JOC Article

Complementary Heterogeneous/Homogeneous Protocols for the Synthesis of Densely Functionalized Benzo[*d*]sultams: C−C Bond Formation by Intramolecular Nucleophilic Aromatic Fluorine Displacement

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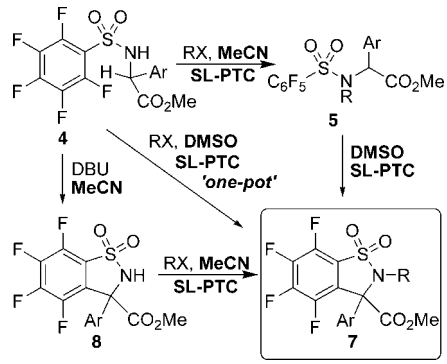

Polyfunctionalized benzo[*d*]sultams **7** and **8**, which contain an α-amino acid unit, have been synthesized from the corresponding open chain (pentafluorobenzene)sulfonamides **4** by complementary solid−liquid phase transfer catalysis (SL-PTC) and homogeneous protocols. The cyclization step proceeds through the intramolecular nucleophilic displacement of an aromatic fluorine atom.

Introduction

Cyclic sulfonamides (sultams),[1] analogously to open chain sulfonamides, find important applications in human therapeutics.[2] In particular, as a result of their biological activity[3] and low toxicity, they have been recently employed in several fields of medicine, as drugs or as carriers of more complex molecules.

Oppolzer's sultam[4] **1** (Figure 1) and saccharin derived 3-alkyl benzosultams[5] **2** are relevant in asymmetric synthesis as chiral auxiliaries in many stereoselective transformations. In contrast to the large number of sultam containing structures reported, few examples of 3-carboxy-substituted benzosultams **3** are known and, despite the fact that they contain an α-amino acid framework, their synthesis is realized through complex protocols[6] that do not involve the participation of any amino acid derivative.

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(1) Recent sultams syntheses: (a) Lee, J.; Zhong, Y.-L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, *5*, 4175. (b) Cleator, E.; Sheen, F. J.; Bio, M. M.; Brands, K. M. J.; Davies, A. J.; Dolling, U.-H. *Tetrahedron Lett.* **2006**, *47*, 4245. (c) Blanchet, J.; Macklin, T.; Ang, P.; Metallinos, C.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 3199. (d) Enders, D.; Moll, A.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1271. (e) Ruppel, J. V.; Kamble, R. M.; Zhang, X. P. *Org. Lett.* **2007**, *9*, 4889. (f) Xie, Y.; Gong, G.; Liu, Y.; Deng, S.; Rinderspacher, A.; Branden, L.; Landry, D. W. *Tetrahedron Lett.* **2008**, *49*, 2320.

(2) (a) Hanessian, S.; Sailes, H.; Therrien, E. *Tetrahedron* **2003**, *59*, 7047. (b) Zhuang, L.; Wai, J. S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P., Jr.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Gregory Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J., Jr.; Michelson, S. R.; Young, S. D. *J. Med. Chem.* **2003**, *46*, 453. (c) Scott, J. P.; Oliver, S. F.; Brands, K. M. J.; Brewer, S. E.; Davies, A. J.; Gibb, A. D.; Hands, D.; Keen, S. P.; Sheen, F. J.; Reamer, R. A.; Robert, D.; Wilson, R. D.; Dolling, U.-H. *J. Org. Chem.* **2006**, *71*, 3086. (d) Tsang, W. Y.; Ahmed, N.; Harding, L. P.; Hemming, K.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2005**, *127*, 8946. (e) Hincliffe, P. S.; Wood, J. M.; Davis, A. M.; Austin, R. P.; Beckett, R. P.; Page, M. I. *Org. Biomol. Chem.* **2003**, *1*, 67. (f) Valente, C.; Guedes, R. C.; Moreira, R.; Iley, J.; Gut, J.; Rosenthal, P. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4115. (g) Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 2001. (h) U.S. Patent, 6 562 850, 2003: Baker, D. C.; Mayasundari, A.; Mao, J.; Johnson, S. C.; Yan, S. *Chem. Abstr.* **2003**, *138*, 368883.

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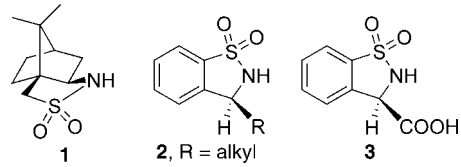
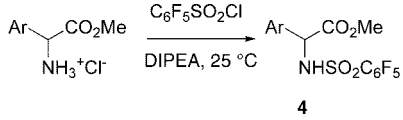


1 **2**, R = alkyl **3**

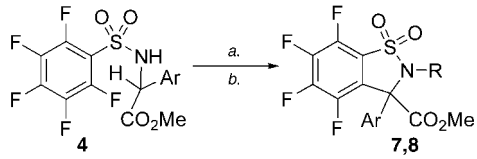
FIGURE 1. Examples of sultams used as chiral auxiliaries in asymmetric synthesis.

In this account we describe the preparation of 3-aryl polyfluorobenzosultams, bearing a carboxylic function in the C-3 position and an alkyl substituent on the sulfonamide *N*-atom. Starting materials are racemic (pentafluorobenzene)sulfonamides **4**, in turn prepared from the corresponding amino esters (eq 1).



4 (1)

Sulfonamides **4** have been cyclized to the corresponding benzo[*d*]sultams through two different and complementary synthetic pathways: *N*-Alkylation of open-chain sulfonamides **4** with an alkyl halide, then cyclization of the intermediate *N*-alkylsulfonamide **5** under solid−liquid phase transfer catalysis (SL-PTC) conditions, gave the corresponding *N*-alkylbenzosultams **7** (eq 2, path a). Alternatively, using DBU as organic-soluble base under homogeneous conditions, sulfonamides **4** were transformed into the unsubstituted benzosultams **8** (eq 2, path b) that, in turn, can be *N*-alkylated to sultams **7**.



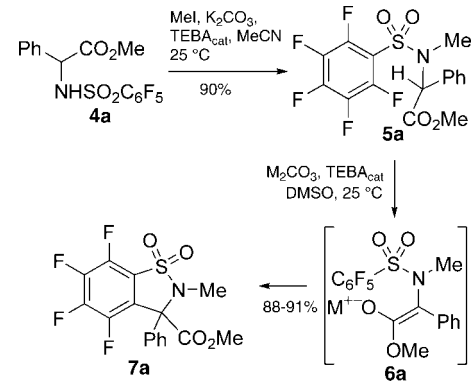
4 **7,8** (2)

a. SL-PTC conditions: **7**, R = alkyl
b. homogeneous conditions: **8**, R = H

Results and Discussion

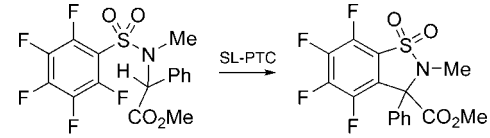
The synthesis of *N*-methyl sultam **7a** was selected as a model to study the reaction parameters that affect the outcome of both protocols. The initial step of the optimized SL-PTC procedure (Scheme 1) was the reaction of (pentafluorobenzene)sulfonamide **4a** with methyl iodide in MeCN, in the presence of anhydrous K_2CO_3 and a catalytic amount (0.1 mol equiv) of triethylbenzylammonium chloride (TEBA). The resulting *N*-methyl sulfonamide **5a** was transformed into the corresponding *N*-methyltetrafluorobenzo[*d*]sultam **7a** by generating, under SL-PTC in DMSO, the enolate **6a**, which rapidly cyclizes through an intramolecular nucleophilic displacement of the aromatic ortho fluorine atom.

SCHEME 1. Synthesis of *N*-Methyl Sultam 7a Under SL-PTC Conditions



4a **5a** **6a** **7a**

TABLE 1. PTC Cyclization of *N*-Methyl Sulfonamide 5a: Effect of the Solvent[a]



5a **7a**

entry	solvent	DMSO[b]	*t* (min)	**7a** (%)[c]
1	DMSO		15	91[d]
2	MeCN	5	90	89
3	MeCN	1	90	86
4	MeCN	0.1	90	68
5	MeCN		90	
6	MeCN		90	5[e]

[a] **5a** (0.2 mmol), Cs_2CO_3 (0.4 mmol), TEBA (0.02 mmol), solvent (1 mL), 25 °C. [b] Mol equivalents. [c] HPLC yields. [d] Isolated yield. [e] At 50 °C.

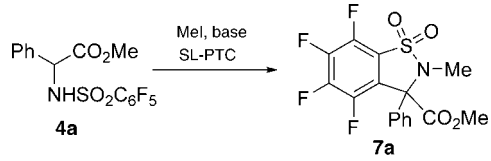
The role of the solvent is particularly crucial for the selectivity of both *N*-alkylation and ring-closing steps (Table 1). Actually, rapid and high cyclization yield of **5a** to sultam **7a** was reached by operating in pure DMSO (entry 1) or in MeCN containing at least 1 mol equiv of DMSO as an additive (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 (**6a**: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 **7a** was obtained (entry 6).

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 **4a** with methyl iodide in DMSO, in the presence of different bases. Using anhydrous cesium carbonate, **7a** was isolated after 75 min in 94% yield (entry 1), whereas the reaction with potassium carbonate required longer reaction times (entries 2 and 3). All the other tested bases gave lower yields of **7a**, but *n*-BuLi produced only byproduct, derived from nucleophilic substitution of aromatic fluorine atom(s) by *n*-butyl anion. Finally, the noncatalyzed process (entry 4) was not complete even after prolonged reaction times and **7a** yield was moderate, thus confirming the effectiveness of the PTC agent.

The interesting results achieved prompted us to investigate the products distribution throughout the "one-pot" methylation/cyclization protocol promoted both by cesium and potassium carbonate (Table 2, entries 1 and 2). By means of HPLC analysis

(3) Clerici, F.; Gelmi, M. L.; Pellegrino, S.; Pocar, D. *Top. Heterocycl. Chem.* **2007**, *9*, 179.
(4) (a) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397. (b) Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Kiran, M. U. *J. Org. Chem.* **2006**, *71*, 337.
(5) (a) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117. (b) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015. (c) Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019. (d) Ahn, K. H.; Ham, C.; Kim, S.-K.; Cho, C.-W. *J. Org. Chem.* **1997**, *62*, 7047. (e) Ahn, K. H.; Kim, S.-K.; Ham, C. *Tetrahedron Lett.* **1998**, *39*, 6321.
(6) Ahn, K. H.; Baek, H.-H.; Lee, S. J.; Cho, C.-W. *J. Org. Chem.* **2000**, *65*, 7690.

TABLE 2. SL-PTC "One-Pot" Methylation/Cyclization of Sulfonamide 4a: Effect of the Base[a]



entry	base (mol equiv)	t (h)	**7a** (%)
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[b]
5	Na_2CO_3 (2)	48	75
6	$NaHCO_3$ (5)	48	70
7	NaH (2.5)	26	28

[a] **4a** (1 mmol), MeI (1.5 mmol), base (2−5 mmol), TEBA (0.1 mmol), anhydrous DMSO (5 mL), 25 °C. [b] Without PTC agent.

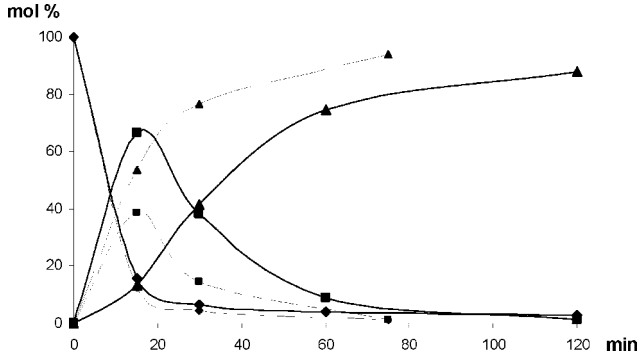


FIGURE 2. HPLC analysis of SL-PTC "one-pot" methylation/cyclization of sulfonamide **4a** (see the Supporting Information for experimental details): (− −) Cs_2CO_3 and (−) K_2CO_3 as a base; (♦) **4a**, (□) **5a**, (■) **7a**.

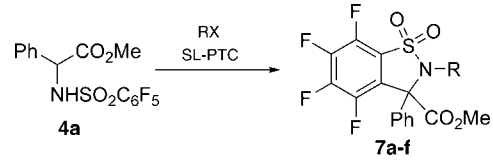
(Figure 2), we found similar *N*-alkylation rates and after 30 min starting material **4a** was less than 10% with both bases; in contrast, the intermediate open chain sulfonamide **5a** cyclized to **7a** much more rapidly in the presence of Cs_2CO_3 and the yield, after 30 min, is about twice (77%) that with K_2CO_3 (42%).

The "one-pot" procedure was applied to the synthesis of different sultams, using several alkyl halides (Table 3). Good to acceptable yields of **7** were reached with ethyl, *n*-propyl, and *n*-butyl iodide, in DMSO at room temperature (entries 2−5). In the reaction with *n*-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 **4a** to the *N*-benzylsulfonamide **5e**, only minor amounts of **7e** 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 **5e** and **5f**, slowing down the cyclization step, as confirmed by the scarce efficiency of the PTC ring-closing of *N*-benzyl sulfonamide **5e** (**7e** in 45% yield), in turn prepared in 88% yield by *N*-benzylation of **4a**.[7]

To overcome the cyclization rate dependence on the stereochemical demand of the alkylating agent and, besides, to have a single scaffold that can be used in the subsequent alkylation

(7) See the Supporting Information for experimental details.

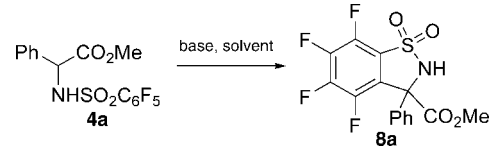
TABLE 3. Synthesis of Sultams 7a−f by SL-PTC "One-Pot" Reaction of Sulfonamide 4a with Different Alkylating Agents (RX)[a]



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

[a] **4a** (1 mmol), RX (1.5 mmol), base (2−4 mmol), TEBA (0.1 mmol), anhydrous solvent (5 mL), 25 °C. [b] At 50 °C. [c] Together with *N*-benzylsulfonamide **5e** (6%) and unknown byproduct. [d] **5e** (75%). [e] **5e** (72%).

TABLE 4. Synthesis of Benzosultam 8a by Direct Cyclization of 4a[a]



entry	base	solvent	T (°C)	t (h)	**8a** (%)
1	Na_2CO_3[b]	DMSO	25	90	
2	Na_2CO_3[b]	MeCN	70	60	
3	Cs_2CO_3[b]	DMSO	80	90	25
4	DBU	MeCN	25	16	98
5	DBU	DME	25	16	96
6	DBU	DMSO	25	48	62
7	TMG[c]	MeCN	25	80	96
8	DBU	MeCN	25	16	75[d]

[a] **4a** (1 mmol), base (4 mmol), anhydrous solvent (5 mL). [b] In the presence of a catalytic amount of TEBA (0.1 mmol). [c] Tetramethylguanidine. [d] In the presence of MeI (1.5 mmol).

step, we decided to prepare the non-*N*-alkylated benzosultam **8a** by direct cyclization of sulfonamide **4a** (Table 4). The SL-PTC technique failed (entry 1), even when drastic conditions were applied (entries 2 and 3). In fact, the aza-anion generated under PTC conditions is unable to form the aza-enolate dianion, the putative species for the cyclization step. On the contrary, the use of DBU as a base in MeCN or in DME (entries 4 and 6), under homogeneous conditions, afforded **8a** in nearly quantitative yields (96−98%). Several other organic bases (TEA, DIPEA, DABCO, and DMAP), tested instead of DBU, were completely ineffective, whereas tetramethylguanidine (entry 7) gave the same yields as DBU, but in longer reaction times.

The homogeneous protocol applied to **4a** in the presence of iodomethane (entry 8) gave sultam **8a** as sole product in 75% yield. The absence of the *N*-methylsultam **7a** indicates probably that, even if DBU is basic enough ($pK_{a(MeCN)}$ 24.34)[8] to deprotonate the sulfonamide NH group, the "tight ion-pair"

SCHEME 2. Ring-Closing Reaction of *N*-Alkylsulfonamides 5a,e

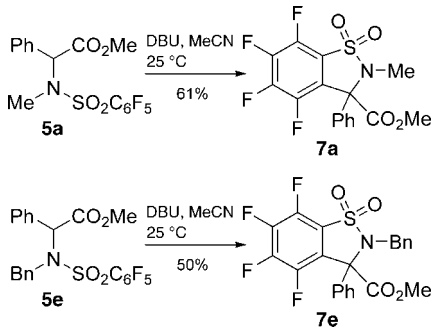
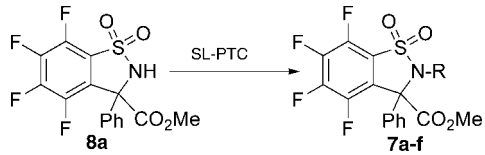


TABLE 5. *N*-Alkylation of Benzosultam 8a Under SL-PTC Conditions[a]



entry	RX	*t* (h)	product	yield (%)
1	MeI	18	**7a**	100
2	EtI	48	**7b**	95
3	*n*-PrI	48	**7c**	88
4	*n*-BuI	48	**7d**	82
5	BnBr	20	**7e**	85
6	AllylBr	20	**7f**	82

[a] Sulfonamide **8a** (1 mmol), RX (1.5 mmol), K_2CO_3 (2 mmol), TEBA (0.1 mmol), MeCN (2 mL), 25 °C.

formed is stable to the alkylation and, hence, that the cyclization proceeds via the resulting base-stabilized enol.

In addition, the cyclization of the *N*-alkylated sulfonamides **5a** and **5e** in the presence of DBU gave very poor amounts of the corresponding benzosultams **7a** and **7e** (Scheme 2), suggesting that the base-stabilized enol is probably more hindered than the enolate **6** formed under PTC conditions.

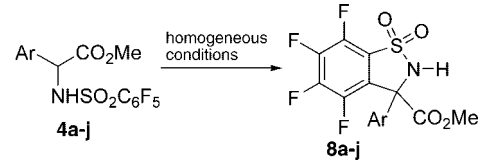
Benzosultam **8a** was then reacted with selected alkyl halides under SL-PTC. Good yields of the corresponding *N*-alkylated products **7a**−**f** (Table 5) were obtained and this procedure emerges as an excellent alternative to the "one-pot" method, especially in the case of the hindered benzyl and allyl derivatives (entries 5 and 6).

To check the reaction scope, a series of 2-arylsulfonamides **4b**−**j** were cyclized under the homogeneous conditions optimized for **4a**, and the resulting benzo[*d*]sultams **8b**−**j** have been isolated in good to excellent yields (Table 6).

Finally, some preliminary experiments were performed on the nonracemic L-phenylglycine derivative *S*-**4a**. While the cyclization with DBU[9] was not stereoselective, and racemic **8a** was isolated, the "one pot" SL-PTC protocol in the presence of MeI[10] gave 94% of (−)-**7a** (15% ee)[11] with TEBA; on the contrary, a low yield (73%) of racemic **7a** was produced with chiral quaternary ammonium Corey's catalyst.[12]

(8) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. *J. Org. Chem.* **2005**, *70*, 1019.
(9) Reaction conditions as in Table 4, entry 5.
(10) Reaction conditions as in Table 2, entry 1.
(11) Determined by chiral HPLC analysis; see the Supporting Information for details.
(12) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

TABLE 6. Synthesis of Benzosultam 8a−j Under Homogeneous Conditions[a]



entry	Ar	**4**	*t* (h)	product	yield (%)
1	Ph	**a**	4	**8a**	96
2	3-F-C_6H_5	**b**	5	**8b**	95
3	4-F-C_6H_5	**c**	5	**8c**	98
4	4-Cl-C_6H_5	**d**	5	**8d**	91
5	4-Br-C_6H_5	**e**	5	**8e**	93
6	4-Me-C_6H_5	**f**	6	**8f**	99
7	3-OMe-C_6H_5	**g**	6	**8g**	98
8	4-OMe-C_6H_5	**h**	8	**8h**	95
9	4-OBn-C_6H_5	**i**	12	**8i**	81
10	3-thienyl	**j**	8	**8j**	88

[a] Sulfonamide **4a**−**j** (1 mmol), DBU (4 mmol), DME (5 mL), 25 °C.

Conclusion

In summary, we have shown that several polysubstituted benzo[*d*]sultams have been prepared in good to excellent yields by two alternative synthetic pathways, using very mild reaction conditions. Research addressed to apply these synthetic methods to starting materials derived from different arylsulfonyl chlorides, i.e. containing less fluorine atoms and/or other functional groups, is underway. Furthermore, research is in progress to improve the enantioselectivity of the ring-closing step in both protocols.

Experimental Section

Synthesis of (Pentafluorobenzene)sulfonamides 4a−j: General Procedure. . To a suspension of methyl amino-arylacetate hydrochloride (10 mmol) in dry dichloromethane (40 mL) was added DIPEA (21 mmol) at 25 °C in 10 min. The reaction mixture was stirred for a further 10 min, then cooled to 0 °C and pentafluorobenzenesulfonyl chloride (10 mmol) was added dropwise. The resulting solution was allowed to reach 25 °C and stirred until no starting material was not detectable by TLC, then was diluted with dichloromethane (20 mL), washed with 3% HCl (3 × 15 mL), saturated $NaHCO_3$ solution (2 × 15 mL), and brine (20 mL), dried over $MgSO_4$, and filtered. After evaporation of the solvent under vacuum (RV), crude recrystallized from ethanol/water (1:9), or purified by FCC or MPLC, gave sulfonamides **4a**−**j**.

Methyl 2-(2,3,4,5,6-Pentafluorophenylsulfonamido)-2-phenylacetate (4a). 4a (3.56 g, 90%); white solid, mp 120−121 °C (EtOH/water 9:1). ^{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.

SL-PTC "One-Pot" Synthesis of *N*-Alkylbenzo[*d*]sultams 7a−f: General Procedure. To a solution of sulfonamide **4a** (395 mg, 1 mmol) and TEBA (23 mg, 0.1 mmol) in dry solvent (5 mL) at 25 °C was added anhydrous alkaline metal carbonate (2−4 mmol). The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent RX (1.5 mmol) was added

and the reaction was monitored by TLC (AcOEt:hexane 1:6) until completion. The mixture was diluted with water and extracted with DCM and concentrated; the residue was diluted with AcOEt (10 mL) and washed with brine (5 × 10 mL), dried over $MgSO_4$, and filtered. After evaporation of the solvent (RV), the crude was purified by MPLC (AcOEt:hexane 1:9).

Methyl 4,5,6,7-Tetrafluoro-1-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-Dioxide (7a). 7a (366 mg, 94%), white solid, mp 166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.40 (m, 3H), 7.26−7.23 (m, 2H), 3.91 (s, 3H), 2.84 (s, 3H). ^{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 166.8, 144.3 (dt, J = 261.6, 13.8 Hz), 143.4 (ddd, J = 261.6, 12.6, 3.8 Hz), 141.5 (dt, J = 261.6, 13.8 Hz), 141.0 (dd, J = 262.8, 13.8 Hz), 132.7, 129.9, 129.2, 127.4, 122.3 (dd, J = 13.4, 3.5 Hz), 118.2 (dd, J = 17.5, 3.1 Hz), 71.8, 53.8, 25.4. IR (nujol) 1748, 1638, 1516, 1495, 1296, 1256, 1230, 1170, 1077, 977, 916, 880, 693, 629, 614 cm^{-1}. Anal. Calcd for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N, 3.60. Found: C, 49.31; H, 2.81; N, 3.64. HRMS (ESI positive) calcd for $C_{16}H_{11}F_4NNaO_4S$ $[M + Na]^+$ 412.02371, found 412.02401.

Synthesis of Benzo[*d*]sultams 8a−j: General Procedure. The solution of sulfonamide **4** (1 mmol) and DBU (609 mg, 4 mmol) in dry DME (5 mL) was stirred at 25 °C until completion (TLC control). The solution was then diluted with AcOEt (10 mL) then 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 sultams **8a**−**j**, without any further purification.

Methyl 4,5,6,7-Tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]-isothiazole-3-carboxylate 1,1-Dioxide (8a). In the case of the synthesis of compound **8a**, sulfonamide **4a** (3.95 g, 10 mmol), DBU (6.09 g, 40 mmol), and DME (50 mL) were used. **8a** (3.60 g, 96%), white solid; mp 98−99 °C. ^{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: C, 47.96; H, 2.44; N, 3.73.

Synthesis of 7a−f by SL-PTC *N*-Alkylation of Benzo[*d*]sultam 8a: General Procedure. To a solution of sultam **8a** (375 g, 1 mmol) and TEBA (23 mg, 0.1 mmol) in dry MeCN (2 mL) at 25 °C was added anhydrous K_2CO_3 (276 mg, 2 mmol). The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent RX was added (1.5 mmol) and the reaction was monitored by TLC (AcOEt:hexane 1:6) until completion. After filtration through a Celite pad and evaporation of the solvent (RV), the crude was purified by MPLC (AcOEt:hexane 1:9). Alkylating agent RX, reaction times, and product yields are given in Table 5. Physical and spectroscopic data for **7a**−**f** match those of products described in the Supporting Information (SL-PTC "One-Pot" Synthesis of *N*-Alkyl-benzo[*d*]sultams **7a**−**f**: General Procedure, p S-9).

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Supporting Information Available: Detailed experimental procedures, physical and spectral data of new compounds, ^{1}H, ^{19}F, and ^{13}C NMR spectra of sulfonamides **4**, **5** and benzosultams **7**, **8**, and chiral HPLC analyses of compounds **4a**, *S*-**4a**, **7a**, and (+)-**7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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