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NEW DEVELOPMENTS IN THE SYNTHESIS OF SACCHARIN RELATED FIVE- AND SIX-MEMBERED BENZOSULTAMS

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Abstract – Recent developments in the novel synthesis of saccharin related five- and six-membered benzosultams are reviewed.

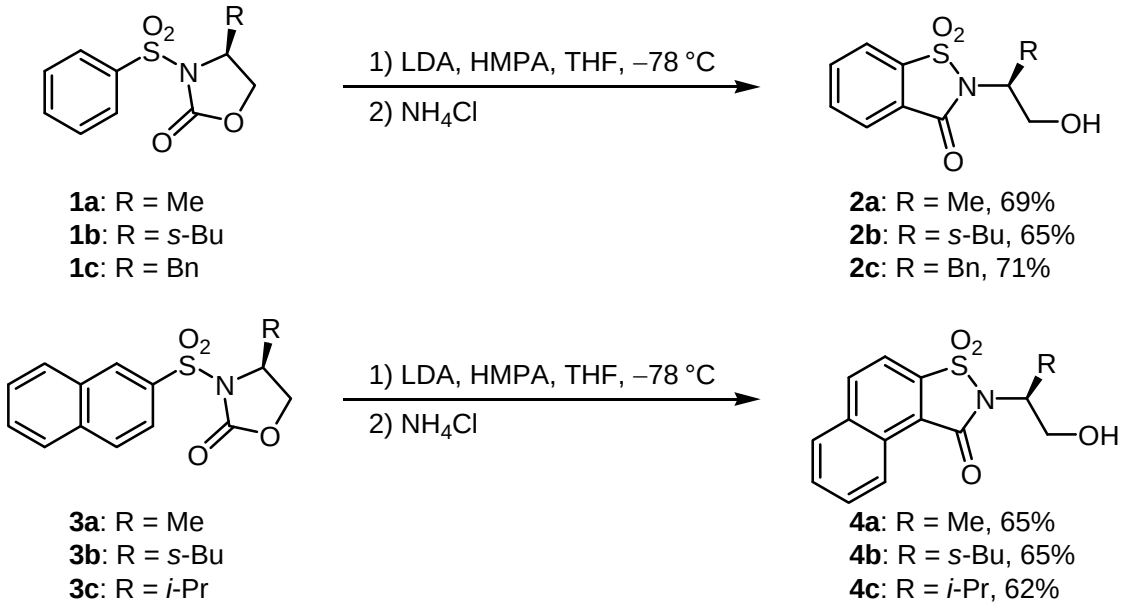
1. INTRODUCTION

The sulfonamide unit has found many applications in medicinal chemistry. It has been incorporated in a still growing number of biologically active compounds, exhibiting antibacterial, anti-carbonic anhydrase, diuretic, hypoglycemic, antithyroid, antiviral and anticancer activity among others.[1] In addition to being a carboxyl isostere, the introduction of the SO_2–N moiety induces an increase of stability, for example, towards protease-catalyzed degradation in the case of sulfonamide-containing peptidomimetics.[2] Recently, high interest has also been directed to the conformationally constrained cyclic counterparts, the sultams, which have served as key functional groups in the development of nonsteroidal antiinflammatory agents, agonists of 5-HT_{1A} receptors, novel serine inhibitors, zinc enzyme carbonic anhydrase inhibitors, etc.[3] Beyond their significance in the treatment of diseases, sultams have also been employed with considerable success as chiral auxiliaries or reagents in modern organic reactions.[4,5] As a sister review to our previous one,[4] this paper will focus on the recent developments in the synthesis of 1,2-benzisothiazoline 1,1-dioxide (saccharin) related five- and six-membered benzosultams, covering the recent literatures published from 2000. For the chemistry of isomeric 2,1-benzisothiazole 2,2-dioxides, please refer to the excellent review by K. Wojciechowski.[6]

2. FIVE-MEMBERED BENZOSULTAMS

2.1. Saccharin Derivatives

Due to the important biological activities of benzisothiazoline 1,1-dioxides, many efforts have been devoted to develop novel methods for the synthesis of analogues of saccharin derivatives. Aliyenne *et al*. reported an efficient way to prepare chiral *N*-substituted saccharin analogues from the readily available chiral 3-*N*-arylsulfonyloxazolin-2-ones.[7] Compounds **1a**–**c** and **3a**–**c** were treated with two equivalents of LDA in anhydrous THF and HMPA at –78 °C, followed by quenching with saturated NH_4Cl solution to afford the corresponding enantiomerically pure benzisothiazolinone 1,1-dioxides **2a**–**c** and naphthoisothiazolinone 1,1-dioxides **4a**–**c** with yields ranging between 62% and 71% (Scheme 1). The additive HMPA proved to be crucial to this reaction. Without HMPA or replacement it with TMEDA, the cyclization failed to proceed. Although *ortho*-lithiation could occur on C1 or C3 of the naphthalene ring, formation of the cyclization products **4a**–**c** proved that the *ortho*-lithiation was regioselective and the deprotonation took place at the C1 position.



1a: R = Me
1b: R = *s*-Bu
1c: R = Bn

2a: R = Me, 69%
2b: R = *s*-Bu, 65%
2c: R = Bn, 71%

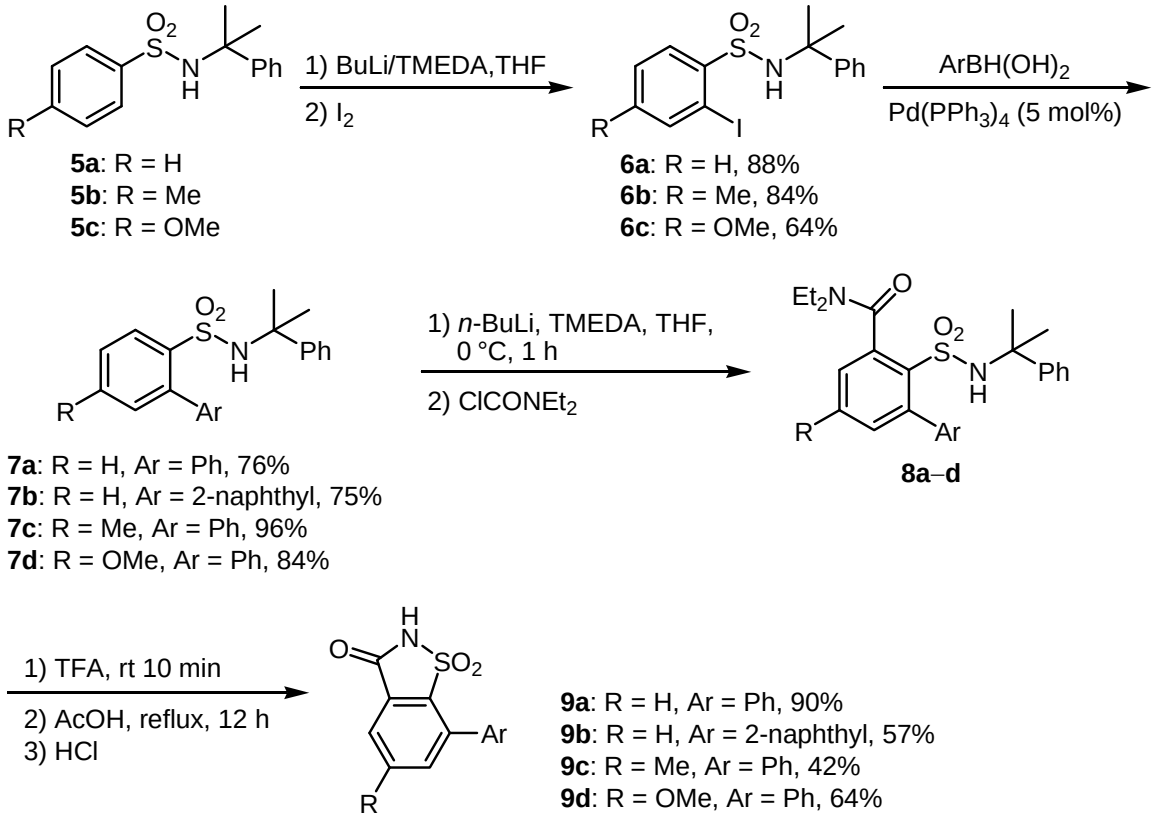
3a: R = Me
3b: R = *s*-Bu
3c: R = *i*-Pr

4a: R = Me, 65%
4b: R = *s*-Bu, 65%
4c: R = *i*-Pr, 62%

Scheme 1. Synthesis of Chiral *N*-Substituted Saccharin Analogues

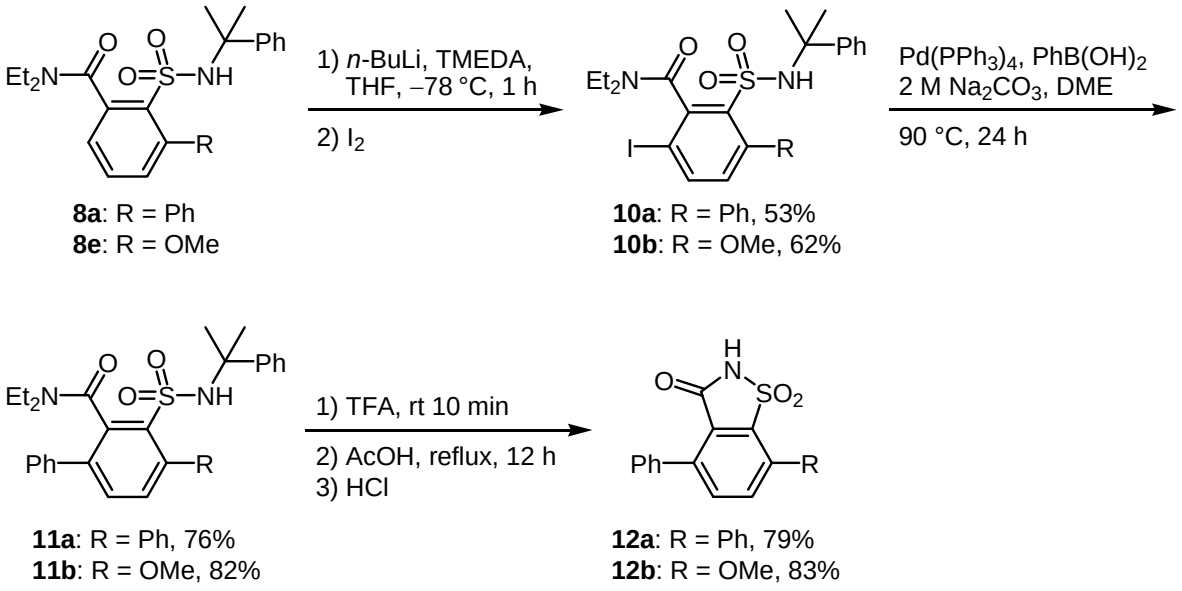
Benzenesulfonamide, both secondary and tertiary, is a powerful Directed Metalation Group (DMG) because of its ability to direct metalation to specific positions on the aryl ring. The sulfonamide Directed *ortho*-Metalation (D*o*M) methodology provides facile and exciting routes to synthesis of benzenesulfonamides and a wide variety of derived heterocycles.[4,8] By using the powerful *N*-cumylsulfonamide directed *ortho* metalation-cross coupling strategies, Snieckus's group developed a facile deprotection and expedient route to 7-substituted and 4,7-disubstituted saccharins.[9]

Treatment of *N*-cumylsulfonamide **5a** with *s*-BuLi, **5b**,**c** with *n*-BuLi in anhydrous THF in the presence of TMEDA at –78 °C, followed by reaction with iodine, gave the 2-iodo derivatives **6a**–**c** in good yields. Suzuki cross coupling of the 2-iodo *N*-cumyl arylsulfonamides with aryl boronic acids led to formation of biaryl *N*-cumylsulfonamides **7a**–**d**. *n*-BuLi/TMEDA *ortho* metalation of **7a**–**d**, followed by *N*,*N*-diethylcarbamoyl chloride quench, gave the expected amide sulfonamides **8a**–**d**. Mostly without isolation, these compounds were conveniently transformed directly by mild TFA decumylation followed by HOAc treatment into the *N*-unsubstituted 7-arylated saccharins **9a**–**d** in modest to excellent yields (Scheme 2).



Scheme 2. Synthesis of 7-Arylated Saccharins

The *n*-BuLi/TMEDA *ortho* metalation and iodination of **8a**,**e** gave the corresponding iodo derivatives **10a**,**b**, respectively. Suzuki cross coupling with phenylboronic acid under the Na_2CO_3 conditions, afforded the tetrasubstituted aromatics **11a**,**b**, which when subjected to the above decumylation and cyclization conditions, produced the 4,7-disubstituted saccharins **12a**,**b** respectively, in good overall yields (Scheme 3).



8a: R = Ph
8e: R = OMe

10a: R = Ph, 53%
10b: R = OMe, 62%

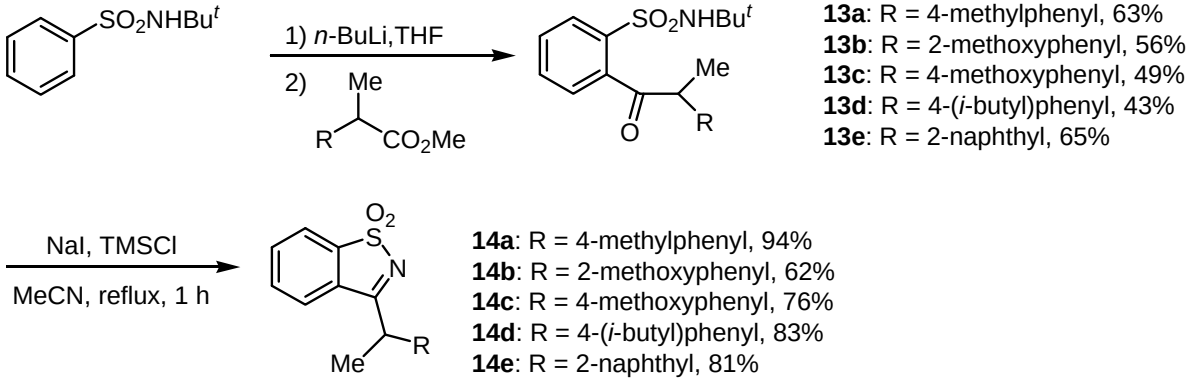
11a: R = Ph, 76%
11b: R = OMe, 82%

12a: R = Ph, 79%
12b: R = OMe, 83%

Scheme 3. Synthesis of 4,7-Disubstituted Saccharins

2.2. Cyclic *N*-Sulfonylimines

3-Substituted benzo[*d*]isothiazole 1,1-dioxides represent an important class of compounds both as bioactive agents and synthetic intermediates for the construction of five- and six-membered benzosultams. The most direct method for the synthesis of such cyclic *N*-sulfonylimines involves the reaction of saccharin with organolithium or Grignard reagents.[4] However, the unavailability and/or poor reactivity of the necessary hindered organometallic species limited the applications of this methodology. By adopting the D*o*M strategy and combining our TMSCl-NaI-MeCN reagent-mediated deprotection/cyclization[10] methodology, we developed a new synthetic approach to benzo[*d*]isothiazole 1,1-dioxides having a secondary alkyl substituent at the 3-position (Scheme 4).[11,12]



13a: R = 4-methylphenyl, 63%
13b: R = 2-methoxyphenyl, 56%
13c: R = 4-methoxyphenyl, 49%
13d: R = 4-(*i*-butyl)phenyl, 43%
13e: R = 2-naphthyl, 65%

14a: R = 4-methylphenyl, 94%
14b: R = 2-methoxyphenyl, 62%
14c: R = 4-methoxyphenyl, 76%
14d: R = 4-(*i*-butyl)phenyl, 83%
14e: R = 2-naphthyl, 81%

Scheme 4. Two-step Synthesis of Cyclic *N*-Sulfonylimines

A solution of *N*-*t*-butylbenzenesulfonamide in THF was treated with an excess of *n*-BuLi (2.5 eq) at 0 °C

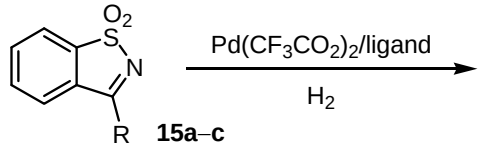
for 1 h, and then allowed to react with methyl 2-arylpropanoate, to give the ketone sulfonamides **13a**–**e** in modest yields. The application of TMSCl-NaI-MeCN reagent-promoted deprotection-cyclization of sulfonamides **13a**–**e** under reflux conditions, afforded the cyclic sulfonylimines **14a**–**e** in good to excellent yields (62–94%).

2.3. Substituted 2,3-Dihydro-benzo[*d*]isothiazole 1,1-Dioxides

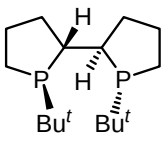
2.3.1. Pd-catalyzed Asymmetric Hydrogenation of Cyclic *N*-Sulfonylimines

Substituted benzosultams are important chiral auxiliaries that were first introduced in 1990 by Oppolzer[13] and have since been successfully applied to a number of asymmetric transformations. Asymmetric hydrogenation of cyclic *N*-sulfonylimines is one of the most widely used synthetic approaches.

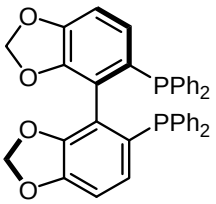
Table 1. Asymmetric Hydrogenation of Cyclic *N*-Sulfonylimines



Entry	R	Ligand	Conv (%)	ee (%)
1	Me (**15a**)	(*S*,*S*,*R*,*R*)-TangPhos	99	94 (*S*)
2	Me (**15a**)	(*S*)-SegPhos	95	92 (*R*)
3	*n*-Bu (**15b**)	(*S*)-SegPhos	95	90 (*R*)
4	Bn (**15c**)	(*S*)-SegPhos	95	88 (*R*)



(*S*,*S*,*R*,*R*)-TangPhos



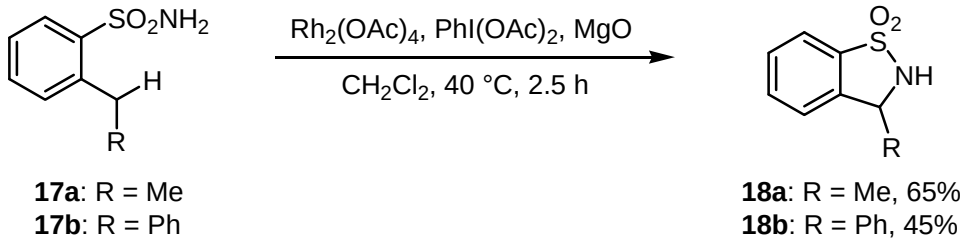
(*S*)-SegPhos

Yang *et al*. developed an efficient Pd-catalyzed asymmetric hydrogenation of *N*-tosylimines.[14] Compound **15a** was hydrogenated in CH_2Cl_2 solution at 40 °C and 75 atm, in the presence of 1.0 mol% $Pd(OCOCF_3)_2$/TangPhos complex, to give the methyl-substituted sultam with enantioselectivity of 94% ee and conversion of more than 99% (Table 1, entry 1). Wang *et al*. also successfully transformed the cyclic *N*-sulfonylimines **15a**–**c** into the chiral sultams with $Pd(OCOCF_3)_2$/(*S*)-SegPhos complex with good enantioselectivities (entries 2–4).[15]

2.3.2. Intramolecular C–H Amination

Amidation of saturated C–H bonds catalyzed by metal complexes based on Fe, Mn, Ru, Cu, or Rh is the established methodologies for C–N bond formation.[16] Fruit *et al*. investigated Rh^{II}-catalyzed intramolecular sulfonamidation with *in situ* generated phenyliodinanes derived from sufonamides.[17] The amidation of **17a**,**b** were carried out under *in situ* conditions with $PhI(OAc)_2$ in the presence of MgO with 5 mol% $Rh_2(OAc)_4$ at 40 °C in CH_2Cl_2 for 2.5 h, to afford the cyclization products **18a**,**b** in 65% and

45% yields, respectively (Scheme 5). Chiral Rh^{II}-catalysts were also tested for intramolecular asymmetric amidation of substrates **17a**,**b**, although the enantioselectivity never exceeded 20%.[17]

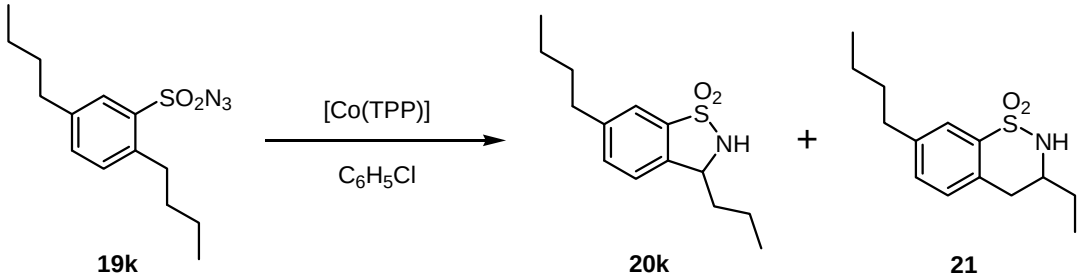


17a: R = Me
17b: R = Ph

18a: R = Me, 65%
18b: R = Ph, 45%

Scheme 5. Rh^{II}-catalyzed Intramolecular Sulfonamidation

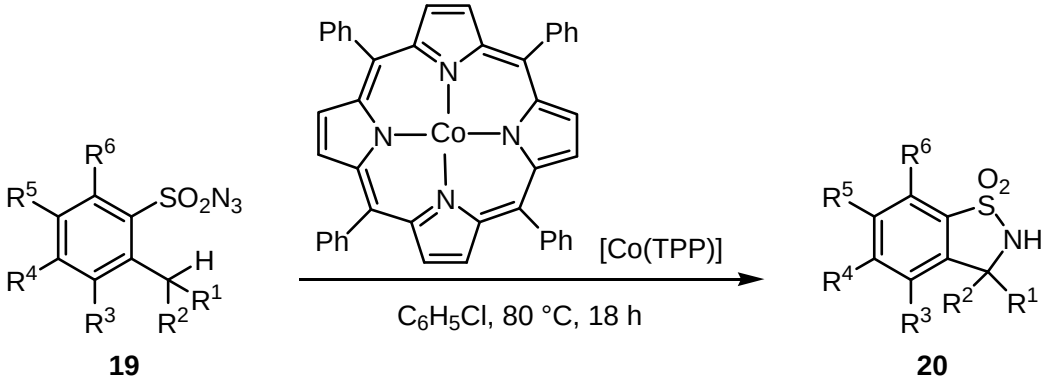
Zhang's group studied Co-catalyzed intramolecular C–H amination with azides as nitrene transfer sources.[18] Using the commercially available 2,4,6-triisopropylbenzenenesulfonyl azide (**19a**) as a model substrate, they surveyed potential catalytic activity of various metalloporphyrins toward intramolecular C–H amination, and found that Co(II) was the most active metal ion with TPP as the supporting ligand. When the reaction was run in chlorobenzene with 2 mol% of Co(TPP) under N_2 in the presence of 5 Å molecular sieves at 40 °C for 18 h, the desired benzosultam **20a** was isolated in 96% yields. The Co(TPP) catalytic system was applied to a broad range of arylsulfonyl azides, having tertiary, secondary, and primary benzyl C–H bonds, containing functional groups such as bromo and nitro at different positions, thus leading to various benzosultam derivatives in excellent yields (Table 2). However, when an azide substrate containing different 2° C–H bonds such as benzylic and non-benzylic types was employed, both five- and six-membered ring formations were observed. For example, Co(TPP)-catalyzed intramolecular C–H amination of azide **19k** with an *n*-butyl group led to the six-membered (**21**) and five-membered (**20k**) compounds (Scheme 6). The ratio of **20k** to **21** was determined to be 72:28, 68:32, and 67:33 at 80 °C, 40 °C, and room temperature, respectively. The increase in the ratio of **20k** to **21** at elevated temperature suggests the higher theromodynamic stability of the five-membered ring structure. Further efforts are necessary to identify suitable catalysts with high regioselctivity towards either five- or six-membered ring formation.



19k **20k** **21**

Scheme 6. Five- and Six-membered Ring Formation via Cobalt-catalyzed Intramolecular C-H Amination

Table 2. [Co(TPP)]-catalyzed Intramolecular C–H Amination of Arylsulfonyl Azides



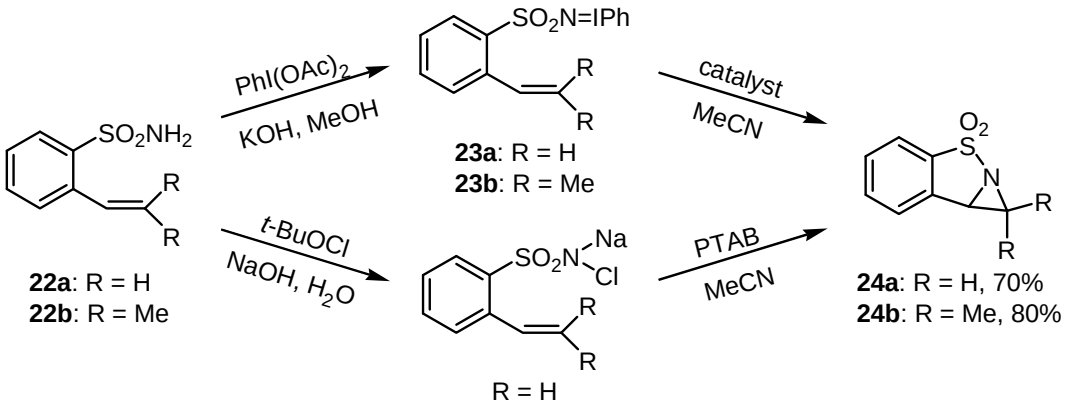
19 **20**

Entry	R^1	R^2	R^3	R^4	R^5	R^6	Yields (%)
a	Me	Me	H	*i*-Pr	H	*i*-Pr	96
b	Me	Me	H	H	*i*-Pr	H	94
c	Me	H	H	Et	H	Et	90
d	Me	H	H	H	Et	H	91
e	H	H	H	Me	H	Me	96
f	H	H	Me	H	Me	Me	91
g	H	H	Me	Me	Me	Me	95
h	Me	H	H	Br	H	H	93
i	Me	H	H	H	NO_2	H	99
j	-$(CH_2)_5$-		H	H	*c*-Hex	H	87

2.3.3. Catalyzed Intramolecular Aziridination

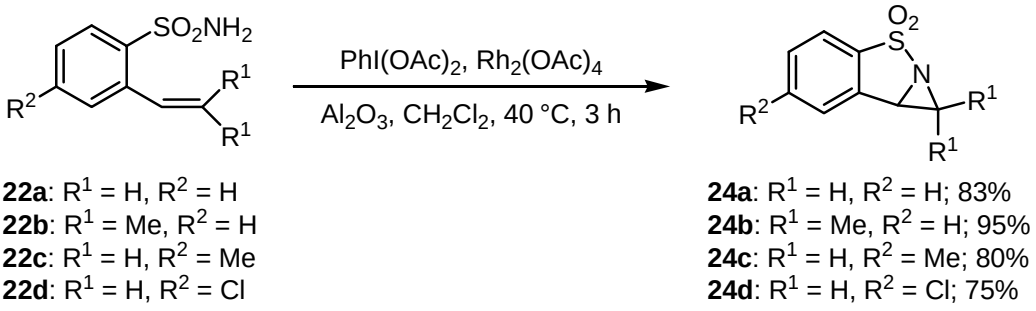
In recent years, metal-catalyzed intramolecular aziridination has become a new strategy for the preparation of cyclic sulfonamides. Dauban and co-workers investigated the copper- and bromine-catalyzed aziridinations.[19,20] When olefinic primary sulfonamides **22a**,**b** were treated with iodobenzene diacetate and potassium hydroxide in methanol, iminoiodiane intermediates **23a**,**b** were formed. Iminoiodiane **23a** underwent phenyltrimethylammonium tribromide (PTAB)-catalyzed intramolecular aziridination to give the desired benzosultam **24a** in 70% yield. On the other hand, **23b** was transformed into the cyclic sulfonamide **24b** when treated with a catalytic amount of copper (I) triflate in acetonitrile in the presence of 4 Å molecular sieves (Scheme 7).[19]

Sulfonamides **22a**,**b** reacted with *tert*-butylhypochlorite (*t*-BuOCl) and sodium hydroxide in water to form the corresponding *N*-chloramine salts, which were directly applied to PTAB-catalyzed intramolecular aziridination to form the aziridines **24a**,**b**, respectively (Scheme 7).[20]



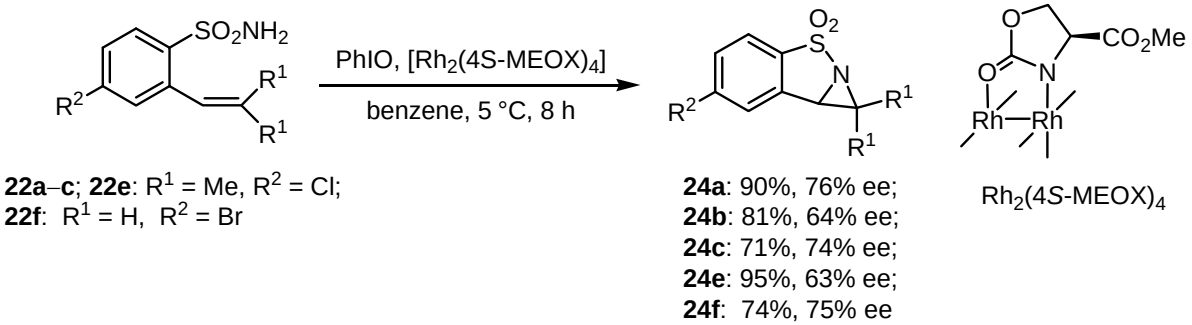
Scheme 7. Copper- and Bromine-catalyzed Intramolecular Aziridinations

Rhodium (II, II) dimer has been studied for the intramolecular aziridination and amidation.[21] Sulfonamides **22a**–**d** underwent direct intramolecular aziridination catalyzed by $Rh_2(OAc)_4$ with $PhI(OAc)_2$ and Al_2O_3 to afford the corresponding sultams in good to excellent yields (Scheme 8).



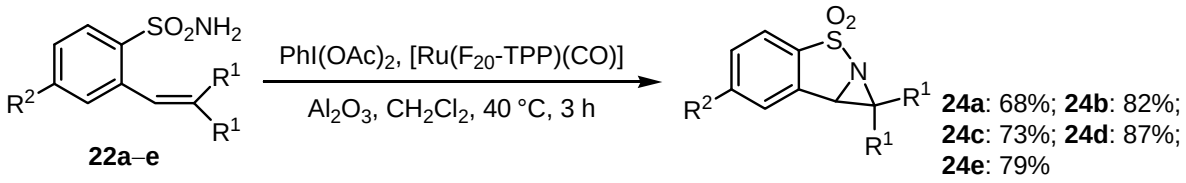
Scheme 8. $Rh_2(OAc)_4$-catalyzed Intramolecular Aziridinations

Chiral rhodium (II, II) dimer was applied to enantioselective intramolecular aziridinations.[22] In the presence of 10 mol% [Rh_2(4*S*-MEOX)$_4$] and 1.5 equiv of PhIO, acyclic sulfonamides **22a**–**c** and **22e**,**f** were transformed into the optically enriched benzosultams in good yields with moderate enantioselectivity up to 76% ee (Scheme 9).



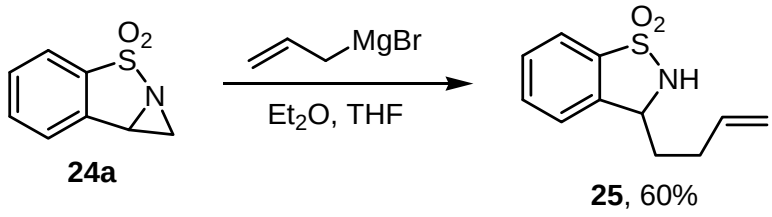
Scheme 9. Chiral Rhodium (II, II) Dimer-catalyzed Enantioselective Intramolecular Aziridinations

Following their work on dirhodium-catalyzed intramolecular aziridination of unsaturated sulfonamides,[21,22] Che's group further applied ruthenium porphyrins as catalysts for this transformation.[23] As shown in Scheme 10, complex [Ru(F_{20}-TPP)(CO)] (F_{20}-TPP = 5,10,15,20-tetrakis(pentafluorophenyl)-porphyrinato dianion) proved to be an active catalyst for intramolecular C–N bond formation. When the reactions were conducted in dichloromethane at 40 °C for 3 h, with catalyst/substrate/$PhI(OAc)_2$/Al_2O_3 molar ratio of 0.02:1:1.5:2.5, the corresponding cyclic aziridines **24a**–**e** were obtained in good yields.



Scheme 10. Ruthenium Porphyrins-catalyzed Intramolecular Aziridinations

Ring opening of the aziridines can lead to 3-substituted five-membered benzosultams. For example, bicyclic sultam **24a** reacted with allylmagnesium bromide to form benzo[*d*]isothiazole **25** (Scheme 11).[19]



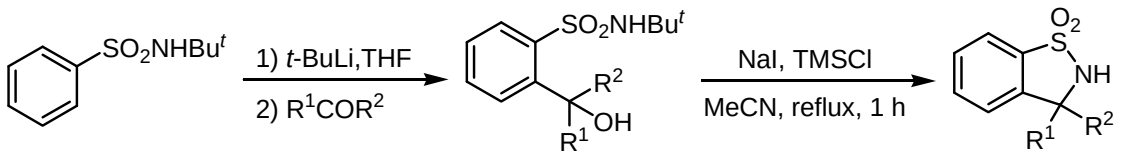
Scheme 11. Aziridine Ring-opening with Allylmagnesium Bromide

2.3.4. TMSCl-NaI-MeCN Reagent-mediated Intramolecular C–N Bond Formation

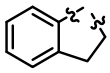
Combining the sulfonamide directed *ortho*-metalation (D*o*M)[8] strategy and TMSCl-NaI-MeCN reagent-mediated cyclization/deprotection methodology,[10] we developed a facile synthesis of 3,3-disubstituted and spiro five-membered benzosultams.[24]

o-Lithiation of *N*-*t*-butylbenzenesulfonamide with *t*-BuLi followed by reaction with ketones gave carbinol sulfonamides **26a**–**g** in modest to good yields. The sulfonamides **26a**–**g** were subjected to TMSCl-NaI-MeCN reagent-mediated cyclization/deprotection under reflux conditions to afford benzosultams **27a**–**g** in excellent yields (Table 3). This two-step synthesis makes 3,3-disubstituted and spiro 2,3-dihydro-benzo[*d*]isothiazole 1,1-dioxides readily available.

Table 3. TMSCl-NaI-MeCN Reagent-mediated Synthesis of Five-membered Benzosultams



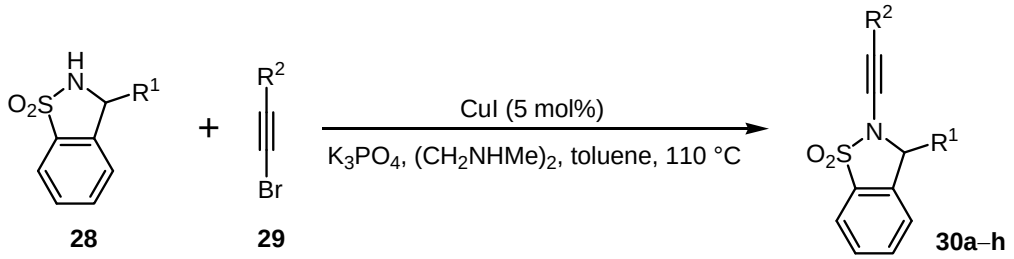
26a–**g** **27a**–**g**

Entry	R^1	R^2	Yields (%) **26a**–**g**	Yields (%) **27a**–**g**
a	Me	Me	85	95
b	Me	Ph	86	99
c	Me	4-methylphenyl	84	92
d	Me	1-naphthyl	55	98
e	-$CH_2CH_2CH_2CH_2$-		76	96
f	-$CH_2CH_2CH_2CH_2CH_2$-		70	92
g			83	96

2.3.5. *N*-1-Alkynylated Benzosultams and Their Synthetic Utilities

Acetylenes are versatile starting materials for transition metal-mediated coupling reactions. Hirano *et al*. developed a practical preparation of *N*-(1-alkynyl)sulfonamides and studied their applications in titanium

Table 4. *N*-Alkynylation of Cyclic Sulfonamides



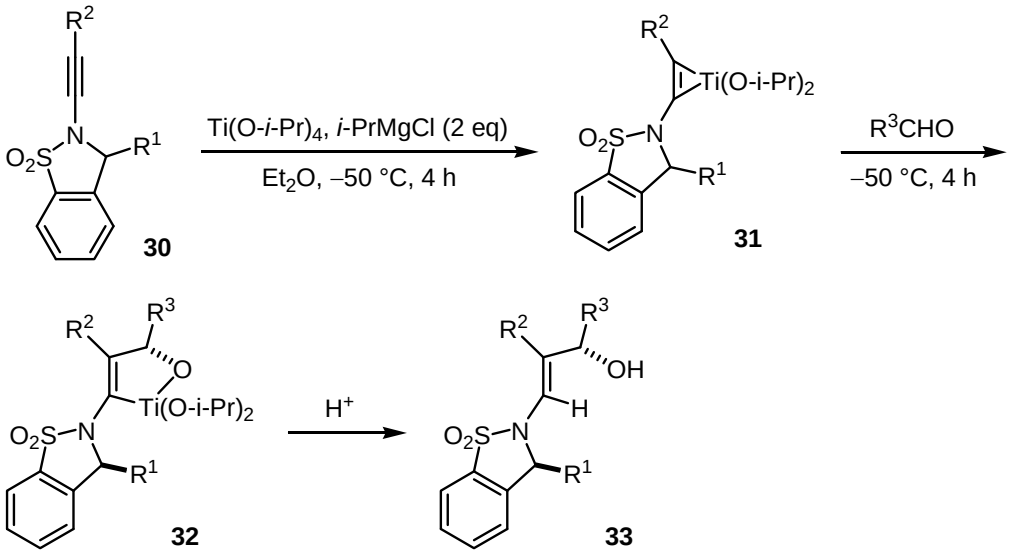
28 **29** **30a**–**h**

Entry	**28**, R^1	R^2	Product **30**	Product Yields (%)
1	**28a**, Me	*n*-hexyl	**30a**	79
2	**28a**, Me	$SiMe_3$	**30b**	74
3	**28b**, *n*-Bu	*n*-hexyl	**30c**	81
4	**28b**, *n*-Bu	$SiMe_3$	**30d**	66
5	(*S*)-**28c**, *t*-Bu	*n*-hexyl	**30e**	94
6	**28c**, *t*-Bu	$SiMe_3$	**30f**	71
7	**28c**, *t*-Bu	-$(CH_2)_3$OTBS	**30g**	81
8	**28d**, Ph	-$(CH_2)_3$OTBS	**30h**	91

alkoxide-mediated coupling reaction.[25] In the alkynylation of benzosultam **28a** (R^1 = Me), the

Pd-catalysts were found to be totally ineffective, while Cu(I) was very efficient in catalyzing this transformation. The best result was obtained when **28a** was treated with one equivalent of 1-bromo-1-octyne (**29**, R^2 = *n*-hexyl) in the presence of 5 mol% CuI and K_3PO_4, with 2.5 mol% *N*,*N*'-dimethylethylenediamine in toluene at 110 °C for overnight, to afford **30a** in 79% yield (Table 4, entry 1). Under the optimum conditions, a variety of benzosultams were alkynylated in good to excellent yields (Table 4). When using a chiral substrate, the enantiomeric purity of optical active sultam (*S*)-**28c** (R^1 = *t*-Bu) was completely retained in the product **30e** (96% ee, entry 5).

Table 5. Remote Diastereoselective Addition of *N*-Alkynylsultams to Aldehydes



Entry	Sultam **30**	Aldehyde		Product		
		R^3	Equiv	**33**	Yields (%)	1,5-Ds
1	**30b**	Ph	0.8	**33a**	87	96:4
2	**30b**	*p*-Cl-C_6H_4-	1.0	**33b**	54	96:4
3	**30b**	(*E*)-C_5H_{11}CH=CH-	0.8	**33c**	73	94:6
4	**30b**	(*E*)-CH_3CH=CH-	1.0	**33d**	52	95:5
5	**30b**	C_8H_{17}	0.8	**33e**	94	88:12
6	**30b**	*c*-C_6H_{11}	0.8	**33f**	89	68:32
7	**30e**	*i*-Pr	1.0	**33g**	88	93:7
8	**30e**	*t*-Bu	0.8	**33h**	93	98:2
9	**30f**	C_8H_{17}	1.0	**33i**	62	88:12
10	**30f**	Ph	1.0	**33j**	74	88:12
11	**30f**	*c*-C_6H_{11}	0.8	**33k**	79	93:7
12	**30f**	(*E*)-CH_3CH=CH-	1.0	**33l**	59	81:19
13	**30g**	*i*-Pr	0.8	**33m**	84	95:5

The amino-substituted acetylenes obtained above were demonstrated to be useful intermediates for diastereoselective synthesis. Sultam **30b** was first treated with titanium (II) alkoxide, Ti(O-*i*-Pr)$_4$/2

i-PrMgBr, to generate the acetylene-titanium complex **31**, which was then allowed to couple with benzaldehyde to give **32**. After hydrolysis, the adduct **33a** was obtained in good yield, showing virtually complete regio- and olefinic stereoselectivities with high 1,5-diastereoselectivity (ds = 96:4). The excellent level of the remote asymmetric induction (1,5-diastereoselectivity) is noteworthy. Other types of aldehydes and sultams underwent the same transformation and the results are summarized in Table 5. Figure 1 shows a proposed stereochemical course of the above reaction. The intermediate shown below, which fulfills (i) the least hindered conformation of the sultam moiety to the substituent (Me_3Si or C_6H_{13}) of the titanated acetylene, (ii) the approach of the aldehyde from the less hindered side (opposite to the Me or *t*-Bu group on the sultam), and (iii) the less hindered orientation of the side chain (R^3) of the aldehyde, may account for the observed stereochemistry of the adducts **33a**–**m**.

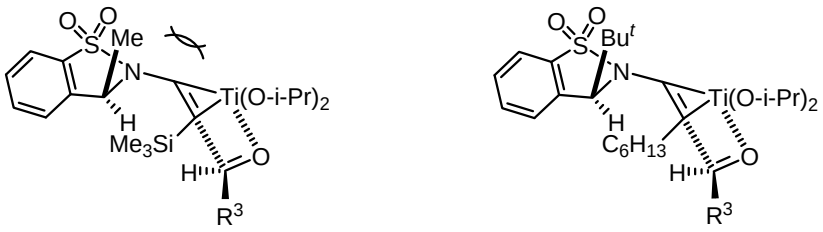
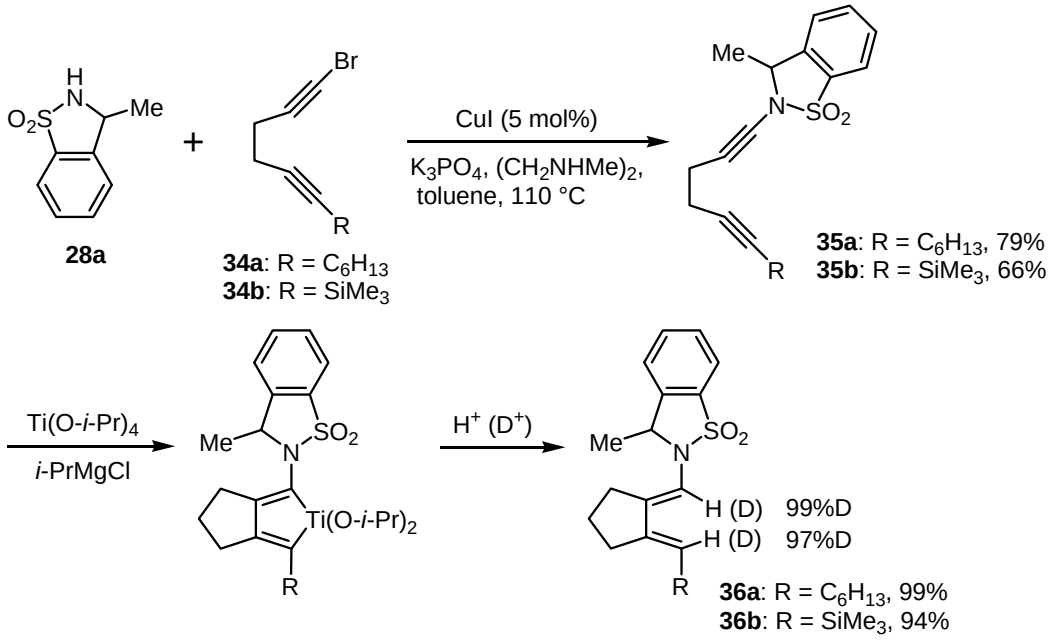


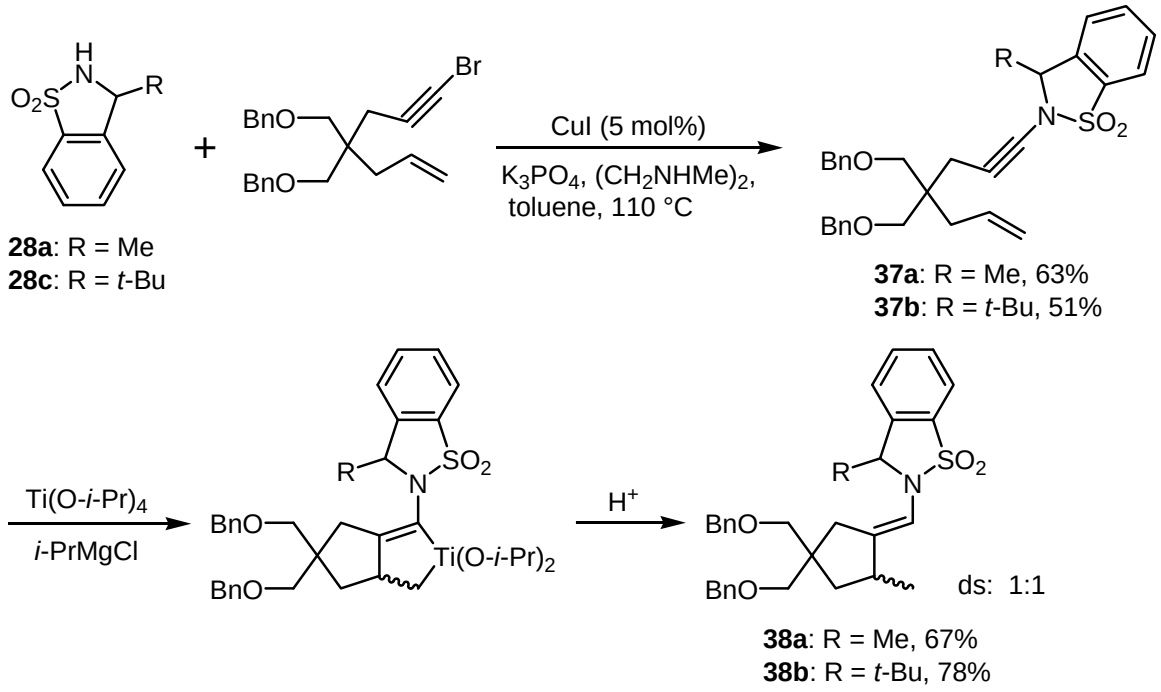
Figure 1. Proposed Stereochemical Course of the Titanium Alkoxide-mediated Coupling Reactions

Copper-catalyzed *N*-alkynylation of sultam **28a** with bromodiynes **34a**,**b**, successfully afforded **35a**,**b**, which were then cyclized with titanium reagent to give, upon hydrolysis or deuteriolysis, the desired amino-substituted *exo*-cyclic dienes **36a**,**b** in excellent yields (Scheme 12). The intramolecular coupling of two acetylenic moieties offers an attractive method to prepare cyclic compounds.



Scheme 12. Preparation of *N*-Alkadiynylsulfonamides and Its Intramolecular Cyclization

The copper-catalyzed *N*-alkynylation of sultam **28a**,**c** with bromoenynes also proceeded as usual, unaffected by the neighboring olefinic moiety in the same molecule, to give *N*-(1-alkynyl)sulfonamides **37a**,**b** having an olefinic appendage. Although the observed diastereoselectivities of the subsequent titanium alkoxide-mediated coupling reaction fell in an unsatisfactory range (ds = 1:1), the desired cyclic products **38a**,**b** were obtained in good yields (Scheme 13).



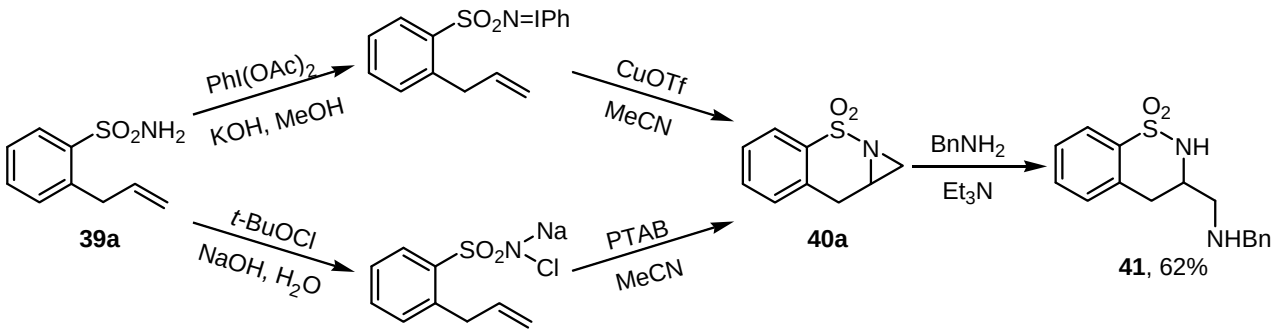
Scheme 13. Preparation of *N*-Alkynylsulfonamides and Intramolecular Enyne Cyclization

3. SIX-MEMBERED BENZOSULTAMS

3.1. Catalyzed Intramolecular Aziridination

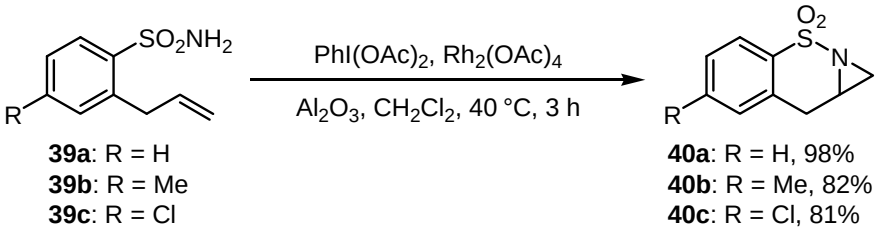
As shown in Scheme 14, olefinic primary sulfonamide **39a** was allowed to react with iodobenzene diacetate and potassium hydroxide in methanol to form an intermediate iminoiodiane, which underwent copper (I) triflate-catalyzed intramolecular aziridination to offer the desired benzosultam **40a** in 60% yield. Ring opening of the aziridine **40a** with benzylamine led to the 3-substituted six-membered benzosultam **41** in 62% yield.[19]

Sulfonamide **39a** was treated with *tert*-butylhypochlorite (*t*-BuOCl) and sodium hydroxide in water to give the *N*-chloramine salt intermediate, which was subjected to an intramolecular reaction in the presence of a catalytic amount of phenyltrimethylammonium tribromide (PTAB) to produce the aziridine **40a** in 46% yield.[20]

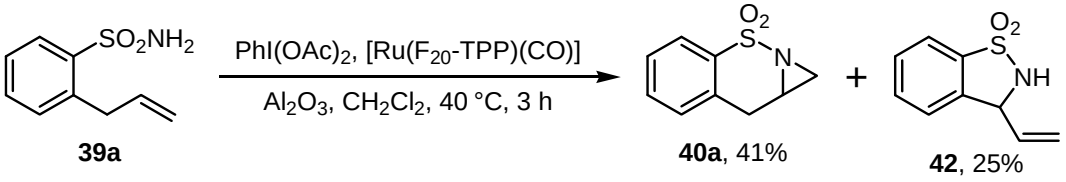


Scheme 14. Copper- and Bromine-catalyzed Intramolecular Aziridinations

Sulfonamide **39a**–**c** underwent direct intramolecular aziridination catalyzed by $Rh_2(OAc)_2$ with $PhI(OAc)_2$ and Al_2O_3 to afford sultams **40a**–**c** in good yields (Scheme 15).[21]



Scheme 15. $Rh_2(OAc)_4$-catalyzed Intramolecular Aziridinations



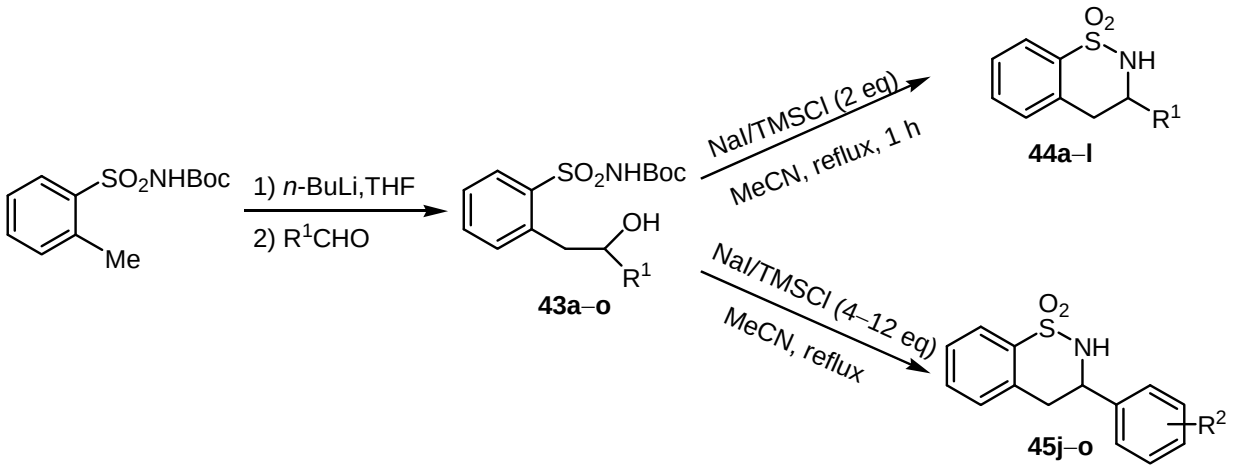
Scheme 16. Ruthenium Porphyrins-catalyzed Intramolecular Aziridinations

In the presence of catalyst [Ru(F_{20}-TPP)(CO)], the reaction between **39a** and $PhI(OAc)_2$ led to the intramolecular aziridination product **40a** (41%) and five-membered benzosultam **42** (25%), as shown in Scheme 16. It is reasonable that unsaturated sulfonamide **39a** that has a benzylic C–H bond can also undergo intramolecular amidation to form the five-membered product **42**.[21]

3.2. TMSCl-NaI-MeCN Reagent-mediated Deprotection/Cyclization

3,3-Disubstituted and spiro six-membered benzosultams can be efficiently prepared via the TMSCl-NaI-MeCN reagent-mediated deprotection/cyclization method which we developed.[10] Some 3-monosubstituted six-membered benzosultams are available from *N*-acyl-*o*-toluenesulfonamides in two

steps via *ortho*-methyl lithiation/cyclization processes followed by Pd/C-catalyzed hydrogenation,[26] but this procedure is not suitable for the preparation of 3-arylated analogues. Recently, we developed a novel two-step method for the facile synthesis of 3-monosubstituted six-membered benzosultams, applying the sulfonamide directed *ortho*-methyl metalation (D*o*M) effect and TMSCl-NaI-MeCN reagent-mediated cyclization/deprotection strategy (Scheme 17).[27,28]



Scheme 17. Two-step Synthesis 3-Monosubstituted Six-membered Benzosultams

N-Boc-*o*-toluenesulfonamide underwent *ortho*-methyl metalation, as well as *N*-metalation, with two equivalents of *n*-BuLi in anhydrous THF under nitrogen atmosphere at –78 °C for 30 min to form dilithiosulfonamide, which reacted with aldehydes to form carbinols **43a**–**o** in good yields. When carbinols **43a**–**l** were treated with two equiv of TMSCl and NaI in acetonitrile under reflux conditions for 1.5 h, the cyclization proceeded smoothly to produce the benzosultams **44a**–**l**. As can be seen from Table 6, this procedure is especially effective for preparation of 3-monoarylated benzosultams with various important functional groups that include both electron donating and withdrawing ones, such as chloro, fluoro, dimethylamino, methoxy, and cyano groups (entries a–e, j–l). For the compounds having less bulky aliphatic substituents at the 3-position, the yields are moderate (entries f and g), but for those having bulky aliphatic substituents such as cyclohexyl and *tert*-butyl groups (entries h and i), the yields are less than satisfactory even for an prolonged reaction time (10 h).

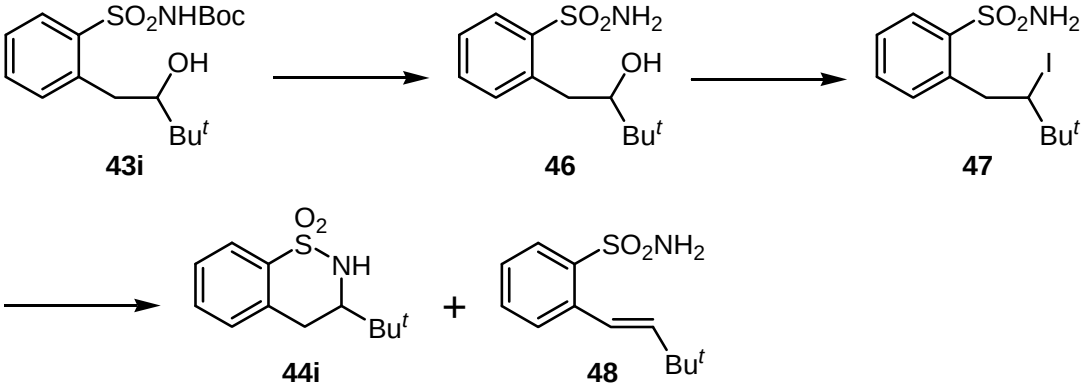
It is also of note, when carbinols **43j**–**o** was treated with 4 equiv of TMSCl and NaI for each methoxy group and refluxed in acetonitrile for a prolonged time, cyclization and demethylation can take place simultaneously and the phenolic benzosultams **45j**–**o** were readily obtained (Table 6, entries j–o).[28] Thus, the TMSCl-NaI-MeCN reagent-mediated cyclization and demethylation strategy provides the most direct way to these phenolic and polyphenolic compounds that have both important phenolic and sulfonamide pharmacophores in the structure.

Table 6. TMSCl-NaI-MeCN Reagent-mediated Facile Synthesis of 3-Monosubstitued Benzosultams

Entry	R^1	Yields (%)		NaI/TMSCl (equiv)	Time (h)	Product		
		43a–**o**	**44a**–**l**			R^2	**45**	Yields (%)
a	Ph	92	84					
b	*p*-Cl-C_6H_4-	87	81					
c	*p*-F-C_6H_4-	79	86					
d	*p*-Me_2N-C_6H_4-	88	82					
e	*p*-CN-C_6H_4-	81	78					
f	Me	78	75					
g	Et	80	72					
h	*c*-Hex	86	46*					
i	*t*-Bu	78	25*					
j	4-MeO-C_6H_4-	86	82	4	5	4-OH	**45j**	81
k	3,4-$(MeO)_2$-C_6H_3-	82	90	8	12	3,4-$(OH)_2$	**45k**	81
l	3,4,5-$(MeO)_3$-C_6H_2-	77	86	12	48	3,4,5-$(OH)_3$	**45l**	66
m	2,3-$(MeO)_2$-C_6H_3-	79		8	24	2,3-$(OH)_2$	**45m**	52
n	2,5-$(MeO)_2$-C_6H_3-	69		8	24	2,5-$(OH)_2$	**45n**	65
o	2,6-$(MeO)_2$-C_6H_3-	86		8	24	2,6-$(OH)_2$	**45o**	79

*refluxed for 10 h

As shown in Scheme 18, the TMSCl/NaI/MeCN reagent-mediated novel cyclization is assumed to proceed through a sequence of consecutive processes, which involve removal of the Boc protective group, conversion of the hydroxy group to iodide, and an intramolecular nucleophilic substitution for the cyclization. When substrate **43i** was treated with two equiv of TMSCl and NaI in acetonitrile at room temperature for 2 h, the *N*-Boc protective group was cleaved thoroughly to form the carbinol sulfonamide **46**, which was converted into the iodide **47** rather slowly at room temperature. Only 25% iodide **47** was formed after 16 h. When heated, substrate **43i** was converted to the iodide **47** much more quickly (in ca. 30 min). After heating for 10 h, the cyclization product **44i** (25%) and the elimination product **48** (42%) were isolated, along with the unreacted iodide **47** (20%).

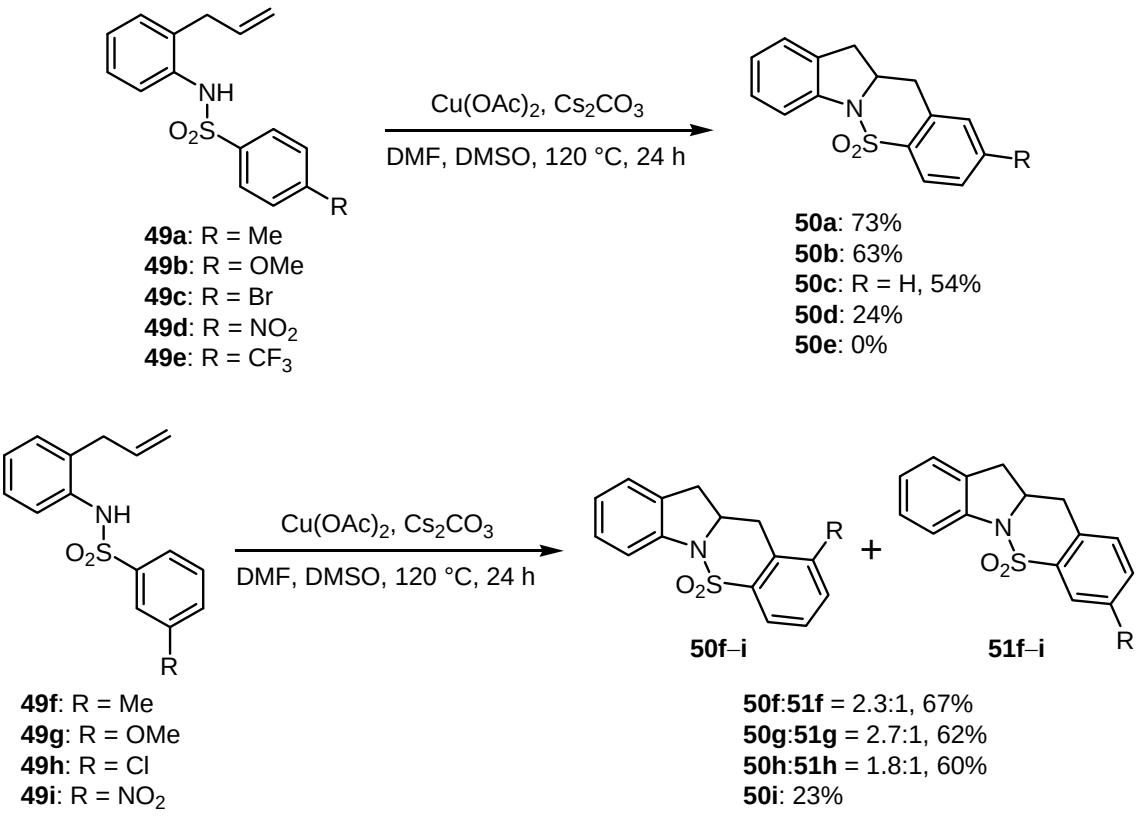


Scheme 18. The Processes of TMSCl-NaI-MeCN Reagent-mediated Cyclization

It is apparent that the intramolecular nucleophilc substitution (cyclization) and elimination reaction are competitive, and the sterically hindered iodide **47** with benzylic hydrogens favors the elimination, so the olefin **48** thus formed is predominant. The bulky alkyl iodides (table 6, entries h and i) are less reactive than the less bulky ones (entries f and g) and the benzyl iodides in the bimolecular nucleophilic substitution. Thus, the 3-monoalkylated benzosultams with bulky substituents such as cyclohexyl and *t*-Bu groups were obtained in much lower yields.

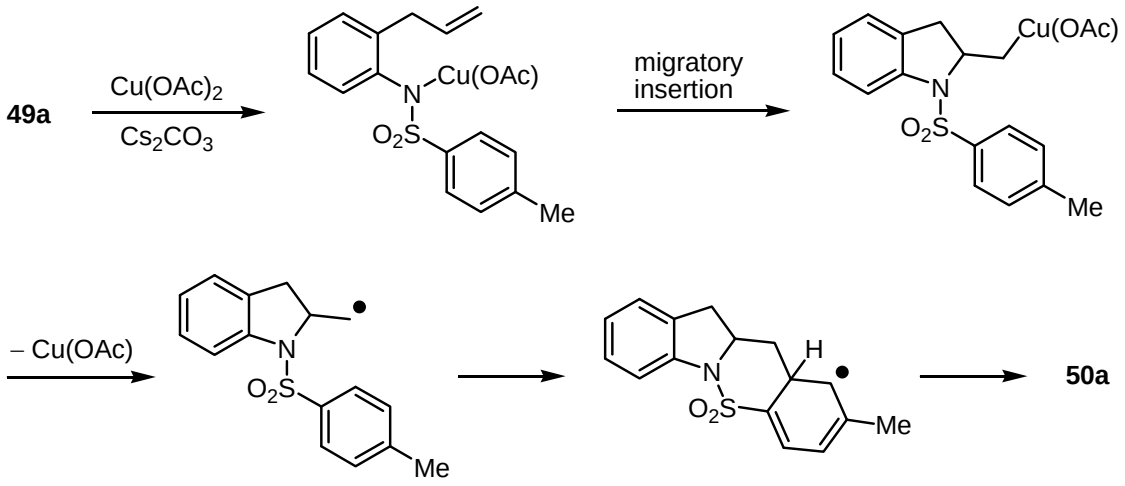
3.3. Copper (II) Carboxylate-promoted Intramolecular Carboamination of Olefins

Sherman *et al*. first reported copper (II) acetate reagent-promoted oxidative cyclization of arylsulfonyl-*o*-allylanilines.[29] When sulfonamides **49a**–**d** in DMF (0.08 M) were treated with $Cu(OAc)_2$ (3 equiv) and Cs_2CO_3 (1 equiv), and heated at 120 °C for 24 h in a pressure tube, the tetracycles **50a**–**d** were obtained in moderate yields (Scheme 19). Substrates with electron donating groups proved most reactive, i.e., 4-methyl, methoxy, and bromoaryl sulfonamides reacted efficiently albeit the bromine was removed under the reaction conditions (**50c**, R = H). On the other hand 4-nitro and 4-trifluoromethyl arylsulfonamides displayed significantly lower reactivity. As for solvent, DMF proved to be better than MeCN and addition of DMSO (4 equiv) increased the yields, sometimes with significant effect.[29]



Scheme 19. Copper (II) Acetate-promoted Oxidative Cyclization of Arylsufonyl-*o*-allylanilines

For *meta*-substituted arylsulfonamides, copper (II) acetate reagent-promoted oxidative cyclization generally led to a mixture of regioisomeric products (Scheme 19, substrates **49f**–**h**), with a preference (ca. 2:1) for the forming of the *ortho*-addition (**50f**–**i**) over the *para*-addition (**51f**–**i**) products. The reaction of *meta*-substituted nitrosulfonamide **49i** afforded the *ortho*-adduct as a sole cyclization product, albeit in low yield. This surprising *ortho* preference (sterically more hindered site) indicated that C–C bond formation might occur via addition of a carbon radical to the aromatic ring. Further studies support the following proposed mechanism shown in Scheme 20.[30] Copper (II) carboxylate-promoted intramolecular carboamination of olefins involves nitrogen-copper (II) bond formation followed by aminocupration (intramolecular migratory insertion), generating an unstable organocopper (II) species that homolyzes to the carbon radical and Cu (I), and subsequent addition of the primary carbon radical to an aromatic ring.

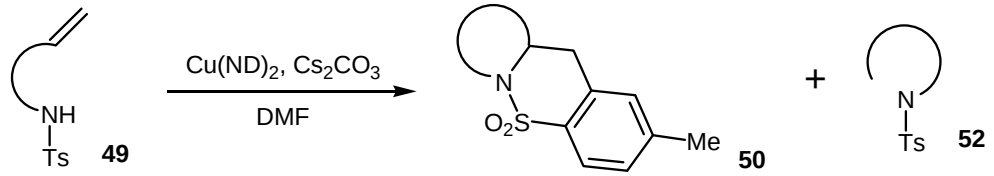


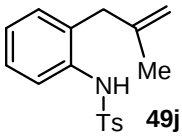
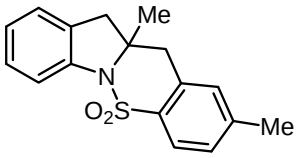
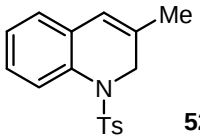
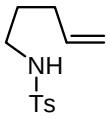
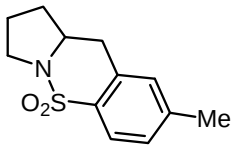
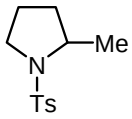
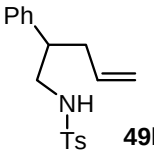
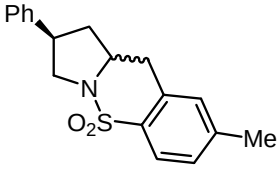
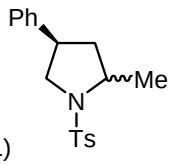
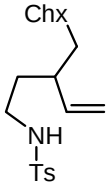
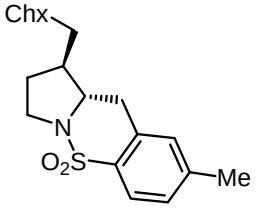
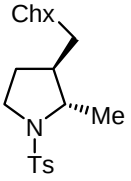
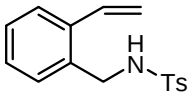
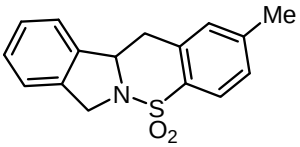
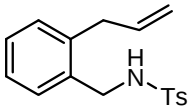
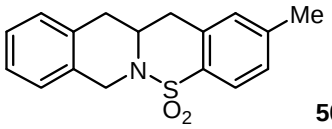
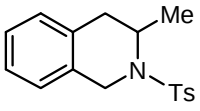
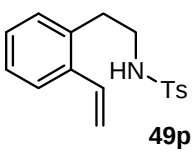
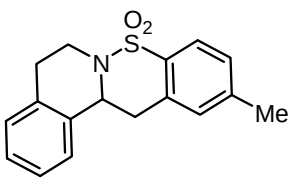
Scheme 20. Proposed Mechanism for Formation of the Carboamination Adducts

In the optimization of the best reaction conditions, the more organic soluble copper (II) neodecanoate [Cu $(ND)_2$] was found to be suitable to promote the intramolecular carboamination. A variety of unactivated olefins, including arylsufonamides derived from aliphilic amines and substrates with different olefin substitution patterns, were applied for $Cu(ND)_2$-mediated oxidative cyclization. The results are summarized in Table 7.[30]

All of the substrates examined in this reaction give exclusively the *exo* cyclization adducts except for the 1,1-disubstitued olefin **49j**, which gave a ca. 1:1 mixture of the *exo* carboamination adduct **50j** and the *endo* oxidative amination adduct **52j** (Table 7, entry 2). Sufonamides **49k**–**m**, derived from aliphilic amines (entries 3–5), underwent the cyclization efficiently. The formation of hydroamination minor products was also observed with some substrates and the carboamination to hydroamination ratio is presumably a function of the relative rates of radical addition to the aromatic ring *vs* hydrogen atom abstraction from the reaction medium (Scheme 20). The carboamination adducts derived from styrenyl

Table 7.Copper (II) Carboxylate-promoted Intramolecular Carboamination of Unactivated Olefins

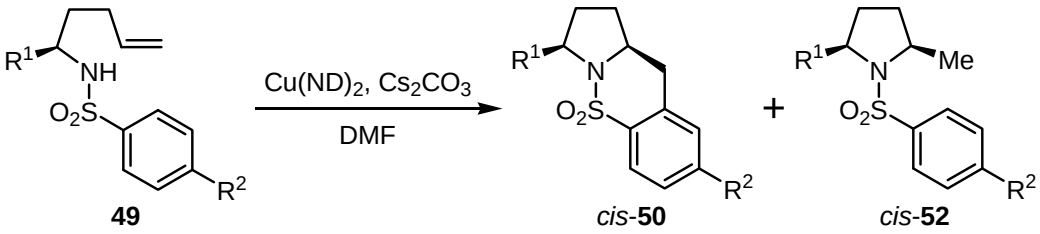


Entry	Substrate **49**	Temp; Time	Product (yield %)	
1	**49a**	120 °C; 24 h	**50a**, 69	
2	 **49j**	120 °C; 24 h	 **50j**, 49	 **52j**, 46
3	 **49k**	160 °C; 72 h	 **50k**, 59	 **52k**, 21
4	 **49l**	210 °C; 72 h (210 °C, μw, 3 h)	 **50l**, 56 (52) *trans* / *cis* (1 / 1)	 **52l**, 16 (20) *trans* / *cis* (1 / 1)
5	 **49m**	180 °C; 72 h	 **50m**, 65 *trans* / *cis* (3 / 1)	 **52m**,33 *trans* / *cis* (3 / 1)
6	 **49n**	200 °C; 72 h	 **50n**, 48	
7	 **49o**	200 °C; 72 h (210 °C, μw, 3 h)	 **50o**, 53 (55)	 **52o**, (14)
8	 **49p**	200 °C; 72 h	 **50p**, 43%	

substrates **49n**,**p** were obtained in modest yields upon heating at 200 °C (entries 6 and 8). Microwave heating was proved to be effective and reduced the reaction time (entries 4 and 7). Further to expand the

scope of the carboamination reactions, several α-substituted γ-alkenyl sulfonamides **49q–v** were examined for the preparation of 2,5-disubstituted pyrrolidines (Table 8).

Table 8. Diasteroselective Formation of 2,5-*cis*-Pyrrolidines



49 *cis*-**50** *cis*-**52**

Entry	Substrate **49**	Temp; Time	Yield (%)	
			50	**52**
1	**49q**, R^1 = *i*-Pr, R^2 = Me	190 °C; 72 h	49	25
2	**49q**	210 °C (μw); 3 h	51	28
3	**49q**	200 °C ; 3 h	40	19
4	**49r**, R^1 = *i*-Pr, R^2 = OMe	190 °C; 72 h	49	23
5	**49r**	210 °C (μw); 3 h	51	23
6	**49s**, R^1 = *t*-Bu, R^2 = Me	170 °C; 72 h	34	15
7	**49s**	210 °C (μw); 3 h	31	17
8	**49t**, R^1 = Me, R^2 = Me	200 °C; 72 h	48	15
9	**49t**	210 °C (μw); 3 h	48	15
10	**49u**, R^1 = *i*-PrCH_2, R^2 = Me	200 °C; 72 h	49	20
11	**49u**	210 °C (μw); 3 h	49	19
12	**49v**, R^1 = Bn, R^2 = Me	200 °C; 72 h	50	22
13	**49v**	210 °C (μw); 3 h	47	21

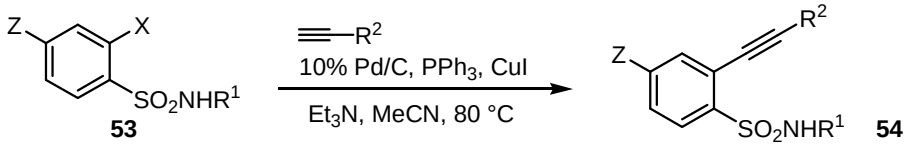
In copper (II)-promoted oxidative cyclization of enantiomerically enriched sulfonamides **49q–v**, *cis*-2,5-disubstituted pyrrolidines **50** were formed with very high diastereoselectivity (>20:1) and in 31–51% yields, using either oil bath heating (sealed tube, 170–210 °C, 72 h) or microwave irradiation (210 °C, 3 h). The net hydroamination adducts **52** were formed in these reactions as well (15–28%) with high 2,5-*cis* selectivity in all cases examined. The products emerged as a ca. 2:1 mixture of carboamination and hydroamination adducts **50** and **52**, respectively.

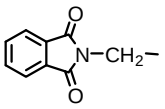
3.4. Pd/C-mediated C–C Coupling Followed by Iodocyclization

A two-step synthesis of iodo benzothiazines, that involved (i) Pd/C-mediated coupling of *o*-halo-benzenesulfonamides with terminal alkynes and (ii) iodocyclization, was developed.[31] In optimizing reaction conditions for the Sonogashira coupling of *o*-halo-benzenesulfonamides with terminal alkynes, it was observed that the use of 10% Pd/C-PPh_3-CuI as a catalyst system in the presence of Et_3N

in acetonitrile produced the best result. Under the optimum conditions, 2-alkynyl-*N*-benzenesulfonamides **54** were prepared (Table 9).

Table 9. Pd/C-mediated Synthesis of 2-Alkynyl-*N*-Benzenesulfonamides



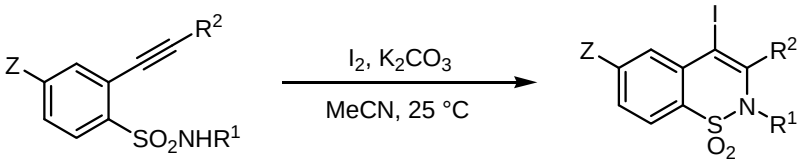
Entry	Substrate				R^2	Time (h)	Product	
	53	Z	R^1	X			**54**	Yield (%)
1	**53a**	H	Et	Br	$HOCH_2CH_2CH_2$-	18	**54a**	85
2	**53a**				*n*-pentyl	8	**54b**	89
3	**53a**				*n*-hexyl	10	**54c**	87
4	**53b**	OMe	Me	I	$HOCH_2CH_2$-	18	**54d**	97
5	**53b**				$HOCH_2CH_2CH_2$-	18	**54e**	94
6	**53b**				phenyl	8	**54f**	90
7	**53c**	Me	Me	I	*n*-pentyl	12	**54g**	87
8	**53c**				*n*-hexyl	7	**54h**	87
9	**53c**				$ClCH_2CH_2CH_2$-	12	**54i**	87
10	**53c**				$NCCH_2CH_2CH_2$-	24	**54j**	94
11	**53c**				4-methylphenyl	8	**54k**	90
12	**53d**	Et	Me	I	*n*-butyl	8	**54l**	90
13	**53d**				phenyl	12	**54m**	94
14	**53d**				4-methylphenyl	10	**54n**	89
15	**53d**					24	**54o**	98

Generally, *o*-halo-benzenesulfonamides exhibited high reactivity towards Pd/C-mediated Sonogashira coupling when all the reactions were carried out using a 1:4:2 ratio of Pd/C-PPh_3-CuI at 80 °C for 8–24 h. Both bromo (**53a**) and iodo (**53b**–**d**) derivatives reacted well with terminal alkynes bearing various substituents such as alkyl, hydroalkyl, chloroalkyl, cyanoalkyl, aryl, and heterocyclic groups. Target compounds were obtained in good to excellent yields (85–97%) in all the cases, irrespective of the nature of the substituents present in the halides as well as alkynes. This allowed the preparation of a variety of functionalized *o*-(1-alkynyl)benzenesulfonamides **54a**–**o**.

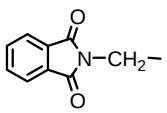
o-(1-Alkynyl)benzenesulfonamides **54a**–**o** underwent smooth iodocyclization under the conditions with 2.5 equiv of iodine and 3 equiv of K_2CO_3 in acetonitrile at room temperature to afford 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides **55a**–**o** in good yields (62–87%, Table 10). Substituents such as methyl, ethyl, and methoxy groups on the benzene ring, and alkyl, chloroalkyl, cyanoalkyl, heterocyclyl alkyl, and aryl groups at the acetylenic end were well tolerated. In general, simple alkyl and

aryl substituents on the triple bond of compounds **54** cyclized more rapidly (e.g. 6–12 h) than others (12–24 h), where various groups such as hydroxyl, chloro or cyano were present at the terminal position of the alkyl side chain (R^2). The present iodocyclization of **54** showed very high selectivity for six-membered ring formed as a result of '6-*endo-dig*' ring closure. No isomeric five-membered ring products were detected under the conditions employed, nor the product involving the simple addition of iodine to the triple bond of **54**.

Table 10. Synthesis of 2*H*-1,2-Benzothiazine 1,1-Dioxides via Iodocyclization

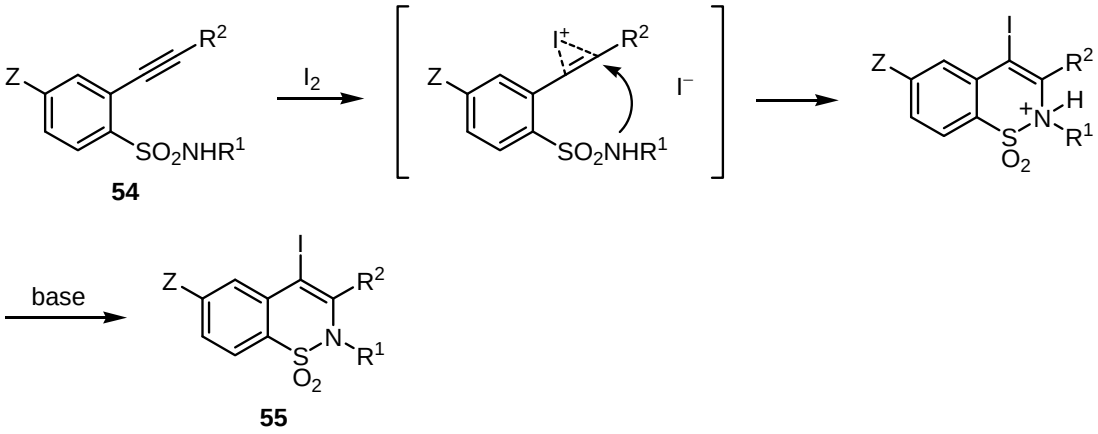


54 **55**

Entry	Substrate				Time (h)	Product	
	54	Z	R^1	R^2		**55**	Yield (%)
1	**54a**	H	Et	$HOCH_2CH_2CH_2$-	16	**55a**	76
2	**54b**			*n*-pentyl	8	**55b**	70
3	**54c**			*n*-hexyl	10	**55c**	62
4	**54d**	OMe	Me	$HOCH_2CH_2$-	12	**55d**	80
5	**54e**			$HOCH_2CH_2CH_2$-	18	**55e**	74
6	**54f**			phenyl	8	**55f**	82
7	**54g**	Me	Me	*n*-pentyl	12	**55g**	74
8	**54h**			*n*-hexyl	6	**55h**	70
9	**54i**			$ClCH_2CH_2CH_2$-	16	**55i**	69
10	**54j**			$NCCH_2CH_2CH_2$-	12	**55j**	80
11	**54k**			4-methylphenyl	8	**55k**	87
12	**54l**	Et	Me	*n*-butyl	8	**55l**	67
13	**54m**			phenyl	8	**55m**	87
14	**54n**			4-methylphenyl	8	**55n**	87
15	**54o**				24	**55o**	85

A plausible mechanism for the formation of 4-iodo-2*H*-benzo[*e*][1,2]thiazine 1,1-dioxides **55** via iodocyclization is shown in Scheme 21.

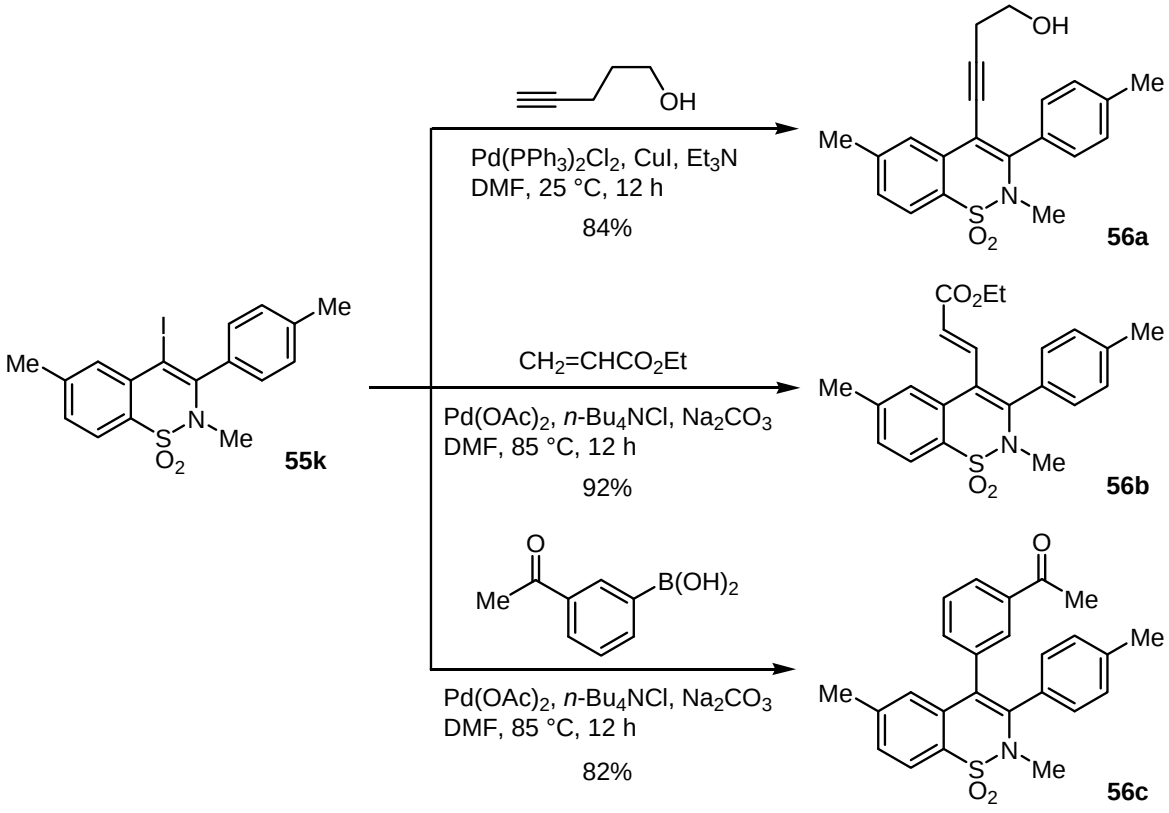
The reaction proceeds via (i) activation of the triple bond of **54** by coordination to I^+ followed by (ii) intramolecular nucleophilic attack by nitrogen of the sulfonamide group in an '*endo-dig*' fashion. Thus, the iodocyclization seems to be facilitated by several factors. (1) The alkyl group enhances the nucleophilicity of the nitrogen of the sulfonamide moiety. (2) The electron withdrawing effect of the sulfonamide moiety makes the vinylic cation susceptible for nucleophilic attack leading to the formation



Scheme 21. Plausible Mechanism of Iodocyclization of **54**

of six-membered ring. (3) The presence of a base facilitates the efficient N–H bond cleavage as cyclization proceeds.

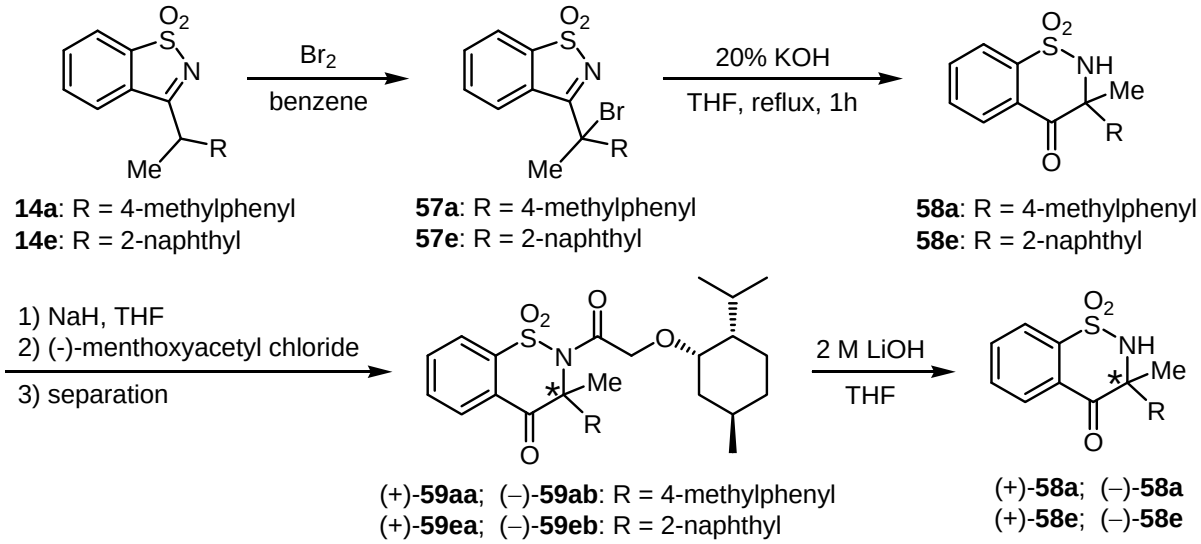
The presence of the iodo group at the C-4 position of the benzothiazine ring allows further structural elaboration through conversion of the iodide functionality into other substituents. Compound **55k** was exposed to Sonogashira, Heck, and Suzuki coupling conditions in the presence of a terminal alkyne, olefin or aryl boronic acid individually, the corresponding products **56a**, **56b**, and **56c** formed via C–C bond forming reactions were isolated in 82–92% yields (Scheme 22).



Scheme 22. Structural Elaboration of the Benzothiazine Ring via Sonogashira, Heck, and Suzuki Reactions

3.5. Abramovitch's Ring Expansion of 3-Bromoalkyl-1,2-benzisothiazole 1,1-Dioxides

Abramovitch's ring-expansion procedure is an efficient way for the preparation of 3,3-disubstituted 2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones.[32] Cyclic *N*-sulfonylimines **14a**,**e** were brominated in benzene to give bromides **57a**,**e** quantitatively, which underwent Abramovitch's ring expansion mediated by 20% KOH (aq.) to form benzosultams **58a**,**e** in excellent yields. Optical resolution of the racemic benzosultams **58a**,**e** was performed by derivatization with (–)-menthoxyacetyl choride followed by the separation of the diastereomers (+)-**59aa** (more polar, 40%) and (–)-**59ab** (less polar, 46%), and (+)-**59ea** (more polar, 39%) and (–)-**59eb** (less polar, 35%) respectively, using column chromatography on silica gel. Removal of the chiral auxiliaries of **59** was achieved with LiOH in aqueous THF to furnish the corresponding enantiomerically pure (+)- and (–)-**58a** and (+)- and (–)-**58e**, respectively (Scheme 23).[12,33] These optically pure benzosultams are useful as chiral auxiliaries for asymmetric synthesis and templates for novel chiral *N*–F agents.



Scheme 23. Preparation of Chiral 3,3-Disubstituted 2*H*-Benzo[*e*][1,2]thiazine 1,1,4-Triones

4. CONCLUSION

In conclusion, much progress has been made in the construction of saccharin related five- and six-membered benzosultams in recent years, especially via the sulfonamide directed *ortho*-metalation (D*o*M)/coupling strategy and cyclization mediated by TMSCl-NaI-MeCN or other reagents, metal-catalyzed intramolecular C–H amination, aziridination, olefin carboaminations, and Pd/C-mediated coupling/iodocyclizations. Further researches will be directed to the development of the asymmetric versions of these novel reactions for the preparation of optically active benzosultams. Considering the diverse biological profiles of sulfonamide containing compounds, functionalized benzosultams are expected to find many application in life science related areas.

ACKNOWLEDGEMENTS

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