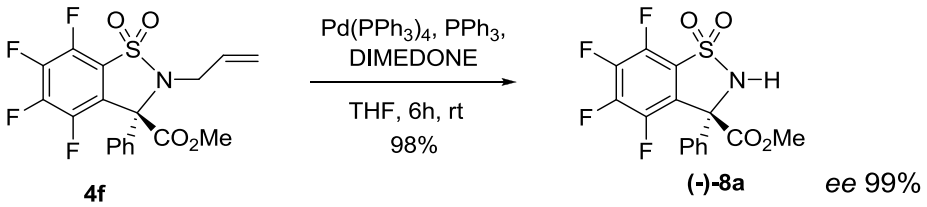
Table 19



4c,f,g

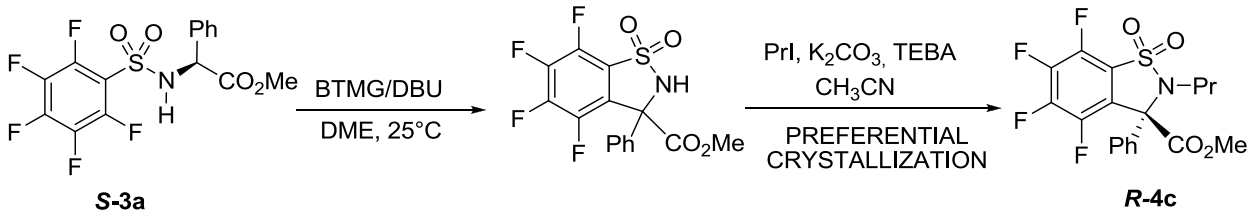
		Solution		Crystallized	
	R^2	yield (%)	*ee* (%)	yield (%)	*ee* (%)
***R*-4f** (*i*Pr_2O/hexane)	Allyl	67	> 99	30	0
***R*-4c** (*i*PrOH)	Pr	30	0	68	> 99
***S*-4g** (*i*PrOH)	Me	86	> 99	14	0

The non-alkylated sultam **(-)-8a** was the unique compound that did not crystallize with this technique, but was obtained through deprotection of the N-allyl derivative **(-)-21c** with tetrakis(triphenylphosphine)palladium and dimedone (Scheme 15).



Scheme 15

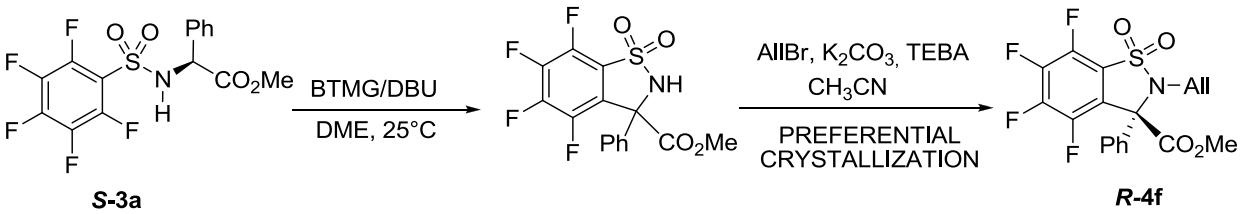
The single crystal X-ray analysis allowed us to assign the right configuration: for the cyclization with DBU/BTMG we observed (Figure 4) the retention product ***R*-4c** starting from ***S*-3a** (Scheme 16); the descriptor change occurs only for a change in priority and the reaction, even if occurring with retention, formally goes through inversion of configuration.



Scheme 16

Figure 4

Furthermore, retention of configuration it is also observed for the cyclization with DBU/BTMG starting from ***S*-3a** (Figure 5, Scheme 17) and using allyl bromide as the alkylating agent.



Scheme 17

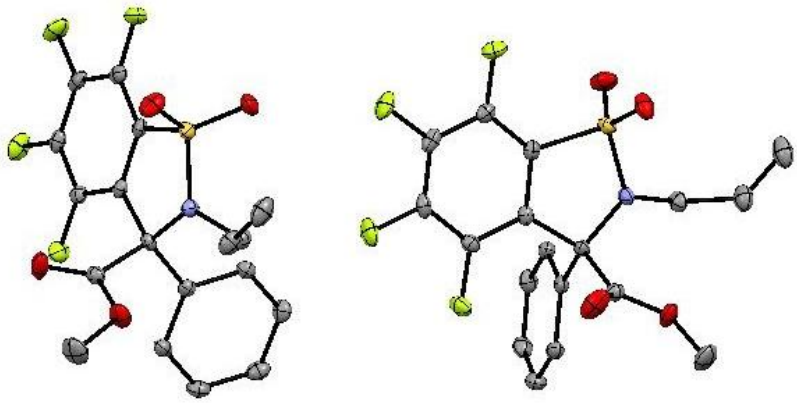
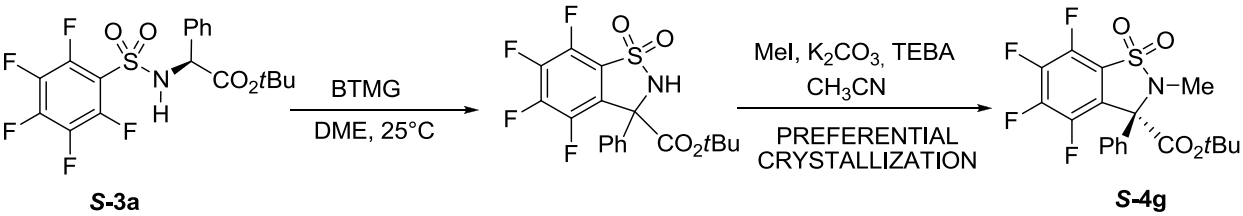


Figure 5

On the other hand, cyclization with BTMG, led to the inversion product (*S*) (Figure 6).



Scheme 18

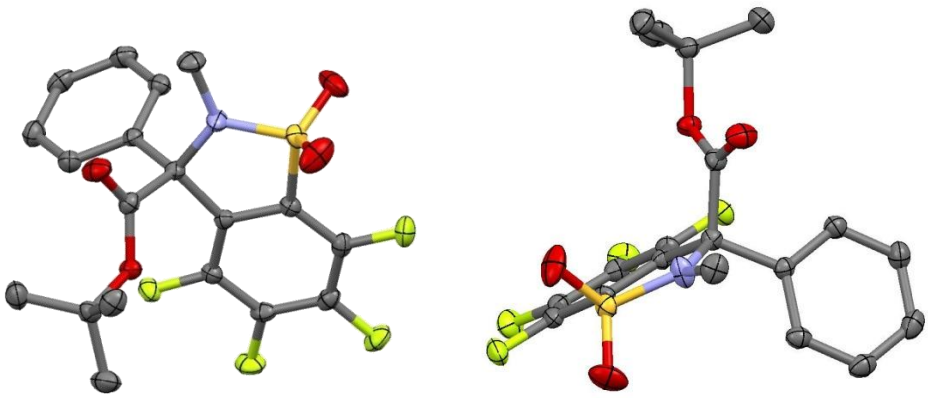
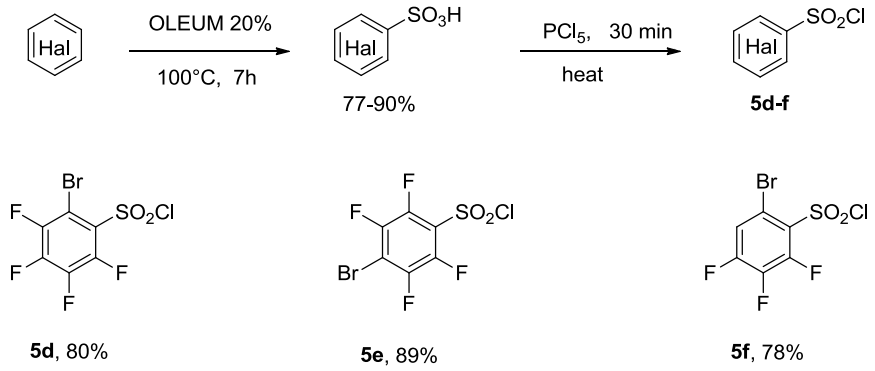


Figure 6

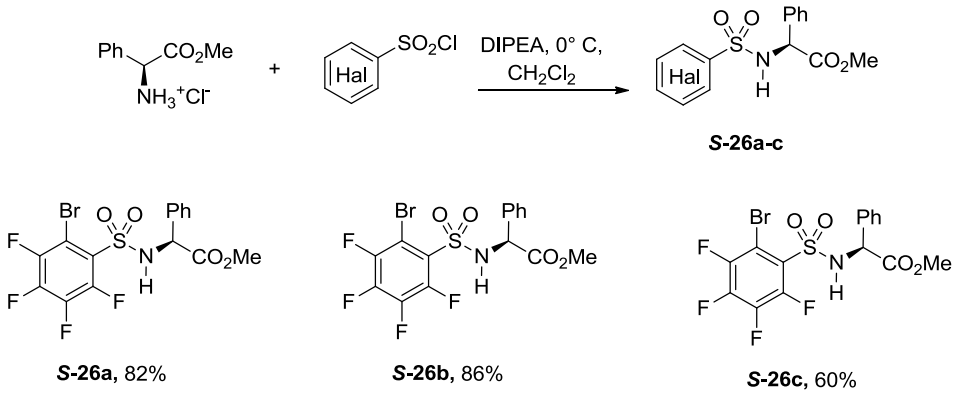
In order to synthesize new and more versatile compounds and to go deeper inside into the reaction mechanism, we decided to investigate the role of the fluorine substituent by preparing and reacting differently halogenated sulfonamides. We prepared a series of sulfonyl chlorides bearing different substituents on the aromatic fluorinated moiety.

We choose, as starting compounds, the commercially available (polyfluoro)halobenzenes that were sulfonated with 20% oleum, following a literature procedure applied on several chlorinated analogues,[91] and good yields were obtained for all the sulfonic acids (Scheme 19). The sulfonic acids were subsequently chlorinated by reaction at 110-120 °C for 30 minutes with neat phosphorus pentachloride, followed by a rapid quench in ice and extraction. With this protocol, we do not observe any substitution at the aromatic ring by the chloride anion.



Scheme 19

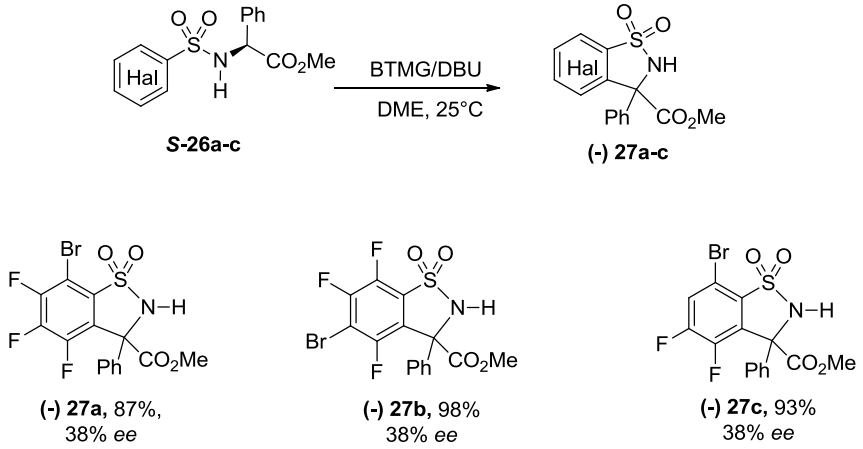
The sulfonyl chlorides **5d-f** were condensed with optically pure phenylglycine methyl ester to give the corresponding sulfonamides ***S*-26a-e** in good yield, after crystallization or chromatographic purification (Scheme 20).



Scheme 20

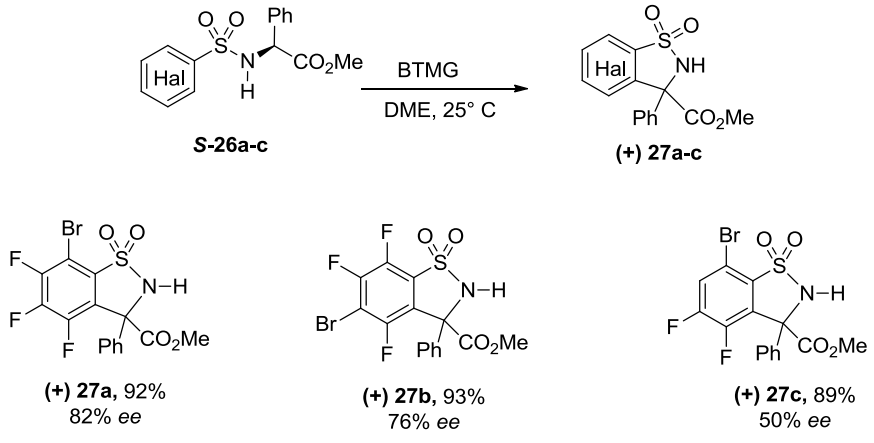
91 Medina, J. C., Roche, D., Shan, B., Learned, R. M., Frankmoelle, W. P., Clark, D. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1843-1846.

The best base/additive conditions, i.e. the DBU/BTMG basic system, were applied to the cyclization of the differently halogenated sulfonamides ***S*-26a-e** (Scheme 21), reaching good yields and modest *ee*'s of the resulting benzosultams.



Scheme 21

As found in the case of the (pentafluorobenzene)sulfonamide ***S*-3a**, the cyclization of (polyhalobenzene)sulfonamides ***S*-26a-c** using BTMG alone, gave **(+)-27a-c** in very good yield and *ee*, that decreases with the decrease of the activation toward the aromatic nucleophilic substitution. Furthermore, analogously to that found for **(+)-8a**, the (polyhalobenzo)sultams **(+)-27a-c** presented an inversion of configuration, respect to that observed with other bases (Scheme 22).



Scheme 22

As regards the mechanism of the enantiodivergent ring-closing reactions (Scheme 23), we suppose that the stronger base (BTMG) first *N*-deprotonates the open-chain sulfonamide ***S*-3a**

forming the tight ion-pair **A**. In the presence of catalytic amounts of the less sterically hindered DBU (*path a*), this base coordinates the α-hydrogen atom through an intermolecular attack from the less crowded side (intermediate **B**) forming the α-enol that, in turn, cyclizes to the sultam with retention of the starting configuration, releasing DBU to the catalytic cycle. In the presence of BTMG alone (*path b*) the ion-pair, through an intramolecular hydrogen bond, is forced to form the more crowded intermediate **C**, which evolves to the β-enol that forms the inversion sultam.

To support our hypothesis, it is worth noting that the DBU/BTMG promoted process is kinetically controlled and it is faster than the BTMG termodinamically controlled process. For this reason, in *path a*, the formation of the retention product is favoured, even if derives from an intermolecular attack by DBU (Scheme 23).

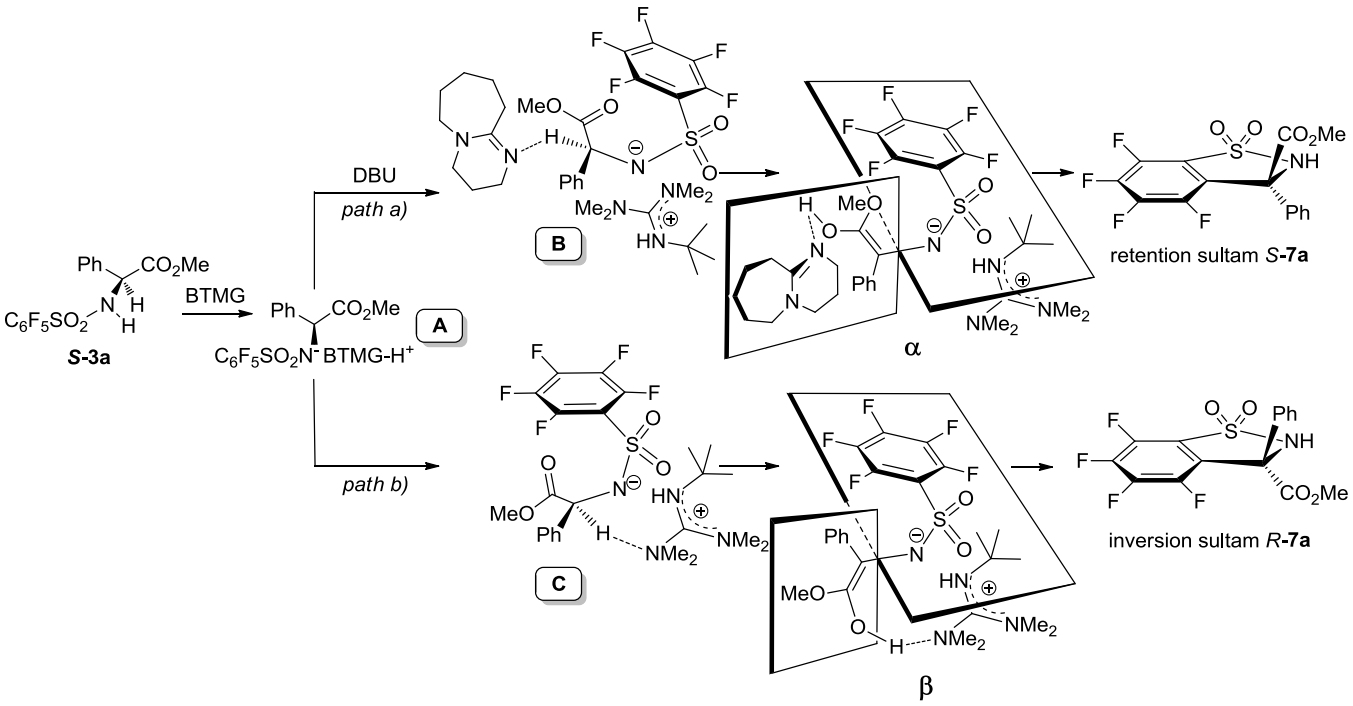
In conclusion, in this thesis I have described the MOC stereodivergent synthesis of a series of enantiomerically enriched polyfluorobenzo[d]sultams. The interest of this protocol resides in the possibility of making use of the chirality of a starting sulfonamide single enantiomer to synthesize the target sultams in both absolute configurations. The choice of the organic base system is the determining factor to direct the cyclization toward either enantiomer. In fact, the steric hindrance of the base regulates its access to the α-hydrogen, that can be approached alternatively through an inter- or an intramolecular attack. A further peculiarity of this protocol is the use, as starting compound, of an α-amino acid derivative bearing a mono-substituted sulfonamidic NH function.

Actually, in our knowledge, *C*-alkylation reactions under MOC conditions of such type of compounds have not been described until now. Furthermore, MOC conditions are ineffective on symmetrically *N*,*N*-disubstitued substrates, therefore all MOC reactions reported were carried out using compounds having two different substituents on the nitrogen atom (e.g., sulfonyl and carbamoyl, or two different carbamoyl, etc.). To explain the reactivity of our starting sulfonamides, we supposed that the very stable tight ion-pair formed by BTMG and the substrate (intermediate **B** in Scheme 23) mimics an asymmetrically *N*,*N*-disubstitued sulfonamide hence, in an analogous way, it stabilizes a specific conformation of the formed enol.

The behaviour of NH sulfonamides shown in the presence of hindered organic bases, open the possibility to study the synthesis under MOC conditions of several amino acid derivatives, without the need of introducing two different *N*-activating groups, thus avoiding the cleavage step of one of them.

REMARKS:

- The use of phenylglycine is essential for the formation of a chiral enol on a secondary solfonamide due to the high acidity of the Cα hydrogen atom.
- The reaction with the couple of bases BTMG/DBU is four times faster than the reaction with BTMG alone.
- In DME, BTMG is more basic than DBU.

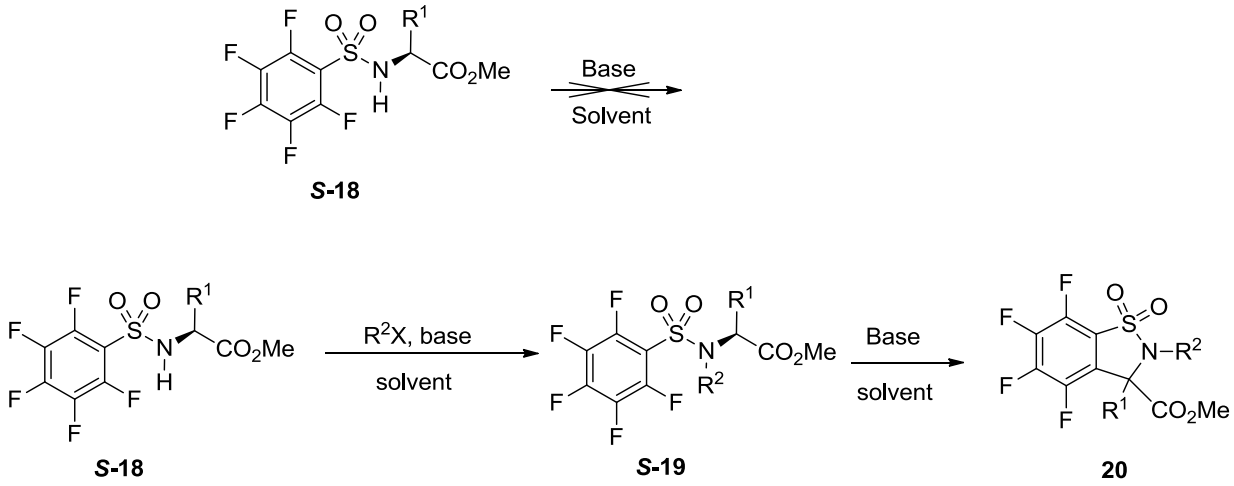


Scheme 23

6.3 Chiral Benzo[d]sultams Derived from Other Optically Pure α-Amino Acids

In an effort to synthesize novel enantiopure chiral benzo[*d*]sultams bearing in the Cα position a substituent different from phenyl, thus having a less acidic Hα than that of phenylglycine, we conducted several experiments on a number of optically pure amino acid derivatives, structurally different from.

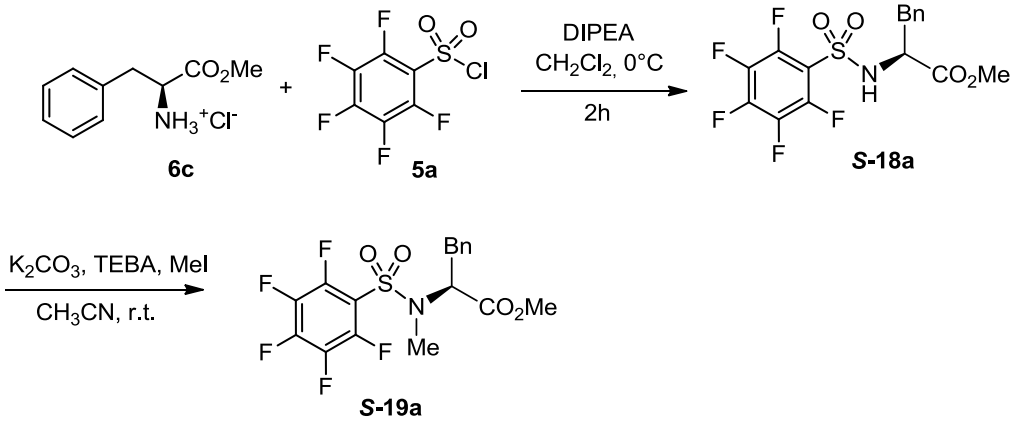
Differently from phenylglycine derivatives, *N*-unsubstituted (polifluoro)benzenesulfonamides derived from alkylglycine did not react under the action of any base (or basic system) that was used in our screening. In fact, in all cases, the starting compounds ***S*-18** (R^1 = Me, Bn, $CH_2CH(CH_3)_2$, $MeSCH_2CH_2$) were recovered unchanged from the crude. As we describe before exhaustively, we found that the benzosultams form only from the corresponding *N*-alkylated sulfonamides ***S*-20** (Scheme 24).



Scheme 24

To identify the best reaction conditions for the enantioselective cyclization of these *N*-alkyl sulfonamides, we chose as model compound the *N*-metyl phenylalaninate sulfonamide ***S*-19a**.

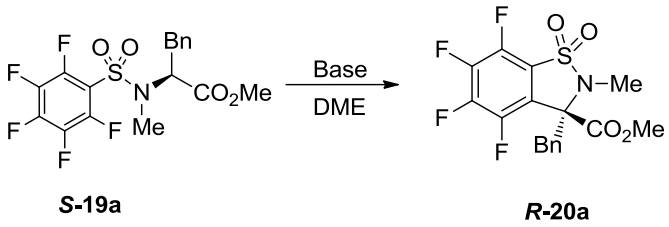
This compound was prepared in good overall yield by *N*-methylation under SL-PTC conditions of sulfonamide ***S*-18a** (Scheme 25) that, in turn, was obtained by condensation, as usual, of methyl phenylalaninate hydrochloride **6c** with (pentafluorobenzene)sulfonyl chloride (**5a**).



Scheme 25

Compound ***S*-19a** was then reacted in DME as solvent, by using several bases (Table 16). The best results were reached by using DBU, at -20 °C: the target benzosultam ***R*-20a**, with retention of configuration, was obtained in moderate yield and 95% *ee* (entry 1). On the contrary, with BTMG (entry 2) ***S*-19a** was unreactive. Very poor yields were reached with the bicyclic bases DBN and MTBD (entries 2 and 4), and also in these cases the retention *R* sultam was the major enantiomer isolated.

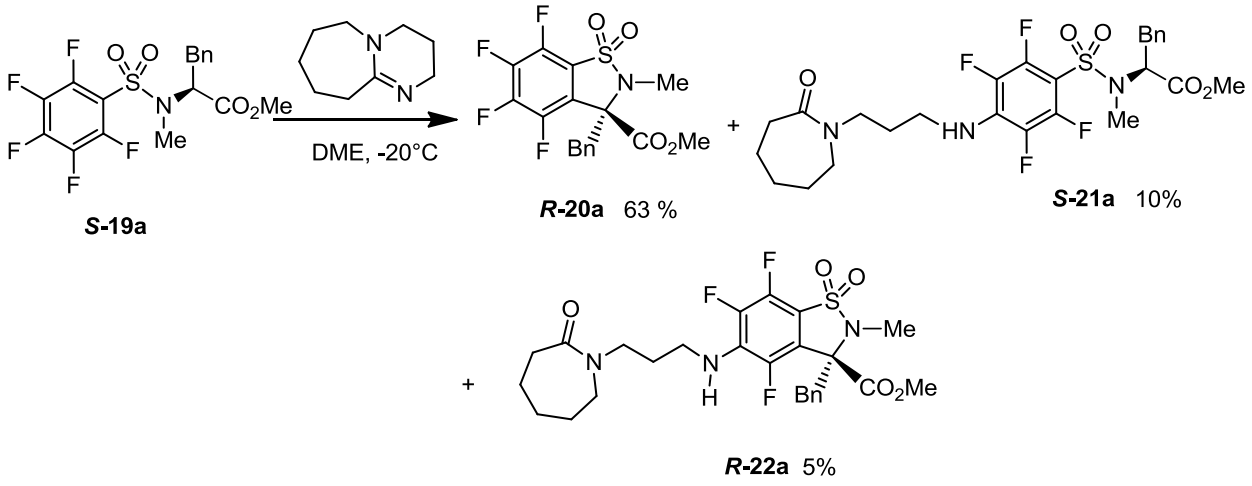
Table 16



entry	base	T (°C)	t	yield (%)	*ee* (%)
1	DBU	-20	2 h	63	95
2	BTMG	-20	20 h	-	-
3	DBN	25	7 d	5	93
4	MTBD	25	7 d	13	87

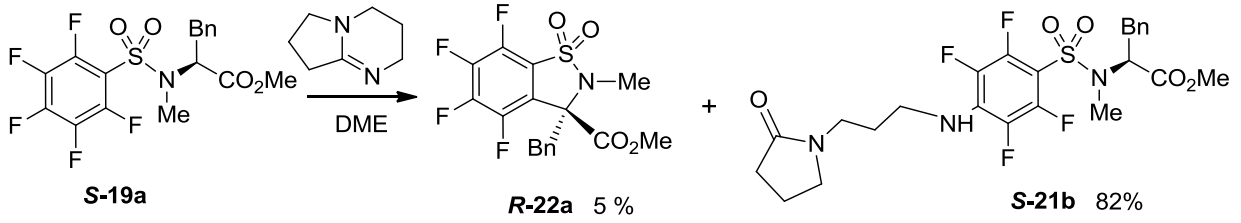
The cyclization reaction gave complete conversion of the starting sulfonamide by using these strong organic bases, but with low selectivity. In fact, together with the desired sultam, relevant amounts of by-products were isolated. After an accurate analysis of the reaction products of ***S*-**

19a with DBU (Table 16, entry 1), we found that two derivatives of nucleophilic attack of DBU on the fluorinated aromatic ring were also formed: the ε-caprolactam containing *para*-substituted sulfonamide ***S*-21a**, and the analogously 4'-substituted sultam ***R*-22a**, in which the 4'-fluorine atom was replaced by this novel DBU derived amino-lactame (Scheme 26).



Scheme 26

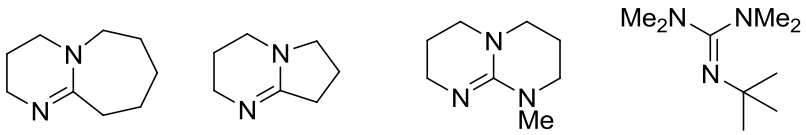
In a similar way, by using DBN (Scheme 27) the corresponding γ-butyrolactam ***S*-21b** was isolated in 82% yield, while very low amounts of the sultam ***R*-20a** were detected in the crude.



Scheme 27

In the literature, is reported that amidines - such as DBU and DBN[92] - and guanidines - such as BTMG and MTBD[93] - are very strong organic nitrogen-bases (23.89 < pK_a < 25.44, in MeCN)[94], but very weak nucleophiles.[95]

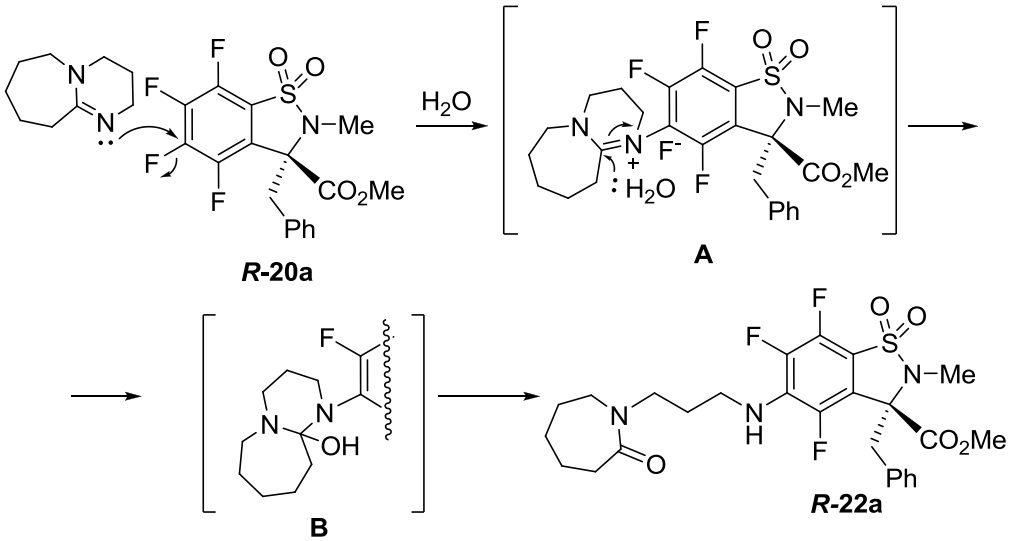
92 (a) Gierczyk, B.; Schroeder, G.; Brzezinski, B. *J. Org. Chem.* **2003**, *38*, 3139-3144. (b) Leffek, K. T.. Pruszynski, P.; Thanapaalasingham, K. *Can. J. Chem*. **1989**, *67*, 590.
93 Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber*. **1994**, *127*, 2435.
94 Gais, H.-J. Vollhardt, J.; Kruger, C. *Angew. Chem*. **1988**, *100*, 108.
95 (a) Schwesinger, R. *Nachr. Chem. Technol. Lab*. **1990**, *38*, 1214. b) Pietzonka, T.; Seebach, D. *Chem. Ber*. **1990**, *124*, 1837.



These tertiary amines are widely used in organic synthesis as bases, especially in dehydrohalogenation. Furthermore, DBU and DBN are described to act as nucleophilic reagents. The nucleophilic behavior of DBU and DBN has also recently been reported in two other cases: Reed *et* al.[96] described them in reactions with halogenated compounds of main group elements; Lammers *et* al.[97] have also observed nucleophility in the reaction with 4-halo-3,5-dimethyl-1-nitro-1*H*-pyrazoles, obtaining lactam-type products in which one of the bicyclic rings in DBU and DBN was opened by water.

Regarding the reaction mechanism, e.g. in the case of DBU as nucleophile (Scheme 28), through 7-N attack on the 4'-F of the sultam ***R*-20a**, the fluoride salt **A** is formed, which by hydrolysis via aminoacetal **B** gives the lactam ***R*-22a**.

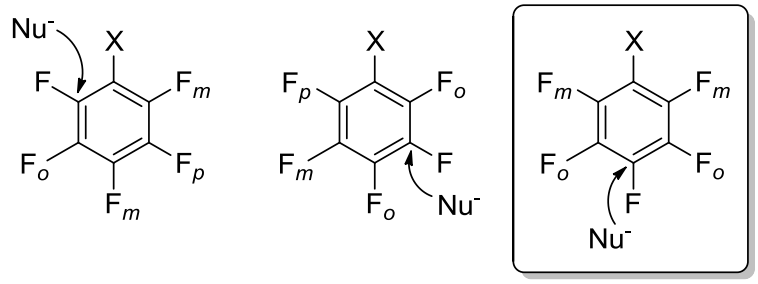
All these results indicate that the fluorine atoms present in the *para* position of the sulfonamide ***S*-19a** and sultam ***R*-20a** are highly susceptible to nucleophilic aromatic substitution (S_NAr).



Scheme 28

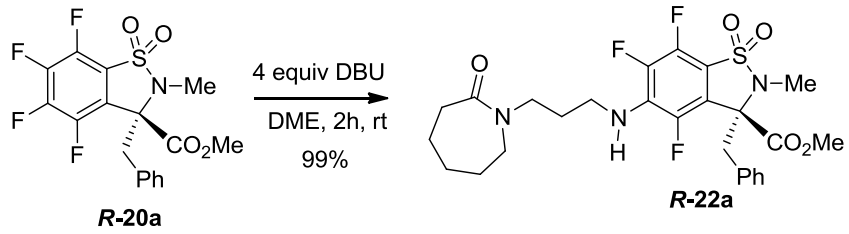
96 Reed, R.; Reau, R.; Dahan, F.; Bertrand, G. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*,399-401.
97 (a) Lammers, H.; Cohen-Fernandes, P.; Habraken, C. L. *Tetrahedron* **1994**, *50*, 865. (b) Sutherland, J. K. *J. Chem. Soc. Chem. Commun*. **1997**, 325. (c) Perbost, M.; Lucas, M.; Chavis, C.; Imbach, J.-L. *J. Heterocycl. Chem*. **1993**, *30*, 627. (d) Chambers, R. D.; Roche, A. J.; Batsanov, A. S.; Howard, J. A. K. *Chem. Commun*. **1994**, 2055.

It is well known that in S_NAr on polyfluorinated substrates the nucleophile attack is governed by the relative fluorine atoms position, rather than by the activating effects of other functional groups possibly present in the aromatic ring. Furthermore, it has been determined that (Scheme 29) for an aromatic a fluorine F leaving group, the *F-meta* is powerfully activating, while the *ortho*-fluorine is less activating, and the *para*-fluorine has an effect similar to a hydrogen substituent. The negatively charged primary addition product is stabilized best by fluorine in the *ortho* position, then by *meta*-F, and least in the *para* position. Only for attack of the nucleophile in the *para* position (right) the complex is stabilized by two *ortho* and two *meta* fluorines.



Scheme 29

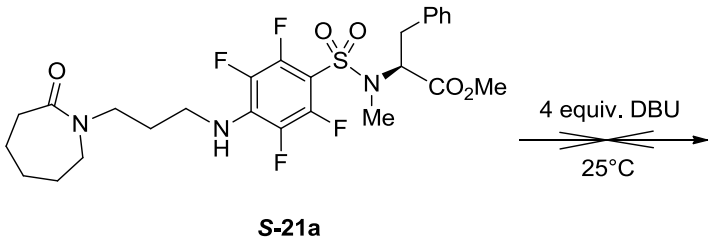
To confirm our hypothesis *N*-methyl (tetrafluorobenzo)sultam ***R*-20a** has been reacted with DBU and the mono-substitution was obtained. The most labile position is the fluorine in 5-position, probably due the activation both by fluorine in 7-position and by the sulfonyl group in 1-position, and the 5(ε-caprolactam)-sultam derivative ***R*-22a** was isolated as sole product in quantitative yield (Scheme 30).



***R*-20a** ***R*-22a**

Scheme 30

On the contrary, treatment of open chain 4'(ε-caprolactam)-sulfonamide ***S*-21a** with DBU at 25 °C in DME did not give the cyclization reaction, and the starting compound was recovered unchanged (Scheme 31).

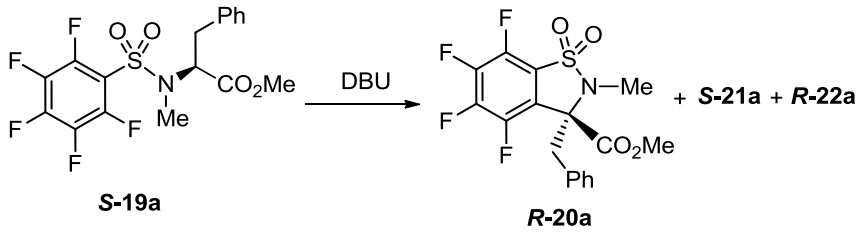


***S*-21a**

Scheme 31

To increase the selectivity of the cyclization step, we carried out several experiments using DBU as base, varying the nature of the solvent and the temperature (Table 17): all these reactions gave low yields of benzosultam ***R*-20a**, but with good enantioselectivity. The best result for this series of reactions was reached in DME at -50 °C (entry 1), where the by-products are reduced to the minimum, confirming once again that this is the solvent of choice.

Table 17

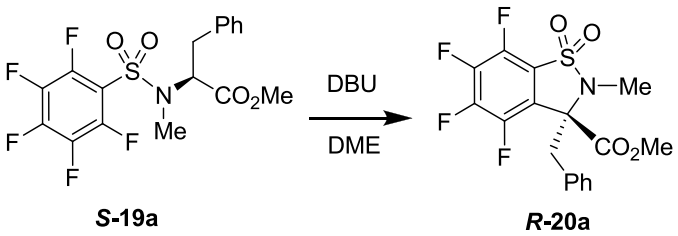


***S*-19a** ***R*-20a**

				***R*-20a**			
entry	solvent	T (°C)	t (h)	yield (%)	*ee* (%)	***S*-21a**(%)	***R*-22a**(%)
1	DME	-50	4	66	95	8	5
2	DMF	-50	12	40	92	14	10
3	CH_2Cl_2	-50	120	39	94	10	7
4	THF	-20	7	50	95	13	8
5	DIOX	25	0.25	-	-	40	11
6	Diglyme	-20	2	50	93	9	6
7	Et_2O	-20	7	37	94	10	8

In light of these results, the reactivity of ***S*-19a** in DME as the solvent and in the presence of variable quantities of DBU was investigated (Table 18). The best results were attained by using 4 equivalents quantitative of DBU (entry 1). By reducing the amounts of DBU (entries 2-5) the benzosultam ***R*-20a** yield progressively decreased, the by-products amount increased, and the reaction time became longer. When a catalytic amount of DBU was used, the reaction rapidly stopped because this base is quenched from HF formed (entry 7).

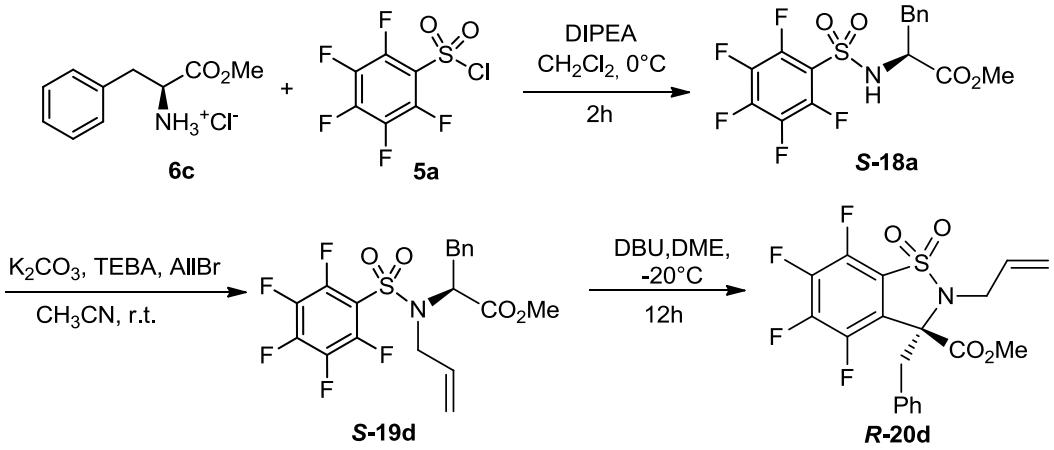
Table 18



***S*-19a** **$\rightarrow$** ***R*-20a**

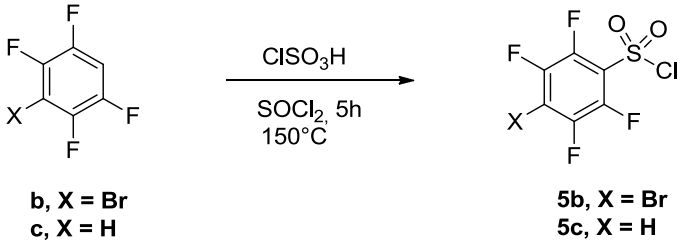
	DBU			***R*-20a**	
entry	(mol equiv.)	T (°C)	t (h)	yield (%)	*ee* (%)
1	4	-20	2	63	95
2	2	-20	8	56	95
3	1	-20	14	50	95
4	1	0	6	38	91
5	1	25	0.5	20	90
6	2	25	0.25	31	90
7	0.1	25	72	–	–

Finally, we decided to investigate the cyclization reaction of the *N*-allyl-phenylalanine derivative ***S*-19d,** which gave the corresponding benzo[*d*]sultam in 70% yield end 96% *ee* (Scheme 32).



Scheme 32

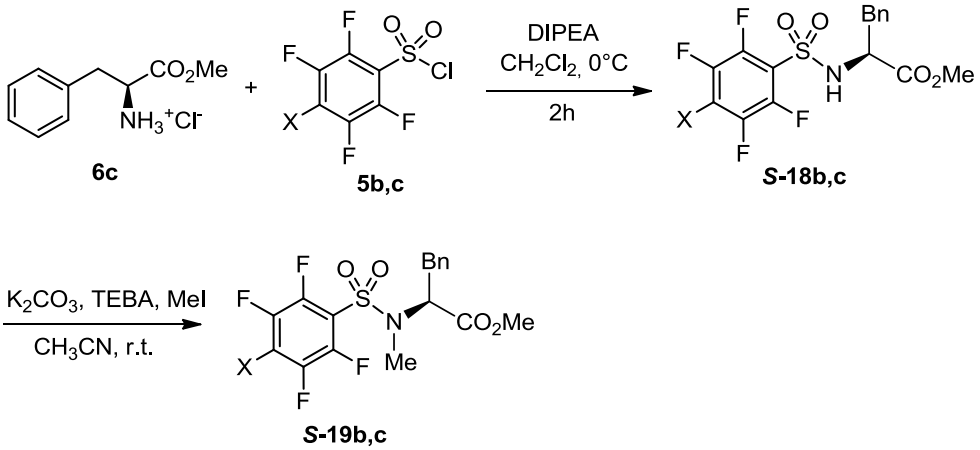
To eliminate in the cyclization process any interference from the S_NAr, which reduces the amount of the target sultam, we decided to synthesize new and more versatile sulfonamides bearing in the 4' position a bromine or a hydrogen atom instead of the fluorine atom. We choose, as starting compounds of the synthetic plan, the commercially available 3-bromo-1,2,4,5-tetrafluorobenzene and 1,2,4,5-tetrafluorobenzene, which have been converted to the corresponding mono-sulfonyl chlorides **5b,c** by chlorosulfonylation with sulfuric chlorohydrin/thionyl chloride, as described in the literature[98] (Scheme 33).



Scheme 33

The corresponding sulfonamides **18b,c** derived from phenylalanine methyl ester, were synthesized in enantiopure form and in good yields (89-92%) (Scheme 31) by condensation with these sulfonyl chlorides at 0−25 °C, in dichloromethane with DIPEA, as usual. Finally the *N*-alkylation with methyl iodide under SL-PTC conditions (Scheme 34) led the desired sulfonamide derivatives **19b,c** in excellent yields (see Experimentals).

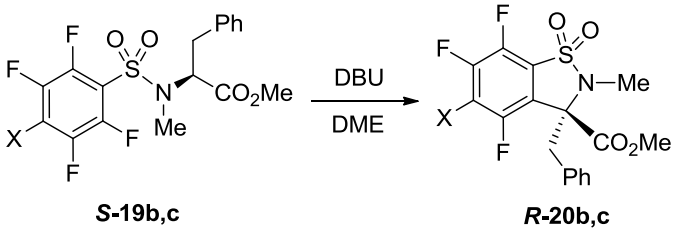
98 Vullo, D.; Pastorek, J.; Scozzafava, A.; Pastorekova, S.; Supuran, C. T.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2351–2356



Scheme 34

The best reaction conditions found, i.e. 4 mol equivalents of DBU and DME as solvent, were applied to the cyclization of this differently substituted sulfonamides ***S*-19b,c** (Table 19), reaching good yields and *ee*'s of the resulting benzosultams ***R*-20b,c**.

Table 19

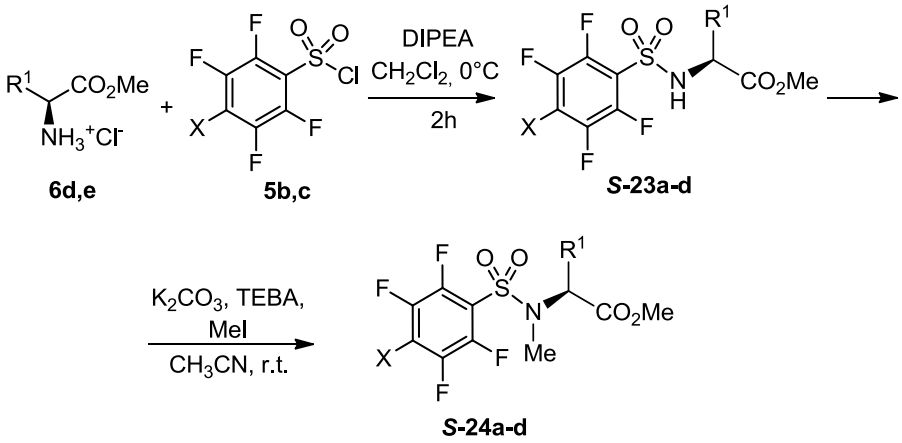


entry	X	T (°C)	t (h)	yield (%)	*ee*
1	Br	-20	8	***R*-20b** 87	96
2	H	25	48	***R*-20c** 82	95

This strategy has been successfully applied to different optically pure α-amino acid derivatives **6d-g** [alanine (**6d**), leucine (**6e**), methionine (**6f**) and tyrosine (**6g**)], thus performing the synthesis of enantio enriched polyfluorobenzo[*d*]sultams in few steps.

The sulfonamide derivatives ***S*-23a–d** were prepared in good yields (78-90 %) by condensation of the α-amino acid methyl ester hydrochlorides **6d-g** and the arylsulfonyl chloride **5b,c** (Table 20). The subsequent *N*-methylation of compounds ***S*-23a–d** under SL-PTC conditions gave the *N*-methyl open chain sulfonamides ***S*-24a–d** in quantitative yields (95-96%) and in enantiopure form (Table 20).

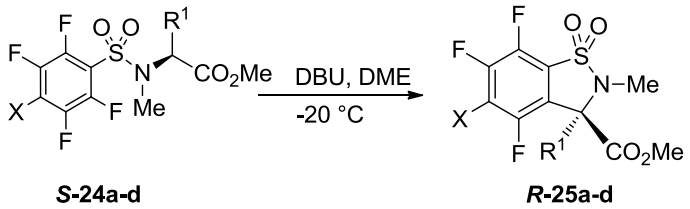
Table 20



entry	R^1	X	yields (%)	yields (%)
1	Me (**6d**)	Br	***S*-23a** 90	***S*-24a** 95
2	Me (**6d**)	H	***S*-23b** 81	***S*-24b** 96
3	Me_2CHCH_2 (**6e**)	Br	***S*-23c** 83	***S*-24c** 96
4	Me_2CHCH_2 (**6e**)	H	***S*-23d** 78	***S*-24d** 96

Sulfonamides ***S*-24a-d** were then cyclized by operating at -20 °C to the corresponding benzo[*d*]sultams ***R*-25a-d** (Table 21) that were isolated in good yields in the case of alanine derivatives (entries 1,2), but in very modest yields when leucine derived sulfonamides were made to react (entries 3,4). On the contrary, as regards the *ee*'s, the larger the amino acid side chain the higher the *ee* value found.

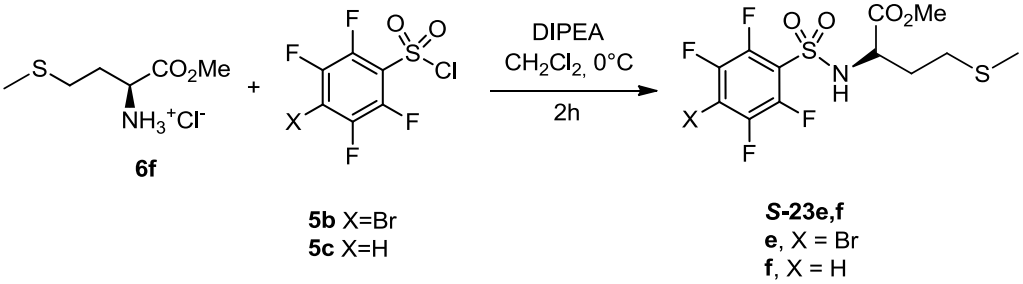
Table 21



***S*-24a-d** **R-25a-d**

entry		R1	X	t (h)	yield (%)	*ee* (%)
1	***S*-24a**	Me	Br	24	***R*-25a** 83	35
2	***S*-24b**	Me	H	5 day	***R*-25b** 75	27
3	***S*-24c**	Me_2CHCH_2	Br	5 day	***R*-25c** 42	95
4	***S*-24d**	Me_2CHCH_2	H	1 week	***R*-25d** 30	69

This methodology was extended also to methionine and methionine derived sulfone and sulfoxide. The sulfonamides ***S*-23e-f** derived of methionine was obtained in good yields (84-89%, respectively) using the classical reaction conditions by condensation of *L*-methionine methyl ester **6f**, with the arylsulfonyl chlorides **5b,c** (Scheme 36).



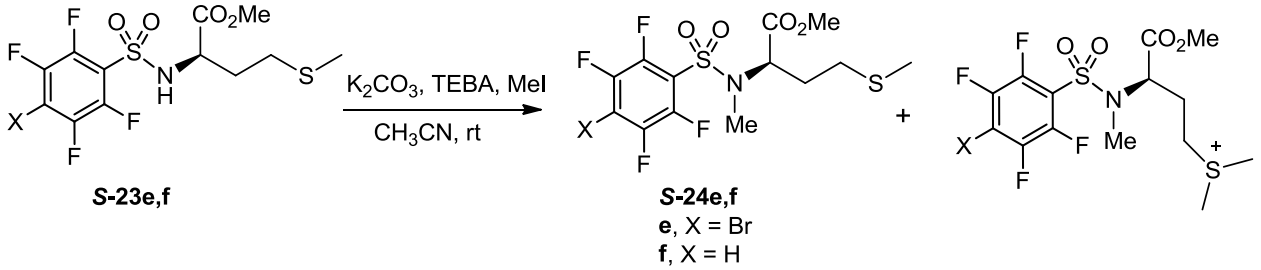
6f

5b X=Br
5c X=H

***S*-23e,f**
e, X = Br
f, X = H

Scheme 36

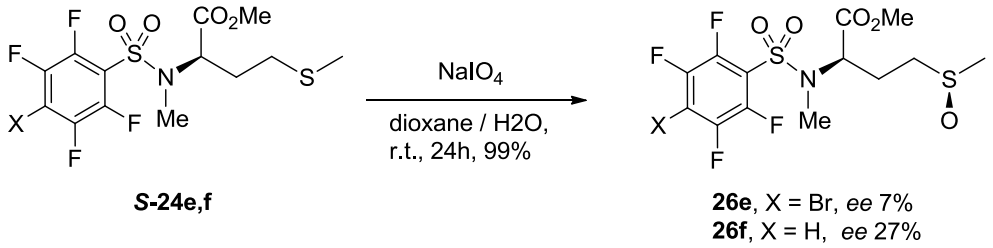
The successive *N*-methylation under SL-PTC conditions with excess MeI, gave the *N*-methyl open chain sulfonamides ***S*-23e,f** in lower yields, because alongside the *N*-alkylation is also present the *S*-alkylation compound (Scheme 37). To eliminate this by-product, we used 1 equimolar amounts of substrate and alkylating agent. Under these conditions, we obtained the target *N*-alkyl sulfonamides ***S*-24e,f** in moderate yields (69-70%).



Scheme 37

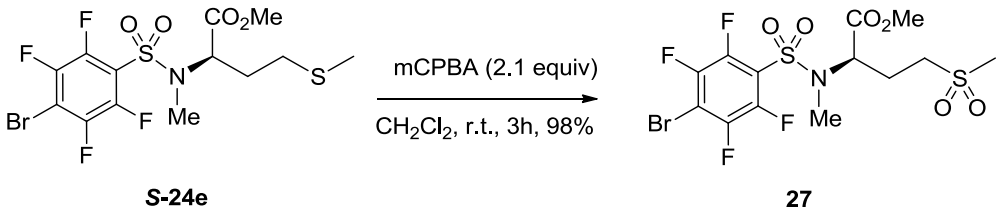
Proteins and peptides are susceptible to oxidative damage through reaction of certain amino acids with oxygen radicals present in their environment. Oxidation can alter protein physiochemical characteristics (e.g., folding and subunit association) and lead to aggregation or fragmentation. Methionine is an essential amino acid and is, together with cysteine, one of the two sulfur-containing amino acids. Met is usually found buried within proteins because of its quite hydrophobic side chain. Met and Cys can be easily oxidized on their sulfur atoms to give the related sulfoxides and sulfones.

With the aim of avoiding the parasitic *S*-methylation reaction and having a more stable Met derivative, we synthesized in quantitative yields (Scheme 38) the methionine derived sulfoxides **26a,b** by oxidation of *N*-alkyl sulfonamides ***S*-24e,f** with $NaIO_4$.



Scheme 38

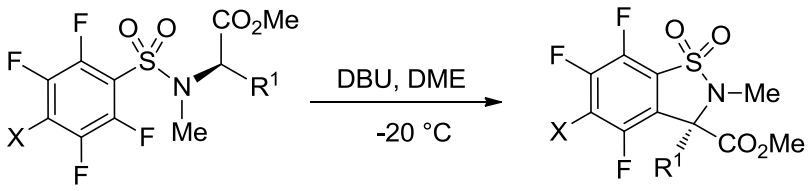
Methionine sulfone **27** was obtained in excellent yield by oxidation of ***S*-24e** at 25 °C with 2.1 mol equivalents of *meta*-chloroperoxybenzoic acid (Scheme 39).



Scheme 39

The sulfonamides of methionine (***S*-24e-f**) and of its *S*-oxidized derivatives (**26e,f** and **27**) were made to react under the best cyclization conditions (DBU in DME), giving the corresponding benzosultams (Table 22) in good (entries 1 and 4) to moderate yields (entries 2,3 and 5). Low *ee*'s were reached from the sulfide and sulfone derivatives (entries 1,2 and 5), while unexpectedly the sulfoxides **26e,f** gave only racemic mixtures of all the possible sultam diastereisomers (i.e. *de* 0%). At this point of the research, our knowledge of the reaction mechanism it is not sufficient for the comprehension of the stereochemical behavior of these sulfur-containing compounds, and further experiments should be done.

Table 22



***S*-24e,f**
26e,f
***S*-27**

***R*-25e,f**
28e,f
***R*-29**

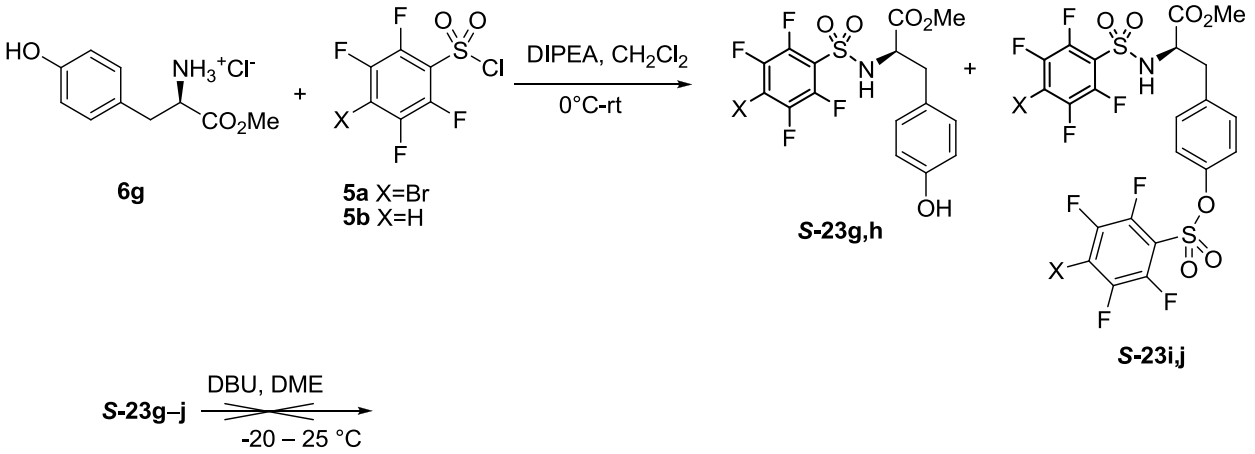
entry	sulfonamide	R^1	X	t (h)	yield (%)	*ee* (%)
1	***S*-24e**	$MeSCH_2CH_2$	Br	18	***R*-25e** 70	57
2	***S*-24f**	$MeSCH_2CH_2$	H	24	***R*-25f** 52	35
3	**26e**	$MeSOCH_2CH_2$	Br	24	**28e** 54	–
4	**26bf**	$MeSOCH_2CH_2$	H	48	**28f** 82	–
5	***S*-27**	$MeSO_2CH_2CH_2$	Br	48	***R*-29** 49	43

The results obtained until now, indicate a strong reactivity dependence on the increasing dimension of starting α-amino acid side chain. As expected, the smaller the steric hindrance near the reacting center, the greater the reaction reactivity.

Finally, we decided to investigate in the synthesis of benzosultams starting from tyrosine, structurally and sterically similar to phenylalanine, but bearing a *para*-hydroxy function that could act as activating element due to its electrodonating ability.

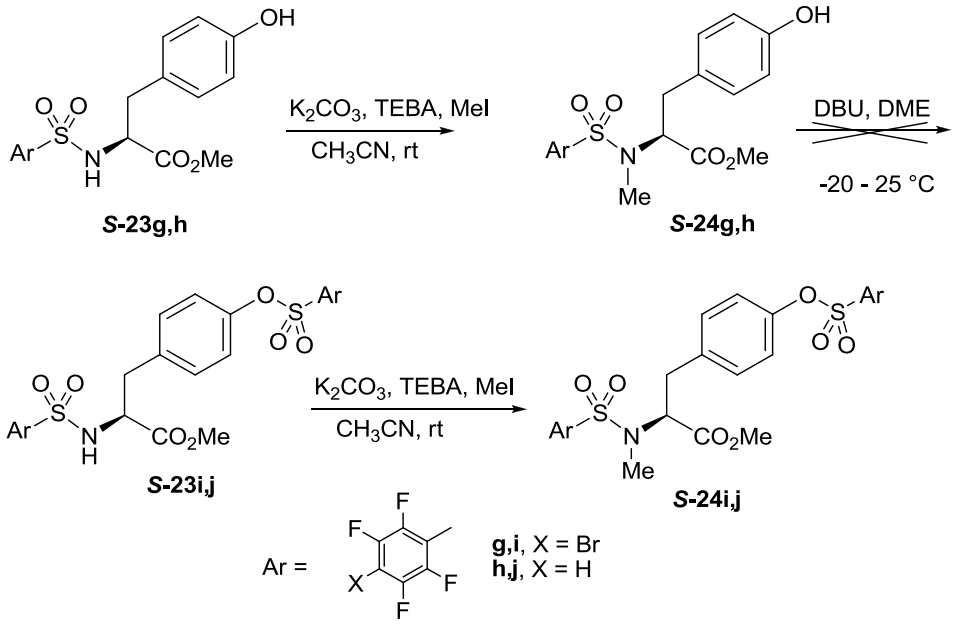
The reaction of L-tyrosine methyl ester (**6g**) with (3-bromo-1,2,4,5-tetrafluorobenzene)sulfonyl chloride **5b**, and (1,2,4,5-tetrafluorobenzene)sulfonyl chloride **5c,** using the classical reaction

conditions (DIPEA, CH_2Cl_2) gave poor yields of the corresponding *N*-sulfonamides ***S*-23g,h** (Scheme 36). The phenol hydroxy group, due to its acidity, was easily deprotonated and the derived phenoxide anion competed with the α-sulfonamido anion as a nucleophile, and significant amounts of *N*,*O*-bis(sulfonyl)tyrosine methyl esters ***S*-23i,j** were produced. Both mono- and bis-sulfonylamides were made to react with DBU, but all these compounds resulted unreactive under the usual cyclization conditions (Scheme 40).



Scheme 40

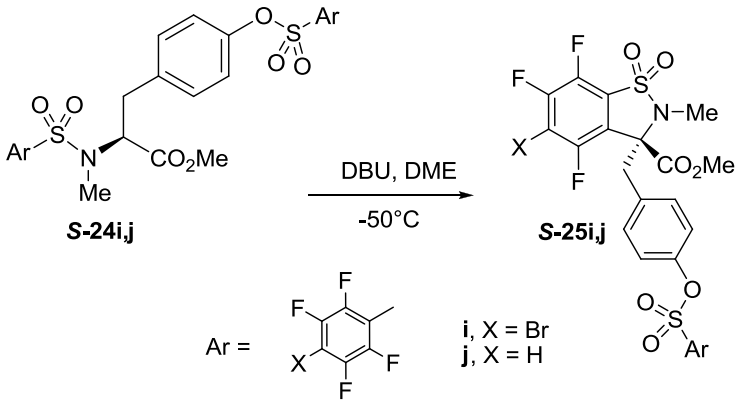
Sulfonamides ***S*-23g–j** were regioselectively *N*-methylated under SL-PTC conditions (Scheme 41). The corresponding *N*-methyl open chain sulfonamides ***S*-24g,h**, having the free phenol hydroxy function, did not react under the action of DBU and were recovered unchanged.



Scheme 41

On the contrary the sulfonamides ***S*-24i,j** have been cyclized with DBU in DME and the corresponding benzosultams were isolated in good yields end excellent *ee*'s (Table 23). These results are similar to that obtained with the phenylalanine derivatives.

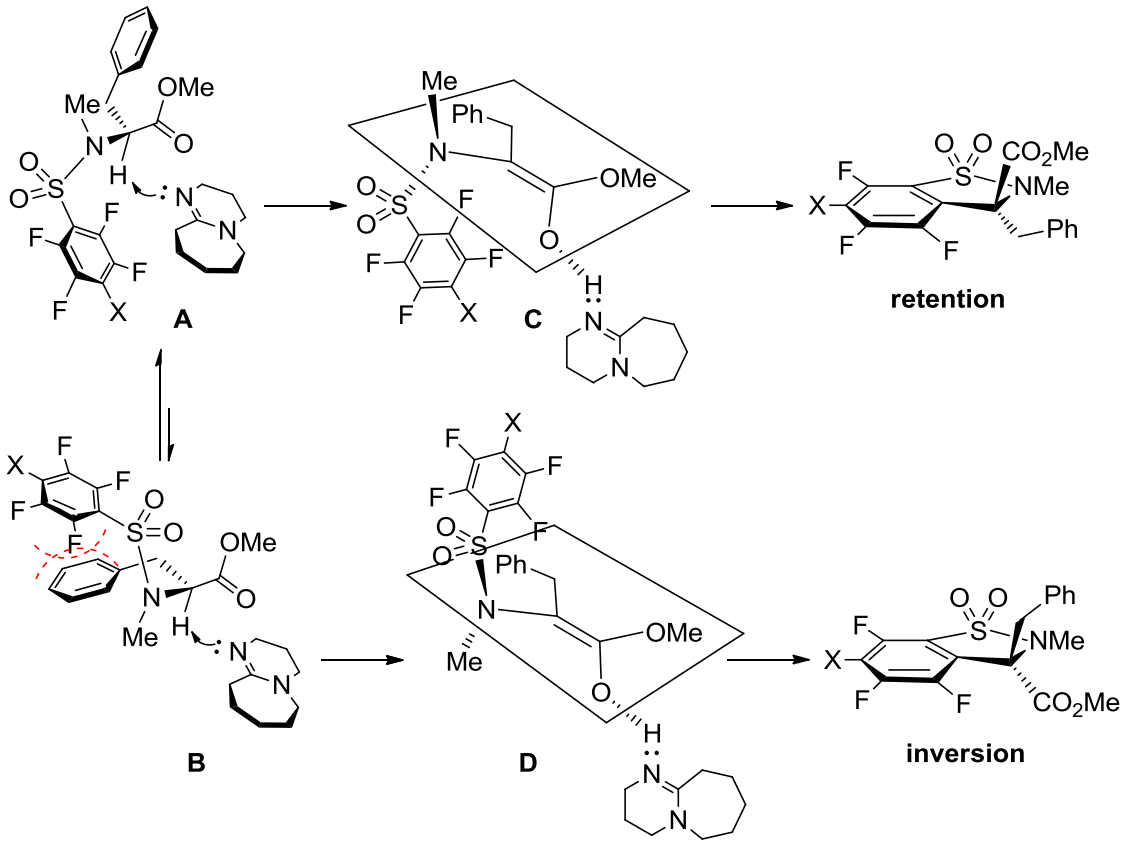
Table 23



entry		X	t (h)	yield (%)	*ee*
1	***S*-24i**	Br	7	***R*-25i** 87	> 99
2	***S*-24j**	H	28	***R*-25j** 75	> 99

As regard the reaction mechanism (Scheme 42) of the cyclization of *N*-alkyl substituted sulfonamides, we can postulate the equilibration of sulfonamide between conformers **A** and **B**. Conformer **A**, which is less sterically hindered, evolves into the enol **C** that, in turn, gives the sultam with complete configuration retention. On the contrary, the less favored conformer **B** shows a strong steric interaction between the fluorinated aromatic ring and the α-amino acid side chain, as shown in Scheme 42. Intermediate **B**, through the enol **D**, could evolve into the inversion sultam that, actually, it is not formed or it is present in very minor amounts.

Due to these final results, it would be very interesting a screening of several *O*-alkylsulfonyl, *O*-arylsulfonyl, *O*-phosphoryl, or *O*-acyl substituted tyrosine sulfonamides.



Scheme 42

6.4 Conclusions

In conclusion, in this research a series of chiral polyfluoro-polyfunctionalized benzosultams were prepared by stereoselective cyclization of enantiopure open-chain sulfonamides obtained, in turn, from natural and unnatural α-amino acids. Starting from the same optically pure arylglycine, it was realized the enantiodivergent synthesis of both the enantiomers of the corresponding benzosultam. The choice of the organic base system is the determining factor to direct the cyclization of the sulfonamide toward either enantiomer.

This process represents the first example of 'Memory Of Chirality' (MOC) principle application to NH-unsubstituted sulfonamides and the unique synthesis of chiral benzosultams bearing a C-3 carboxy function.

Part of our researches was also devoted to the study of the cyclization of *N*-alkylsulfonamides derived from α-amino acids having an alkyl side chain. These compounds were transformed, under homogeneous mild conditions, into the corresponding benzosultams with retention of configuration, confirming once again the validity of the MOC rules.

These new benzosultams could find application as chiral auxiliaries or catalysts in asymmetric synthesis, or they could be tested as biologically active compounds.

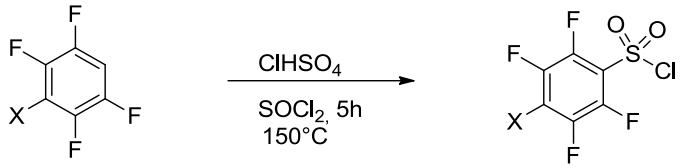
Furthermore, through straightforward chemical manipulations of sultams, new and more functionalized products are easily accessible: actually, the fluorine atoms, due to their good aromatic leaving group aptitude, can be substituted by all the classes of nucleophiles, while the bromine-containing sultams can easily undergo a number of Pd-catalyzed coupling reactions (Suzuki, Stille, Sonogashira, Buchwald-Hartwig, Heck, Hiyama, Negishi, etc.).

7 Experimental section

7.1 Materials and Methods

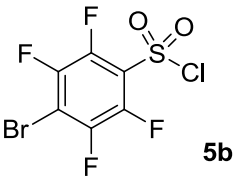
All reactions were carried out in flame-dried glassware with magnetic stirring. Isolated yields refer to homogeneous materials (TLC, HPLC, NMR). Reagent-grade commercially available reagents and solvents were used; anhydrous solvents (MeOH, Et_2O, DCM, DMSO, MeCN and DME) were used as purchased. TLC was performed using 0.25 mm silica-gel pre-coated plates and visualized by UV-254 light and CAM staining. Silica-gel (particle size 0.040–0.063 mm) was used for flash column chromatography (FCC) and medium pressure liquid chromatographic (MPLC). Melting points are corrected. HPLC analyses were performed using an EC 250/4.6 NUCLEOSIL 100-5 column and, for chiral HPLC analyses, a 250/4.6 Chiracel OD column, Chiralpak AD column, and Chiralcel OJ-H column; IR spectra are reported in frequency of absorption (cm^{-1}). $[\alpha]_D$'s were measured at 589 nm, using a 10 cm x 5 ml cell and *c* is in g/100 ml. NMR spectra were recorded at: 300.13 MHz for ^{1}H; 75.00 MHz for ^{13}C; 282.407 MHz for ^{19}F. TMS was used as external reference; δ are in ppm and *J* are in Hz.

7.2 Synthesis of Sulfonyl Chlorides 5b-c: General Procedure.



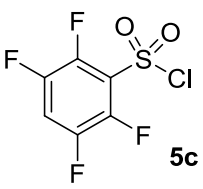
5b, X = Br
5c, X = H

Chlorosulfonic acid of 5 equiv (9.7 g; 5.53 mL) were addedto 2.5 g of 3-bromo-1,2,4,5-tetrafluorobenzeneor 1,2,4,5-tetrafluorobenzene and the obtainedsolution was heated at 150 °C. After 2h, the heating washalted in order to allow the solution to reach roomtemperature and 2 equiv of thionyl chloride (3.99 g; 2.43 mL) were added. The obtained mixture was heatedfor 3 h at 150 °C. The brown solution obtained was thenadded dropwise under stirring to a mixture of 25 g ice and 10 mL water. The obtained suspension was extracted three times with 15 mL of ethyl acetate. The organicfractions were collected and dried by solvent evaporationunder depression. The obtained brown oil was collected and stored at) - 20 °C.



5b

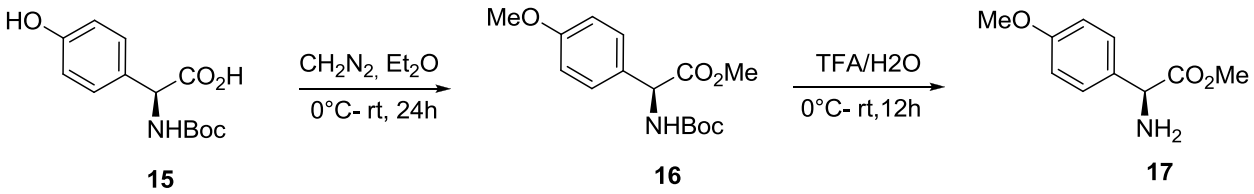
4-bromo-2,3,5,6-tetrafluorobenzene-1-sulfonyl chloride(5b)(3,1 g, 86%); brawn solid, mp 48-49°C,^{19}F NMR (282 MHz, $CDCl_3$) δ -127.9 (m, 2F), -134.2 (m,2F).



5c

2,3,5,6-tetrafluorobenzene-1-sulfonyl chloride (5c)(3,5 g, 70%); white solid, mp 50-52°C, ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.9 (m, 2F), -135.2 (m,2F).

7.3 Synthesis of (S)-Methyl 2-amino-2-(4-methoxyphenyl)acetate (17)



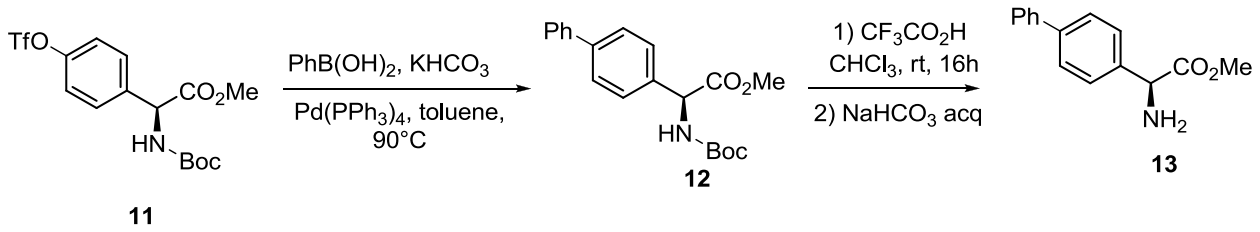
15 **16** **17**

To a solution of (*S*)-2-(*tert*-butoxycarbonylamino)-2-(4-hydroxyphenyl)acetic acid **15** (267 mg, 1 mmol) and $AlCl_3$ (13 mg, 0.1 mmol) in dry MeOH (3 ml) at 0 °C, CH_2N_2 in Et_2O was added dropwise until the solution remains yellow.[99] After evaporation under vacuum (RV) and filtration under silica (AcOEt/hexane – 1 : 2) the pure (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(4-methoxyphenyl)acetate **16** (24h, 269 mg, 91%) was obtained. White solid, mp 77-78 °C; FCC - AcOEt/hexane (1 :2); $[\alpha]_D^{20}$ +134.2 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 6.89-6.86 (m, 2H), 5.49-5.45 (m, 1H), 5.26-5.24 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 160.0, 155.0, 128.3, 128.2, 114.1, 79.8, 56.9, 55.1, 25.3, 28.1.

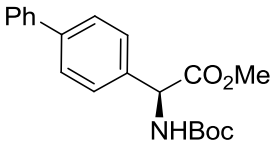
Compound **16**(269 mg, 0.91 mmol) was then dissolved in $CHCl_3$ (1.9 ml); TFA (0.1 ml) was added at 0 °C and this solution was warmed at room temperature and stirred over night. The crude was quenched with $NaHCO_3$ and extracted with DCM (2×20 mL). The organic layer was dried over $MgSO_4$, evaporated (RV) and the pureproduct **17** was obtained without any further purification. **17**(176 mg, 99%). White wax; $[\alpha]_D^{20}$ -121.0 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 6.90-6.87 (m, 2H), 4.56 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 1.70 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 159.2, 132.3, 127.9, 114.0, 57.9, 55.1, 52.2; IR (nujol) 3543, 3321, 1685, 1563,1243, 815 cm^{-1}.

99The CH_2N_2 solution must be kept at -78 °C.

7.4 Synthesis of (S)-methyl 2-amino-2-(biphenyl-4-yl)acetate (13)



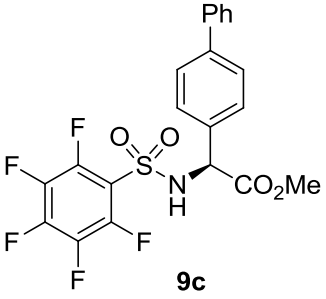
Starting (*S*)-Methyl 2-amino-2-(biphenyl-4-yl)acetate**11**was synthesised following literature method.[100] NMR spectra and physical data completely matched with the reported data. We used $KHCO_3$ instead of K_2CO_3 in the Suzuky coupling since the Bello *et al*'s reaction conditions lead to the *N*-Boc phenyl glycinederivative**9c**in 34% enantiomeric excess. We were able to estimate the enantiomeric excess value only when we isolated the sulphonamide derivative **9c**.



12

$[\alpha]_D^{20}$ +115.1 (*c* 1, $CHCl_3$), *ee* = 34%

$[\alpha]_D^{20}$ +306.8 (*c* 1, $CHCl_3$), *ee*> 99%



9c

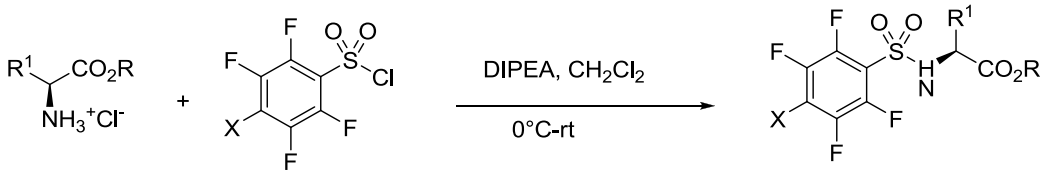
$[\alpha]_D^{20}$ +50.2 (*c* 1, $CHCl_3$), *ee* = 34%

$[\alpha]_D^{20}$ +137.0 (*c* 1, $CHCl_3$), *ee*> 99%

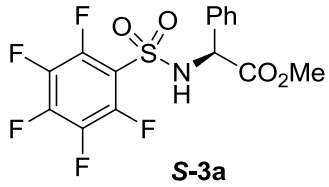
[CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 13 bar, t_1 = 13.8 min, t_2 = 15.8 min].

100Bello, C. *Bioorg. Med. Chem.*, **2010**, 18,3320-3334

7.5 Synthesis of sulfonamides S-3a-d, 9a-e, S-18a-c, S-23a-j : General Procedure

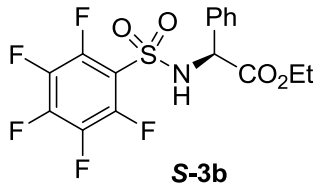


To a suspension of alkyl or 2-arylaminoacetate hydrochloride (10 mmol) in drydichloromethane (40 mL), DIPEA (21 mmol) was added at 25 °C in 10 min. Thereaction mixture was stirred for furhter 10 min, then cooled to 0°C and sulfonylchloride (10 mmol) was added dropwise. The resulting solution was allowed to reach25 °C and stirred until no starting material was not detectable by TLC, then wasdiluted with dichloromethane (20 mL), washed with 3% HCl (3×15 mL), saturated$NaHCO_3$ solution (2×15 mL) and brine (20 mL), dried over $MgSO_4$, filtered. Afterevaporation of the solvent under vacuum (RV), the crude recrystallized fromethanol/water (1 : 9), or purified by FCC or MPLC, gave the desired sulfonamides.Starting materials, product, yield, chromatographic eluant, physical and analyticaldata are as follows.



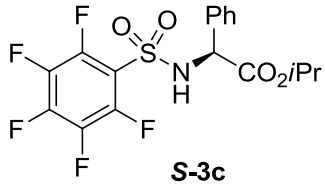
***S*-3a**

(*S*)-Methyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3a). (3h, 356 mg, 90%). White solid, mp 120-121 °C (EtOH/water – 9 : 1); $[\alpha]_D^{20}$ +79.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.19 (m, 5H), 6.42 (d, 1H, *J* = 7.5 Hz,), 5.28 (d, 1H, *J* = 7.5 Hz), 3.72 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.9 (m, 1F), -159.8 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 143.9 (dm, *J* = 258.6 Hz), 143.6 (dm, *J* = 261.6 Hz), 137.4 (dm, *J* = 258.4 Hz), 133.8, 129.2, 128.9, 127.3, 116.7, 59.9, 53.4; IR (nujol) 3331, 1741, 1644, 1522, 1300, 1214, 1101, 985, 885 cm^{-1}. Anal. Calcd. for $C_{15}H_{10}F_5NO_4S$: C, 45.58; H, 2.55; N, 3.54. Found: C, 45.52; H, 2.58; N, 3.59.



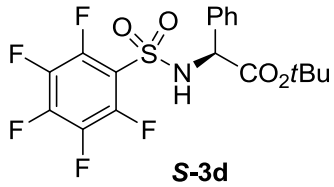
***S*-3b**

(*S*)-Ethyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3b) (20h, 302,9 mg, 74%); FCC - AcOEt/hexane (1 : 6); white solid, mp 100-102°C, $[\alpha]_D^{20}$+71.5 (c 1, CHCl3).^{1}H NMR (300 MHz, CDCl3) δ 7.26-7.20 (m, 5H), 6.25 (d,1H, *J* = 7.5 Hz,), 5.24 (d, 1H, *J* = 7.8 Hz), 4.27-4.06 (m, 2H),1.73 (t, 3H, *J* = 7.2 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -136.5 (m, 2F), -146.9 (m, 1F), -159.8 (m, 2F); IR (nujol) 3342, 1746, 1642, 1522, 1301, 1216, 1110, 973cm^{-1}.Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 43.11; H, 2.94; N,3.14. Found: C, 43.08; H, 2.92; N, 3.12.



***S*-3c**

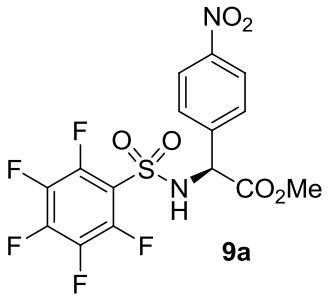
(*S*)-Isopropyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3c).(20h, 317,5 mg, 75%);FCC - AcOEt/hexane (1 : 8), white solid, mp 91-92°C, $[\alpha]_D^{20}$+54.9 (c 1, CHCl3).^{1}H NMR (300 MHz, CDCl3) δ7.25-7.17 (m, 5H), 6.27 (d,1H, J = 7.6 Hz), 5.21 (d, 1H, J = 7.6 Hz), 5.05-4.97 (m, 1H),1.22 (d, 3H, J = 6.3 Hz), 1.04 (d, 3H, J = 6.3 Hz).^{19}F NMR (282 MHz, CDCl3) δ -136.6 (m, 2F), -147.0 (m,1F), -159.9 (m, 2F).^{13}C NMR (75 MHz, CDCl3) δ 168.6, 144.1 (dm, J = 261.7Hz), 143.6 (dm, J = 259.5 Hz), 137.4 (dm, J = 257.3 Hz),134.1, 129.0, 128.8, 127.2, 119.0, 70.9, 60.1, 21.5, 21.1.Anal. Calcd. for $C_{17}H_{14}F_5NO_4S$: C, 48.23; H, 3.33; N,3.31. Found: C, 45.24; H, 2.34; N, 3.33.



***S*-3d**

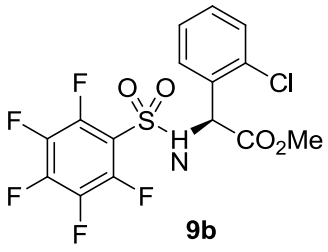
(*R*)-tert-butyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3d).(24h, 389,3 mg, 89%);FCC - AcOEt/hexane (1 : 12), white solid, mp 91-92°C, $[\alpha]_D^{20}$+82.4 (c 1, CHCl3).^{1}H NMR (300 MHz, CDCl3) δ 7.24-7.17 (m, 5H), 6.23 (d,1H, J = 7.6 Hz), 5.14 (d, 1H, J = 7.7 Hz), 1.34 (s, 9H).^{19}F NMR (282 MHz, CDCl3) δ -136.5 (m, 2F), -147.3 (m,1F), -160.1 (m, 2F).^{13}C NMR (75 MHz, CDCl3) δ 168.5, 144.4 (dm, J = 266.0Hz), 144.0 (dm, J = 258.4 Hz), 138.0 (dm, J = 265.9Hz),134.8, 129.3, 129.2, 127.6, 119.3, 84.4, 60.8, 28.0. IR

(nujol) 3333, 1739, 1645, 1526, 1298, 1218, 1106, 981,888 cm^{-1}.Anal. Calcd. for $C_{18}H_{16}F_5NO_4S$: C, 49.43; H, 3.69; N,3.20. Found: C, 49.40; H, 3.70; N, 3.21.



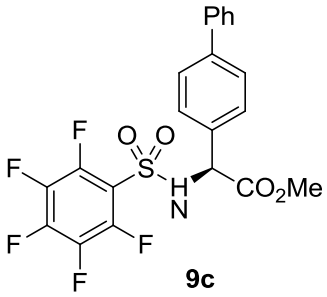
9a

(*S*)-Methyl 2-(4-nitrophenyl)-2-(perfluorophenylsulfonamido)acetate (9a). Compound (*S*)-Methyl 2-(perfluorophenylsulfonamido)-2-phenylacetate***S*-3a**(395 mg, 1 mmol) was dissolved in H_2SO_{4conc} (1 ml); HNO_3 (95 mg, 1.5 mmol, 70 μl) was added dropwise and this solution was stirred at -10 °C for 2 h. The crude was diluted with water (20 mL), extracted with AcOEt (2×20 mL) and dried over $MgSO_4$. After evaporation of the solvent under vacuum (RV), the crude was purified by FCC (AcOEt/hexane 1 : 3). **9a** (431 mg, 98%). White solid, mp 111-112 °C; $[\alpha]_D^{20}$ +76.8 (*c* 1.1 $CHCl_3$) *ee* 70% [CHIRALPAK OD ®, Hexane – Isopropanol 8 : 2 + 0.2% TFA, Flow rate 0.7 mL/min, P= 15 bar, t_1 = 4.9 min, t_2 = 6.3 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.17 (m, 2H), 7.54-7.51 (m, 2H), 6.60 (d, 1H, *J* = 6.3 Hz), 5.40 (d, 1H, *J* = 6.3 Hz), 3.74 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.8 (m, 2F), -145.3 (m, 1F), -158.9 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 148.2, 144.2 (dm, *J* = 255.5 Hz), 144.1 (dm, *J* = 243.6 Hz), 141.7, 141.4, 137.7 (dm, *J* = 262.2 Hz), 128.3, 124.1, 59.1, 53.9 IR (nujol) 3310, 1741, 1644, 1575, 1278, 1214, 1101 cm^{-1}. Anal. Calcd. for $C_{15}H_9F_5N_2O_6S$: C, 40.92; H, 2.06; N, 6.36. Found: C, 45.21; H, 2.89; N, 3.31.



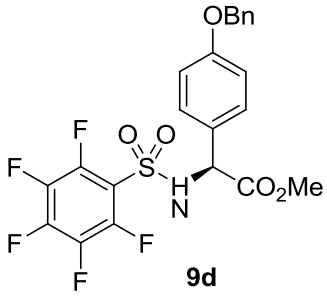
9b

(*S*)-Methyl 2-(2-chlorophenyl)-2-(perfluorophenylsulfonamido)acetate (9b). (*S*)-Methyl 2-amino-2-(2-chlorophenyl)acetate hydrochloride **6b**, 236 mg. **9b**(4h, 313 mg, 73%). White solid, mp 110-110 °C; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ +75.6 (*c* 1.1 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.24 (m, 4H), 6.35 (d, 1H, *J* = 7.5 Hz), 5.58 (d, 1H, *J* = 7.5 Hz), 3.74 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.0 (m, 1F), -159.2 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 143.7 (dm, *J* = 260.9 Hz), 143.2 (dm, *J* = 260.1 Hz), 137.0 (dm, *J* = 252.8 Hz),132.8, 132.1, 132.0, 130.1, 129.9, 129.5, 126.8, 57.7, 53.0; IR (nujol) 3274, 1745, 1634, 1510, 1294, 1160, 1100, 990 cm^{-1}. Anal. Calcd. for $C_{15}H_9ClF_5NO_4S$: C, 41.92; H, 2.11; N, 3.26. Found: C, 45.21; H, 2.89; N, 3.31.



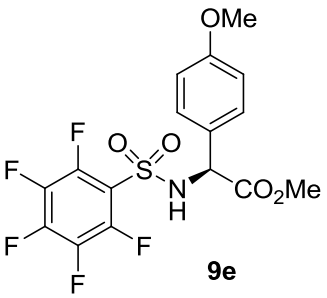
9c

(*S*)-Methyl 2-(biphenyl-4-yl)-2-(perfluorophenylsulfonamido)acetate (9c). (*S*)-Methyl 2-(biphenyl-4-yl) acetate**13**, 308 mg. **9c** (212 mg, 45%). White solid, mp 103-104 °C; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$+137.0 (*c* 1, $CHCl_3$). ^{1}H NMR (300MHz, DMSO) δ 7.47-7.39 (m, 7H), 7.30-7.26 (m, 2H), 6.30 (d, 1H, *J* = 7.5 Hz), 5.33 (d, 1H, *J* = 7.5 Hz), 3.76 (s, 3H); ^{19}F NMR (282 MHz, DMSO) δ -136.5 (m, 2F), -147.7 (m, 1F), -160.2 (m, 2F); ^{13}C NMR (75 MHz, DMSO) δ 169.3, 143.6 (dm, *J* = 256.0 Hz), 143.0 (dm, *J* = 251.8 Hz), 137.1 (dm, *J* = 253.9 Hz), 140.3, 139.3, 134.0, 130.0, 128.8, 128.2, 127.6, 126.6, 121.6, 59.2, 52.6; IR (nujol) 3275, 1741, 1627, 1518, 1310, 1176, 1100, 996, 884 cm^{-1}. Anal. Calcd. for $C_{21}H_{14}F5NO_4S$: C, 53.51; H, 2.99; N, 2.97. Found: C, 52.74; H, 3.19; N, 2.83.



9d

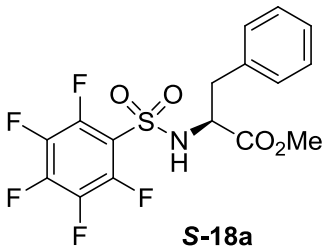
(*S*)-Methyl 2-[4-(benzyloxy)phenyl]-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (9d). (*S*)-Methyl 2-amino-2-[4-(benzyloxy)phenyl]acetate hydrochloride, 308 mg. **9d**(416 mg, 83%). White solid, mp 103-104 °C; FCC - AcOEt/hexane (1 : 12); $[\alpha]_D^{20}$ +48.4 (*c* 0.9 $CHCl_3$). ^{1}H NMR (300MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 7.13-7.10 (m, 2H), 6.83-6.79 (m, 2H), 6.20 (d, 1H, *J* = 7.1 Hz), 5.22 (d, 1H, *J* = 7.1 Hz), 4.97 (s, 2H), 3.71 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.0 (m, 1F), -159.8 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 159.5, 144.0 (dm, *J* = 263.0 Hz), 143.8 (dm, *J* = 260.0 Hz), 137.4 (dm, *J* = 257.9 Hz), 136.3, 126.1, 126.0, 128.7, 127.4, 126.1, 116.9 (t, *J* = 13.0 Hz), 115.0, 70.2, 59.4, 53.3; IR (nujol) 3275, 1741, 1627, 1518, 1310, 1176, 1100, 996, 884 cm^{-1}. Anal. Calcd. for $C_{22}H_{16}F_5NO_5S$: C, 52.70; H, 3.22; N, 2.79. Found: C, 52.74; H, 3.19; N, 2.83.



9e

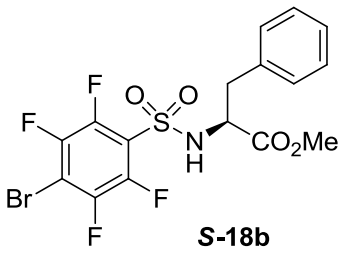
(*S*)-Methyl 2-(4-methoxyphenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (9e). (*S*)-Methyl 2-amino-2-(4-methoxyphenyl)acetate hydrochloride**17**, 232 mg. **9e**(16h, 340 mg, 80%). White solid, mp 115-116 °C; FCC - AcOEt/hexane (1 : 9); $[\alpha]_D^{20}$ +84.7 (*c* 1.1 $CHCl_3$). ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.13-7.10 (m, 2H), 6.74-6.71 (m, 2H), 6.27 (d, 1H, *J* = 7.5 Hz), 5.22 (d, 1H, *J* = 7.5 Hz), 3.74 (s, 3H), 3.71 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.2 (m, 1F), -160.0 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 160.9, 144.6 (dm, *J* = 262.1 Hz), 144.2 (dm, *J* = 258.6 Hz), 138.4 (dm, *J* = 267.2 Hz), 129.3, 126.5, 114.8, 60.8, 55.9, 53.9; IR (nujol) 3263, 1748, 1610, 1518, 1303, 1174, 1091, 990 cm^{-1}. Anal. Calcd. for $C_{16}H_{12}F_5NO_5S$: C, 45.18; H, 2.84; N, 3.29. Found: C, 45.21; H, 2.89; N, 3.31.



***S*-18a**

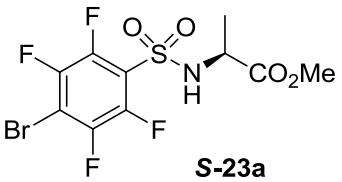
(*S*)-methyl 2-(perfluorophenylsulfonamido)-3-phenylpropanoate(*S*-18a). (1,5 h, 286,5 mg, 70%). White solid, mp 130-131 °C; FCC - AcOEt/hexane (1 : 7). ^1H NMR (300MHz, CDCl3) δ 7.22-7.19 (m, 3H), 7.11-7.07 (m, 2H), 5.60 (d, 1H, J = 9.2 Hz), 4.54-4.47 (m, 1H),3.73 (s, 3H), 3.19 (dd, 1H, J = 13.9, 4.8 Hz), 2.97 (dd, 1H, J= 13.9, 8.1 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -136.6 (m, 2F), -147.2 (m,1F), -159.7 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 145.2 (dm, *J* = 260.1 Hz), 141.7 (dm, *J* = 257.3 Hz), 138.7 (dm, *J* = 264.6 Hz), 134.6, 128.0, 126.7, 57.2, 52.4, 38.4;IR (nujol) 3225, 1722, 160', 1501, 1342, 1171, 1110, 1096,998 cm^{-1}.Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 46.95; H, 2.95; N,3.42. Found: C, 46.96; H, 2.98; N, 3.44.



***S*-18b**

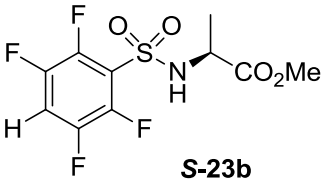
(S)-methyl 2-(4-bromo-2,3,5,6-tetrafluorophenylsulfonamido)-3-phenylpropanoate (*S*-18b). (4 h, 300,5 mg, 80%). White solid, mp 117-118 °C; FCC - AcOEt/hexane (1 : 9)**;** $[\alpha]_D^{20}$ -22.3 (*c* 0.3 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 17.4 min]. ^1H NMR (300MHz, CDCl3) δ 7.21-7.18 (m, 3H), 7.10-7.07 (m, 2H), 5.61 (d, 1H, J = 9.0 Hz), 4.56-4.49 (m, 1H),3.74 (s, 3H), 3.20 (dd, 1H, J = 13.7, 4.5 Hz), 2.95 (dd, 1H, J= 13.8, 8.1 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -130.9 (m, 2F), -136.2 (m,2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 146.6 (dm, *J* = 245.5 Hz), 144.9 (dm, *J* = 261.7 Hz), 143.3 (dm, *J* = 242.2 Hz), 141.5 (dm, *J* = 261.7 Hz), 136,3, 129.1, 128.4, 127.0, 109.5, 105.2, 57.9, 52.9, 38.7;IR (nujol) 3226, 1724, 160', 1501, 1345, 1169,

1109, 1092,994 cm^{-1}.Anal. Calcd. for $C_{16}H_{12}BrF_4NO_4S$: C, 40.87; H, 2.57; N, 2.98. Found: C, 41.23; H, 2.72; N, 3.20.



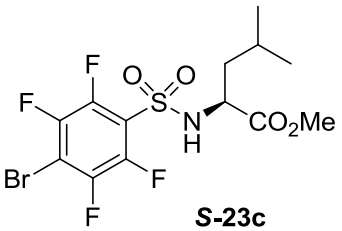
***S*-23a**

(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluorophenylsulfonamido)propanoate (*S*-23a). (4 h, 322,5 mg, 82%). Brown wax, FCC - AcOEt/hexane (1 : 9)**;** $[\alpha]_D^{20}$ -38.4 (*c* 1.3 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 9.3 min]. ^{1}H NMR (300MHz, CDCl3) δ 5.78 (d, 1H, J = 8.1 Hz), 4.33-4.28 (m, 1H),3.68 (s, 3H), 1.50 (d, 3H, J = 7.2 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -128.4 (m, 2F), -134.6 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 146.9 (dd, J = 251.2,19.5 Hz), 145.5 (dd, *J* = 258.0, 15.0 Hz), 143.6, 142.0,120.4 (t, *J* = 14.5 Hz), 105.3 (t, *J* = 21.9 Hz), 52.9, 52.22, 19.38;IR (nujol) 3224, 1750, 156, 1495, 1330, 1068,993 cm^{-1}.Anal. Calcd. for $C_{10}H_8BrF_4NO_4S$: C, 30.47; H, 2.05; N, 3.55;. Found: C, 30.63; H, 2.25; N, 3.69.



***S*-23b**

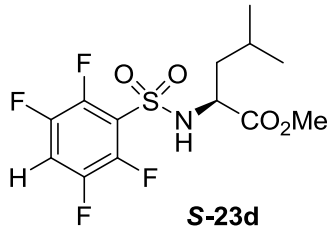
(*S*)-methyl 2-(2,3,5,6-tetrafluorophenylsulfonamido)propanoate (*S*-23b)(4,5h, 267.7 mg, 83%). White solid, FCC - AcOEt/hexane (1 : 9)**;** $[\alpha]_D^{20}$ -23.0 (*c* 1.3 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 9 : 1, Flow rate 0.8 mL/min, P= 30 bar, t_1 = 20.4 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.34-7.32 (m, 1H), 5.84 (d, 1H, J = 7.8 Hz), 4.35-4.25 (m, 1H),3.67 (s, 3H), 1.49 (d, 3H, J = 7.2 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -134.2 (m, 2F), -135.7 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 147.5 (dd, J = 247.5, 6.0 Hz), 145.1 (dd, *J* = 261.7, 15.1 Hz), 144.2, 141.6,121.2 (t, *J* = 15.0 Hz), 109.9 (t, *J* = 22.5 Hz), 61.9, 54.7, 18.8;IR (nujol) 3227, 1745, 153, 1485, 1327, 1059,989 cm^{-1}.Anal. Calcd. for $C_{10}H_9F_4NO_4S$: C, 38.10; H, 2.88; N, 4.44. Found: C, 39.23; H, 2.92; N, 4.52.



***S*-23c**

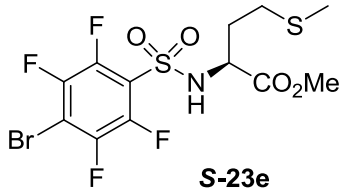
(S)-methyl 2-(4-bromo-2,3,5,6-tetrafluorophenylsulfonamido)-4-methylpentanoate (*S*-23c) (4 h, 388.7 mg, 89%). wax, FCC - AcOEt/hexane (1 : 9)**;** $[\alpha]_D^{20}$ -36.6 (*c* 0.5 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 9 : 1, Flow rate 0.8 mL/min, P= 30

bar, t_1 = 9.2 min]. ^{1}H NMR (300MHz, CDCl3) δ 5.49 (d, 1H, J = 9.3 Hz), 4.30-4.22 (m, 1H),3.61 (s, 3H), 1.84-1.77 (m, 1H), 1.63-1.55 (m, 2H), 0.97-0.93 (m, 6H); ^{19}F NMR (282 MHz, CDCl3) δ -130.7 (m, 2F), -136.3 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 146.3 (dd, J = 248.2, 18.7 Hz), 145.0 (dd, *J* = 262.5, 16.5 Hz), 143.1, 141.5, 119.6, 104.8 (t, *J* = 22.5 Hz), 54.5, 52.0, 41.4, 23.8, 22.1, 20.7;IR (nujol) 3220, 1755, 147, 1460, 1318, 1042,982 cm^{-1}.Anal. Calcd. for $C_{13}H_{14}BrF_4NO_4S$: C, 35.79; H, 3.23; N, 3.21. Found: C, 35.84; H, 3.50; N, 3.40.



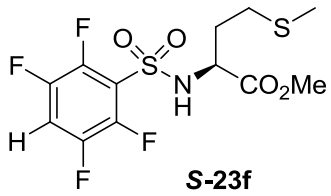
***S*-23d**

(S)-methyl 4-methyl-2-(2,3,5,6-tetrafluorophenylsulfonamido)pentanoate (*S*-23d) (4,5 h, 310.8 mg, 87%). Brown wax, FCC - AcOEt/hexane (1 : 7)**;** $[\alpha]_D^{20}$ +17.6 (*c*1 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 9 : 1, Flow rate 0.8 mL/min, P= 30 bar, t_1 = 11.1 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.28-7.25 (m, 1H), 5.52 (d, 1H, J = 9 Hz), 4.26-4.23 (m, 1H),3.59 (s, 3H), 1.81-1.79 (m, 1H), 1.62-1.56 (m, 2H), 0.93 (d, 6H, J = 6 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -136.7 (m, 2F), -137.5 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 147.7 (dm, J = 255.7 Hz), 145.3 (dm, *J* = 254.2 Hz), 144.3, 141.9, 121.3 (t, *J* = 15.0 Hz), 110.1 (t, *J* = 22.5 Hz), 54.9, 52.4, 41.7, 24.3, 22.5, 21.1;IR (nujol) 3214, 1752, 157, 1475, 1314, 1038,970 cm^{-1}.Anal. Calcd. for $C_{13}H_{15}F_4NO_4S$: C, 43.70; H, 4.23; N, 3.92. Found: C, 43.77; H, 4.30; N, 3.87.



***S*-23e**

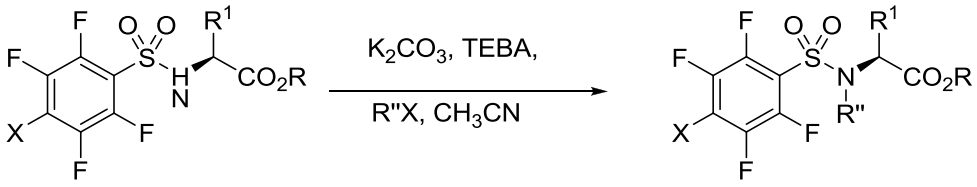
(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluorophenylsulfonamido)-4-(methylthio)butanoate (*S*-23e) (4h, 336.1 mg, 74%). Wax, FCC - AcOEt/hexane (1 : 5). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.5 mL/min, P= 27 bar, t_1 = 11.2 min]. ^{1}H NMR (300MHz, CDCl3) δ 5.95 (d, 1H, J = 10.8 Hz), 4.43-4.39 (m, 1H),3.69 (s, 3H), 2.60-2.53 (m, 2H), 2.19-2.02 (m, 5H); ^{19}F NMR (282 MHz, CDCl3) δ -130.8 (m, 2F), -136.7 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 146.8 (dd, J = 248.2, 21.7 Hz), 145.5 (dd, *J* = 258.0, 15.7 Hz), 143.5, 142.0, 119.6 (t, *J* = 13.5 Hz), 105.4 (t, *J* = 22.5 Hz), 55.2, 52.8, 31.8, 29.5,15.2;IR (nujol) 3234, 1740, 148, 1465, 1308, 1027,967 cm^{-1}.Anal. Calcd. for $C_{12}H_{12}BrF_4NO_4S_2$: C, 31.73; H, 2.66; N, 3.08;. Found: C, 31.82; H, 2.70; N, 3.13.



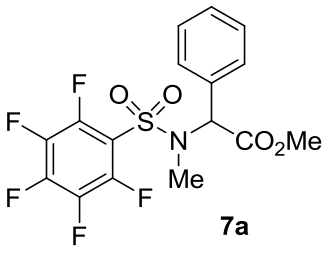
***S*-23f**

(*S*)-methyl 4-(methylthio)-2-(2,3,5,6-tetrafluorophenylsulfonamido)butanoate (*S*-23f) (4h, 292.5 mg, 78%). Wax, FCC - AcOEt/hexane (1 : 3). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 13.2 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.31-7.26 (m, 1H), 6.24 (d, 1H, J = 9 Hz), 4.39-4.32 (m, 1H),3.62 (s, 3H), 2.60-2.54 (m, 2H), 2.13-1.98 (m, 5H); ^{19}F NMR (282 MHz, CDCl3) δ -134.1 (m, 2F), -135.3 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 147.8 (dd, J = 255, 7.5 Hz), 145.4 (dd, *J* = 255.0, 13.5 Hz), 144.4, 142.0, 121.1, 110.1 (t, *J* = 22.5 Hz), 55.2, 52.8, 31.9, 29.5,15.1;IR (nujol) 3272, 1735, 139, 1454, 1312, 1015,953 cm^{-1}.Anal. Calcd. for $C_{12}H_{13}F_4NO_4S_2$: C, 38.40; H, 3.49; N, 3.73. Found: C, 38.50; H, 3.53; N, 3.82.

7.6 SL-PTC N-Alkylation of Sulfonamides 7a-b, S-19a-d, S-24a-j: General Procedure.

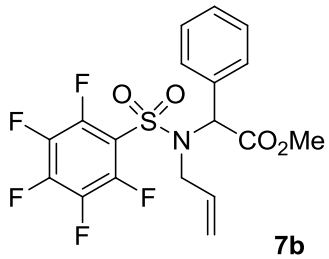


To a solution of sulfonamide (1 mmol) and TEBA (23 mg, 0.1 mmol) in dry MeCN (2 mL) at 25 °C, anhydrous K_2CO_3 (276 mg, 2 mmol) was added. This suspension was stirred for 10 min,then a solution of the alkylating agent (1.5 mmol) in MeCN (1 mL) was added under vigorousstirring, and the reaction was monitored by TLC (AcOEt : hexane – 1 : 9) until completion. Themixture was then diluted with AcOEt (5 mL), washed with brine (2 × 2 mL), dried over $MgSO_4$and filtered. The solvent was removed under vacuum, the crude was purified by column chromatography ; alkylating agent, product, yield, chromatographic eluant, physical andanalytical data are as follows.



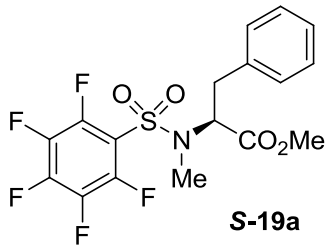
7a

Methyl 2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)-2-phenylacetate (7a) (24 h, 368 mg, 90%);white solid, mp 67-69 °C (EtOH/water – 9 : 1).^{1}H NMR (300 MHz, CDCl3) δ7.42-7.23 (m, 5H), 6.04 (s,1H), 3.72 (s, 3H), 2.84 (s, 3H).^{19}F NMR (282 MHz, CDCl3) δ-135.3 (m, 2F), -146.4 (m,1F), -159.7 (m, 2F).IR (nujol) 1744, 1644, 1541, 1296, 1271, 1222, 1173, 1098,1025, 699, 678 cm^{-1}.Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 46.95; H, 2.95; N,3.42. Found: C, 47.02; H, 3.00; N, 3.37.



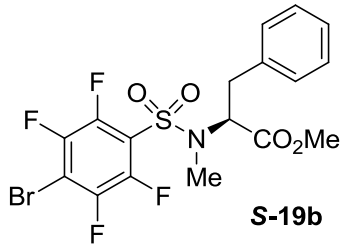
7b

Methyl 2-(N-allyl-2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (7b) (40 h, 122 mg, 48%);FCC - AcOEt/hexane (1 : 12), white wax.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.35 (m, 3H), 7.28-7.26 (m, 2H), 6.06 (s, 1H), 5.42-5.28 (m, 1H), 4.82 (d, 1H, J= 17.0 Hz), 4.77 (d, 1H, J = 9.9 Hz), 3.98 (dd, 1H, J = 16.4,4.7 Hz), 3.82 (dd, 1H, J = 16.4, 6.9 Hz), 3.74 (s, 3H).^{19}F NMR (282 MHz, $CDCl_3$)δ-135.0 (m, 2F), -146.4 (m,1F), -159.6 (m, 2F).Anal. Calcd. for $C_{18}H_{14}F_5NO_4S$: C, 49.66; H, 3.24; N,3.22. Found: C, 49.63; H, 3.24; N, 3.20.



***S*-19a**

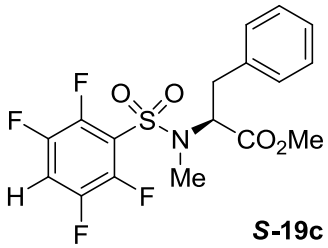
(*S*)-methyl 2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)-3-phenylpropanoate (*S*-19a) (12 h, 410.8 mg, 96%). Wax, FCC - AcOEt/hexane (1 : 3). [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 13 bar, t_1 = 15.5 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.27-7.14 (m, 5H), 4.97-4.89 (m, 1H), 3.74 (s, 3H), 3.36 (dd, 1H, J = 21.0, 6 Hz), 3.09 (s, 3H), 2.93 (dd, 1H, J= 21.0, 18 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -137.0 (m, 2F), -147.1 (m, 1F), -159.8 (m, 2F);^{13}C NMR (75 MHz, $CDCl_3$) δ169.9, 145.9 (dm, J = 263.2 Hz), 145.2 (dm, J = 262.5 Hz), 139.6 (dm, J = 252.7 Hz),135.9, 128.7, 128.4, 127.0, 61.5, 52.6, 35.1, 30.6;IR (nujol) 3268, 1742, 128, 1446, 1316, 1012,946 cm^{-1}.Anal. Calcd. for $C_{17}H_{14}F_5NO_4S$: C, 48.23; H, 3.33; N, 3.31. Found: C, 48.50; H, 3.52; N, 3.53.



***S*-19b**

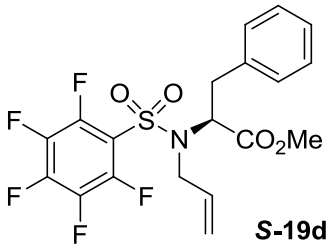
(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-3-phenylpropanoate(*S*-19b) (12 h, 409.5 mg, 85%).FCC - AcOEt/hexane (1 : 8)**;** $[\alpha]_D^{20}$ -24.9 (*c* 0.3 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 20.3 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.16-7.15 (m, 5H), 4.94-4.89 (m, 1H),3.30 (s, 3H), 3.34 (dd, 1H, J = 15.0, 6.0 Hz), 3.11 (s, 3H), 2.92 (dd, 1H, J= 15, 12 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -130.9 (m, 2F), -136.2 (m,2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 146.6 (dd, *J* = 251.2, 15 Hz), 144.9 (dd, *J* = 264.0, 16.9 Hz), 143.1, 141.4, 135,5, 128.2, 128.0, 126.6, 109.1, 104.6, 61.2, 52.3, 34.8, 30.4;IR (nujol)

3218, 1720, 157', 1514, 1334, 1157, 1105, 1083,970 cm^{-1}.Anal. Calcd. for $C_{17}H_{14}BrF_4NO_4S$: C, 42.16; H, 2.91; N, 2.89. Found: C, 42.20; H, 2.98; N, 2.97.



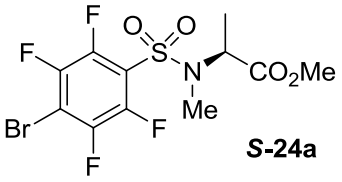
***S*-19c**

(*S*)-methyl 3-phenyl-2-(2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)propanoate (*S*-19c) (12 h, 376.9 mg, 93%). White wax, FCC - AcOEt/hexane (1 : 8)**;** $[\alpha]_D^{20}$ -24.4 (*c*1 $CHCl_3$). [CHIRALCEL OJ ®, Hexane – Isopropanol 8 : 2, Flow rate 0.8 mL/min, P= 33 bar, t_1 = 19.4 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.23-7.15 (m, 5H), 4.56-4.49 (m, 1H),3.68 (s, 3H), 3.19 (dd, 1H, J = 15.0, 6.0 Hz), 3.07 (s, 3H), 2.92 (dd, 1H, J= 15, 12 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -136.0 (m, 2F), -136.8 (m,2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 147.1 (dm, *J* = 243.7 Hz), 144.8 (dm, *J* = 255.0 Hz), 143.9, 141.4, 135,3, 128.2, 127.9, 126.7, 109.3 (t, *J* = 22.5 Hz), 60.9, 51.9, 34.8, 30.1;IR (nujol) 3222, 1718, 149, 1508, 1329, 1148, 1117, 1076,968 cm^{-1}.Anal. Calcd. for $C_{17}H_{15}F_4NO_4S$: C, 50.37; H, 3.73; N, 3.46. Found: C, 50.42; H, 3.80; N, 3.53.



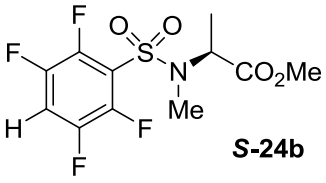
***S*-19d**

(*S*)-methyl 2-(N-allyl-2,3,4,5,6-pentafluorophenylsulfonamido)-3-phenylpropanoate (*S*-19d) (24 h, 359.2 mg, 80%);FCC - AcOEt/hexane (1 : 9), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.21 (m, 5H), 5.86-5.75 (m, 1H), 5.26 (d, 1H, J= 17.0 Hz), 5.17 (d, 1H, J = 9.0 Hz), 4.94-4.89 (m, 1H), 4.81-4.08 (m, 2H), 3.69 (s, 3H), 3.36 (dd, 1H, J = 15.0, 6.0 Hz), 3.04 (dd, 1H, J = 15.0, 9.0 Hz).^{19}F NMR (282 MHz, $CDCl_3$)δ-134.8 (m, 2F), -147.0 (m,1F), -159.8 (m, 2F).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 145.7 (dm, *J* = 255.0 Hz), 144.8 (dm, *J* = 245.0 Hz), 142.3, 139.0, 135,6, 135.4, 133.0, 128.5, 128.0, 126.5, 118.6, 61.2, 51.9, 48.6, 35.7.Anal. Calcd. for $C_{19}H_{16}F_5NO_4S$: C, 50.78; H, 3.59; N, 3.12. Found: C, 50.85; H, 3.62; N, 3.23.



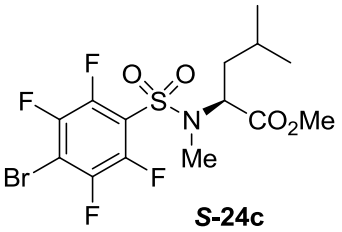
***S*-24a**

(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)propanoate (*S*-24a) (12 h, 370.2 mg, 91%) Brown wax, FCC - AcOEt/hexane (1 : 5)**;** $[\alpha]_D^{20}$ -12.2 (*c*2 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 11.0 min]. ^{1}H NMR (300MHz, CDCl3) δ 4.87-4.80 (m, 1H),3.60 (s, 3H), 2.94 (s, 3H), 1.48 (d, 3H, J = 9.0 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -131.1 (m, 2F), -135.0 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 147.0 (dd, J = 247.5, 15.0 Hz), 145.8 (dd, *J* = 262.5, 15.0 Hz), 143.6, 142.3, 105.0 (t, *J* = 21.9 Hz), 55.4, 52.41, 29.9, 15.7;IR (nujol) 3218, 1720, 156, 1329, 1053,985 cm^{-1}.Anal. Calcd. for $C_{11}H_{10}BrF_4NO_4S$: C, 32.37; H, 2.47; N, 3.43. Found: C, 32.52; H, 2.60; N, 3.57.



***S*-24b**

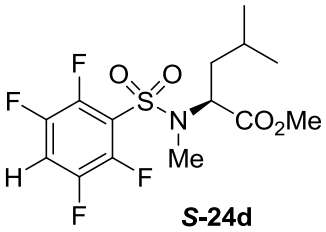
(*S*)-methyl 2-(2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)propanoate (*S*-24b)(6 h, 292.9 mg, 89%) White wax, FCC - AcOEt/hexane (1 : 5)**;** $[\alpha]_D^{20}$ -20.2 (*c*1 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 13.6 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.31-7.25 (m, 1H), 4.82 (q, 1H, J = 12.0, 6.0 Hz),3.58 (s, 3H), 2.93 (s, 3H), 1.46 (d, 3H, J = 9.0 Hz); ^{19}F NMR (282 MHz, CDCl3) δ -136.3 (m, 2F), -136.6 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 147.8 (dd, J = 247.5, 15.0 Hz), 145.5 (dd, *J* = 240.0, 15.0 Hz), 144.5, 142.3, 121.8, 109.9 (t, *J* = 22.5 Hz), 55.3, 52.3, 29.9, 15.6;IR (nujol) 3224, 1718, 158, 1320, 1047,978 cm^{-1}.Anal. Calcd. for $C_{11}H_{11}F_4NO_4S$: C, 40.12; H, 3.37; N, 4.25. Found: C, 40.30; H, 3.42; N, 4.32.



***S*-24c**

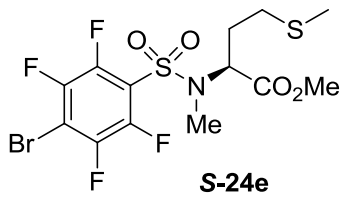
(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-4-methylpentanoate (*S*-24c) (12 h, 414.9 mg, 92%). wax, FCC - AcOEt/hexane (1 : 9)**;** $[\alpha]_D^{20}$ -30.8 (*c*1.3 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.5 mL/min, P= 27 bar, t_1 = 11.2 min]. ^{1}H NMR (300MHz, CDCl3) δ 4.84-4.78 (m, 1H),3.60 (s, 3H), 2.95 (s, 3H)1.72-1.69 (m, 3H), 1.02-0.98 (m, 6H); ^{19}F NMR (282 MHz, CDCl3) δ -129.2 (m, 2F), -132.6 (m, 2F); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 170.5, 145.4 (dd, J = 248.2, 18.7 Hz), 145.0 (dd, *J* = 262.5, 16.5 Hz), 143.1, 141.7, 126.5, 104.8 (t, *J* = 22.5 Hz), 57.6, 51.7, 37.3, 29.4, 23.9, 22.5, 20.2;IR (nujol) 3240, 1747, 138, 1452, 1309, 1037,975 cm^{-1}.Anal. Calcd. for $C_{14}H_{16}BrF_4NO_4S$: C, 37.35; H, 3.58; N, 3.11. Found: 37.42; H, 3.70; N, 3.35.



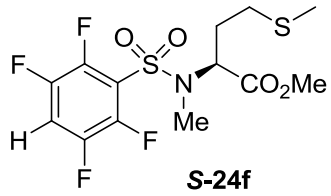
***S*-24d**

(*S*)-methyl 4-methyl-2-(2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)pentanoate(*S*-24d)(12 h, 330.2 mg, 89%). Brown wax, FCC - AcOEt/hexane (1 : 7)**;** $[\alpha]_D^{20}$ +23.6 (*c*1 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 6.9 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.30-7.24 (m, 1H), 4.82-4.77(m, 1H),3.57 (s, 3H), 2.96 (s, 3H), 1.71-1.68 (m, 3H), 1.01-0.97 (m, 6H);^{19}F NMR (282 MHz, CDCl3) δ -133.8 (m, 2F), -134.8 (m, 2F);IR (nujol) 3220, 1748, 1489, 1318, 1030,960 cm^{-1}.Anal. Calcd. for $C_{14}H_{17}F_4NO_4S$: C, 45.28; H, 4.61; N, 3.77. Found: C, 45.38; H, 4.75; N, 3.82.



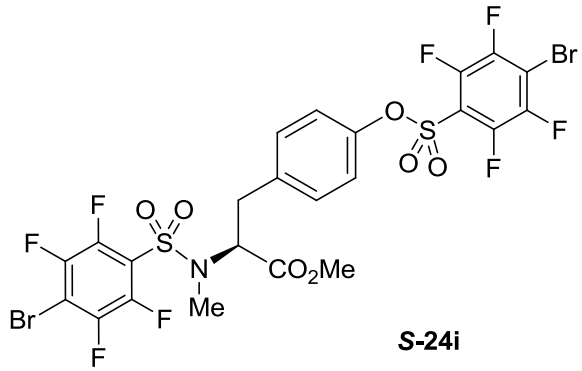
***S*-24e**

(S)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-4-(methylthio)butanoate (*S*-24e) (12 h, 331.6 mg, 73%). Wax, FCC - AcOEt/hexane (1 : 5), $[\alpha]_D^{20}$ +2.5 (*c*1 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 9 : 1, Flow rate 0.8 mL/min, P= 29 bar, t_1 = 24.1 min]. ^{1}H NMR (300MHz, CDCl3) δ 4.92-4.87 (m, 1H),3.63 (s, 3H), 2.97 (s, 3H), 2.63-2.52 (m, 2H), 2.28-2.25 (m, 1H), 2.13 (s, 3H), 2.04-1.97 (m, 1H); ^{19}F NMR (282 MHz, CDCl3) δ -131.7 (m, 2F), -135.0 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 146.6 (dd, J = 247.5, 15.0 Hz), 145.5 (dd, *J* = 262.5, 12.5 Hz), 143.5, 142.3, 118.8, 105.1, 58.8, 52.4, 30.1, 29.5, 28.4,15.2;IR (nujol) 3223, 1736, 136, 1452, 1312, 1016,952 cm^{-1}.Anal. Calcd. for $C_{13}H_{14}BrF_4NO_4S_2$: C, 33.34; H, 3.01; N, 2.99. Found: C, 33.52; H, 3.35; N, 3.16.



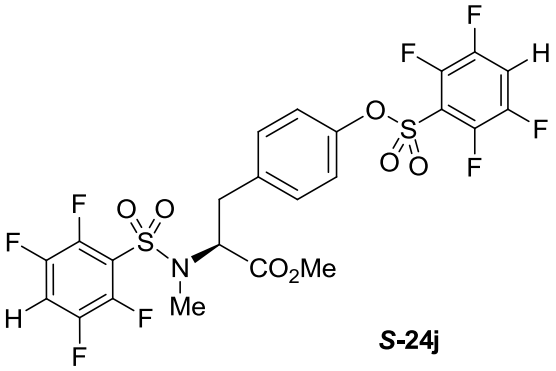
***S*-24f**

(*S*)-methyl 4-(methylthio)-2-(2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)butanoate (*S*-24e) (12 h, 291.7 mg, 75%). Brown wax, FCC - AcOEt/hexane (1 : 5)**;** $[\alpha]_D^{20}$ +19.4 (*c*1.3 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 9 : 1, Flow rate 0.8 mL/min, P= 28 bar, t_1 = 30.5 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.34-7.26 (m, 1H), 4.92-4.87 (m, 1H),3.62 (s, 3H), 2.97 (s, 3H), 2.63-2.53 (m, 2H), 2.28-2.25 (m, 1H), 2.14 (s, 3H), 2.04-1.97 (m, 1H); ^{19}F NMR (282 MHz, CDCl3) δ -135.8 (m, 2F), -136.3 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 147.7 (dm, J = 238.5 Hz), 145.6 (dm, *J* = 255.0 Hz), 144.6, 142.2, 109.9 (t, *J* = 22.5 Hz), 58.8, 52.3, 30.2, 28.5, 15.4;IR (nujol) 3220, 1762, 163, 1482, 1320, 1041,969 cm^{-1}.Anal. Calcd. for $C_{13}H_{15}F_4NO_4S_2$: C, 40.10; H, 3.88; N, 3.60. Found: C, 40.35; H, 3.90; N, 3.80.



***S*-24i**

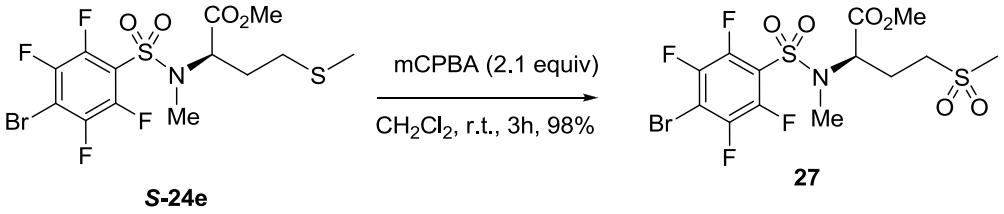
(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-3-(4-(4-bromo-2,3,5,6-tetrafluorophenylsulfonyloxy)phenyl) propanoate (*S*-24i) (24 h, 654,7 mg, 83%).FCC - AcOEt/hexane (1 : 7)**;** $[\alpha]_D^{20}$ -8.6 (*c*1.2 $CHCl_3$). [CHIRALCEL OD-H®, Hexane – Isopropanol 8 : 2, Flow rate 0.8 mL/min, P= 38 bar, t_1 = 30.7 min]. ^{1}H NMR (300MHz, CDCl3) δ 7.26-7.15 (m, 4H),4.87 (q, 1H, J = 9.0, 6.0 Hz), 3.65 (s, 3H), 3.34 (dd, 1H, J = 15.0, 6.0 Hz), 2.98 (dd, 1H, J= 15.0, 9.0 Hz), 2.94 (s, 3H9; ^{19}F NMR (282 MHz, CDCl3) δ -129.5 (m, 2F), -131.3 (m, 2F), -135.1 (m, 2F), -135.2 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 148.7, 147.0 (dm, *J* = 255.0 Hz), 145.7 (dm, *J* = 247.5 Hz), 143.6 (dm, *J* = 255.0 Hz), 142.4 (dm, *J* = 246.5 Hz), 136,0, 130.8, 128.7, 121.5, 118.8, 114.6 (d, *J* = 15.0 Hz), 108.2 (t, *J* = 22.5 Hz), 105.3 (t, *J* = 22.5 Hz), 61.3, 52.6, 34.6, 30.4, 29.6;IR (nujol) 3230, 1735, 158, 1514, 1356, 1158, 1106, 1085,980 cm^{-1}.Anal. Calcd. for $C_{23}H_{13}Br_2F_8NO_7S_2$: C, 34.91; H, 1.66; N, 1.77. Found: C, 35.02; H, 1.86; N, 1.81.



***S*-24j**

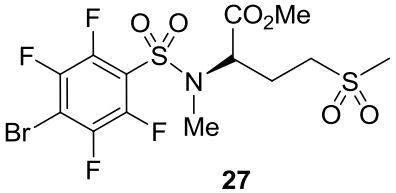
(*S*)-methyl 2-(2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-3-(4-(2,3,5,6-tetrafluorophenylsulfonyloxy)phenyl)propanoate (*S*-24j) (12 h, 519.0 mg, 82%). White wax, FCC - AcOEt/hexane (1 : 5)**;** $[\alpha]_D^{20}$ -10.6 (*c*1.2 $CHCl_3$). ^{1}H NMR (300MHz, CDCl3) δ 7.26-7.15 (m, 6H), 4.93 (q, J= 9.0, 6 Hz 1H),3.65 (s, 3H), 3.64 (dd, 1H, J = 15.0, 6.0 Hz), 2.99 (dd, 1H, J= 15, 12 Hz),2.97 (s, 3H); ^{19}F NMR (282 MHz, CDCl3) δ -134.3 (m, 2F), -134.9 (m,2F)-135.9 (m, 2F), -136.5 (m,2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 147.8 (dm, *J* = 195.0 Hz), 146.1 (dm, *J* = 262.5 Hz), 145.3, 144.3, 142,4, 142.1, 136.1, 130.7, 121.5, 120.2(t, *J* = 15.0 Hz), 116.1 (t, *J* = 7.5 Hz), 112.5 (t, *J* = 22.5 Hz), 109.9 (t, *J* = 22.5 Hz), 61.0, 52.4, 34.6, 30.4;IR (nujol) 3242, 1725, 132, 1523, 1328, 1145, 1114, 1079,971 cm^{-1}.Anal. Calcd. for $C_{23}H_{15}F_8NO_7S_2$: C, 43.61; H, 2.39; N, 2.21. Found: C, 43.83; H, 2.45; N, 2.48.

7.7 Synthesis of (S)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-4-(methylsulfonyl)butanoate (27)



***S*-24e** **27**

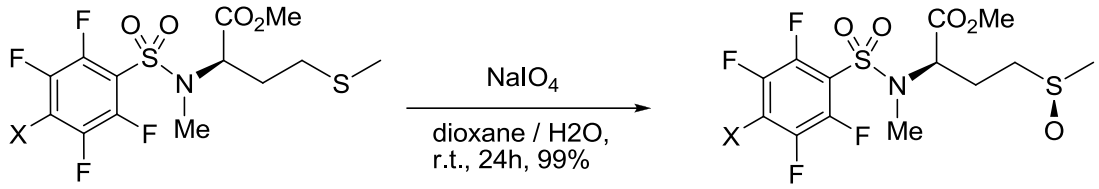
(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-4-(methylthio)butanoate **(*S*-24e)**(93.3 mg, 0.2 mmol) was addedto a round bottom flask and dissolved in DCM (1 mL). The stirred solutionwas cooled to 0 ºC and 3-chloroperoxybenzoic acid (70%, 103.5mg, 0.42 mmol) wasadded as a suspension in 0.3 mL of DCM by pipette over a period of 5 min. Anadditional 0.3 mL of DCM was used to complete the transfer of oxidant. The reactionwas stirred for 1.5 hours at room temperature at which time it was diluted with diethylether (10 mL) and sodium hydrogen carbonate (5 mL of a saturated aqueoussolution). The layers were separated and the organic fraction was washedsuccessively with sodium hydrogen carbonate (2 x 10 mL of a saturated aqueoussolution) and brine (15 mL). The organics were dried (MgSO4), filtered, andconcentrated under reduced pressure. The product was purified by flash columnchromatography (ethyl acetate/hexane, 1:1) to afford the corresponding sulfone **27**



27

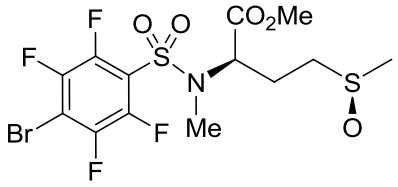
(*S*)-methyl 2-(4-bromo-2,3,5,6-tetrafluoro-N-methylphenylsulfonamido)-4-(methylsulfonyl)butanoate (27) (12 h, 331.6 mg, 73%). White solid, p.f. 130°C,FCC - AcOEt/hexane (1 : 1), $[\alpha]_D^{20}$ +2.7 (*c*1 $CHCl_3$). [CHIRALPAK AD®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 17 bar, t_1 = 52.8 min]. ^{1}H NMR (300MHz, CDCl3) δ 4.82-4.77 (m, 1H),3.63 (s, 3H), 3.21-3.12 (m, 2H), 2.98 (s, 3H), 2.93 (s, 3H), 2.62-2.50 (m, 1H), 2.31-2.20 (m, 1H); ^{19}F NMR (282 MHz, CDCl3) δ -131.1 (m, 2F), -135.1 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 146.8 (dd, J = 247.5, 15.0 Hz), 145.7 (dd, *J* = 255.0, 15.0 Hz), 143.5, 142.3, 118.2, 105.6 (t, J =22.5 Hz), 58.8, 52.7, 50.9, 41.1, 30.1, 20.9;IR (nujol) 3240, 1742, 141, 1457, 1317, 1022,948 cm^{-1}.Anal. Calcd. for $C_{13}H_{14}BrF_4NO_6S_2$: C, 31.21; H, 2.82; N, 2.80. Found: C, 31.48; H, 2.93; N, 2.97.

7.8 Synthesis of methionine sulfoxide sulfonamide 26e,f: General procedure.



***S*-24e-f** **26e,f**

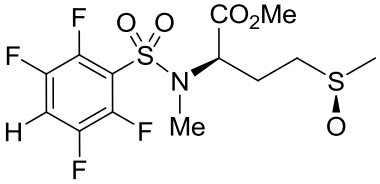
In a round-bottomed flask equipped with a magnetic stirrer are placed 34.1 mg. (0.159 mmole) of powdered sodium metaperiodate and 2 ml. of water. The mixture is stirred and cooled in an ice bath, and 600 mg. (1.59 mmole) of sulphonamide ***S*-24e,f** is added. The reaction mixture is stirred for 15 hours at ice-bath temperature and is then filtered through a Büchner funnel. The filter cake of sodium iodate is washed with three 3 ml portions of methylene chloride. The water-methylene chloride filtrate is transferred to a separatory funnel, the lower methylene chloride layer is removed, and the water layer is extracted with three 10 ml portions of methylene chloride. The combined methylene chloride extracts are treated with activated carbon and dried over anhydrous sodium sulfate. The solvent is removed at reduced pressure to yield 98% of sulfoxide derivatives as a thick clear wax, and as a mixture of diastereomers.Starting sulfonamides, reaction time, product, yield, physical and analytical data are as follows.



26e

Methionine sulfoxide sulfonamide 26a (20 h, 100.6 mg, 98%, mixture of diastereomers 1:1). wax, FCC - AcOEt/hexane (1 : 1), $[\alpha]_D^{20}$ +1.5 (*c* 1 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.5 mL/min, P= 27 bar, t_1 = 17.9 min, t_2 = 21.5 min]. ^{1}H NMR (300MHz, CDCl3) δ 4.85-4.77 (m, 1H),3.59 (s, 3H), 2.92 (s, 3H), 2.82-2.71 (m, 2H), 2.61 (s, 3H), 2.59-2.49 (m, 1H), 2.25-2.16 (m, 1H); ^{19}F NMR (282 MHz, CDCl3) δ -131.2 (m, 2F), -135.1 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 147.0 (dd, J = 255.0, 7.5 Hz), 145.8 (dd, *J* = 265.5, 16.5 Hz), 143.6, 142.3,

118.2, 105.6 (t, J = 22.5 Hz), 58.8, 52.7, 50.3, 38.8, 30.1, 21.9;IR (nujol) 3238, 1738, 145, 1448, 1306, 1018,952 cm^{-1}.Anal. Calcd. for $C_{13}H_{14}BrF_4NO_5S_2$: C, 32.24; H, 2.91; N, 2.89. Found: C, 32.52; H, 3.23; N, 2.97.

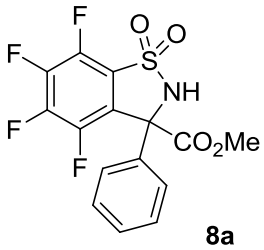


26f

Methionine sulfoxide sulfonamide 26b (12 h, 399.6 mg, 94%, mixture of diastereomers 2:1). wax, FCC - AcOEt/MeOH(13 : 1), $[\alpha]_D^{20}$ - 27.8 (*c* 1.1 $CHCl_3$). [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 21.3 min, t_2 = 28.0 min]. ^{1}H NMR (300MHz, CDCl3) δ7.33-7.27 (m, 1H), 4.88-4.83 (m, 1H),3.62 (s, 3H), 2.96 (s, 3H), 2.85-2.69 (m, 2H), 2.64 (s, 3H), 2.59-2.51 (m, 1H), 2.27-2.22 (m, 1H); ^{19}F NMR (282 MHz, CDCl3) δ -133.6 (m, 2F), -134.4 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 147.7 (dd, J = 247.5, 7.5 Hz), 145.6 (dd, *J* = 247.5, 15.0 Hz), 144.4, 142.2, 118.2, 110.2 (t, J = 22.5 Hz), 59.3, 52.5, 50.2, 38.7, 30.0, 21.8;IR (nujol) 3248, 1758, 136, 1457, 1316, 1025,964 cm^{-1}.Anal. Calcd. for $C_{13}H_{15}F_4NO_5S_2$: C, 38.52; H, 3.73; N, 3.46. Found: C, 38.65; H, 3.89; N, 3.72.

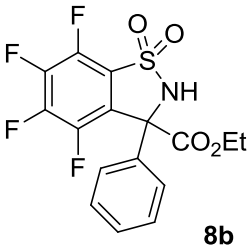
7.9 Synthesis of Benzo[d]sultams 8a-d: General Procedure.

To a solution of sulfonamide (1 mmol) in dry DME (4 mL), base (4 mmol) in DME(1mL) was added and the mixture was stirred at 25°C until completion (TLC control).The solution was then diluted with AcOEt (10 mL), washed with aqueous 5% citric acid(3×10 mL), saturated $NaHCO_3$ solution (2×10 mL), and brine (10 mL). The organic phasewas dried over $MgSO_4$, filtered, and concentrated under reduced pressure (RV), givingthe sultams, in some case without any further purification. Starting sulfonamides,reaction time, product, yield, physical and analytical data are as follows.



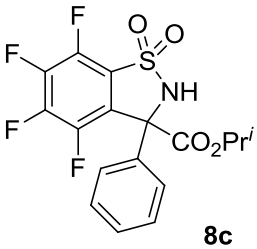
8a

Methyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8a).4 h, 3.60 g, 96%;white solid; mp 98-99°C.^{1}H NMR (300 MHz, CDCl3) δ 7.42-7.34 (m, 5H), 6.38 (s,1H), 3.93 (s, 3H).^{19}F NMR (282 MHz, CDCl3) δ -132.5 (m, 1F), -140.1 (m,1F), -144 (m, 1F), -147.9 (m, 1F).^{13}C NMR (75 MHz, CDCl3) δ 168.0, 144.6 (dt, J = 262.2,14.3 Hz), 143.6 (ddd, J = 261.8, 12.4, 3.3 Hz), 141.6 (dt, J =262.1, 14.2 Hz), 140.9 (dd, J = 261.6, 12.5 Hz), 135.4, 129.6,129.0, 126.2, 121.8 (d, J = 14.3 Hz), 119.6 (d, J = 17.8 Hz),69.9, 54.3.IR (nujol) 3280, 1748, 1637, 1512, 1376, 1319, 1257, 1173,1035, 914 cm^{-1}.Anal. Calcd. for $C_{15}H_9F_4NO_4S$: C, 48.01; H, 2.42; N, 3.73.Found: C, 47.96; H, 2.44; N, 3.73.



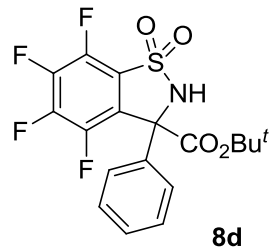
8b

Ethyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8b).16 h, 366 mg, 94%;white solid; mp 83.5-84.5°C.^{1}H NMR (300 MHz, CDCl3) δ 7.43-7.37 (m, 5H), 5.98 (s,1H), 4.50-4.08 (m, 2H), 3.93 (t, 3H, J = 6.3 Hz).^{19}F NMR (282 MHz, CDCl3) δ-132.1 (m, 1F), -139.6 (m,1F), -143.8 (m, 1F), -147.5 (m, 1F).IR (nujol) 3245, 1742, 1643, 1518, 1369, 1314, 1252, 1173,1033, 909 cm^{-1}.Anal. Calcd. for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N,3.60. Found: C, 49.34; H, 2.82; N, 3.59.



8c

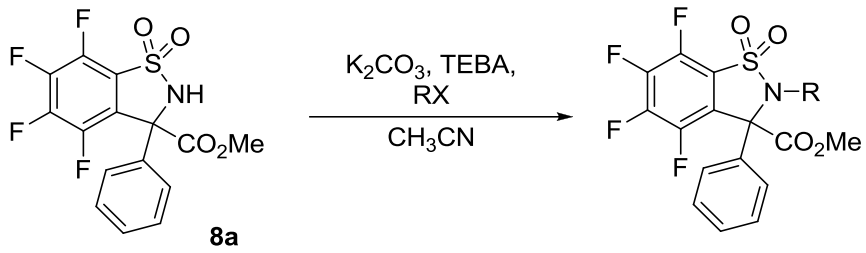
Isopropyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate1,1-dioxide (8c).20 h, 379,1 mg, 94%;white solid; mp 95.5-96.5°C.^{1}H NMR (300 MHz, CDCl3) δ7.41-7.36 (m, 5H), 6.09 (s,1H), 5.27-5.18 (m, 1H), 1.34 (d, 3H, J = 6.3 Hz), 1.29 (d,3H, J = 6.3 Hz).^{19}F NMR (282 MHz, CDCl3) δ -131.9 (m, 1F), -139.8 (m,1F), -144.0 (m, 1F), -147.7 (m, 1F).^{13}C NMR (75 MHz, CDCl3) δ167.5, 145.2 (dt, J = 261.1,14.4 Hz), 144.2 (dd, J = 257.6, 11.6 Hz), 142.1 (dt, J =260.7, 14.4 Hz), 141.4 (dd, J = 260.6, 11.7 Hz), 136.2, 129.9,129.5, 126.8, 122.5 (d, J = 15.2 Hz), 120.4 (d, J = 17.6 Hz),73.5, 70.5, 21.8.IR (nujol) 3229, 1746, 1644, 1523, 1362, 1315, 1256, 1171,1033, 920 cm^{-1}.Anal. Calcd. for $C_{17}H_{13}F_4NO_4S$: C, 50.62; H, 3.25; N,3.47. Found: C, 50.60; H, 3.26; N, 3.45.



8d

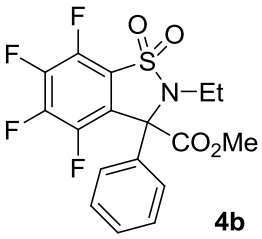
***tert*-Butyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate1,1-dioxide (8d).** 16 h, 379,8 mg, 91%;white solid; mp 108-109°C.^{1}H NMR (300 MHz, CDCl3) δ 7.41-7.39 (m, 5H), 6.16 (s,1H), 1.52 (s, 9H).^{19}F NMR (282 MHz, CDCl3) δ -132.0 (m, 1F), -140.1 (m,1F), -144.4 (m, 1F), -148.1 (m, 1F).^{13}C NMR (75 MHz, CDCl3) δ 166.4, 146.5-139.1 (4 C-FAr), 136.1, 129.5, 129.1, 125.9, 120.5, 119.5, 86.6, 70.5, 27.9.IR (nujol) 3233, 1745, 1641, 1523, 1363, 1315, 1257, 1171,1040, 903 cm^{-1}.Anal. Calcd. for $C_{18}H_{15}F_4NO_4S$: C, 51.80; H, 3.62; N,3.36. Found: C, 51.81; H, 3.63; N, 3.39.

7.10 N-Alkylation of Racemic Benzo[d]sultams 8a: General Procedure.



8a

To a solution of sultam (0,25 mmol) and TEBA (5,7 mg, 0,025 mmol) in dryacetonitrile (1 mL) at 25 °C, anhydrous potassium carbonate (51,8 mg, 0,375 mmol)was added. The resulting heterogeneous mixture was stirred for 10 min, then thealkylating agent RX (0,375 mmol) was added and the reaction was monitored byTLC until completion. The mixture was filtered through a celite pad and, afterevaporation of the solvent (RV), the crude was purified by FCC. Starting sulfonamideand alkylating agent (RX), reaction time, product, yield and eluant are as follows.



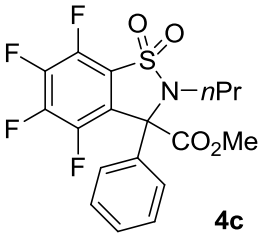
4b

Methyl 4,5,6,7-tetrafluoro-2-ethyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4b).

Starting sultam **8a**, 93,8 mg; EtI, 58,5 mg;

sultam **4b**, 87,2 mg, 95%,

MPLC (AcOEt : esano – 1 : 12).



4c

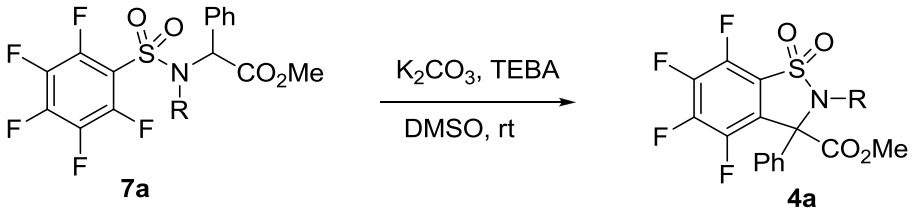
Methyl 4,5,6,7-tetrafluoro-2-n-propyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (4c).

Starting sultam **8a**, 93,8 mg; n-PrI, 63,7 mg;

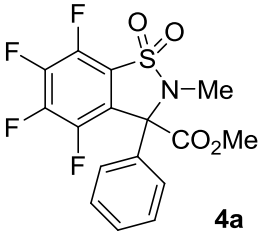
sultam **4c**, 83,9 mg, 88%,

MPLC (AcOEt : esano – 1 : 12).

7.11 SL-PTC Ring Closing Reactions of N-Alkylsulfonamide 7a.



To a solution of N-alkyl-sulfonamide (0.2 mmol) and TEBA (5 mg, 0.02 mmol) in dry DMSO (1mL) at 25 °C, anhydrous Cs_2CO_3 (130 mg, 0.4 mmol) was added. This suspension wasvigorously stirred for 15 min, monitoring by TLC (AcOEt : hexane – 1 : 9), then diluted withwater (2 mL), extracted with DCM (3×10 mL). The solvent was removed under vacuum (RV).The residue was diluted with AcOEt (10 mL), washed with brine (5×2mL), dried over Mg_2SO_4filtered and, after evaporation of the solvent (RV), purified by MPLC (AcOEt : hexane – 1 : 12) togive the desired *N*-alkyl benzosultam. Starting sulfonamides, product, yield andchromatographic eluants are as follows.



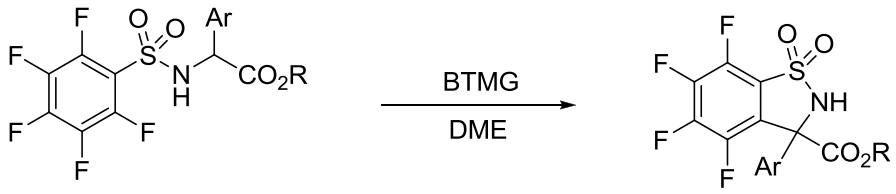
Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carbossilate 1,1-dioxide (4a).

Starting sultam **8a**, 93,8 mg; MeI, 53,2 mg;

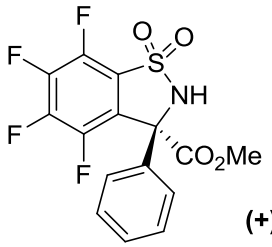
sultam **4a**, 142 mg, 91%,

MPLC (AcOEt : hexane – 1 : 12).

7.12 Synthesis of Benzo[d]sultams (+)8a,d, (+)18a-e: General Procedure

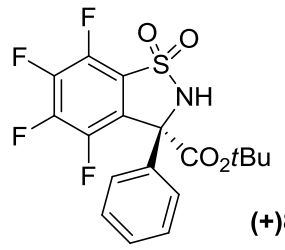


To a solution of sulfonamide ***S*-3a,d**(1 mmol) in dry DME (3 mL), was added BTMG(609 mg, 4 mmol)in dry DME (3 mL) at 0°C. The solution was stirred at 25 °C until completion (TLC control). The crude was then diluted with AcOEt (10 mL), washed with aqueous 5% citric acid (2×10 mL), saturated $NaHCO_3$ solution (2×10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (RV), giving the sultam **(+)8a,d** and **(+)18a-6**. Starting sulfonamide ***S*-3a,d**, reaction time, product, yield, physical and analytical data are as follows.



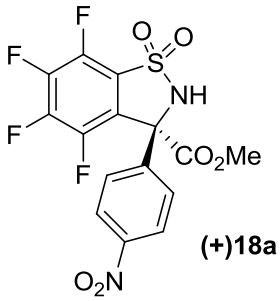
(+)8a

(*R*)-Methyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide [(+)8a]. Sulfonamide***S*-3a** 395 mg. **(+)8a** (4d, 360 mg, 96%). White solid; mp 98-99°C; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20.}$+ 61.2 (*c* 1.1, $CHCl_3$) *ee* 80% [CHIRALCEL OD®, Hexane – Isopropanol 8 : 2+ 0.2% TFA, Flow rate 0.7 mL/min, P= 10 bar, t_1 = 9.9 min, t_2 = 10.7 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 6.38 (s, 1H), 3.93 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.5 (m, 1F), -140.1 (m, 1F), -144 (m, 1F), -147.9 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 144.6 (dt, *J* = 262.2, 14.3 Hz), 143.6 (ddd, *J* = 261.8, 12.4, 3.3 Hz), 141.6 (dt, *J* = 262.1, 14.2 Hz), 140.9 (dd, *J* = 261.6, 12.5 Hz), 135.4, 129.6, 129.0, 126.2, 121.8 (d, *J* = 14.3 Hz), 119.6 (d, *J* = 17.8 Hz), 69.9, 54.3; IR (nujol) 3280, 1748, 1637, 1512, 1376, 1319, 1257, 1173, 1035, 914 cm^{-1}. Anal. Calcd. for $C_{15}H_9F_4NO_4S$: C, 48.01; H, 2.42; N, 3.73. Found: C50.13; H, 2.68; N, 3.92.



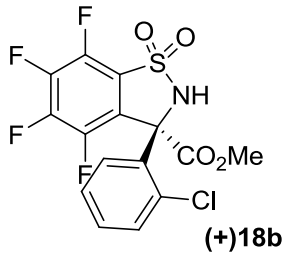
(+)8d

(*R*)-*tert*-butyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide [(+)8d]. Sulfonamide***S*-3d** 437 mg. **(+)8d**(6d, 146 mg, 35%). White solid; mp 108-109°C; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ +90.7 (*c* 0.8, $CHCl_3$) *ee* 87% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1+ 0.2% TFA, Flow rate 1 mL/min, P= 13 bar, t_1 = 6.2 min, t_2 = 7.0 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.39 (m, 5H), 6.16 (s, 1H), 1.52 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.0 (m, 1F), -140.1 (m, 1F), -144.4 (m, 1F), -148.1 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 144.7 (dd, *J* = 261.5, 14.9 Hz), 143.7 (ddd, *J* = 257.5, 13.1, 4.2 Hz), 141.3 (dd, *J* = 260.3, 13.7 Hz), 140.9 (dd, *J* = 260.4, 14.6 Hz), 136.1, 129.6, 129.1, 126.4, 128.5, 126.4, 126.0, 86.6, 70.5, 27.7; IR (nujol) 3233, 1745, 1641, 1523, 1363, 1315, 1257, 1171, 1040, 903 cm^{-1}.Anal. Calcd. for $C_{18}H_{15}F_4NO_4S$: C, 51.80; H, 3.62; N, 3.36. Found: C, 51.87; H, 3.75; N, 3.45.



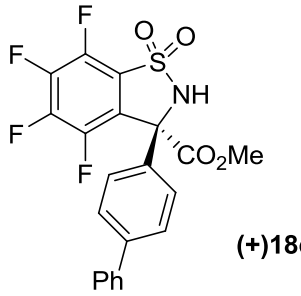
(+)18a

(*R*)-Methyl 4,5,6,7-tetrafluoro-3-(4-nitrophenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide [(18a)]. Sulfonamide**9a**, 440 mg. **18a** (16h, 189 mg, 45%). Yellow wax; FCC - AcOEt/hexane (1 : 2); *ee* 0% [CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1+ 0.2% TFA, Flow rate 1 mL/min, P= 13 bar, t_1 = 13.7 min, t_2 = 23.0 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.66-7.63 (m, 2H), 6.2 (s, 1H), 3.99 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -133.2 (m, 1F), -138.7, -142.9 (m, 1F), -146.1 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 148.6, 144.9 (dd, *J* = 262.1, 13.1 Hz), 143.7 (dd, *J* = 256.9, 11.3 Hz), 142.1(dm, *J* = 264.0 Hz), 142.0, 141.4 (dd, *J* = 260.9, 10.7 Hz), 127.9, 124.2, 120.4, 119.9 (d, *J* = 10.8 Hz), 69.7, 55.2**.** Anal. Calcd. for $C_{15}H_8F_4N_2O_6S$: C, 42.87; H, 1.92; N, 6.67. Found: C, 42.97; H, 2.13; N, 6.84.



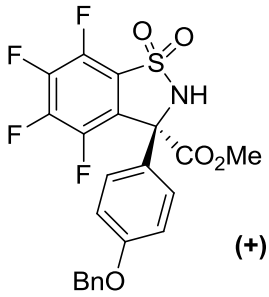
(+)18b

(*R*)-Methyl 4,5,6,7-tetrafluoro-3-(4-chlorophenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide [(+)18b]. Sulfonamide**9b**, 429 mg. **(+)18b** (7d, 135 mg, 33%). White wax; FCC - AcOEt/hexane (1 : 4); *ee*<10% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 13 bar, t_1 = 11.7 min, t_2 = 15.0 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.39 (dt, 1H, *J* = 7.8, 1.5 Hz), 7.25 (dt, 1H, *J* = 7.5, 1.2 Hz), 6.84 (dd, 1H, *J* = 8.1, 1.8 Hz), 6.5 (s, 1H), 3.92 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -131.6 (m, 1F), -138.4 (m, 1F), -143.8 (m, 1F), -146.3 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 144.6 (dm, *J* = 261.2 Hz), 143.5 (dm, *J* = 259.2 Hz), 142.1(dm, *J* = 264.0 Hz), 142.0, 141.3 (dm, *J* = 258.1 Hz), 131.5, 131.1, 128.3, 127.2, 120.3, 115.0, 69.3, 55.2**;** IR (nujol) 3274, 1731, 1634, 1288, 1160, 911 cm^{-1}.Anal. Calcd. for $C_{15}H_8ClF_4NO_4S$: C, 43.97; H, 1.97; N, 3.42. Found: 44.20; H, 2.35; N, 3.76.



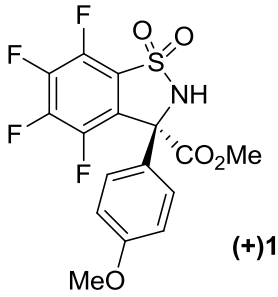
(+)18c

***R*-Methyl 4,5,6,7-tetrafluoro-3-(4-phenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide ((+)18c)** sulfonamide **49c**, 501 mg, **(+)18c** (4d, 169 mg, 98%), white wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$= +35.2 (*c* 0.8 $CHCl_3$) *ee*64% [.CHIRALCEL OD®, Hexane – Isopropanol 9 : 1 + 0.2% TFA, Flow rate 1 mL/min, P= 15 bar, t_1 = 18.7 min, t_2 = 34.0 min.].^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.55 (m, 4H), 7.47-7.38 (m, 5H), 7.20 (bs, 1H), 3.98 (s, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ -132.6 (m, 1F), -139.9 (m, 1F), -144.0 (m, 1F), -147.8 (m, 1F). Anal. Calcd. for $C_{21}H_{13}F_4NO_4S$: C, 55.88; H, 2.90; N, 3.10. Found: C, 56.12; H, 3.06; N, 3.25.



(+)18d

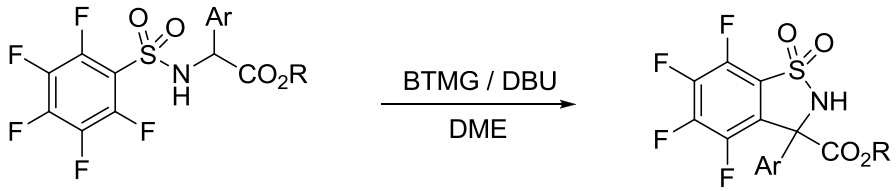
(*R*)-Methyl 4,5,6,7-tetrafluoro-3-(4-benzyloxyphenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(+)18d]. Sulfonamide**9d**, 501 mg. **(+)18d** (4d, 169 mg, 35%). White wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ +59.2 (*c* 0.8 $CHCl_3$) *ee* 96% [CHIRALCEL OD®, Hexane – Isopropanol 8 : 2 + 0.2% TFA, Flow rate 1 mL/min, P= 15 bar, t_1 = 9.5 min, t_2 = 14.0 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 7.31-7.25 (m, 2H), 7.00-6.96 (m, 2H), 6.13 (s, 1H), 5.06 (s, 2H), 3.93 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.5 (m, 1F), -140.0 (m, 1F), -143.9 (m, 1F), -147.9 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 159.3, 144.4 (dt, *J* = 274.4, 13.9 Hz), 143.3 (dd, *J* = 259.9, 11.4 Hz), 141.4 (dt, *J* = 260.8, 13.4 Hz), 140.7 (dd, *J* = 261.6, 10.8 Hz), 135.9, 129.9, 128.2, 127.7, 127.4, 127.0, 121.7 (d, *J* = 13.6 Hz), 119.4 (d, *J* = 17.4 Hz), 115.0, 69.8, 69.3, 54.1; IR (nujol) 3284, 1739, 1645, 1508, 1371, 1304, 1255, 1170, 1022, 906 cm^{-1}. Anal. Calcd. for $C_{22}H_{15}F_4NO_5S$: C, 54.89; H, 3.14; N, 2.91. Found: C, 54.92; H, 3.23; N, 3.20.



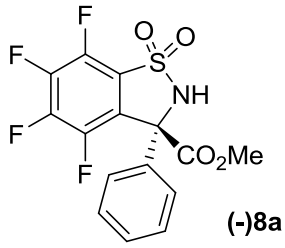
(+)18e

(*R*)-Methyl 4,5,6,7-tetrafluoro-3-(4-methoxyphenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide [(+)18e]. Sulfonamide**9e**, 425 mg. **(+)18e** (4d, 385 mg, 95%). White wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ +39.5 (*c* 1 $CHCl_3$) *ee* 94% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 13 bar, t_1 = 12.2 min, t_2 = 18.4 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.23 (m, 2H), 6.88-6.85 (m, 2H), 5.9 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.7 (m, 1F), -140.2 (m, 1F), -144.1 (m, 1F), -148.1 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 160.5, 144.7 (dt, *J* = 264.2, 14.3 Hz), 143.7 (dd, *J* = 261.9, 12.1 Hz), 141.6 (dt, *J* = 264.2, 14.4 Hz), 140.9 (dd, *J* = 261.9, 12.1 Hz), 127.7, 127.2, 122.2 (d, *J* = 13.6 Hz), 119.8 (d, *J* = 17.4 Hz), 114.1, 69.7, 55.3, 54.4; IR (nujol) 3270, 1750, 1600, 1458, 1436, 1352, 1326, 1258, 1170, 1050, 912 cm^{-1}. Anal. Calcd. for $C_{16}H_{11}F_4NO_5S$: C, 47.41; H, 2.74; N, 3.46. Found: C, 47.64; H, 2.83; N, 3.68.

7.13 Synthesis of Benzo[d]sultams (-)8a,d, (-)18a-e: General Procedure BTMG/DBU

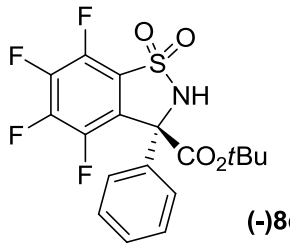


To a solution of sulfonamide ***S*-3a,d** (1 mmol) in dry DME (3 mL), was added a solution of DBU (46 mg, 0.3 mmol) and *BTMG* (291 mg, 1.7 mmol)in dry DME (3 mL) at 0°C. The solution was stirred at 25 °C until completion (TLC control). The crude was then diluted with AcOEt (10 mL), washed with aqueous 5% citric acid (3×10 mL), saturated $NaHCO_3$ solution (2×10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (RV), giving the sultam **(-)8a,d** and **(-)18a-e**.



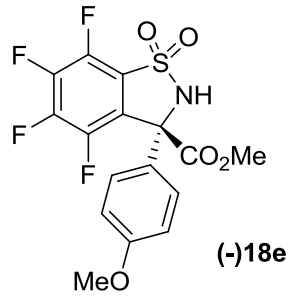
(-)8a

(*S*)-Methyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(-)8a]. Sulfonamide***S*-3a** 395 mg. **(-)8a** (16h, 364 mg, 97%). White wax; $[\alpha]_D^{20}$ -52.8 (*c* 1 $CHCl_3$) *ee* 68% [CHIRALCEL OD®, Hexane – Isopropanol 8 : 2+ 0.2% TFA, Flow rate 0.7 mL/min, P= 10 bar, t_1 = 9.9 min, t_2 = 10.7 min]. NMR spectra match those of **(+)8a**.



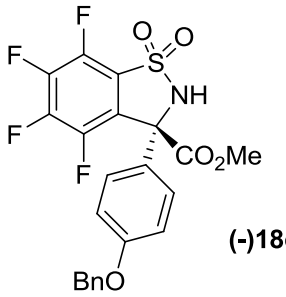
(-)8d

(*S*)-*tert*-butyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(-)8d)]. Sulfonamide***S*-3d** 437 mg. **(-)8d**(24h, 379.8 mg, 91%). Clare wax; $[\alpha]_D^{20}$ +90.7 (*c* 0.8 $CHCl_3$) *ee* 82% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1+ 0.2% TFA, Flow rate 1 mL/min, P= 13 bar, t_1 = 6.2 min, t_2 = 7.0 min]. NMR spectra match those of **(+)8d**.



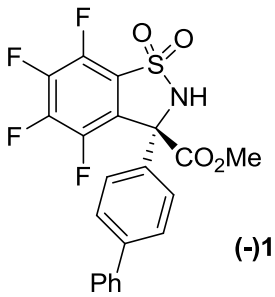
(-)18e

(*S*)-Methyl 4,5,6,7-tetrafluoro-3-(4-methoxyphenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(-)18e]. Sulfonamide**9e**, 425 mg. **(-)18e** (4d, 401 mg, 99%). White wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ -37.1 (*c* 0.7 $CHCl_3$) *ee* 94% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 13 bar, t_1 = 12.2 min, t_2 = 18.4 min]. NMR spectra match those of **(+)18e**.



(-)18d

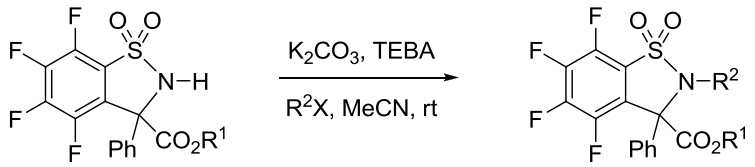
(*S*)-Methyl 4,5,6,7-tetrafluoro-3-(4-benzyloxyphenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(-)18d]. Sulfonamide**9d**, 501 mg. **(-)18d** (4d, 390 mg, 81%). White wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ -59.2 (*c* 1.1 $CHCl_3$) *ee* 94% [CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2 + 0.2% TFA, Flow rate 1 mL/min, P= 15 bar, t_1 = 9.53 min, t_2 = 13.94 min.]. NMR spectra match those of **(+)18d**.



(-)18c

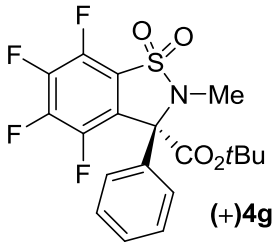
(*S*)-Methyl 4,5,6,7-tetrafluoro-3-(4-phenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(-)18c]. Sulfonamide**9c**, 471 mg. **(-)18c** (16h, 424 mg, 94%). White wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ -27.7 (*c* 0.7 $CHCl_3$) *ee* 56% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1 + 0.2% TFA, Flow rate 1 mL/min, P= 15 bar, t_1 = 18.7 min, t_2 = 34.0 min.]. NMR spectra match those of **(+)18c**.

7.14 N-Alkylation of enantiopure Benzo[d]sultams 8a,d: General Procedure.



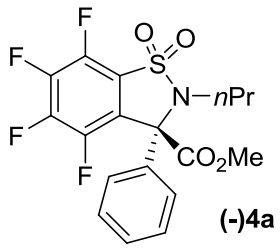
8a,d **4c,f,g**

To a solution of sultam **8a,d** (1 mmol) and TEBA (23 mg, 0.1 mmol) in dry acetonitrile (4 mL) at 25 °C, anhydrous potassium carbonate (208 mg, 1.5 mmol) was added. The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent R^2X (1.5 mmol) was added and the reaction was monitored by TLC until completion. The mixture was filtered through a celite pad and, after evaporation of the solvent (RV), the crude was purified by FCC and recrystallized giving the enantiomerically pure sultams **4c,f,g**. Starting sulphonamide and alkylating agent (RX), reaction time, product, yield and eluant are as follows.



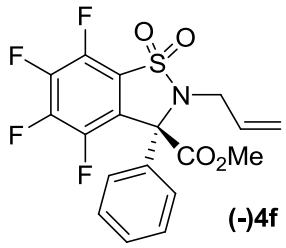
(+)4g

(*S*)-Methyl 4,5,6,7-tetrafluoro-1-methyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide [(+)4g]. MeI, 213 mg; sultam **(+)8d**, 375 mg. **(+)4g** (8h, 3702 mg, 95%). White solid, mp 165-166°C (*i*PrOH. Solution: 86%, *ee*>99%; crystallized: 14%, *ee* 0%); FCC - AcOEt/hexane (1 : 7); $[\alpha]_D^{20}$ -119.8 (*c* 1 $CHCl_3$) *ee*>99% [CHIRALCEL OD®, Hexane – Isopropanol 8 : 2, Flow rate 1 mL/min, P= 15 bar, t_1 = 5.4 min, t_2 = 6.7 min.]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42- 7.26 (m, 5H), 2.84 (s, 3H), 1.53(s, 9H); ^{19}F NMR (282, MHz, $CDCl_3$) δ 135 (m, 1F), -140.3 (m, 1F), -145.3 (m, 1F), -149 (m, 1F); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 144.1 (dt, *J* = 259.4, 14.3 Hz), 143.3 (ddd, *J* = 259.0, 13.5, 2.8 Hz), 141.3 (dt, *J* = 259.3, 14.3 Hz), 140.8 (dd, *J* = 259.2, 13.7 Hz), 133.1, 129.6, 129.1, 127.4, 123.0 (d, *J* = 13.7 Hz), 120.3 (d, *J* = 16.1 Hz), 85.5, 72.2, 27.7, 25.4; IR (nujol) 1748, 1638, 1516, 1495, 1296, 1256, 1230, 1170, 1077, 977, 916, 880, 693, 629, 614 cm^{-1}. Anal. Calcd. for $C_{19}H_{17}F_4NO_4S$: C, 52.90; H, 3.97; F, N, 3.25. Found: C, 53.01; H, 3.95; N, 3.64.



(-)4a

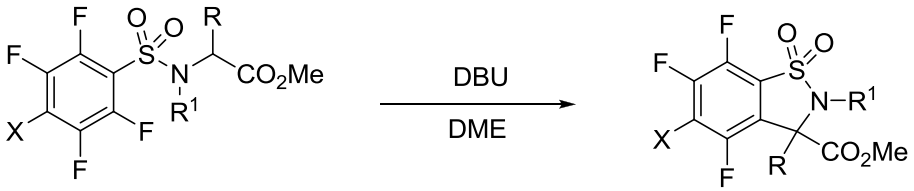
(*R*)-Methyl 4,5,6,7-tetrafluoro-2-propyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(-)4a]. *n*PrI, 255 mg; sultam **(-)8a,**375 mg. **(-)4a** (8h, 363 mg, 87%). White solid, mp 56-57°C (*i*PrOH. Solution: 30%, *ee* 0; crystallized: 68%, *ee*>99%); FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ +122.6 (*c* 1 $CHCl_3$) *ee*>99% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 0.6 mL/min, P= 7 bar, t_1 = 8.7 min, t_2 = 10.6 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H), 3.90 (s, 3H), 3.34-3.10 (m, 2H), 1.71-1.56 (m, 2H), 0.79 (t, 3H, *J* = 7.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.4 (m, 1F), -140.5 (m, 1F), -145.3 (m, 1F), -149.1 (m, 1F); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 144.2 (dt, *J* = 258.7, 16.1 Hz), 143.0 (dd, *J* = 257.9, 9.4 Hz), 141.4 (dt, *J* = 260.0, 13.4 Hz), 140.9 (dd, *J* = 258.6, 11.2 Hz), 133.7, 129.7, 129.0, 127.6, 122.3 (d, *J* = 16.1 Hz), 118.3, 72.4, 53.7, 44.7, 22.4, 11.2; IR (nujol) 1748, 1639, 1510, 1497, 1300, 1232, 1209, 1167, 1078, 993, 876, 699 cm^{-1}. Anal. Calcd. for $C_{18}H_{15}F_4NO_4S$: C, 51.80; H, 3.62; N, 3.36. Found: C, 51.75; H, 3.60; N, 3.41.



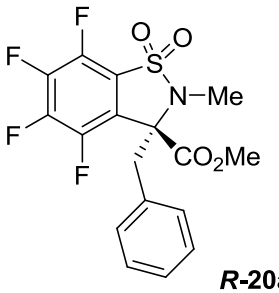
(-)4f

(*S*)-Methyl 4,5,6,7-tetrafluoro-2-allyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide [(-)4f]. AllBr, 181 mg; sultam **(-)8a,** 375 mg. **(-)4f** (8h, 142 mg, 91%). White solid, mp 111-112°C (*i*Pr_2O/hexane – 1 : 1. Solution: 67%, *ee*>99%; crystallized: 30%, *ee* 0%); FCC - AcOEt/hexane (1 : 6); $[\alpha]_D^{20}$ +122.6 (*c* 1 $CHCl_3$) *ee*>99% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 0.7 mL/min, P= 8 bar, t_1 = 8.3 min, t_2 = 9.5 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 3H), 7.31-7.27 (m, 2H), 5.88-5.75 (m, 1H), 5.20-5.08 (m, 2H), 4.03-3.78 (m, 2H), 3.89 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.2 (m, 1F), -140.5 (m, 1F), -145.2 (m, 1F), -149.1 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 144.3 (dt, *J* = 260.0, 13.6 Hz), 143.2 (dd, *J* = 257.7, 11.9 Hz), 141.4 (dt, *J* = 259.7, 14.0 Hz), 140.7 (dd, *J* = 259.1, 10.8 Hz), 133.5, 132.3, 129.8, 129.1, 127.6, 122.3 (d, *J* = 13.7 Hz), 118.8, 118.3, 72.2, 53.8, 44.9; IR (nujol) 1748, 1643, 1516, 1498, 1302, 1262, 1230, 1171, 1077, 977, 916, 880, 691 cm^{-1}. Anal. Calcd. for $C_{18}H_{13}F_4NO_4S$: C, 52.05; H, 3.15; N, 3.37. Found: C, 52.00; H, 3.19; N, 3.34.

7.15 Synthesis of Benzo[d]sultams R-20a-d, R-25a-j, 28e,f, R-29: General Procedure (DBU)

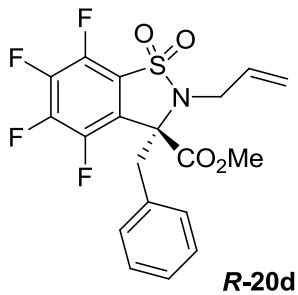


To a solution of sulfonamide ***S*-19a-d, 24a-j,26e,f** or **27** (0.2 mmol) in dry DME (0.5 mL), was added a solution of DBU (121.7 mg, 0.8 mmol) in dry DME (0.3 mL) at -20°C. The solution was stirred at -20 °C until completion (TLC control). The crude was then diluted with AcOEt (10 mL), washed with aqueous 5% citric acid (3×3 mL), saturated $NaHCO_3$ solution (2×5 mL), and brine (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (RV), giving the sultam.



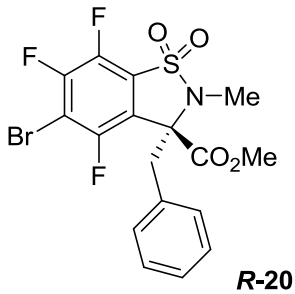
***R*-20a**

(*S*)-Methyl 4,5,6,7-tetrafluoro-2-methyl-3-benzyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-20a. sultam ***R*-20a** (2h, 50.7 mg, 63%). Wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ +78.5 (*c* 1 $CHCl_3$) *ee*>95% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 13 bar, t_1 = 10.8 min, t_2 = 16.2 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.17 (m, 3H), 7.01-7.00 (m, 2H), 3.81 (s, 3H), 3.58-3.56 (m, 2H), 3.01 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -137.5 (m, 1F), -139.5 (m, 1F), -146.2 (m, 1F), -148.7 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 144.3 (dt, *J* = 262.5, 15.0 Hz), 144.1 (dd, *J* = 255.7, 14.2 Hz), 142.8 (dd, *J* = 262.5, 18.7 Hz), 142.1 (dt, *J* = 262.5, 15.0 Hz), 140.8 (dd, *J* = 255.7, 14.2 Hz), 139.5 (dd, *J* = 262.5, 18.7 Hz), 132.5, 129.5, 128.5, 127.9, 70.1, 53.9, 36.6, 24.9; IR (nujol) 1753, 1635, 1522, 1483, 1314, 1254, 1227, 1163, 1068, 967, 878, 685 cm^{-1}. Anal. Calcd. for $C_{17}H_{13}F_4NO_4S$: C, 50.62; H, 3.25; N, 3.47. Found: C, 50.75; H, 3.34; N, 3.52.



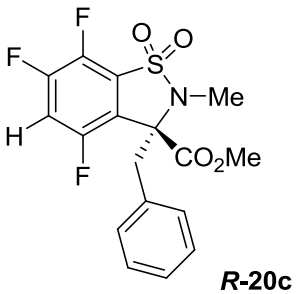
***R*-20d**

(*S*)-Methyl 4,5,6,7-tetrafluoro-2-allyl-3-benzyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-20d. sultam ***R*-20d**(2h, 40.7 mg, 650%). Wax; FCC - AcOEt/hexane (1 : 6); $[\alpha]_D^{20}$ +78.5 (*c* 1 $CHCl_3$) *ee*>96% [CHIRALCEL OD®, Hexane – Isopropanol 9 : 1, Flow rate 1 mL/min, P= 13 bar, t_1 = 11.6 min, t_2 = 17.9 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.18 (m, 3H), 7.04-7.03 (m, 2H), 6.12-5.99 (m, 1H), 5.45-5.32 (m, 2H), 4.08-4.05 (m, 2H), 3.77 (s, 3H), 3.60 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -138.1 (m, 1F), -139.3 (m, 1F), -145.9 (m, 1F), -148.4 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 143.8 (dd, *J* = 255.0, 15.0 Hz), 143.0 (dt, *J* = 262.5, 19.5 Hz), 140.4(dd, *J* = 255.0, 15.0 Hz), 139.4 (dt, *J* = 262.5, 15.0 Hz), 132.5, 131.2, 129.6, 128.4, 127.8, 120.5, 69.4, 53.1, 45.5, 43.5, 36.7; IR (nujol) 1748, 1642, 1505, 1467, 1308, 1247, 1236, 1153, 1054, 956, 868, 675 cm^{-1}. Anal. Calcd. for $C_{19}H_{15}F_4NO_4S$: C, 53.15; H, 3.52; N, 3.26. Found: C, 53.27; H, 3.64; N, 3.31.



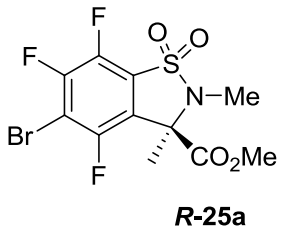
***R*-20b**

(*S*)-Methyl 6-bromo-4,5, 7-trifluoro-2-methyl-3-benzyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-20b. sultam ***R*-20b** (8h, 80.7 mg, 87%). Wax; FCC - AcOEt/hexane (1 : 1); $[\alpha]_D^{20}$ +149.2 (*c* 1.2 $CHCl_3$) *ee*>95% [CHIRALCEL OJ-H®, Hexane – Isopropanol 8 : 2, Flow rate 0.8 mL/min, P= 33 bar, t_1 = 17.8 min, t_2 = 24.4 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.16 (m, 3H), 7.01-6.97 (m, 2H), 3.82 (s, 3H), 3.59-3.50 (m, 2H), 3.00 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -106.2 (m, 1F), -117.5 (m, 1F), -138.6 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 151.8, 150.5 (dd, *J* = 255.0, 15.0 Hz), 148.5, 147.1 (dd, *J* = 255.0, 15.0 Hz), 142.5 (dd, *J* = 265.5, 15.0 Hz), 139.0 (dd, *J* = 265.5, 15.0 Hz), 132.6,129.6, 128.4, 127.8, 132.6 (d, *J* = 15.0 Hz), 119,0 (d, *J* = 15.0 Hz), 105.6 (t, *J* = 22.5Hz), 70.1, 53.8, 36.5, 24.9; IR (nujol) 1747, 1625, 1518, 1476, 1306, 1248, 1216, 1154, 1052, 957, 868, 682 cm^{-1}. Anal. Calcd. for $C_{17}H_{13}BrF_3NO_4S$: C, 43.98; H, 2.82; N, 3.02. Found: C, 44.02; H, 2.94; N, 3.16.



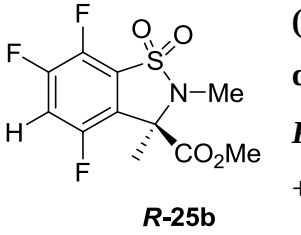
***R*-20c**

(*S*)-Methyl 4,5, 7-trifluoro-2-methyl-3-benzyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-20c. sultam ***R*-20c** (12h, 63.0 mg, 82%). Wax; FCC - AcOEt/hexane (1 : 1); $[\alpha]_D^{20}$ +64.2 (*c* 1 $CHCl_3$) *ee*>95% [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 46 bar, t_1 = 18.1 min, t_2 = 20.8 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.12 (m, 3H), 6.99-6.98 (m, 2H), 3.79 (s, 3H), 3.63-3.48 (m, 2H), 3.99 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.4 (m, 1F), -128.1 (m, 1F), -143.9 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 153.3 (dd, *J* = 250.5, 7.5 Hz), 151.7 (dt, *J* = 255.0, 11.2 Hz), 149.9 (dd, *J* = 250.5, 15.0 Hz), 142.5 (dt, *J* = 255.0, 15.0 Hz), 142.1 (dd, *J* = 255.0, 15.0 Hz), 138.7 (dd, *J* = 255.0, 22.5 Hz), 132.2, 129.1, 127.8, 127.2, 118.8 (d, *J* = 15.0 Hz), 109.9 (t, *J* = 24.7Hz), 69.3, 53.2, 35.9, 29.2, 24.3; IR (nujol) 1752, 1631, 1515, 1464, 1306, 1236, 1214, 1148, 1042, 953, 875, 679 cm^{-1}. Anal. Calcd. for $C_{17}H_{14}F_3NO_4S$: C, 52.99; H, 3.66; N, 3.63. Found: C, 53.09; H, 3.78; N, 3.71.



***R*-25a**

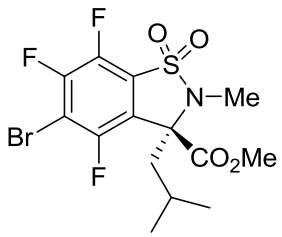
(*S*)-Methyl 6-bromo-4,5, 7-trifluoro-2-methyl-3-methyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-25a. sultam ***R*-25a** (24h, 64.1 mg, 83%). Wax; FCC - AcOEt/hexane (1 : 6); $[\alpha]_D^{20}$ -5.2 (*c* 1.0 $CHCl_3$) *ee*>35% [CHIRALCEL OJ-H®, Hexane – Isopropanol 8 : 2, Flow rate 0.8 mL/min, P= 32 bar, t_1 = 15.2 min, t_2 = 16.6 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ3.76 (s, 3H), 2.87 (s, 3H), 1.82 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.6 (m, 1F), -118.4 (m, 1F), -138.8 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 152.1, 150.7, 150.5, 148.8, 142.7, 139.2, 109.8, 106.3, 65.4, 53.7, 24.4, 19.3; IR (nujol) 1762, 1311, 1253, 1217, 1162, 1047, 943, 675 cm^{-1}. Anal. Calcd. for $C_{11}H_9BrF_3NO_4S$: C, 34.04; H, 2.34; N, 3.61. Found: C, 34.11; H, 2.42; N, 3.59.



***R*-25b**

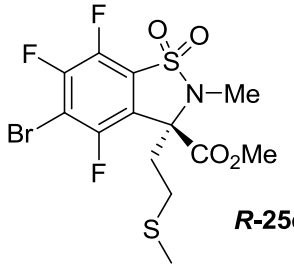
(*S*)-Methyl 4,5, 7-trifluoro-2-methyl-3-methyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-25b. sultam ***R*-25b** (5 day, 46.7 mg, 75%). Wax; FCC - AcOEt/hexane (1 : 6); $[\alpha]_D^{20}$ +4.2 (*c* 1 $CHCl_3$) *ee*>27% [CHIRALCEL OJ-H®, Hexane – Isopropanol 7

: 3, Flow rate 0.8 mL/min, P= 46 bar, t_1 = 15.6 min, t_2 = 16.2 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.19 (m, 1H), 3.75 (s, 3H), 2.88 (s, 3H), 1.81 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.4 (m, 1F), -118.1 (m, 1F), -123.9 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 153.5 (dd, *J* = 255.0, 7.5 Hz), 151.8 (dt, *J* = 256.5, 16.5 Hz), 150.2 (dd, *J* = 255.0, 7.5 Hz), 148.4 (dt, *J* = 256.5, 15.0 Hz), 142.2 (d, *J* = 15.0 Hz), 138.8 (d, *J* = 15 Hz), 130.7 (d, *J* = 15 Hz), 128.5 (t, *J* = 15 Hz), 121.2 (d, *J* = 22.5 Hz), 110.3 (t, *J* = 22.5 Hz), 64.8, 53.1, 23.9, 18.9; IR (nujol) 1748, 1628, 1512, 1457, 1137, 1035, 947, 867, 682 cm^{-1}. Anal. Calcd. for $C_{11}H_{10}F_3NO_4S$: C, 42.72; H, 3.26; N, 4.53. Found: C, 42.81; H, 3.32; N, 4.64.



***R*-25c**

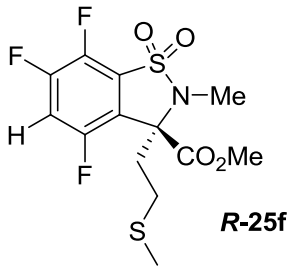
(*S*)-Methyl 6-bromo-4,5, 7-trifluoro-2-methyl-3-(2-methyl, propyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-25c. sultam ***R*-25c**(5 day, 35.3 mg, 42%). Wax; FCC - AcOEt/hexane (1 : 6); $[\alpha]_D^{20}$+15.2 (*c* 1.0 $CHCl_3$) *ee*>95% [CHIRALCEL OJ-H®, Hexane – Isopropanol 9 : 1, Flow rate 0.8 mL/min, P= 27 bar, t_1 = 9.5 min, t_2 = 12.1 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ3.74 (s, 3H), 2.86 (s, 3H), 2.31-2.17 (m, 2H), 0.94 (d, *J* = 6.0 Hz, 3H), 0.65 (d, *J* = 9.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.0 (m, 1F), -120.1 (m, 1F), -140.6 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 153.8, 151.7, 150.3, 148.4, 145.8, 142.4, 138.8, 129.3, 126.7, 110.2 (t, J = 22.5, Hz),53.1, 37.7, 29.2, 23.2; IR (nujol) 1771, 1308, 1248, 1215, 1158, 1056, 936, 681 cm^{-1}. Anal. Calcd. for $C_{14}H_{15}BrF_3NO_4S$: C, 39.08; H, 3.51; N, 3.26. Found: C, 39.11; H, 3.59; N, 3.31.



***R*-25e**

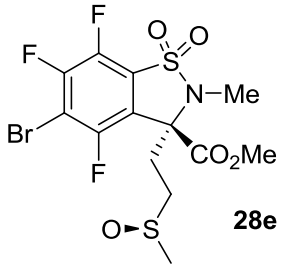
(*S*)-Methyl 6-bromo-4,5, 7-trifluoro-2-methyl-3-(methyl(propyl)sulfane)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-25e. sultam ***R*-25e**(18h, 61.8 mg, 70%). Wax; FCC - AcOEt/hexane (1 : 4); $[\alpha]_D^{20}$ + 15.2 (*c* 1.0 $CHCl_3$) *ee*>57% [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 46 bar, t_1 = 15.5 min, t_2 = 19.1 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ3.78 (s, 3H), 2.87 (s, 3H), 2.75-2.65 (m, 1H), 2.59-2.48 (m, 1H), 2.39-2.31 (m, 1H), 2.10-1.99 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.2 (m, 1F), -120.0 (m, 1F), -140.9

(m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 152.1, 150.7 (dd,*J* =255.0, 7.5 Hz), 148.7, 147.4 (dd, *J* = 255.0, 7.5 Hz), 142.7 (dd, *J* = 262.5, 15.0 Hz), 139.2(dd, *J* = 262.5, 15.0 Hz), 128.2, 118.2 (d, J = 22.5, Hz), 106.0 (t, J = 22.5, Hz), 68.6, 53.7, 30.4, 27.2, 24.3, 15.6; IR (nujol) 1764, 1305, 1236, 1211, 1149, 1051, 929, 674 cm^{-1}. Anal. Calcd. for $C_{14}H_{15}BrF_3NO_4S$: C, 39.08; H, 3.51; N, 3.26. Found: C, 39.11; H, 3.64; N, 3.29.



***R*-25f**

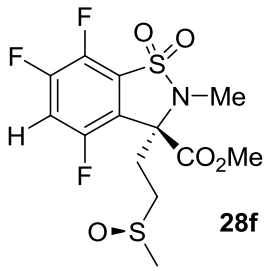
(*S*)-Methyl 4,5, 7-trifluoro-2-methyl-3-(methyl(propyl)sulfane)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-25f. sultam ***R*-25f** (24 h, 38.4 mg, 52%). Wax; FCC - AcOEt/hexane (1 : 2); *ee*>37% [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 46 bar, t_1 = 18.1 min, t_2 = 20.8 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.28-7.18 (m, 1H), 3.75 (s, 3H), 2.86 (s, 3H), 2.78-2.64 (m, 1H), 2.56-2.50 (m, 1H), 2.38-2.28 (m, 1H), 2.15-1.99 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.2 (m, 1F), -127.4 (m, 1F), -143.2 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 154.2 (dd, *J* = 255.0, 7.5 Hz), 152.5 (dm, *J* = 265.2 Hz), 150.7 (dd, *J* = 255.0, 7.5 Hz), 142.9 (d, *J* = 15.0 Hz), 139.4 (d, J = 15.0 Hz), 110.8 (t, J = 22.5, Hz), 69.5, 53.7, 30.6, 27.3, 24.3, 15.7; IR (nujol) 1756, 1309, 1228, 1209, 1147, 1049, 917, 669 cm^{-1}. Anal. Calcd. for $C_{13}H_{14}F_3NO_4S_2$: C, 42.27; H, 3.82; N, 3.79. Found: C, 42.31; H, 3.93; N, 3.83.



28e

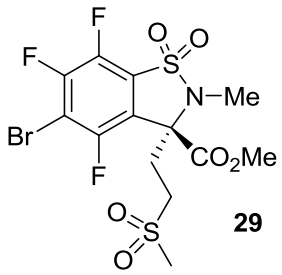
(*S*)-Methyl 6-bromo-4,5, 7-trifluoro-2-methyl-3-(1-(methylsulfinyl)propane)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide 28e. sultam **28e** (28 h, 40.8 mg, 54%, mixture of diastereomers 1:1). Wax; FCC - AcOEt/MeOH(9 : 1); $[\alpha]_D^{20}$ + 10.5 (*c* 1.1 $CHCl_3$) [CHIRALPAK AB®, Hexane – Isopropanol 9 : 1, Flow rate 0.8 mL/min, P= 18 bar, t_1 = 34.2 min, t_2 = 39.7 min, t_3 = 47.5 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ3.80 (s, 3H), 2.89-2.83 (m, 5H), 2.54-2.47 (m, 4H), 2.26-2.16 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.9 (m, 1F), -119.0 (m, 1F), -140.3 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 152.2 (dd, *J* = 255.0, 7.5 Hz), 151.1(dd, *J* = 255.0, 15 Hz), 148.8, (dd, *J* = 255.0, 7.5 Hz), 147.7 (dd, *J* = 255.0, 15 Hz), 142.8 (dd, *J* = 262.5, 15.0 Hz), 139.3 (dd, *J* = 262.5, 15.0 Hz), 123.9 (d, J = 15.0 Hz), 117.9 (d, J = 22.5 Hz), 106.5 (t, J = 22.5, Hz), 68.1, 54.0, 47.8, 47.0, 39.2, 38.5, 29.6,

24.6, 24.3, 23.6; IR (nujol) 1757, 1308, 1228, 1209, 1145, 1049, 926, 679 cm^{-1}. Anal. Calcd. for $C_{13}H_{13}BrF_3NO_5S_2$: C, 33.63; H, 2.82; N, 3.02. Found: C, 33.69; H, 2.88; N, 3.06.



28f

(*S*)-Methyl 4,5, 7-trifluoro-2-methyl-3-(1-(methylsulfinyl)propane)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide 28f. sultam **28f** (48 h, 63.4 mg, 82%, mixture of diastereomers 1:1). Wax; FCC - AcOEt/MeOH(9 : 1); $[\alpha]_D^{20}$ + 10.5 (*c* 1.1 $CHCl_3$) [CHIRALCELOJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 21.3 min, t_2 = 25.9 min, t_3 = 29.2 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.29-7.23 (m, 1H), 3.78 (s, 3H), 2.89-2.67 (m, 5H), 2.59-2.43 (m, 4H), 2.27-2.14 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.3 (m, 1F), -126.8 (m, 1F), -143.1 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 154.0 (dt, *J* = 255.0, 7.5 Hz), 152.7 (dt, *J* = 255.0, 7.5 Hz), 150.6, (dt, *J* = 255.0, 7.5 Hz), 149.3 (dt, *J* = 255.0, 15 Hz), 142.9 (dd, *J* = 262.5, 15.0 Hz), 139.4 (dd, *J* = 262.5, 15.0 Hz), 125.5 (d, J = 15.0 Hz), 118.1 (d, J = 22.5 Hz), 111.3 (t, J = 7.5, Hz), 68.3, 67.9, 53.8, 47.9, 47.2, 39.1, 38.6, 24.4, 24.3, 24.1, 23.7; IR (nujol) 1762, 1306, 1231, 1205, 1144, 1051, 928, 680 cm^{-1}. Anal. Calcd. for $C_{13}H_{14}F_3NO_5S_2$: C, 40.52; H, 3.66; N, 3.63. Found: C, 40.59; H, 3.71; N, 3.69.



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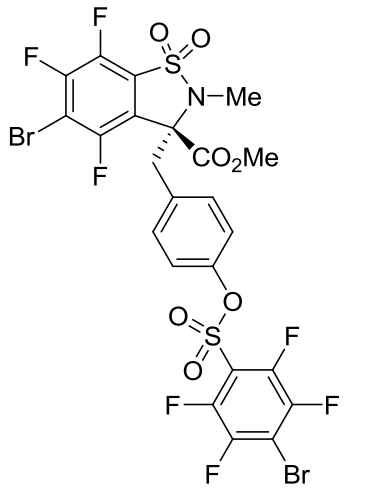
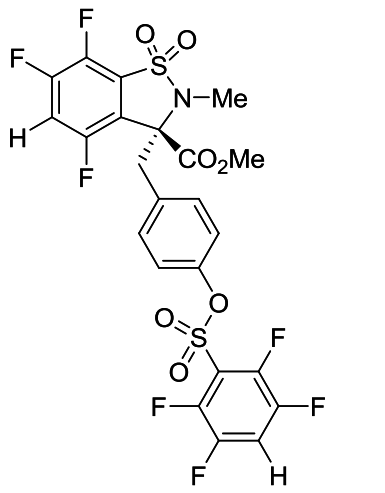
(*S*)-Methyl 6-bromo-4,5, 7-trifluoro-2-methyl-3-(1-(methylsulfonyl) propane)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide 28e. sultam **28e** (48 h, 37.7 mg, 59%). Wax; FCC - AcOEt/Hexane (1 : 1); $[\alpha]_D^{20}$ + 7.6 (*c* 1.0 $CHCl_3$) [CHIRALPAK AB®, Hexane – Isopropanol 85 : 15, Flow rate 0.8 mL/min, P= 18 bar, t_1 = 18.5 min, t_2 = 22.7 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ3.81 (s, 3H), 2.92-2.98 (m, 6H), 2.61-2.49 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.1 (m, 1F), -118.4 (m, 1F), -139.8 (m, 1F); IR (nujol) 1757, 1308, 1217, 1209, 1145, 1049, 926, 679 cm^{-1}. Anal. Calcd. for $C_{13}H_{13}BrF_3NO_6S_2$: C, 32.51; H, 2.73; N, 2.92. Found: C, 32.57; H, 2.70; N, 2.98.



***R*-25i**

(*S*)-Methyl 6-bromo-4,5, 7-trifluoro-2-methyl-3-(4-ethylphenyl 4-bromo-2,3,5,6-tetrafluorobenzenesulfonate)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-25i. sultam ***R*-25i** (7 h, 668.8 mg, 87%). Wax; FCC - AcOEt/Hexane(1 : 3); $[\alpha]_D^{20}$ + 121.3 (*c* 1.0 $CHCl_3$) [CHIRALCELOD-H®, Hexane – Isopropanol 8 : 2, Flow rate 0.8 mL/min, P= 38 bar, t_1 = 21.5 min, t_2 = 25.1 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.03-6.96 (m, 4H),3.81 (s, 3H), 3.62-3.46 (m, 2H), 2.92 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.5 (m, 1F), -119.0 (m, 1F), -129.4 (m, 2F), -134.4 (m, 2F), -140.6 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ166.9, 151.6, 150.7 (dd, *J* = 255.0, 15 Hz), 148.3, 147.2 (dm, *J* = 255.0 Hz), 145.9, (dd, *J* = 255.0, 22.5 Hz), 143.8 (dm, *J* = 255.0 Hz), 142.5 (dm, *J* = 255.0 Hz), 139.1 (d, *J* = 15.0 Hz), 133.0, 131.4, 121.5, 118.4 (d, J = 22.5 Hz), 108.3 (t, J = 22.5 Hz), 105.8 (t, J = 22.5, Hz), 69.8, 54.0, 35.9, 29.6, 24.9; IR (nujol) 1761, 1309, 1226, 1204, 1139, 1053, 928, 680 cm^{-1}. Anal. Calcd. for $C_{23}H_{12}Br_2F_7NO_7S_2$: C, 35.82; H, 1.57; N, 1.82. Found: C, 35.87; H, 1.61; N, 1.85.



***R*-25j**

(*S*)-Methyl 4,5, 7-trifluoro-2-methyl-3-(4-ethylphenyl -2,3,5,6-tetrafluorobenzenesulfonate)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide *R*-25j. sultam ***R*-25j** (50 h, 460.0 mg, 75%). Wax; FCC - AcOEt/Hexane(1 : 3); $[\alpha]_D^{20}$ + 19.2 (*c* 1.0 $CHCl_3$) [CHIRALCEL OJ-H®, Hexane – Isopropanol 7 : 3, Flow rate 0.8 mL/min, P= 48 bar, t_1 = 23.9 min]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.34 (m, 1H), 7.16-7.12 (m, 1H), 7.08-6.95 (m, 4H), 3.79 (s, 3H), 3.62-3.43 (m, 2H), 2.93 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.6 (m, 1F), -126.9 (m, 1F), -134.8 (m, 4F), -134.4 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ167.1, 153.5 (dd, *J* = 255.0, 7.5 Hz), 152.3 (dm, *J* = 247.5 Hz), 150.1 (dd, *J* = 255.0, 7.5 Hz), 148.3, 147.8 (dm, *J* = 247.5 Hz), 145.9 (dm, *J* = 247.5 Hz), 144.5 (dm, *J* = 247.5 Hz), 142.5 (dm, *J* = 262.5 Hz), 239.1 (d, *J* = 15.0 Hz), 133.0, 131.4, 130.8, 121.3, 115.2, 112.2 (t, J = 22.5 Hz), 110.5 (t, J = 22.5, Hz), 69.6, 53.7, 35.7, 35.7, 29.6, 24.7; IR (nujol) 1767, 1305, 1218, 1207, 1141, 1057, 926, 683 cm^{-1}. Anal. Calcd. for $C_{23}H_{14}F_7NO_7S_2$: C, 45.03; H, 2.30; N, 2.28. Found: C, 45.09; H, 2.37; N, 2.31.