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BENZOSULTAMS: SYNTHESIS AND APPLICATIONS

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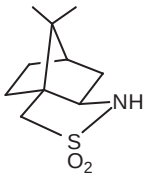
Abstract- Recent developments on the synthesis and applications of benzosultams are reviewed.

1. INTRUDUCTION

Oppolzer's camphorsultam (**1**)[1] and its antipode were introduced in 1984[2] and rank today among the most practical of chiral auxiliaries available for organic synthesis. The structurally more simple relatives, the benzosultams (**2**) (R = Me, *t*-Bu, *etc.*), also make up an important class of chiral auxiliaries (Figure 1). These sultams have many important applications as chiral auxiliaries in asymmetric versions of several reactions, including alkylations,[3] acylations,[3] aldol reactions,[3] Diels-Alder reactions,[4] and azidations.[5] Synthesis of *N*-fluorobenzosultam templates has become one of the important strategies for the development of novel electrophilic fluorinating agents.[6–11] Recently, such benzosultams have also received much attention as potent HIV-1 inhibitors.[12] In this article, recent developments on the synthesis and applications of benzosultams are reviewed.



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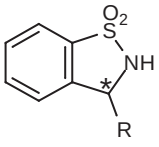


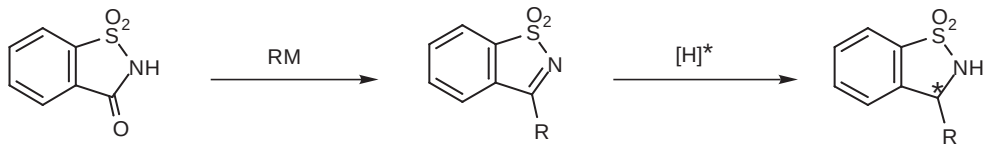
2

Figure 1

2. FIVE-MEMBERED BENZOSULTAMS

2.1. Oppolzer's Chiral 3-Monosubstituted Five-membered Benzosultams

Chiral 3-monosubstituted five-membered benzosultams have been developed as alternatives to the well-known Oppolzer camphorsultam auxiliary. The benzosultams have simpler structures and also possess a benzene chromophore that makes their detection easier. These chiral benzosultams (**2**) are usually prepared by asymmetric reduction[3,13] of the corresponding *N*-sulfonylimines (**4**), which can be derived from saccharin (**3**) *via* reaction with organometallic agents (Scheme 1).[4,8,13–16] There are also other approaches reported for the preparation of the *N*-sulfonylimines (**4**).[17–19]



3 **4** **2**

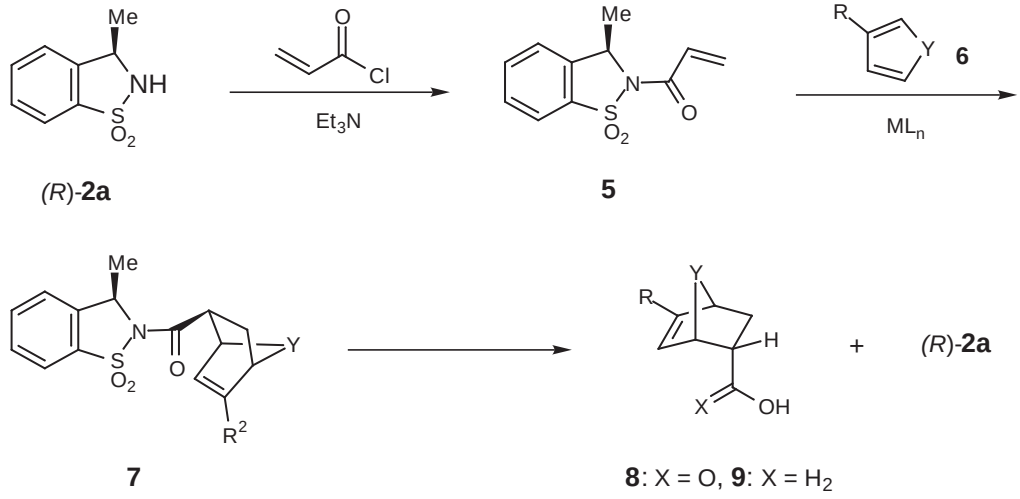
a: R = Me, **b**: R = *t*-Bu, **c**: R = Bn

Scheme 1

Addition of methyllithium, *tert*-butyllithium or benzylmagnesium chloride to saccharin (**3**) furnished prochiral imine (**4a**) (R = Me),[1] (**4b**) (R = *t*-Bu),[4] and (**4c**) (R = Bn) in 73, 66, and 67% yields, respectively.[13] Asymmetric hydrogenation of imine (**4a**), catalyzed by $Ru_2Cl_4[(R)\text{-}(+)\text{-BINAP}]_2(NEt_3)$ or $Ru_2Cl_4[(S)\text{-}(-)\text{-BINAP}]2(NEt3)$[20] under H_2 (4 atm), afforded enantiomerically pure sultam ((*R*)-**2a**) (72%) or ((*S*)-**2a**) (71%).[1] Transfer hydrogenation of the sulfonylimines (**4b**) and (**4c**), in the presence of Noyori's (*S*,*S*)-RuCl(TsDPEN) (benzene) catalyst,[21] produced optically pure (*S*)-**2b** (75%) and (*S*)-**2c** (59%), respectively.[13]

Benzosultams (**2**) served as dienophile auxiliaries, thus extending the scope of asymmetric Diels-Alder reactions.[4] In the presence of $EtAlCl_2$ or Me_2AlCl, cyclopentadiene added smoothly to the acryloyl sultam (**5**) to form adducts (**7**) with excellent *endo*- as well as π-face selectivities. Diels-Alder addition of butadiene and isoprene also proceeded readily with 90 and 92% diastereoselectivities, respectively (Scheme 2, Table 1). Removal of the sultam moiety from adducts (**7**) using $LiOH/H_2O_2$/aq. THF[22] or $LiAlH_4$[2]

furnished carboxylic acids (**8**) or alcohols (**9**).



Scheme 2

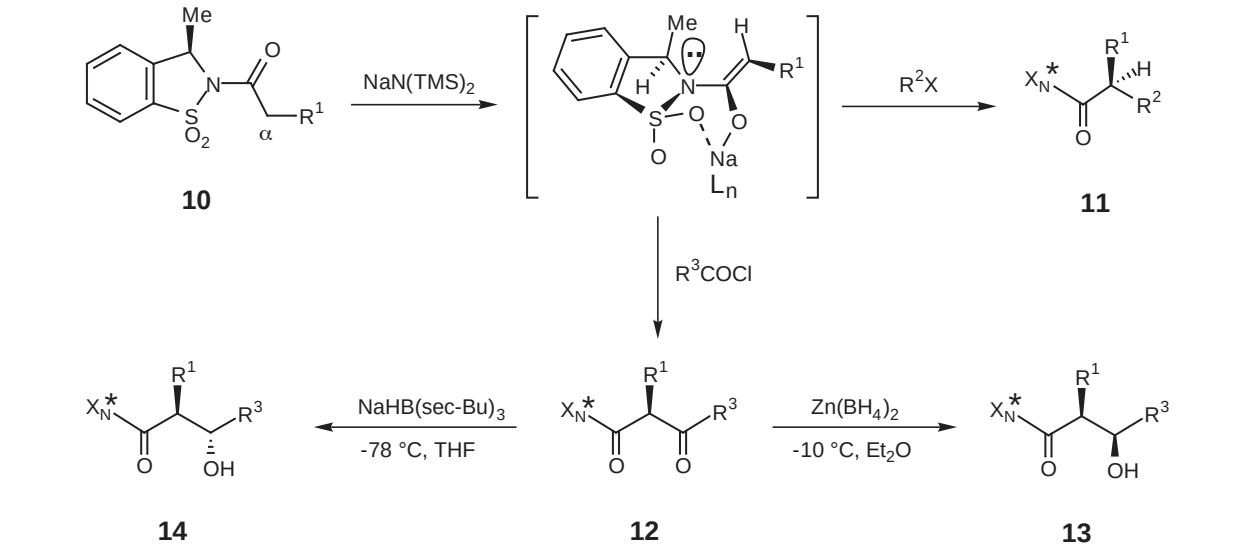
Table 1. Asymmetric Diels-Alder Reactions of **5**

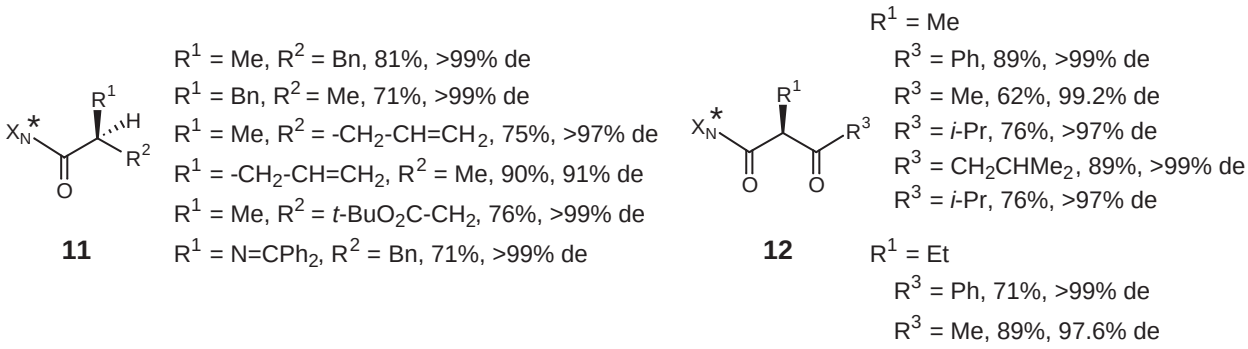
Entries	Diene (**6**)		ML_n (eq.)	Temp (°C)	Product (**7**)		
	R	Y			Yield (%)	endo/exo	de
1	H	CH_2	$EtAlCl_2$ (2.0)	-78	94	>99:1	91
2	H	CH_2	Et_2AlCl (2.0)	-78	93	>99:1	94
3	H	CH_2	Me_2AlCl (2.0)	-98	97	>99:1	93
4	H	H_2	$EtAlCl_2$ (1.6)	-78	79	-	90
5	Me	H_2	Me_2AlCl (1.6)	-98	97	-	92

Deprotonation of **10** with NaHMDS in THF, followed by alkylation or acylation reactions, gave **11** or **12** in high yield and diastereomeric purity after flash chromatography and/or crystallization. Chelate-controlled reduction[23] of *N*-(3-oxoacyl)sultams (**12**) with zinc borohydride proceeded without epimerization and afforded selectively "*syn*"-aldols (**13**). "*Anti*"-aldols (**14**) were obtained almost exclusively and in high diastereomeric purity by reducing the keto group of **12** with sodium tris-*s*-butylborohydride (Scheme 3).[3]

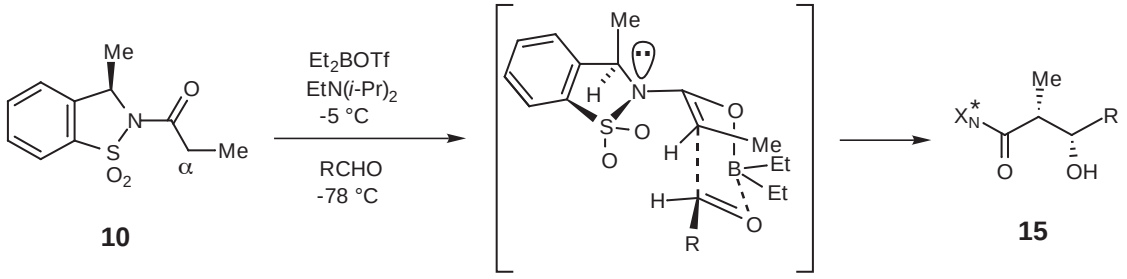
Treatment of acylsultam (**10**) with *in situ* prepared diethylboryl triflate/EtN(*i*-Pr)$_2$ (2 eq) and a variety of aldehydes furnished, without exception, pure "*syn*"-aldols (**15**) in high yields (R = Ph, 84%; R = Me, 71%; R = *i*-Pr, 95%; R = *i*-Bu, 78%) (Scheme 4).[3] These aldol reactions reflect an electrophilic attack to the opposite "enolate" π-face than observed with alkylations and acylations. In the transition state

described in Scheme 4, the (*Z*)-"enolate", with the boron atom being fully coordinated (and thus incapable of chelation with a SO_2 oxygen atom), adopts an electrostatically favored N-SO_2/$COML_n$ *s-trans* configuration.





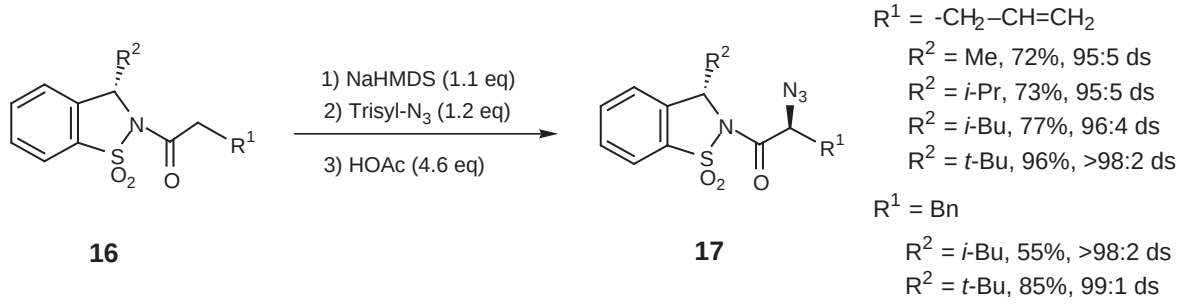
Scheme 3



Scheme 4

Ahn and co-workers reported[5] asymmetric azidation of acylsultams (**16**) using 2,4,6-triisopropyl-

benzenesulfonyl azide (trisyl-N_3) as an azide-transferring agent and MHMDS as a base[24] to give the azidation products with diastereoselectivities (de) of 95:5 or more. Excellent π-face selectivities and high yields were observed when R^2 is *tert*-butyl (Scheme 5).

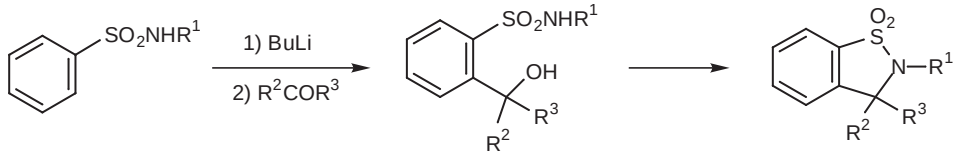


16 **17**

Scheme 5

2.2. 3,3-Disubstituted Five-membered Benzosultams

There are several methods for the synthesis of 3,3-disubstituted five-membered benzosultams. *ortho*-Metalation of *N*-methyl- and *N*-phenylbenzenesulfonamides (**18**) followed by reaction with a variety of ketones produced carbinol sulfonamides (**19**). These were cyclized under thermal or hydrobromic acid conditions to give benzosultams (**20**) (Scheme 6).[25] However, difficulty in removing the *N*-protective groups limits subsequent applications of these products.

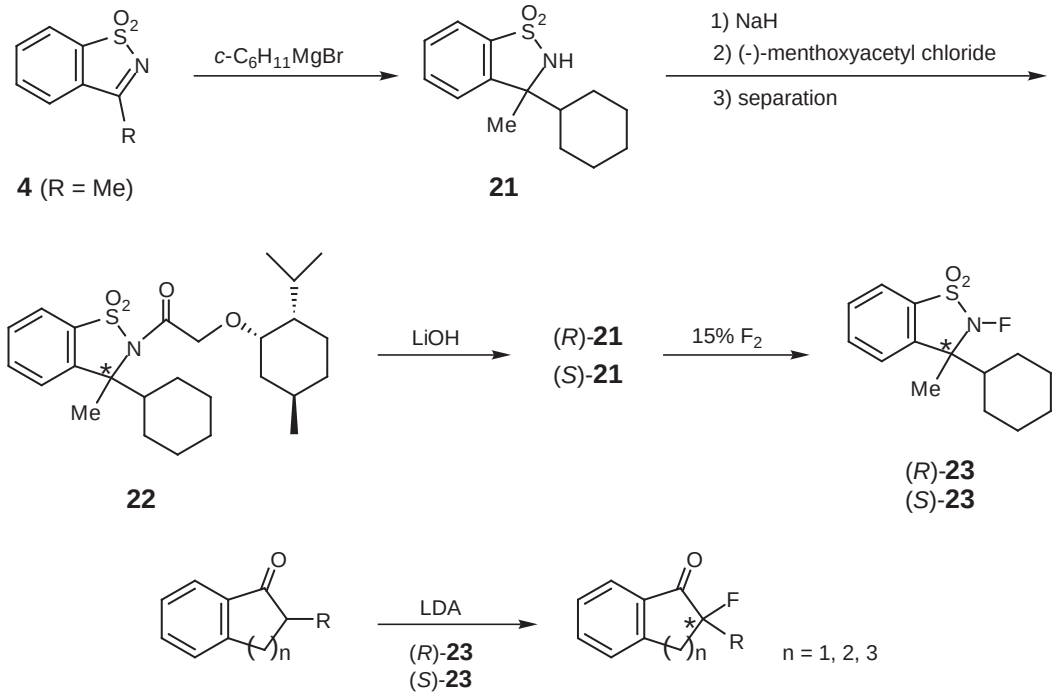


18 **19** **20**

Scheme 6

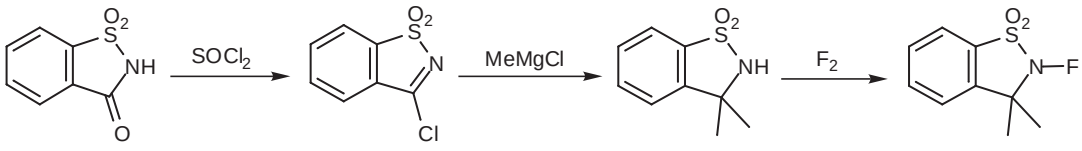
3,3-Disubstituted five-membered benzosultams are usually prepared by addition of organolithium compounds or Grignard reagents to the *N*-sulfonylimine (**4**).[8] By this way, we have prepared racemic 3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]isothiazole 1,1-dioxide (**21**). Chemical resolution of **21** with (–)-menthoxyacetyl chloride and removal of the chiral auxiliaries from the two diastereomers thus formed gave optically pure sultams ((*R*)-**21**) and ((*S*)-**21**). Finally, chiral *N*-fluorosultams (**23**) were

developed and proved to be efficient agents for electrophilic asymmetric fluorination of lithium enolates of indanone, tetralone, and benzosuberone derivatives. Yields (39-—73%) and ee's (18—74%) ranged from poor to modest. In the best result, an ee of 88% and isolated yield of 79% were obtained when (*R*)-**2 3** was employed for fluorination of 2-benzyl-1-tetralone (Scheme 7).[8]



4 (R = Me) **21** **22** (*R*)-**23** (*S*)-**23**

Scheme 7



3 **24** **25** **26**

R^1 = Ph, R^2 = OMe, 78%
R^1 = MeCO, R^2 = *t*-BuO, 70%
R^1 = R^2 = , 90%

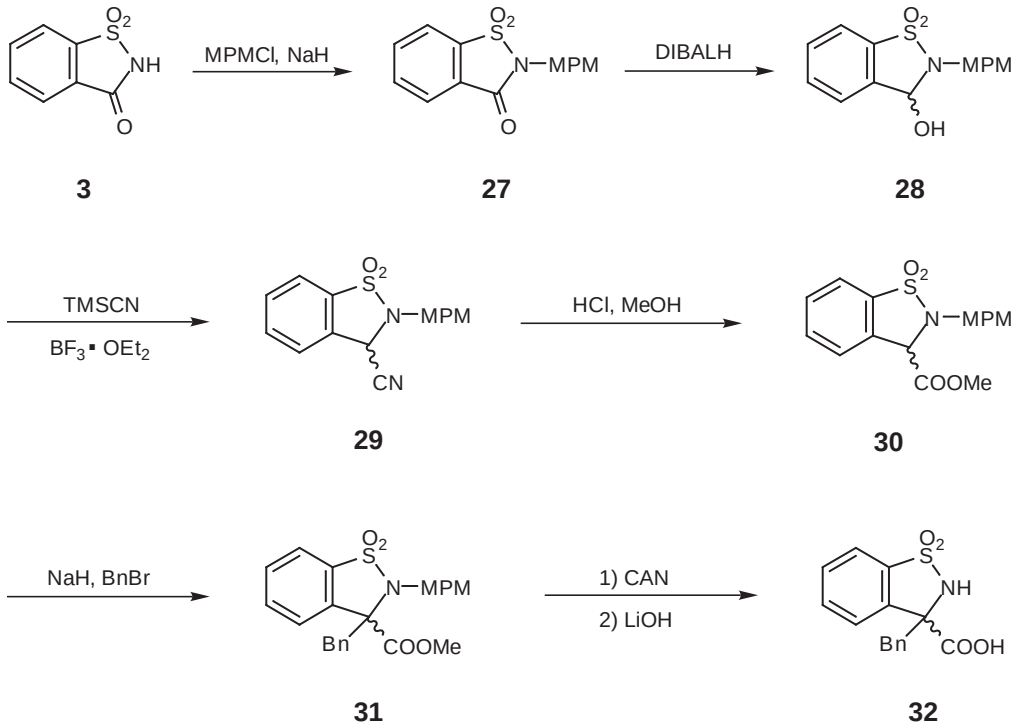
R^1 = Ph, R^2 = OMe, 33%
R^1 = Me, R^2 = Ph, 53%
R^1 = Me, R^2 = OBn, 58%

R^1 = Ph, R^2 = OMe, 53%
R^1 = Me, R^2 = Ph, 64%

Scheme 8

N-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (**26**) was derived from the corresponding benzosultam (**25**), which can be easily prepared from saccharin (**3**) *via* the 3-chloro compound (**24**).[26] *N*-Fluorosultam (**26**) can be used not only for the fluorination of disubstituted enolates,[26] but also for the fluorination of monosubstituted enolates to give selectively either mono- or difluorinated carbonyl derivatives.[27] Monofluorination was achieved using a slight excess of a base (1.2 eq) and 1.3—1.6 equivalents of **26**, while double fluorination could be done using 2.4—3.6 equivalents of base in THF at –78 ℃ followed by addition of 2.6—3.6 equivalents of **26** (Scheme 8).

Recently, Ahn *et al.* developed a method for the synthesis of 3-functionalized 1,2-benzisothiazoline 1,1-dioxides.[28] *N*-Protected saccharin (**27**) was treated with DIBALH to give semi-aminal (**28**), which was converted into methyl ester (**30**) *via* nitrile (**29**). Treatment of ester (**30**) with NaH in DMF followed by benzylation gave 3-benzylated product (**31**). Deprotection of the MPM group of **31** with CAN and hydrolysis of the ester produced racemic 3-benzyl-3-carboxysultam (**32**), which was obtained from saccharin in an overall yield of 63% (Scheme 9). Optically pure sultams (**32**) were available through chemical resolution of racemic **32** with (–)-brucine.



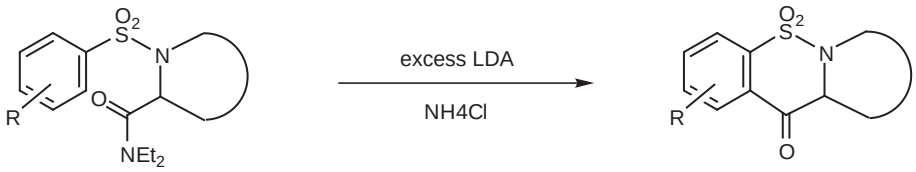
Scheme 9

3. SIX-MEMBERED BENZOSULTAMS

Six-membered benzosultams that have no substituents at 3-position can be prepared by usual way.[29] In this part, we focused on novel methods developed for the synthesis of 3-monosubstituted and 3,3-di-substituted six-membered benzosultams.

3.1. 3-Monosubstituted Six-membered Benzosultams

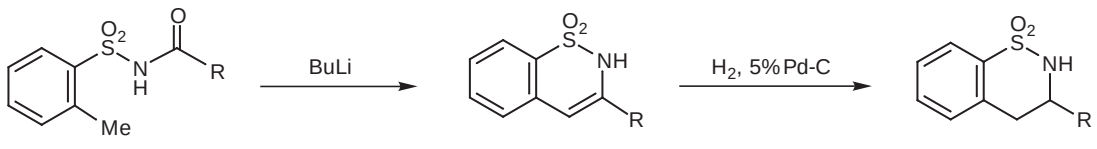
Snieckus and co-workers reported on the convenient synthesis of benzothiazine 1,1,4-trione compounds (**34**) from readily available *N*-arylsulfonylated amino amides (**33**) using mild standard LDA conditions (Scheme 10).[30] Scope and limitations, structure of the amino amides, reaction conditions, and cyclization regiochemistry were discussed.



33 **34**

Scheme 10

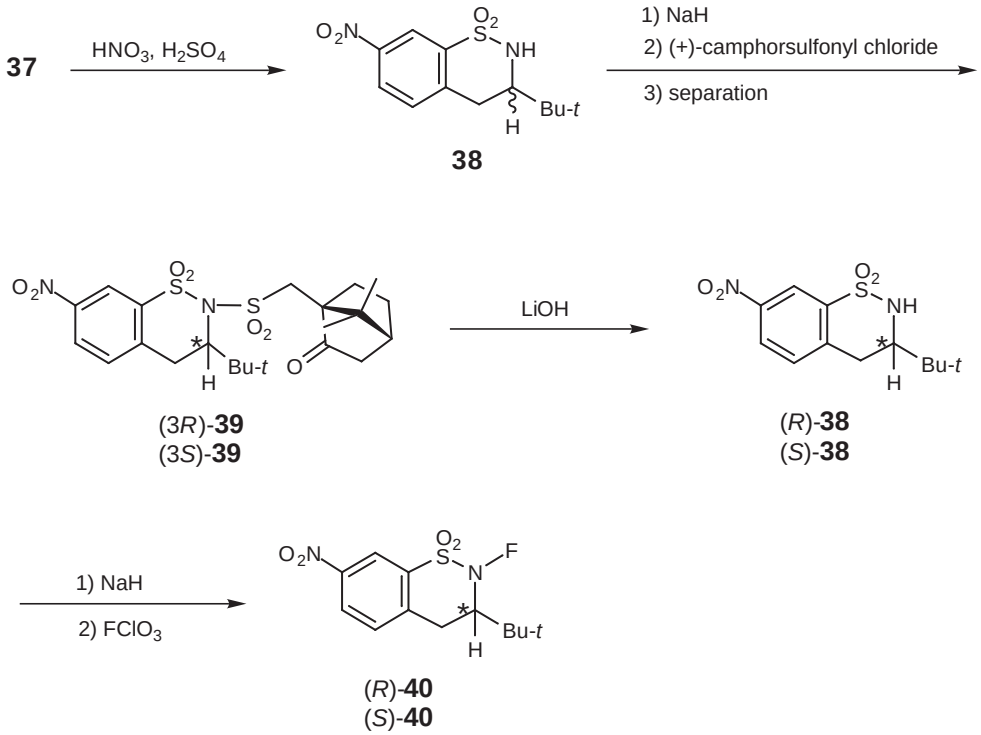
In the development of chiral *N*-fluoro agents based on the benzosultam templates, we discovered an expeditious method for the synthesis of 3-monosubstituted benzosultams.[31] *N*-Acyl-*o*-toluenesulfonamides (**35**) were treated with BuLi (2 eq) to give the sultams (**36**) *via ortho*-methyl lithiation/cyclization processes.[32] The yields were dependent on the bulkiness of R substituents (R = *t*-Bu, 74%; *c*-Hex, 54%; *i*-Pr, 46%; *i*-Bu, 20%; Ph, 25%). Hydrogenation of **36** produced the saturated sultams (**37**) in high yields (Scheme 11).



35 **36** **37**

Scheme 11

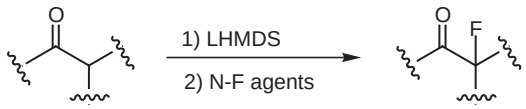
Compound (**37**) (R = *t*-Bu) was nitrated to give racemic sultam (**38**), which was condensed with (+)-10-camphorsulfonyl chloride to furnish two separable diastereomers ((3*R*)-**39**) and ((3*S*)-**39**). Removal of the chiral auxiliary with LiOH in aqueous THF gave optically pure sultams ((*R*)-**38**) and ((*S*)-**38**), respectively, which were subjected to fluorination with $FClO_3$ to afford the corresponding *N*-fluorosultams ((*R*)-**40**) and ((*S*)-**40**). These were evaluated as enantioselective electrophilic fluorinating agents (Scheme 12).[11]



Scheme 12

In the asymmetric fluorination of lithium enolates of a series of indanones and tetralones, *N*-fluorosultams ((*R*)-**40**) and ((*S*)-**40**) could be used to produce the two enantiomers of optically active quaternary α-fluoro carbonyl compounds. The fluorinations proceeded with modest enantioselectivities to give products with ee's of 43—69%. It is worthy of note that (*R*)-**40** exhibited *R* selectivity in the fluorination of 2-methyl-1-tetralone and furnished (*R*)-2-fluoro-2-methyl-1-tetralone in 79% yield and 62% ee, while *N*-fluorosultam ((*R*)-**23**) showed *S* selectivity (Table 2, entries 9,10).[8] Different working models were proposed for (*R*)-**40** and (*R*)-**23**.[8,11]

Table 2. Asymmetric Fluorination of Ketone Enolates Using Chiral *N*-Fluorosultams



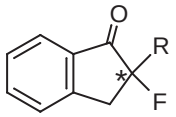
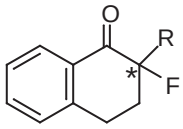
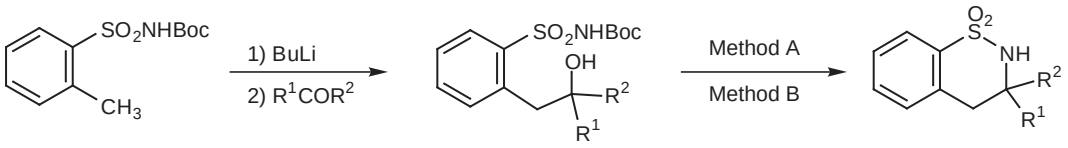
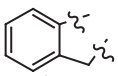
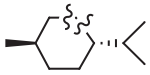
entry	*N*-F Sultam	Products	R	ee (%)	config.	isolated yield(%)
1	(*R*)-**23**		Me	54	*S*	54
2	(*S*)-**40**		Me	52	*S*	74
3	**44a**		Me	40	*S*	76
4	**44b**		Me	13	*R*	69
5	(*R*)-**23**		Bn	54	*S*	63
6	(*R*)-**40**		Bn	57	*R*	40
7	**44a**		Bn	54	*S*	59
8	**44b**		Bn	24	*R*	42
9	(*R*)-**23**		Me	74	*S*	67
10	(*R*)-**40**		Me	62	*R*	79
11	**44a**		Me	70	*S*	65
12	(*R*)-**23**		Bn	88	*R*	79
13	(*S*)-**40**		Bn	49	*R*	55
14	**44a**		Bn	56	*R*	61

Table 3. Synthesis of Six-membered Benzosultams



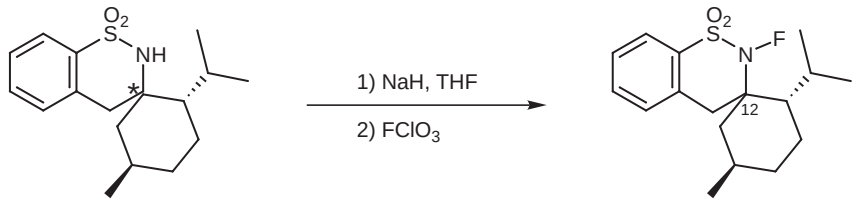
41 **42a–g** **43a–h**

Entry	R^1	R^2	Yield (%) **42a–g**	Yield (%) **43a–h** A	Yield (%) **43a–h** B
a	Me	Me	77	94	96
b	Me	Bu^t	94	90	93
c	Me	Ph	96	92	99
d	CF_3	Ph	85	89	94
e	$-CH_2CH_2CH_2CH_2CH_2-$		84	90	95
f			75	93	98
g			95[a]	35[b]	98[c]

[a]only one isomer. [b]**43g**: (11*S*,12*R*,14*R*)-isomer, **43h**: (11*S*,12*S*,12*R*)-isomer. **43g** : **43h** = 1 : 2.5.
[c]**43g** : **43h** = 5.5 : 1

3.2. 3,3-Disubstituted and Spiro Six-membered Benzosultams

We also developed efficient methods for the construction of 3,3-disubstituted and spiro six-membered benzosultams.[10] *o*-Methyl lithiation of *N*-Boc-*o*-toluenesulfonamide (**41**) followed by reaction with a variety of ketones gave carbinol sulfonamides (**42**). These underwent a novel cyclization mediated by $MeSO_3H/CH_2Cl_2$ or NaI/TMSCl/MeCN to afford sultams (**43**). Upon treatment with $MeSO_3H/CH_2Cl_2$ (Method A), the carbinol sulfonamide underwent a sequence of consecutive process, including rapid dehydration, slow removal of the Boc protective group, and then an acid-catalyzed addition to form the anticipated benzosultam. In most cases, this method worked well and gave sultams (**43**) in good yields (Table 3, entries a—f, Method A). However, when this procedure was applied to the sterically hindered carbinol sulfonamide (**42g**), a mixture of two separable diastereomers (**43g**,**h**) was obtained in only 35% yield, in a ratio of 1:2.5 (Table 3, entry g, Method A). When NaI/TMSCl/MeCN was employed (Method B), the cyclization went smoothly to produce sultams (**43g**,**h**) in 91% yield, with a reversed ratio of 5.5:1. By the same procedure, sultams (**43a**—**f**) were obtained in almost quantitative yields (Table 3, Method B). Finally, both **43g** and **43h** were separately subjected to $FClO_3$ fluorination in the presence of NaH in THF to give the corresponding diastereomerically pure *N*-fluorosultams (**44a**) [(11*S*,12*R*,14*R*)-isomer] and (**44b**) [(11*S*,12*S*,14*R*)-isomer] in 81 and 44% yields, respectively (Scheme 13).[10]



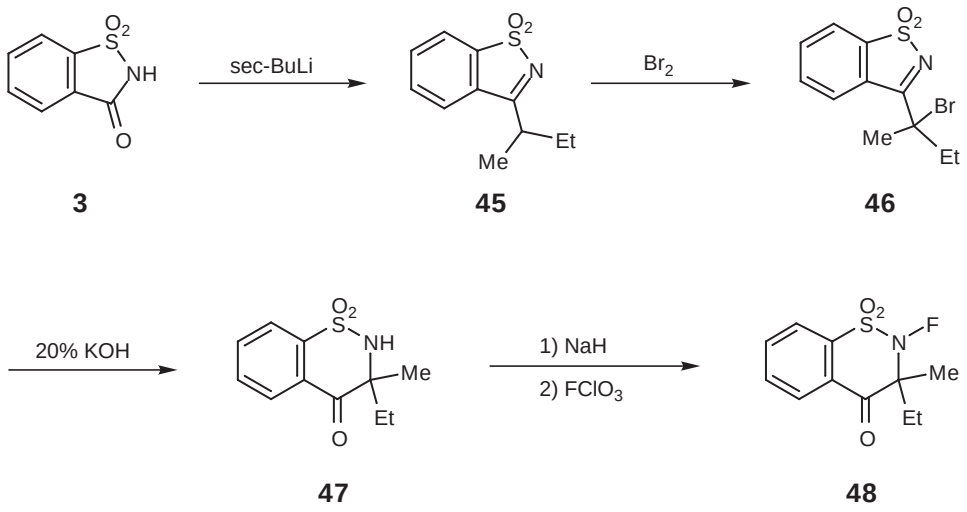
43g,**h** **44a**,**b**

Scheme 13

The chiral N–F agent (**44a**) showed better asymmetric induction than did **44b** in the enantioselective fluorinations of 2-methylindanone and 2-benzylindanone enolates (Table 2, entries 3,4,7,8). It is also of interest that **44a** showed *S* selectivity in the fluorination of 2-methyl-1-tetralone and gave the corre-

sponding 2-fluoro compound in 65% yield and with an ee of 70% (Table 2, entry 11). Based on the sense of chiral induction, it seems possible that **44a** may operate through a different mechanism than (*R*)-**40**, and similar to the model proposed for (*R*)-**23**.

3,3-Disubstituted 2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione represents another type of benzosultam that has been used as a template for developing an N–F agent.[9] *N*-Fluoro-3-ethyl-3-methylbenzo[*e*][1,2]thiazine 1,1,4-trione (**48**) was readily prepared by the route outlined in Scheme 14.

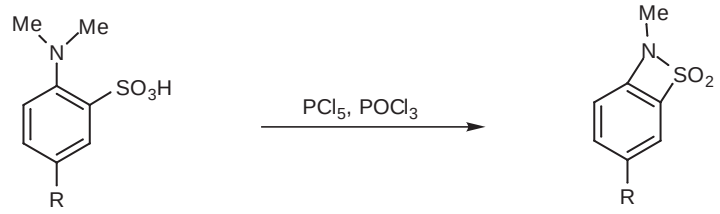


Scheme 14

Saccharin (**3**) was converted into benzosultam (**47**) in three steps consisting of sequential alkylation, bromination, and ring expansion according to Abramovitch's procedures.[33] Fluorination of the sodium salt of **47** with $FClO_3$ gave the stable N–F agent (**48**) in 71% yield. Racemic **48** in general showed good reactivity towards lithium and sodium enolates generated from indanones, tetralones, and benzosuberones to give the corresponding α-fluoro carbonyl compounds in good yields (64—100%).[9]

4. OTHER MEMBERED BENZOSULTAMS

Wu has recently synthesized four-membered benzosultams *via* a demethylative cyclization.[34] When sulfonic acid (**49a**) (R = Me) was heated with phosphorus oxychloride in the presence of phosphorus pentachloride, the four-membered benzosultam (**50a**) was formed in good yield. By the same procedure, **50b** (R = H) was obtained from **49b** (Scheme 15).

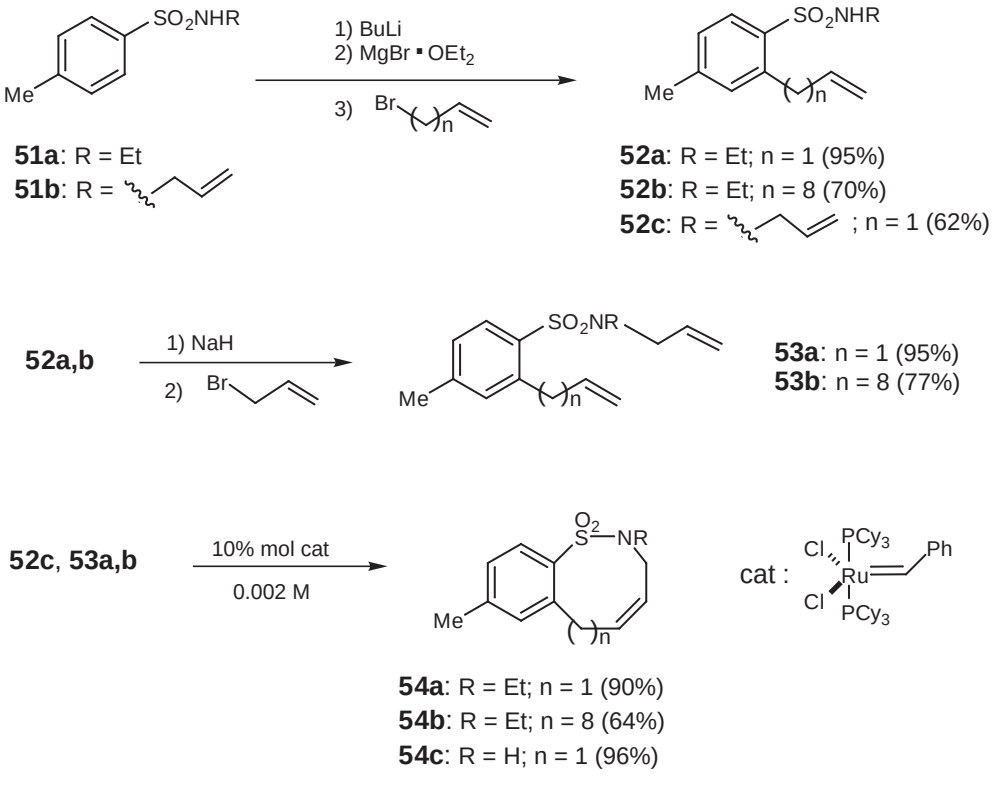


49a: R = Me
49b: R = H

50a: R = Me
50b: R = H

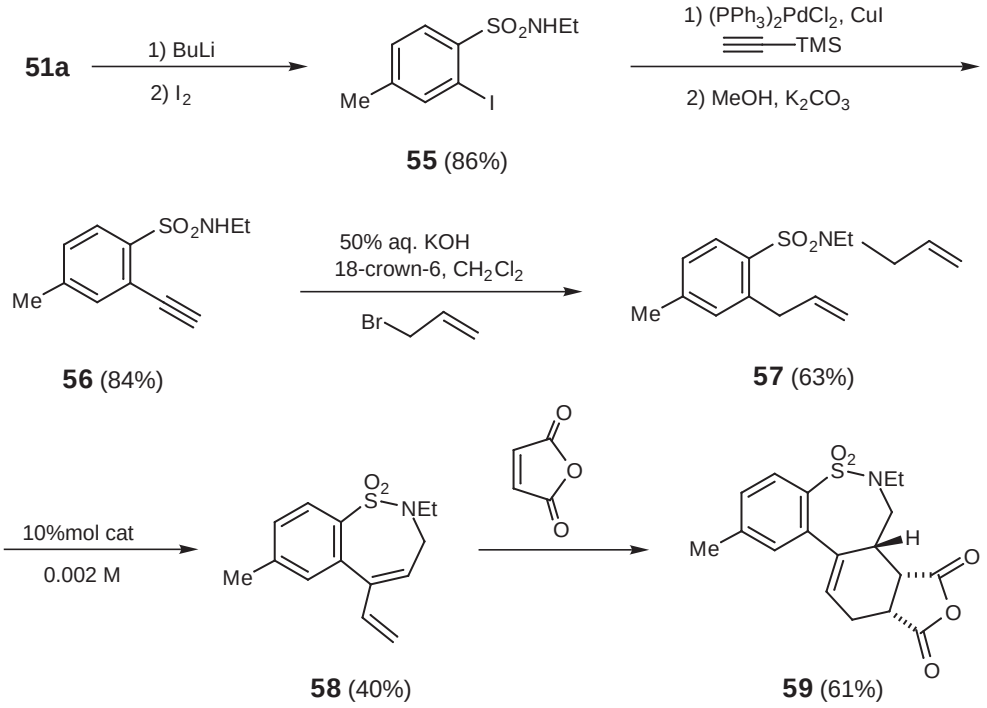
Scheme 15

In addition to the seven membered benzosultam synthesis by Snieckus,[30] higher membered benzosultams can be approached using methodology based on the new Directed *ortho* Metalation (D*o*M)[35] – Ring Closure Metathesis (RCM)[36] connection.[37] A D*o*M – Mg transmetalation – allylation and/or alkylation sequence on *p*-tolylsulfonamides (**51a**) and (**51b**) afforded the products (**52a**–**c**). NaH-Mediated allylation of **52a** and **52b** gave **53a** and **53b**, respectively. When subjected to metathesis conditions, sulfonamides (**52c**, **53a**, and **53b**) were transformed into the sultams (**54a**–**c**), respectively (Scheme 16).



Scheme 16

To illustrate further the scope of the sulfonamide D*o*M – RCM methodology, an ene-yne RCM,[38] allowing further annelation chemistry *via* Diels-Alder reactions, was demonstrated. D*o*M – iodination of **51a** afforded **55** which, upon Sonogashira coupling[39] and desilylation, gave **56**. Under phase transfer conditions, the required ene-yne precursor (**57**) was obtained. Exposure of **57** to standard RCM conditions yielded the diene (**58**). A Diels-Alder reaction was carried out on **58** to give the cycloadduct (**59**) (Scheme 17).[37]



Scheme 17

5. CONCLUSION

In conclusion, there has been much progress in benzosultam chemistry in recent years. However, additional methods are still needed for the synthesis of 3,3-disubstituted and spiro five-membered benzosultams and 3,3-disubstituted 2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones. The methods presently available for the synthesis of these types of benzosultams are limited due to the unavailability or poor reactivity of the corresponding organometallic species towards saccharin. At present there are no methods for the synthesis of spiro five-membered benzosultams. We are making progress in our own research in this area. Considering the diverse biological profiles of sulfonamide containing compounds, benzosultams

can be expected to find many applications in life science related areas. An example would be their application as substrates for developing sulfonamide peptidomimetics.[40]

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