CHEMICAL REVIEWS

REVIEW

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Recent Developments in the Synthesis of Fused Sultams

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1. INTRODUCTION

The sulfonamide is an important functional group. The sulfonamides have been extensively used as pharmaceutical and agricultural agents because of their diverse biological properties. The ability to serve as amide surrogates, with unique physical properties, have made them ideal functional groups for the development of novel peptidomimetics.[1−3] Recently, enormous interest has also been directed to its cyclic counterpart, the sultams, because of their biological activities and diverse medicinal uses.[4,5] They have shown promising bioactivities, such as antiviral, anticancer, antimicrobial, antimalarial, antileukemic, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulatory properties with potential for treating disorders of the brain, novel serine inhibitors, zinc enzyme carbonic anhydrase inhibitors, etc.[6−12] In particular, a number of fused sultams have recently been reported to exhibit broad inhibitory properties against a variety of enzymes including COX-2,[5] HIV integrase,[13] lipoxygenase,[14] Calpain I,[15] and MMP-2.[16] Besides their significance in the treatment of diseases, fused sultams have found many important applications in organic synthesis including use as protecting groups, chiral auxiliaries, and directed metalation groups (DMGs). For example, Oppolzer's sultam **1**[17] and benzosultam **2**[18] (Figure 1) are relevant in asymmetric synthesis as chiral auxiliaries in many stereoselective transformations.

Reflecting their diverse roles, many powerful methodologies have been developed for the synthesis of sultams, e.g., Pictet-Spengler reactions,[9] Friedel−Craft reactions,[19,20] sulfonamide dianion alkylation,[21] cyclization of aminosulfonyl chlorides,[22] [3 + 2]-cycloadditions,[23] Diels−Alder reactions,[24] and a number of transition-metal catalyzed cyclizations.[25−31] Some review articles highlighting their biological activities, synthesis, and important uses have also appeared.[6,32−34] This review compiles the recent developments (focusing on the publications during the period 2000−2010) of fused sultams.

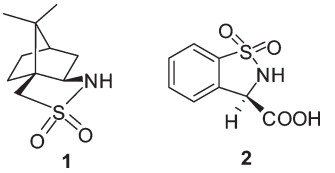

Figure 1. Examples of sultams used as chiral auxiliaries in asymmetric synthesis.

2. BICYCLIC SULTAMS

In the development of condensed sultams, much attention has recently been directed to the synthesis of bicyclic sultams. For clear presentation, the bicyclic sultams have been classified into four classes, e.g., benzosultams, pyrido-annelated sultams, chiral and enantiomerically pure sultams, and other sultams.

2.1. Benzosultams

Benzosultams are important targets for drug discovery because of their potent biological activities. For example, benzothiadiazin-3-one-1,1-dioxides and their derivatives have shown promising activities, e.g., hypoglycemic,[35] anti-HIV,[36,37] etc. The most important example of this family is 1,2-benzisothiazoline 1,1-dioxide, which is commonly known as saccharin. Its X-ray structure complexed to carbonic anhydrase II has been reported, allowing a very nice opportunity for drug design.[38] Other benzosultam representatives that have an impact because they are widely used drugs are the benzothizine diuretics, such as trichloromethiazide, chlorthalidone, indapamide, and furosemide.[39] They also significantly inhibit carbonic anhydrases (CAs) and the X-ray crystal structures of their CA adducts exhibit a different behavior as compared to classical inhibitors, e.g., acetazolamide, methazolamide,and ethoxyzolamide. The newly found binding modes of these diuretics may be exploited for designing better CA II inhibitors as well as compounds with selectivity/affinity for various isoforms with medicinal applications. Because of the important biological activities of benzisothiazoline 1,1-dioxides, much efforts have been devoted to develop novel methods for the sythesis of analogues of the saccharin derivatives.[34]

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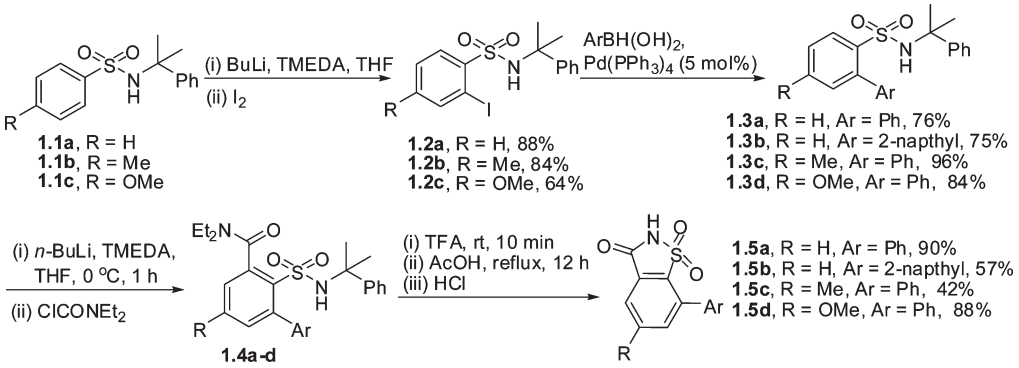
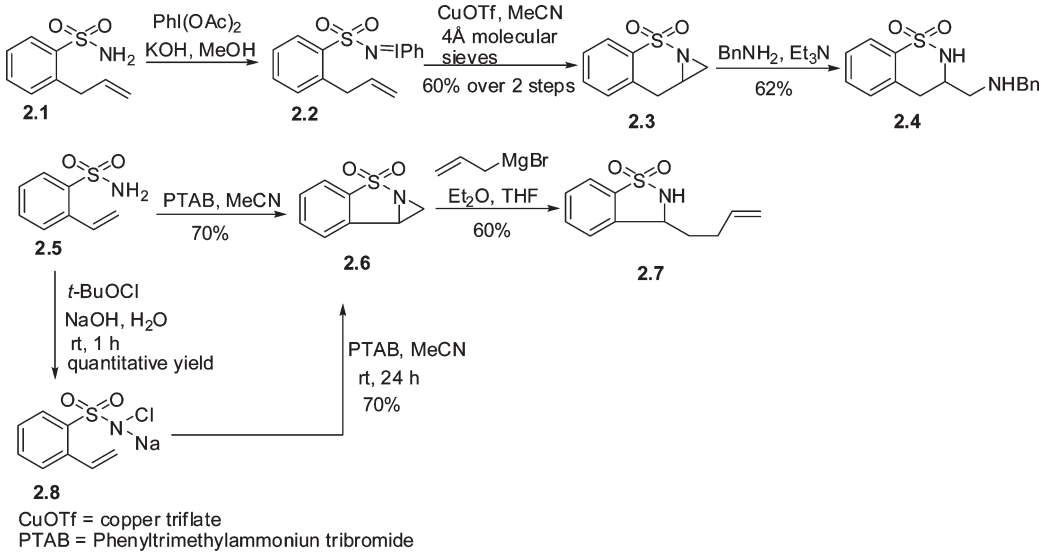
Scheme 1. Synthesis of 7-Arylated Saccharins



Scheme 2. Synthesis of Benzosultams via Aziridine Formation



Recently, Snieckus and co-workers developed[40] the synthesis of 7- and 4,7-substituted saccharins from *N*-cumyl arylsulfonamides by combining directed ortho metalation (D*o*M) and Suzuki cross-coupling reactions. Treatment of *N*-cumylsulfonamide **1.1a** with *s*-BuLi, **1.1b,c** with *n*-BuLi in anhydrous tetrahydrofuran (THF) in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at −78 °C, followed by reaction with iodine, gave the 2-iodo derivatives **1.2a**−**c** in good yields. Suzuki cross-coupling of the 2-iodo *N*-cumyl arylsulfonamides **1.2a**−**c** with aryl boronic acids led to the formation of biaryl *N*-cumylsulfonamides **1.3a**−**d**. *n*-BuLi/TMEDA ortho metalation of **1.3a**−**d**, followed by quenching with *N*,*N*-diethylcarbamoyl chloride gave the amide sulfonamides **1.4a**−**d**. The latter compounds were directly treated with mild trifluoroacetyl (TFA) decumylation followed by HOAc to give the *N*-unsubstituted 7-arylated saccharins **1.5a**−**d** in modest to excellent yields (Scheme 1). The same methodology has been utilized for the synthesis of 4,7-disubstituted saccharins.

In 2000, Dauban and Dodd described a new methodology for the preparation of benzosultams based on copper- or bromine-catalyzed aziridination.[41] Olefinic primary sulfonamide **2.1** was treated with iodobenzene diacetate and potassium hydroxide in methanol to give the intermediate iminoiodinane **2.2**, which was immediately treated with a catalytic amount of copper triflate to give the aziridine **2.3**. However, no reaction occurred with the iminoiodinane derived from vinylic compound **2.5** because of the instability of the intermediate. However, application of the bromine-catalyzed aziridination procedure[42] to **2.5** led to the formation of aziridine **2.6**. The aziridines (**2.3** and **2.6**) were opened by various nucleophiles to give the corresponding sultams (**2.4** and **2.7**) (Scheme 2).

In a subsequent report,[43] the same group extended their work with an alternative route for the formation of aziridine **2.6**. For this purpose, sulfonamide **2.5** was treated with 1 equiv of *tert*-butyl hypochlorite and 1 equiv of sodium hydroxide in water to give the corresponding *N*-chloramine salt **2.8**. It was directly treated with a catalytic amount of phenyltrimethylammonium tribromide (PTAB) in acetonitrile to afford the aziridine **2.6**. Later, Che and co-workers[44] reported another alternative for the asymmetric intramolecular aziridation of unsaturated sulfonamides catalyzed by dirhodium (II, II) complexes in good yields (up to 95%) and with significant enantioselectivity (up to 76% ee).

The synthesis of 3,3-disubstituted benzosultams **3.3** was achieved[45] by *o*-lithiation of *N*-*tert*-butylbenzenesulfonamide **3.1** and subsequent reaction with ketones followed by TMSCl−NaI mediated cyclization in refluxing acetonitrile (Scheme 3).

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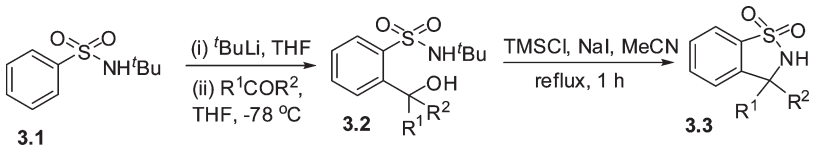
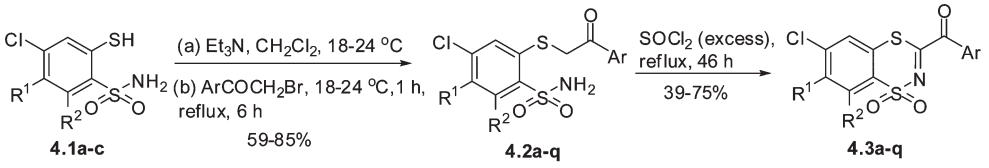
Scheme 3. Synthesis of Benzosultams Mediated by TMSCl−NaI−MeCN Reagent



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

Scheme 4. Synthesis of Benzenesulfonamides and Their Transformation into Benzodithiazines



Compd.	R^1	R^2	Ar	Compd.	R^1	R^2	Ar
4.1a, 4.2a, 4.3a	Me	H	C_6H_5	**4.1a, 4.2j, 4.3j**	Me	H	2-naphthyl
4.1a, 4.2b, 4.3b	Me	H	4-$MeOC_6H_4$	**4.1b, 4.2k, 4.3k**	H	Me	4-ClC_6H_4
4.1a, 4.2c, 4.3c	Me	H	4-BrC_6H_4	**4.1b, 4.2l, 4.3l**	H	Me	3,4-$Cl_2C_6H_3$
4.1a, 4.2d, 4.3d	Me	H	4-ClC_6H_4	**4.1b, 4.2m, 4.3m**	H	Me	2-naphthyl
4.1a, 4.2e, 4.3e	Me	H	4-FC_6H_4	**4.1c, 4.2n, 4.3n**	H	H	4-ClC_6H_4
4.1a, 4.2f, 4.3f	Me	H	4-$O_2NC_6H_4$	**4.1c, 4.2o, 4.3o**	H	H	3-$O_2NC_6H_4$
4.1a, 4.2g, 4.3g	Me	H	3-$O_2NC_6H_4$	**4.1c, 4.2p, 4.3p**	H	H	3,4-$Cl_2C_6H_3$
4.1a, 4.2h, 4.3h	Me	H	3,4-$Cl_2C_6H_3$	**4.1c, 4.2q, 4.3q**	H	H	2-naphthyl
4.1a, 4.2i, 4.3i	Me	H	4-PhC_6H_4				

Saczewski and co-workers[46] demonstrated that 1,4,2-benzodithiazines constitute a novel class of HIV-1 integrase (IN) inhibitors; they exhibit antiviral activity, albeit at high concentrations, but are essentially nontoxic. They synthesized the benzodithiazines **4.3a−q** from the derivatives **4.2a−q** by heating with thionyl chloride under reflux. The *S*-substituted derivatives **4.2a−q** were obtained from the reactions of 4-chloro-2-mercaptobenzenesulfonamides **4.1a−c** with bromomethyl ketones in dichloromethane in the presence of triethylamine (Scheme 4).

Che and co-workers reported a series of benzosultams formed by Au(PPh_3)OTf-catalyzed cycloisomerization of terminal alkenes.[47] The cyclizations of compounds **5.1**, when carried out using AgOTf, Au(PPh_3)Cl, and AuCl/AgOTf, failed to give the desired cyclic products **5.2** in good yields. However, when the same reactions were performed using a combination of 5 mol % of Au(PPh_3)Cl and AgOTf as a catalyst in toluene, the desired products were formed in nearly quantitative yields. They also employed microwave heating to complete the reaction in a much shorter time (Scheme 5).

Hanson and co-workers reported[48] a new route to benzosultams **6.2** by a domino process whereby a classical Heck reaction was coupled to an aza-Michael reaction, ultimately resulting in a one-pot protocol for a sequential three-component reaction of α-bromobenzenesulfonyl chlorides **6.1**, amines, and Michael acceptors (Scheme 6).

For example, a subset of benzosultams were prepared using this one-pot protocol (Table 1). First, α-bromobenzenesulfonyl chlorides were coupled with a range of aromatic, cyclic, and alkylamines to yield the intermediate sulfonamides. After 2 h, Et_3N, Bu_4NCl, $Pd_2(dba)_3 \cdot CHCl_3$, and the appropriate Michael

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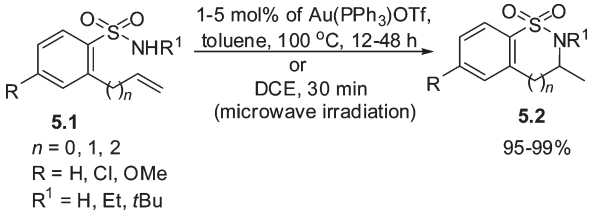
Scheme 5. Synthesis of Benzosultams by Phosphine Gold(I)-Catalyzed Intramolecular Hydroamination



Scheme 6. Synthesis of Benzosultams by Domino Heck−aza-Michael Reactions

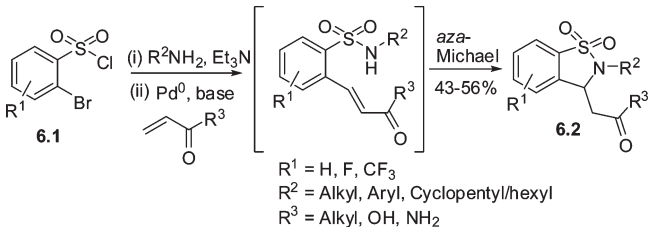
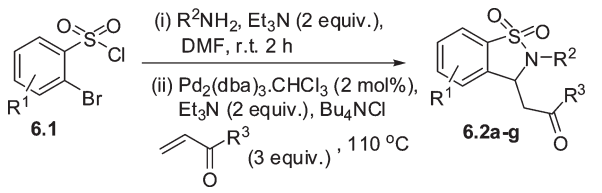


Table 1. One-Pot Domino Protocol for the Synthesis of Benzosultams

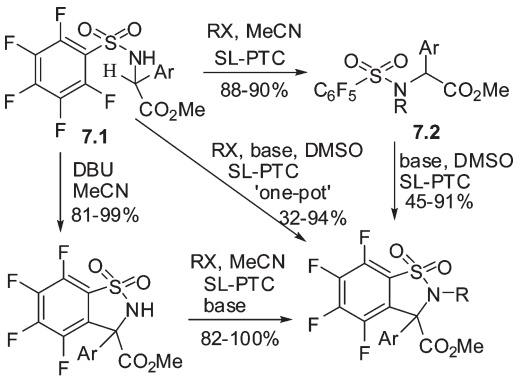


entry	R^1	R^2	R^3	product	yield (%)
1	H	*c*-C_5H_9	Me	**6.2a**	74
2	H	*c*-C_5H_{11}	OH	**6.2b**	86
3	4-F	Bn	OEt	**6.2c**	84
4	4-F	C_8H_{17}	OH	**6.2d**	90
5	H	4-ClC_6H_4	OEt	**6.2e**	81
6	4-F	*c*-C_6H_{11}	OH	**6.2f**	84
7	H	4-$MeOC_6H_4$	OMe	**6.2g**	84

acceptor were added to the reaction mixture, which was subsequently heated at 110 °C and subjected to workup after 14 h to afford the desired sultams **6.2**.

In 2008, Penso et al.[49] synthesized tetrafluoro benzosultams from pentafluorophenylsulfonamides **7.1** by two different complementary routes: *N*-alkylation of the open-chain pentafluorophenylsulfonamides **7.1** with an alkyl halide, followed by cyclization of the intermediate *N*-alkylsulfonamides **7.2** under basic solid−liquid phase-transfer catalysis (SL-PTC) conditions, afforded the corresponding *N*-alkylbenzosultams **7.3**. Alternatively, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a soluble organic base under homogeneous conditions, sulfonamides **7.1** were transformed into the unsubstituted benzosultams **7.4**, which, in turn, could be *N*-alkylated to sultams **7.3** (Scheme 7). The cyclization proceeds through an intramolecular displacement of an aromatic fluorine atom. Here the

Scheme 7. Synthesis of Benzosultams by Solid−Liquid Phase-Transfer Catalysis (SL-PTC) and Homogeneous Protocols



triethylbenzylammonium chloride (TEBA) was used as a solid−liquid phase-transfer catalyst. Both procedures give racemic products, which is the only drawback of the procedures.

Recent studies in 2009 have demonstrated the facile formation of bicyclic sultams by an intramolecular cyclodialkylation reaction.[50] The parent *N*-allylaniline **8.3a** was prepared in 78% overall yield by allylation of formanilide **8.1** followed by deformylation. Other *N*-(ω-alkenyl)anilines were prepared starting from 2-nitrobenzenesulfanilides **8.5** obtained from the sulfonyl chloride **8.4** and the appropriate aniline. Alkylation of the compounds **8.5** with allyl, homoallyl, and 4-pentenyl bromides afforded the *N*-(2-nitrophenylsulfonyl)anilines **8.6b−k**, from which the protective and at the same time the activating 2-nitrophenylsulfonyl group could be cleanly removed by treatment with thiophenol/potassium carbonate in dimethylformamide (DMF) to give the compounds **8.3b−k**. The overall yields of the three steps in this sequence ranged from 61 to 77%. The *N*-alkenylanilines **8.3a−k** reacted smoothly with methyl (chlorosulfonyl)acetate to give the corresponding sulfonamides **8.7** in good yields. Addition of bromine to the C=C double bonds in sulfonamides **8.7** occurred quantitatively to give the corresponding dibromoalkyl derivatives **8.8**. Upon treatment with potassium carbonate in DMF, the (dibromoalkyl)-sulfonamides **8.8** underwent intramolecular cyclodialkylation at their C,H-acidic positions to yield the bicyclic sultams **8.9** (n = 1 and 2). Under the established conditions, the dibromoalkyl derivative **8.8** with n = 3 gave an inseparable complex mixture (Scheme 8).

A two-step, one-pot protocol was developed by Hanson and co-workers for the synthesis of benzosultams.[51] The first step is a copper-catalyzed *N*-arylation of α-bromobenzenesulfonamides **9.1** with different amines to generate the corresponding 2-aminobenzenesulfonamides **9.2**, which then undergo cyclization to the desired sultams **9.3** upon treatment with carbonyldiimidazole (CDI). To carry out this two-step reaction in one pot, the CDI-mediated cyclization was conducted under microwave irradiation following the initial copper-catalyzed step in the same vial (**9.4** to **9.5**). This required a change of solvent to DMF, which was found

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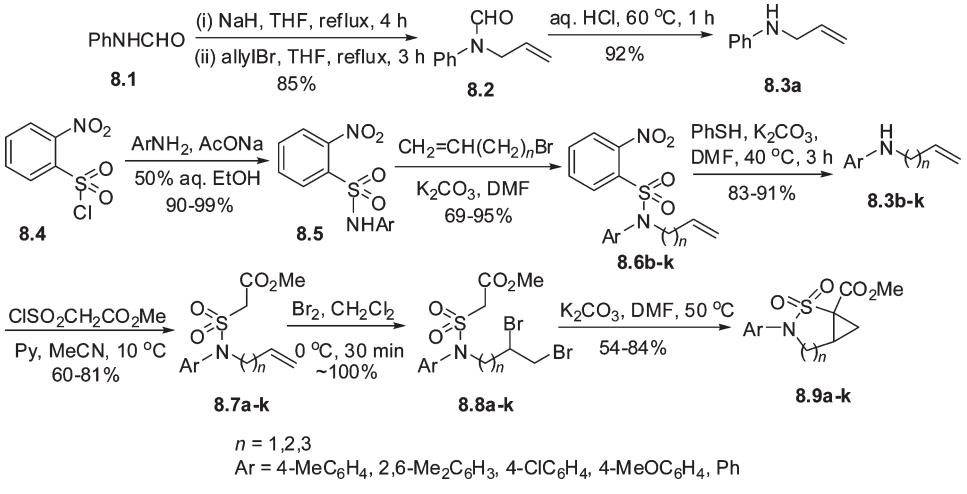
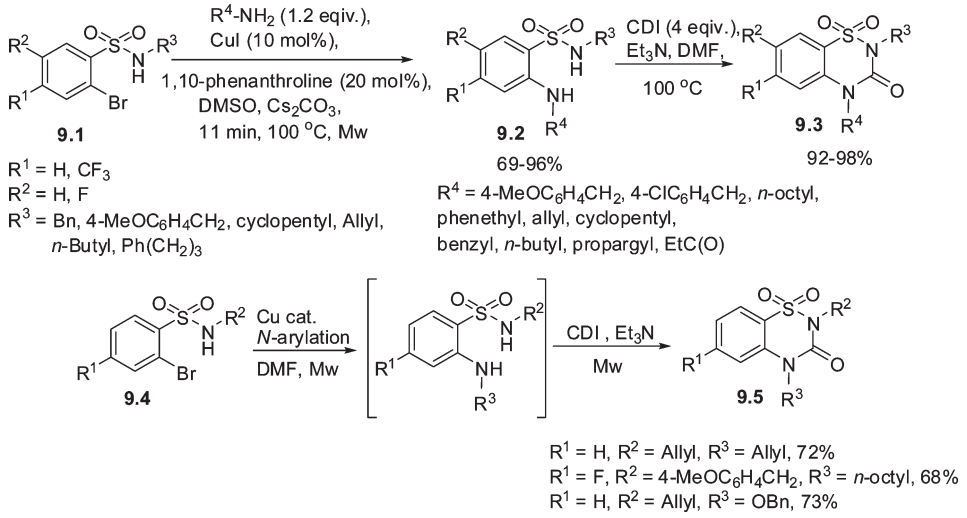
Scheme 8. Synthesis of Benzosultams by Intramolecular Cyclodialkylation



Scheme 9. Sequential One-Pot Synthesis of Benzothiadiazin-3-one-1,1-dioxides



to be the optimum compatible solvent for both the *N*-arylation and the CDI-mediated cyclization steps (Scheme 9).

Very recently, Hanson and co-workers[52] reported a reagent-based, diversity-oriented synthetic (DOS) strategy termed "Click, Click, Cyclize" en route to structurally diverse sultams **10.3**, **10.6**, **10.9**, and **10.10** from the common sulfonamide linchpins **10.2**, **10.5**, and **10.8** (Scheme 10). The yield (96%) reported in the conversion of **10.1** to **10.2** over two steps is notable in view of the fact that a recent publication by Deng and co-workers[53] reported only 70% yield after column chromatography in the first step with a 10-fold excess of $(CH_2NH_2)_2$, although the aryl sulfonyl chlorides bear different substituents on the phenyl ring.

In a recent communication, Thibaudeau and co-workers[54] described the synthesis of benzosultams **11.2** or fluorinated sulfonamides **11.3** starting from *N*-allylsulfonamides **11.1** through activation in the superacidic medium HF/SbF_5 (Scheme 11).

The reactions are very selective with respect to the acidity of the medium. When the medium is more acidic due to higher SbF_5 content, the Friedel−Crafts-type cyclization process to give sultams **11.2** is favored, and when the medium is less acidic, the hydrofluorination of the allyl group in **11.1** to give compounds **11.3** is favored (see Table 2). The reason for the selectivity is that, when the SbF_5 concentration is lower than 10 mol %, SbF_6^- is practically the only anionic species present and $H_3F_2^+$ is the predominant cationic species. However, when the SbF_5 concentration is 10−22 mol %, essentially the anions SbF_6^- and $Sb_2F_{11}^-$ are in slow equilibrium and only the cation $H_3F_2^+$ is present. Therefore, the increase in the concentration of SbF_5 strongly decreases the nucleophilicity of the fluoride ion source. Subsequently, they have also reported[55] the synthesis of 4-aminobenzosultam using the same methodology.

2.2. Pyrido-annelated Sultams

Aza-*ortho*-xylylenes (6-methylene-2,4-cyclohexadien-1-imines) are potential building blocks for the construction of condensed heterocyclic systems.[56] Aza-*ortho*-xylylenes can be easily obtained from pyridosultams.[57]

Pyridosultams were synthesized[58] from 3-amino-2-chloropyridine (**12.1**). Aminopyridine **12.1** was subjected to 2-fold

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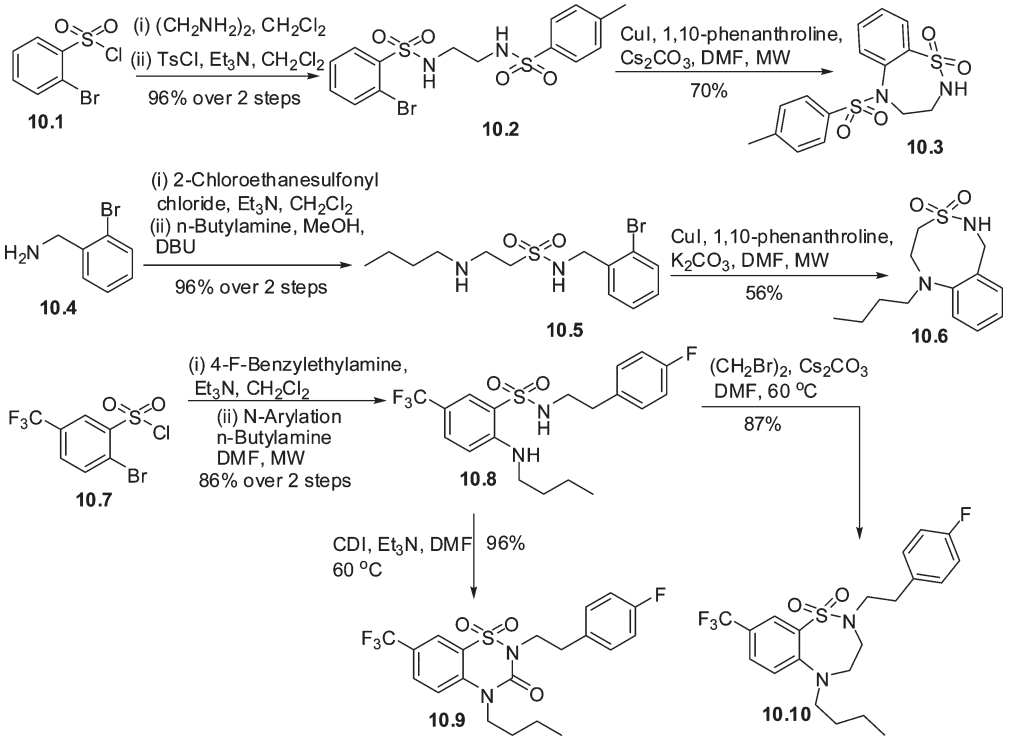
Scheme 10. Synthesis of Benzosultams by "Click, Click, Cyclize" Protocol



Scheme 11. Intramolecular Friedel–Crafts and Hydrofluorination Reactions in Superacid

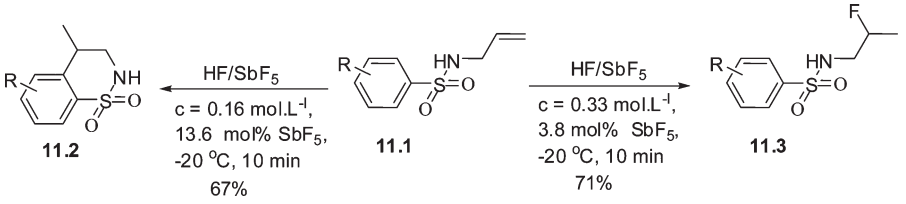
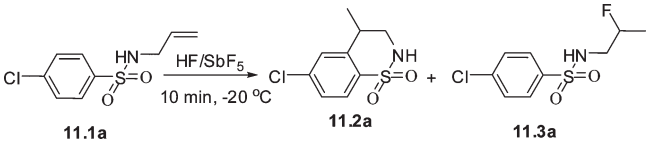


Table 2. Competition between Intramolecular Friedel–Crafts and Hydrofluorination Reactions in Superacid



entry	concentration[a] (mol·L^{-1})	acidity (mol % SbF_5)	products (yield, %)[b]	
1	0.33	8.4	**11.2a** (55)	**11.3a** (17)
2	0.33	3.8	**11.2a** (13)	**11.3a** (71)
3	0.33	27	**11.2a** (64)	**11.3a** (0)
4	0.66	13.6	**11.2a** (49)	**11.3a** (0)
5	0.16	13.6	**11.2a** (67)	**11.3a** (0)

[a] Substrate concentration. [b] After column chromatography.

sulfonylation, and subsequently one of the sulfonyl groups was removed with aqueous sodium hydroxide to give the monosulfonylated products **12.3a,b** in high yields. The latter products were subsequently *N*-alkylated with a methyl iodide in the presence of K_2CO_3 in dimethylformamide. Cyclization of the *N*-alkylsulfonamides **12.4a,b** upon treatment with solid NaOH or *t*BuOK in dimethylsulfoxide (DMSO) gave the pyridosultams **12.5a,b** in good yields. In the synthesis of 1,3-dimethylpyridosultam **12.5b**, the cyclization required anaerobic conditions, because the anion of the formed sultam **12.5b** is oxidized in the presence of air to the pyridinylethanone derivative **12.6** (Scheme 12).

In a subsequent publication,[59] the same group reported the application of vicarious nucleophilic substitution (VNS) of hydrogen for the synthesis of pyrido- and quinolinosultams. Compounds **13.4a,b** were prepared according to the earlier procedure[58] (Scheme 13). However, attempted cyclization of **13.4a,b** by intramolecular VNS under standard conditions (powdered NaOH in DMSO or *t*-BuOK in DMF) for the synthesis of sultams failed. This is probably due to the lack of reactivity toward nucleophilic substitution of the pyridine ring. The electrophilicity of the pyridine ring was enhanced by either *N*-oxidation (by 30% hydrogen peroxide in acetic acid) or by

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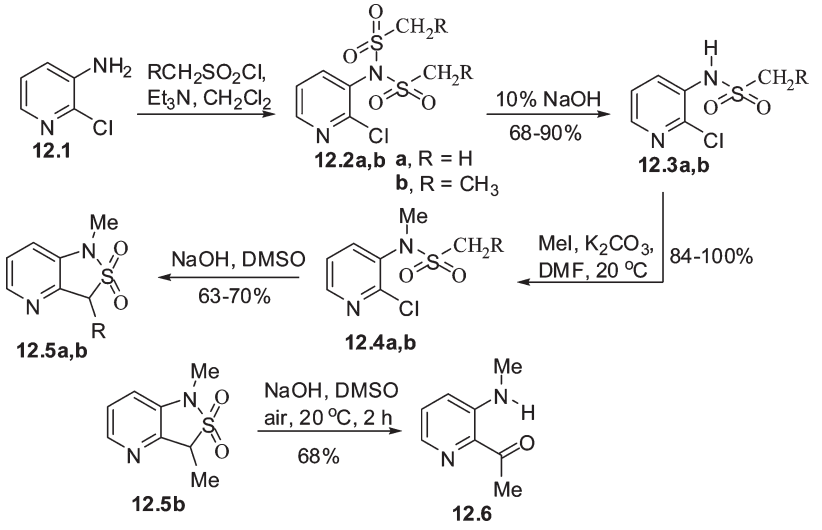
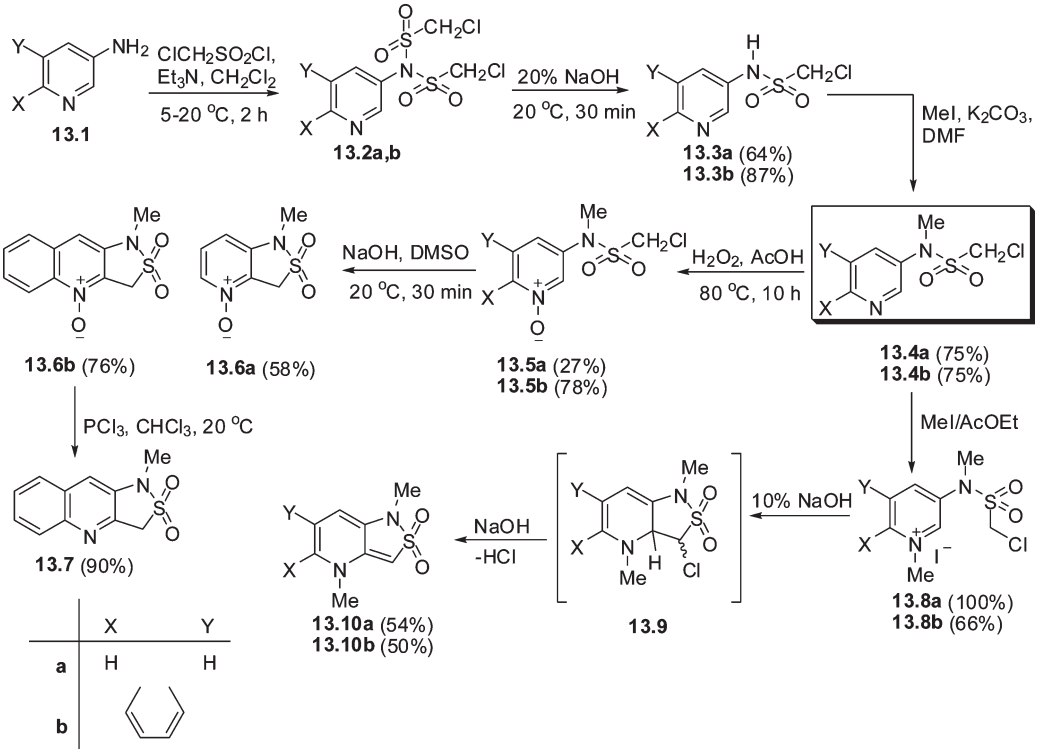
Scheme 12. Synthesis of Pyridosultams from 3-Amino-2-chloropyridine



Scheme 13. Synthesis of Pyrido- And Quinolinosultams by Vicarious Nucleophilic Substitution (VNS) of Hydrogen



quaternization of the nitrogen atom (using MeI) to give the derivatives **13.5a,b** and **13.8a,b** respectively. The *N*-oxides **13.5a, b** in the presence of NaOH in DMSO and the salts **13.8a,b** in the presence of 10% aqueous NaOH underwent fast intramolecular VNS reactions to afford the corresponding sultams **13.6a,b** and **13.10a,b**, respectively (Scheme 13).

2.3. Chiral and Enantiomerically Pure Sultams

Chiral sultams have been widely exploited as chiral auxiliaries in asymmetric synthesis. For example, the application of the Oppolzer chiral sultam for asymmetric carbon−carbon bond formation has been well documented.[60,61] The chiral bicyclic sultams can be subdivided into two parts: (i) simply chiral (which can be racemic) and (ii) enantiopure sultams.

2.3.1. Simple Chiral Sultams. In 2000, Tozer and co-workers synthesized chiral bicyclic sultams by the implementation of intramolecular Diels−Alder reactions of suitable triene derivatives.[62] The intramolecular Diels−Alder reactions of compounds **14.1** and **14.2** were carried out at 145 °C in toluene, in a sealed screw-cap vessel under argon. Under these conditions,

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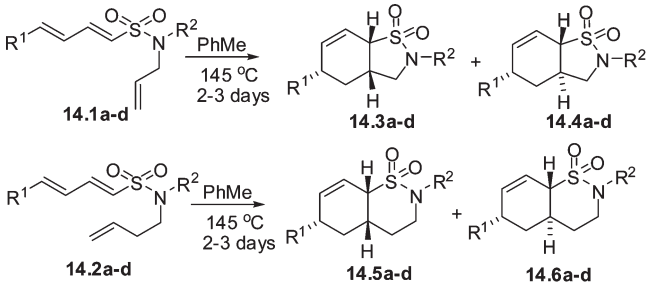
Scheme 14. Synthesis of Chiral Sultams by Intramolecular Diels–Alder Reactions



triene	R^1	R^2	product (ratio)	yield (%)
14.1a	H	4-Cl-$C_6H_4CH_2$	**14.3a, 14.4a** (6:1)	76
14.1b	Me	4-Cl-$C_6H_4CH_2$	**14.3b, 14.4b** (6:1)	71
14.1c	Ph	4-Cl-$C_6H_4CH_2$	**14.3c, 14.4c** (3:1)	92
14.1d	Ph	*n*-Bu	**14.3d, 14.4d** (3:1)	87
14.2a	H	4-Cl-$C_6H_4CH_2$	**14.5a, 14.6a** (5:1)	66
14.2b	Me	4-Cl-$C_6H_4CH_2$	**14.5b, 14.6b** (6:1)	74
14.2c	Ph	4-Cl-$C_6H_4CH_2$	**14.5c, 14.6c** (4:1)	92
14.2d	Ph	*n*-Bu	**14.5d, 14.6d** (4:1)	80

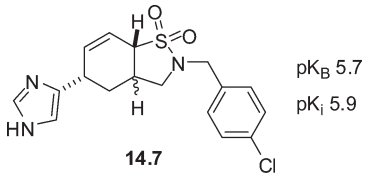


Figure 2. Histamine H_3 antagonist.

racemic mixtures of the diastereomeric [4.3.0]-bicyclic products **14.3** and **14.4** and the [4.4.0]-bicyclic products **14.5** and **14.6** were obtained in good yields (Scheme 14). Notably the sultams **14.3** and **14.4** are closely similar to the compound **14.7** (Figure 2), which is a histamine H_3 antagonist.

Chan and co-workers[63] also reported the synthesis of a number of bicyclic chiral sultams for use as chiral auxiliaries in asymmetric Diels–Alder reactions based on 1,3-dipolar cycloadditions of nitrile oxides and nitrones with prop-1-ene-1,3-sultone. Nucleophilic ring-opening of the racemic sultone adducts **15.3a,b** obtained from 1,3-dipolar cycloaddition of **15.1** and nitrile oxides **15.2a,b** with (*S*)-(−)-α-methylbenzylamine in refluxing THF afforded a mixture of diastereomeric internal ammonium sulfonate salts. $POCl_3$-mediated cyclization of the internal salts furnished 1:1 mixtures of the diastereomers **15.4a,b** and **15.5a,b**. Treatment of **15.4a,b** and **15.5a,b** with concentrated formic acid at 70–80 °C for 5 h followed by subsequent hydrolysis under basic conditions afforded **15.6a,b** and **15.7a,b**, respectively. Using a similar approach, homochiral diastereomeric **15.13a,b** and **15.14a,b** were obtained. For the use of these chiral sultams as chiral auxiliaries in asymmetric Diels–Alder reactions, *N*-acylation by successive treatment with *n*-butyllithium and acid chlorides were carried out to give the corresponding *N*-acryloyl sultams **15.8c,g** and *N*-crotonyl sultams **15.8a,b,d,e,f,h** (Scheme 15).

Using the "Click, Click, Cyclize" protocol, Hanson and co-workers synthesized a number of chiral sultams from vinyl sulfonamide linchpins.[64] The vinyl sulfonamide linchpin **16.3** was prepared from vinyl sulfonylation of valine methyl ester **16.1** with 2-chloro ethanesulfonyl chloride **16.2**. Subsequent alkylation with propargyl bromide followed by intramolecular Pauson Khand cyclization afforded sultam **16.5** (Scheme 16).

2.3.2. Enantiopure Sultams. In an effort to synthesize novel enantiopure chiral bicyclic sultams, Chiacchio et al. exploited the intramolecular 1,3-dipolar cycloaddition of different dipoles, in which the sulfonamide group is located at the α-position with respect to the reactive center.[23] The aminoalcohols **17.1a–d** were treated with *trans*-2-phenylethenesulfonyl chloride to give the corresponding sulfonamide alcohols **17.2a–d**, which were then converted into the α-sulfonamido aldehydes **17.3a–d** by oxidation with Dess–Martin periodinane (DMP). Subsequent treatment with different nucleophilic reagents followed by intramolecular cycloaddition gave the corresponding sultams **17.4–17.8** in enantiomerically pure form and good yields (Scheme 17).

In a subsequent report,[65] the work for the synthesis of stereoisomeric chiral bicyclic sultams (**18.6a,b** and **18.7a,b**) was extended using the same methodology (Scheme 18). The major compounds **18.6a,b** were isolated enantiomerically pure by flash chromatography. Here it is important to note that they have used the chiral bicyclic sultams as chiral auxiliaries in asymmetric conjugate additions of the Grignard reagents.

In 2002, Metz and co-workers[66] described the synthesis of enantiopure bicyclic bridged sultams by intramolecular Diels–Alder reactions of furan-containing ethenylsulfonamides. It is notable that when ethenylsulfonamide **19.4** was refluxed in toluene, the sultams **19.5** and **19.6** were formed in 80% yield with diastereomeric ratio 62:38, but when refluxed in dichloromethane under a pressure of 13 kbar at room temperature, sultams **19.5** and **19.6** were isolated in high yield but in low diastereoselectivity (**19.5**/**19.6** = 1:1). These sultams could be easily separated by flash chromatography (Scheme 19).

An application of ring-closing metathesis (RCM) in the synthesis of enantiopure bicyclic sultams was reported[67] by Hanessian et al. in 2003. The 4-*cis*-(2-propenyl)-*N*-Boc-L-proline benzyl ester **20.1** was deprotected with trifluoroacetic acid, and the product **20.2** was then sulfonated with ethenesulfonyl chloride prepared from 2-chloroethylsulfonyl chloride and triethylamine, to give **20.3** in excellent overall yield. Treatment of **20.3** with the first-generation Grubbs catalyst **A** triggered a ring-closing metathesis to give the bicyclic sulfonamide **20.4** in 22% yield. Analogously, the products from **20.1** with prop-2-ene-1-sulfonyl and but-3-ene-1-sulfonyl chloride gave the sultams **20.6** and **20.8**, respectively, in good yields. This methodology was applied for the synthesis of the sultam **20.18**, which is an analogue of the constrained proline derivative **20.19**, an inhibitor of thrombin (Scheme 20).

Metz and co-workers described the application of a Heck cyclization for the synthesis of bicyclic sultams.[68] The precursors **21.4**, **21.8**, and **21.11** were prepared in good yields by treatment of 1-bromoethenesulfonyl chloride **21.3** with the cyclopentenyl and cyclohexenylamines **21.2**, **21.7**, and **21.10**, respectively. However, the Heck cyclizations of the α-bromovinylsulfonamides (**21.4**, **21.8**, and **21.11**) under established standard conditions [5 mol % $Pd(PPh_3)_4$, 2 equiv Et_3N, MeCN, reflux, 2 h or 5 mol % $Pd(OAc)_2$, 11 mol % P(*o*-Tol)$_3$, 2 equiv Bu_4NCl, 2 equiv Na_2CO_3, MeCN, reflux, 1 h] afforded the desired sultams **21.5**, **21.9**, and **21.12** along with the undesired products arising from a double-bond migration due to readdition of the hydridopalladium bromide and occasionally also a complementary

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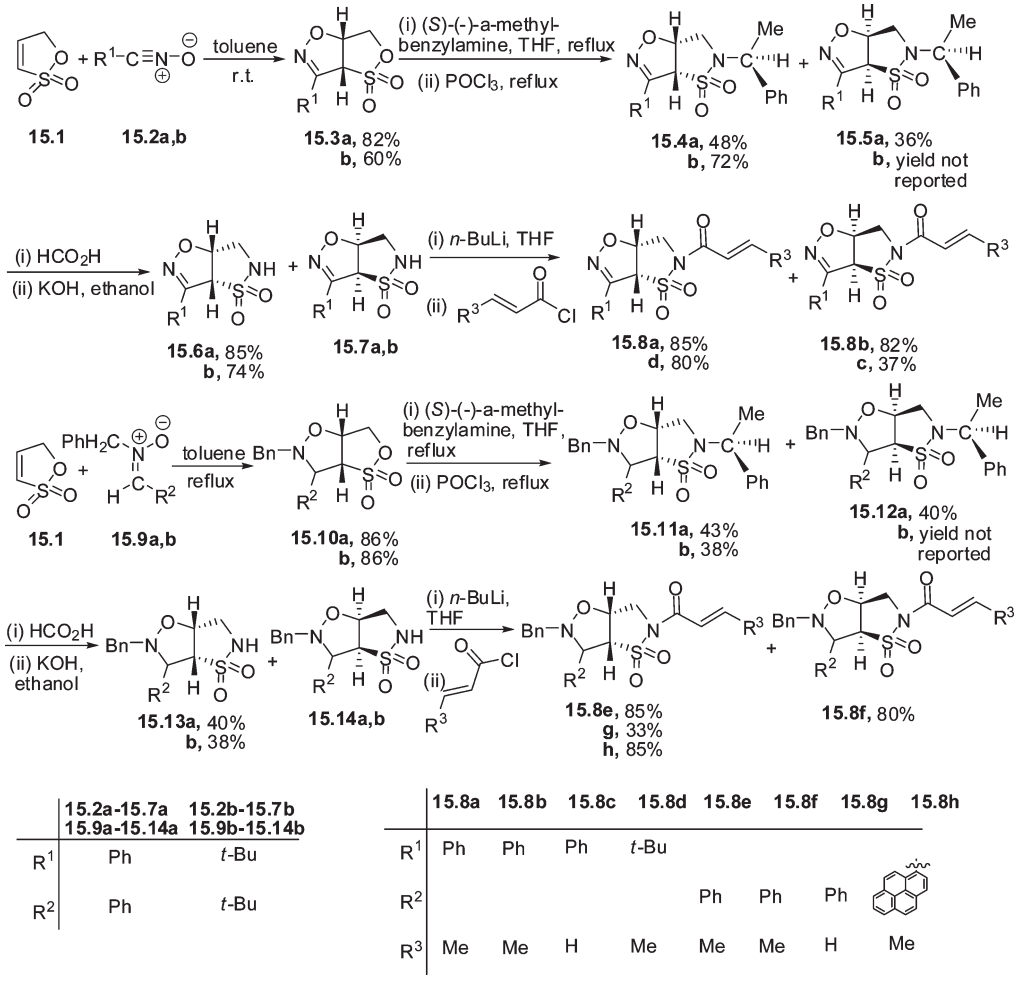
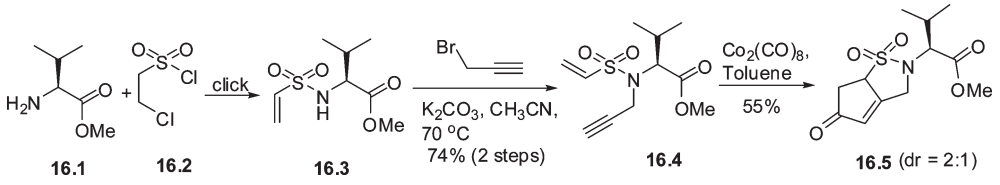
Scheme 15. Preparation of Bicyclic Chiral Sultams Based on 1,3-Dipolar Cycloadditions



Scheme 16. "Click, Click, Cyclize" Protocol for Sultams



regioselectivity of carbopalladation (6-endo cyclization instead of the desired "5-exo" cyclization). To avoid these undesired features, silver and thallium additives were used to enhance the selectivity. The optimized conditions for the Heck cyclizations of the precursors **21.4** and **21.8** for the formation of the corresponding sultams **21.5** and **21.9** were 10 mol % $Pd(OAc)_2$, 11 mol % $P(o\text{-}Tol)_3$, 2 equiv TlOAc, MeCN, reflux. However, the substrate **21.11** failed to give the corresponding sultam **21.12** under this condition (Scheme 21).

In a subsequent report,[69] Hanson and co-workers disclosed a Heck-type cyclization for the synthesis of skeletally diverse benzofused sultams from *o*-bromobenzene sulfonyl chlorides **22.1** (Scheme 22).

Recently, Hanson, Organ, and co-workers explored the synthesis of chiral benzothiaoxazepine-1,1-dioxides containing a secondary sulfonamide in enantiomerically pure form via an intramolecular S_NAr *o*-arylation route.[70] Addition of α-fluorobenzenesulfonyl chloride **23.2** to a vigorously stirring CH_2Cl_2/H_2O biphasic system of 1,2-amino alcohols **23.1** in the presence of $NaHCO_3$ furnished the β-hydroxy α-fluorobenzene sulfonamides **23.3a**−**h** in excellent yields. These products were thereafter subjected to microwave irradiation at 140 °C for 30 min in DMF in the presence of Cs_2CO_3 to yield a variety of chiral benzothiaoxazepine-1,1-dioxides **23.4a**−**h** in excellent yields (Scheme 23).

Simultaneously, Hanson and co-workers also described[71] another alternative route for the synthesis of benzothiaoxazepine-1,1′-dioxides via a formal [4 + 3]-epoxide cascade protocol. Epoxide ring-opening followed by either intramolecular S_NAr cyclization or intramolecular oxa-Michael cyclization affords these sultams (Scheme 24).

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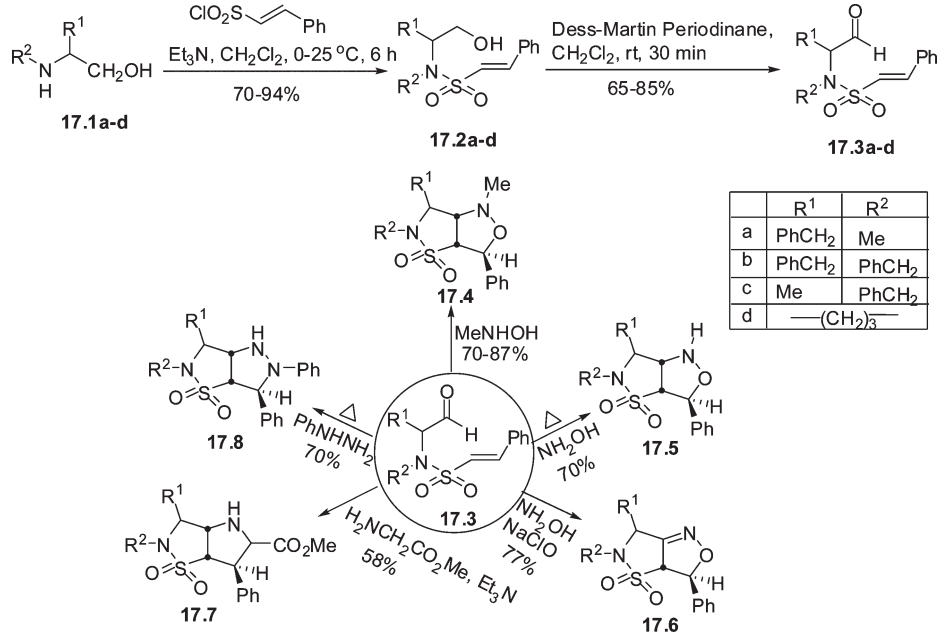
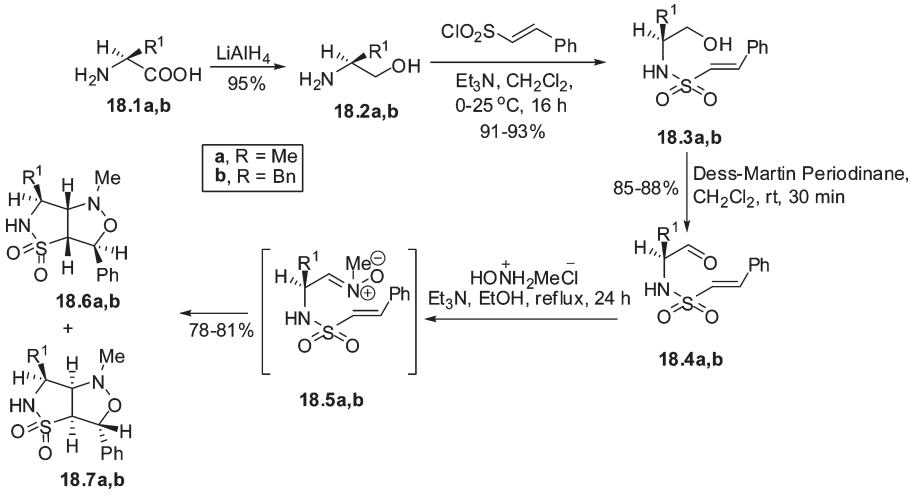
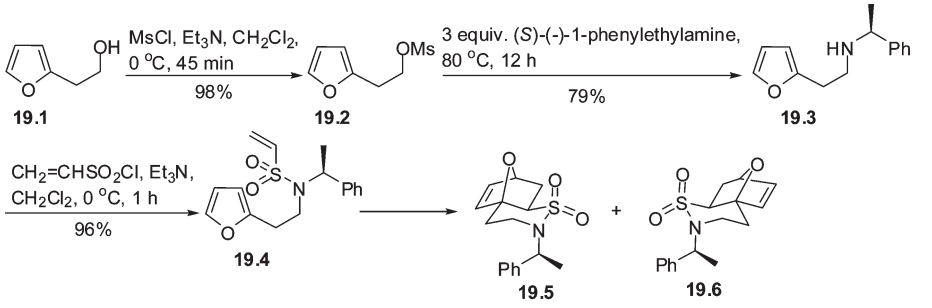
Scheme 17. Stereoselective Synthesis of Chiral Sultams by Intramolecular Cycloadditions



Scheme 18. Synthesis of Chiral Sultams by Intramolecular Cycloaddition Reactions



Scheme 19. Preparation of Enantiopure Sultams by Intramolecular Diels−Alder Reaction



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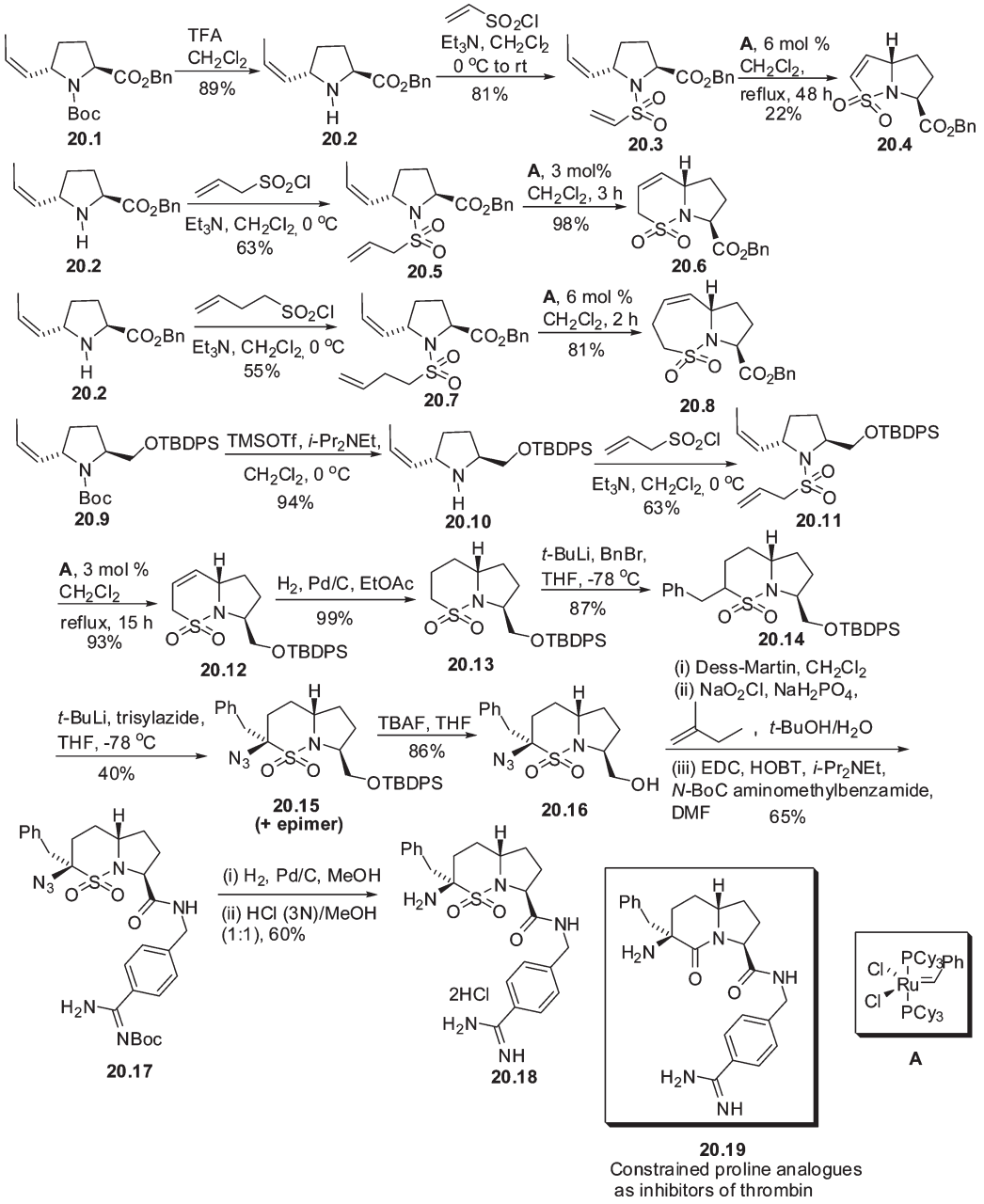
Scheme 20. Synthesis of Bicyclic Enantiopure and Functionalized Sultams by Ring-Closure Metathesis Reaction



Zhou and Hanson developed the intramolecular oxa-Michael and Baylis−Hillman approaches for the synthesis of enantiomerically pure chiral sultams.[72] The *tert*-butyldimethylsilyl (TBS)-protected prolinol-derived vinyl sulfonamide **25.2** was treated with tetrabutylammonium fluoride (TBAF), which resulted in the production of the bicyclic sultam **25.3** in excellent yields via an oxa-Michael pathway. In contrast, treatment of **25.2** with the orthogonal Baylis−Hillman conditions involving acidic deprotection, oxidation, and addition of 1,4-diaza[2.2.2]bicyclooctane (DABCO) yielded the bicyclic sultam **25.5** with good yield and excellent diastereoselectivity (Scheme 25).

Moreover, Chen et al.[73] synthesized a number of bicyclic chiral sultams like **25.6**, the sultam moiety of which is a part of the compounds **25.7**, novel potent inhibitors of hepatitis C virus (HCV) (Figure 3).

2.4. Other Sultams

The synthesis of the hydroperoxy sultams **26.8a**−**d**, chemoselective oxidants of a wide range of nitrogen-, sulfur-, and phosphorus-containing compounds, has been reported[74] by Gelalcha and Schulze. The cycloalkenones **26.1** were subjected to a Vilsmeier reaction with $POCl_3$ in DMF to give the β-chlorovinylaldehydes **26.2** in high yields. Subsequent reaction with NH_4SCN furnished the thiocyanates **26.3**. The latter product reacted with suitably substituted anilines **26.4** in the presence of stoichiometric amounts of perchloric acid in glacial acetic acid by intramolecular cyclocondensation of the intermediate imines to give the bicyclic isothiazolium salts **26.5** in a one-pot reaction at room temperature. Treatment of these salts **26.5** with an excess of 30% H_2O_2 in glacial acetic acid gave the sultams **26.8a**−**d** in high yields as crystalline products, which are ready to be used as oxidants (Scheme 26).

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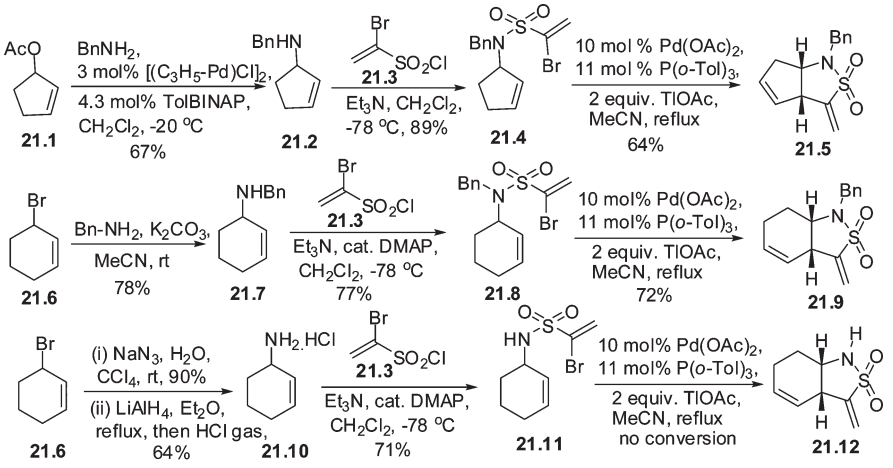
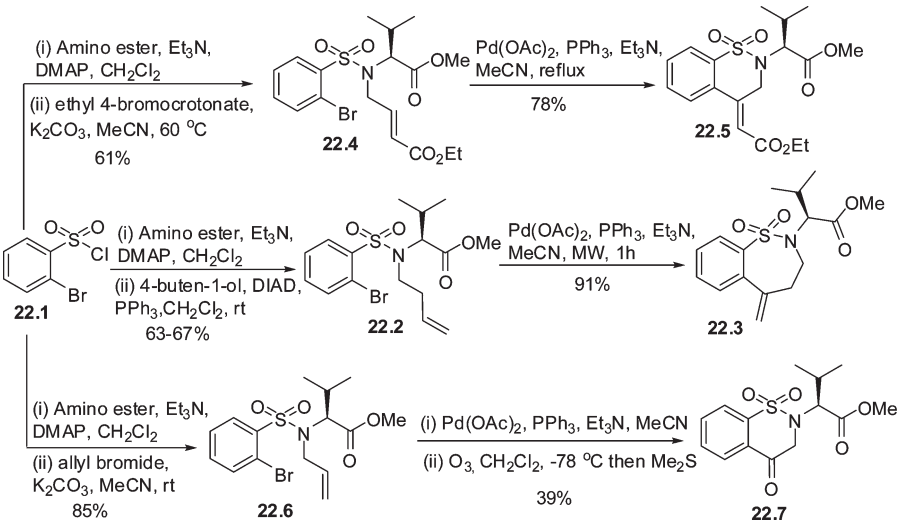
Scheme 21. Intramolecular Heck Reactions for the Synthesis of Enantiopure Sultams

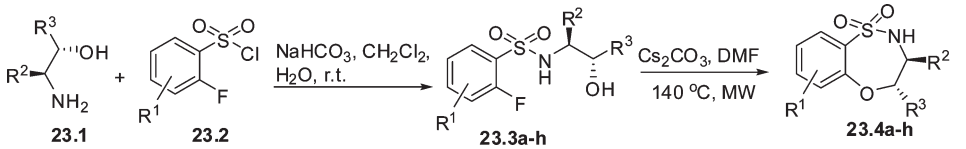


TolBINAP = 2,2'-bis(di-4-tolylphosphino)-1,1'-binaphthyl

Scheme 22. Synthesis of Benzosultams by Intramolecular Heck Reaction



Scheme 23. Click-Cyclize Protocol to Diverse Benzothiaoxazepine-1,1-dioxides



23.3a, R^1 = 4-Br, R^2 = Ph, R^3 = H, 93%
23.3b, R^1 = 4-Br, R^2 = *i*Pr, R^3 = H, 96%
23.3c, R^1 = 4-Br, R^2 = *i*Bu, R^3 = H, 97%
23.3d, R^1 = 4-Br, R^2 = Bn, R^3 = H, 89%
23.3e, R^1 = 4-Br, R^2 = Me, R^3 = Ph, 92%
23.3f, R^1 = 6-F, R^2 = *i*Bu, R^3 = H, 93%
23.3g, R^1 = 6-F, R^2 = Me, R^3 = Ph, 94%
23.3h, R^1 = 4-F, R^2 = *i*Bu, R^3 = H, 95%

23.4a, R^1 = 4-Br, R^2 = Ph, R^3 = H, 89%
23.4b, R^1 = 4-Br, R^2 = *i*Pr, R^3 = H, 87%
23.4c, R^1 = 4-Br, R^2 = *i*Bu, R^3 = H, 94%
23.4d, R^1 = 4-Br, R^2 = Bn, R^3 = H, 83%
23.4e, R^1 = 4-Br, R^2 = Me, R^3 = Ph, 95%
23.4f, R^1 = 6-F, R^2 = *i*Bu, R^3 = H, 88%
23.4g, R^1 = 6-F, R^2 = Me, R^3 = Ph, 92%
23.4h, R^1 = 4-F, R^2 = *i*Bu, R^3 = H, 93%

Recently, the hydroperoxy bicyclic sultam 2-(6-bromo-pyrid-2-yl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazol-1,1-dioxide (HPS) was prepared[75] as a reagent for the catalyzed selective epoxidation of cyclooctene. HPS **27.4** was obtained by oxidation of the isothiazolium salt **27.3** with 30% H_2O_2 in glacial acetic acid at room temperature (Scheme 22). The isothiazolium

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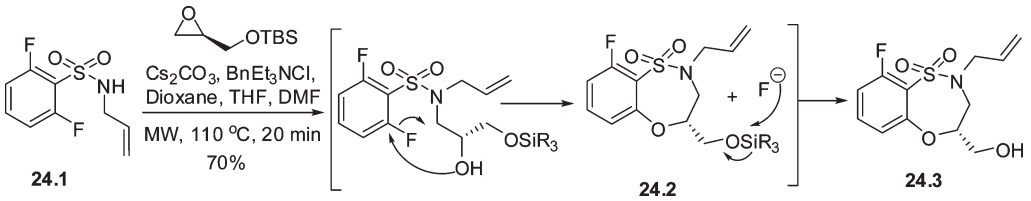
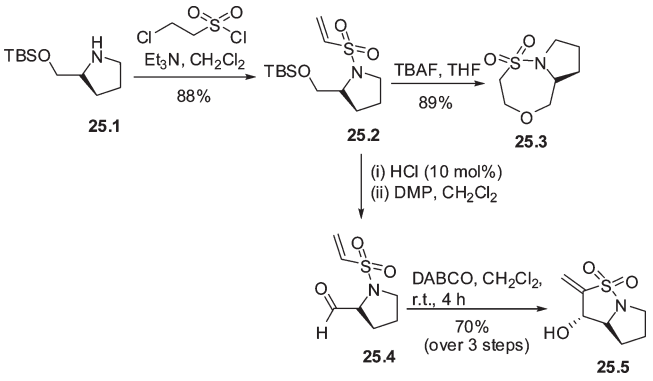
Scheme 24. One-Pot Epoxide, S_NAr Cascade Protocol to Benzothiaoxazepine-1,1′-dioxides



Scheme 25. oxa-Michael and Baylis−Hillman Approaches to Sultams



salt **27.3** was in turn prepared by the intermolecular cyclocondensation of β-thiocyanatocyclohexenyl aldehyde **27.1** and 2-amino-6-bromopyridine **27.2** in the presence of perchloric acid in glacial acetic acid (Scheme 27).

The synthesis of β-lactam-fused sultams using a ring-closing metathesis (RCM) reaction has been reported.[76] β-Lactams **28.3** were synthesized by the cycloaddition of chlorosulfonyl isocyanate (**28.2**) with 1,3-butadiene (**28.1a**) and isoprene (**28.1b**), which were then converted to *N*-sulfonyl derivatives **28.4** with alkenesulfonyl chlorides. The *N*-sulfonyl derivatives **28.4** under standard RCM conditions formed the desired bicyclic sultams **28.5** as crystalline materials (Scheme 28).

Another method for the preparation of bicyclic sultam **29.3** with a pyramidal nitrogen at the bridgehead and a sulfur atom at the apex position was reported by Paquette and co-workers.[77] This method relies on the ring-closing metathesis reaction of the precursor **29.1**, followed by an intramolecular cycloalkylation in the seven-membered sultam **29.2**. de Meijere and co-workers reported[78] the third method for the synthesis of bicyclic sultams with a pyramidal bridgehead nitrogen atom and a sulfur atom in the apex position by sequential inter/intramolecular dialkylations of sultams of the type **29.4** with a free NH group and an additional nucleophilic center with different bifunctional alkylating agents **29.5** (Scheme 29).

3. TRICYCLIC SULTAMS

Recently a number of tricyclic sultams have been prepared by ring-closing metathesis, Diels−Alder reactions, cycloisomerizations, or metal-mediated cyclizations. Wróbel synthesized tricyclic sultams[79] by a cascade cyclization of *N*-alkyl-*N*-(2-X-5-nitrophenyl)prop-2-enyl sulfonamides. The *N*-alkyl-*N*-(2-X-5-nitrophenyl)propen-3-yl sulfonamides **30.3** required for these cyclizations were obtained from commercial 2-X-5-nitroanilines **30.1** (X = H, Cl) by sulfonylation with propen-3-ylsulfonyl chloride (Py/CH_2Cl_2, −30 °C to room temperature (rt); 55−76%) to yield **30.2**, followed by alkylation with alkyl halides (K_2CO_3/DMF/cat. KI, rt; 70−90%). Sequential ring closure was accomplished under the action of a base in the presence of a catalytic amount of $MgCl_2$ in DMSO to afford the tricyclic sultams in moderate yields (Scheme 30).

A cascade ring-closure metathesis/isomerization and subsequent radical cyclization was utilized to generate tricyclic sultams from bisallylsulfonamides by Piva and co-workers.[80] Sulfonamides **31.2a,b** were obtained by condensation of 2-bromobenzenesulfonyl chloride **31.1** with allylamine and bisallylamine, respectively. *N*-substitution of the secondary sulfonamide **31.2a** with 4-bromobutene was achieved under mild conditions to give **31.2c** in high yield. RCM of **31.2b,c** in the presence of Grubbs' catalyst **I** gave the full conversion to the expected sulfonamide derivatives, which in turn were converted to the double-bond isomerized products **31.3b,c** in the presence of sodium hydride. Finally, radical cyclizations of **31.3b,c** in the presence of 2,2′-azobisisobutyronitrile (AIBN) and tris(trimethylsilyl)silane (TTMSS) afforded the tricyclic sultams **31.4b,c** in good yields (Scheme 31).

After achieving the synthesis of tricyclic sultams in three individual steps, they developed a one-pot procedure by combining the ring-closing metathesis, isomerization, and radical cyclization steps. To a solution of the sulfonamides **31.2b,c** (0.5 mmol) in toluene was added Grubbs' catalyst **I** (2.5% mol), and the mixture was stirred at rt for 1 h to complete the disappearance of the starting material. Then NaH (1.5 mmol) was added at once, and the reaction mixture was heated to reflux. A new addition of both Grubbs' catalyst **I** (2.5% mol) and NaH (1.5 mmol) was performed after 12 h of heating, and this sequence was repeated three more times. After cooling to rt, AIBN (0.05 mmol) was added. The mixture was bubbled with a stream of dry nitrogen and then heated. A solution of TTMSS (1 mmol) in toluene (10 mL) containing AIBN (0.05 mmol) was slowly added to the reaction mixture in 10 min, and then it was heated at 130 °C for 6 h to afford the tricyclic sultams **31.4b,c** in good yields.

The development of a ring-opening metathesis/ring-closing metathesis/cross-metathesis (ROM−RCM−CM) cascade strategy for the synthesis of diverse tricyclic sultams was reported by Hanson and co-workers.[81] For example, the tricyclic sultam scaffold bearing an ester functional handle **32.5** was synthesized from furfurylamine **32.1**. First, the furfurylamine was mesylated and subsequently allylated to give the sulfonamide **32.2** in 82% yield over two steps. Generation of the phosphonate, followed by Horner−Wadsworth−Emmons reaction, yielded a mixture of uncyclized sulfonamide **32.3** and the sultam **32.4**. Addition of hexane to the crude mixture led to the sole precipitation of **32.4**. Then the sultam **32.4** in the presence of ethylene in CH_2Cl_2 was

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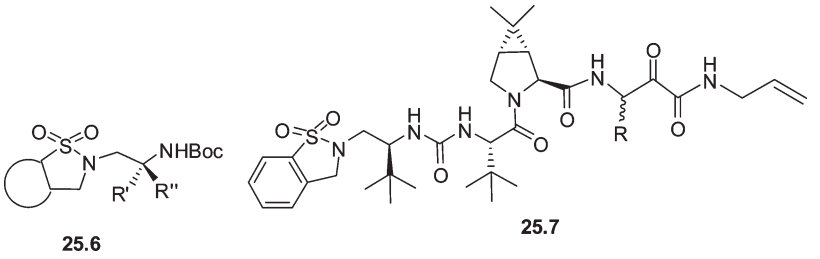
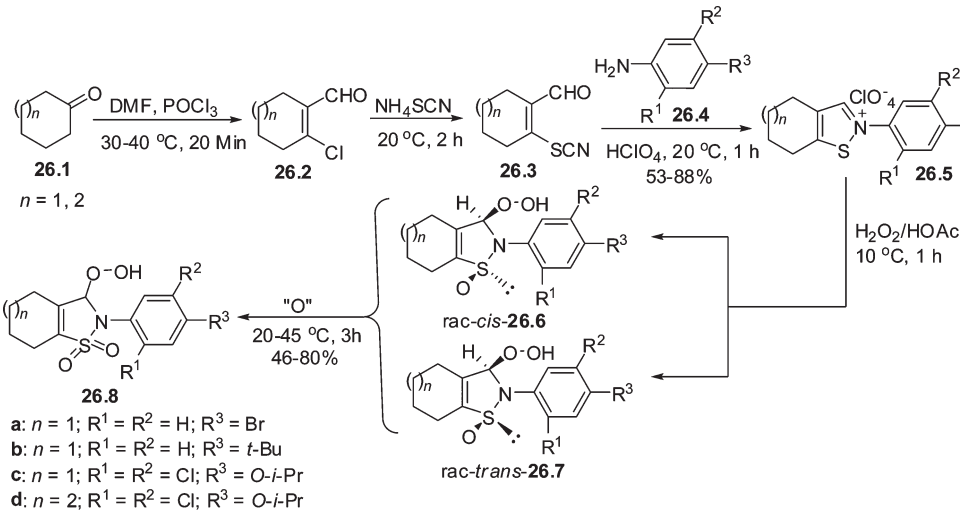
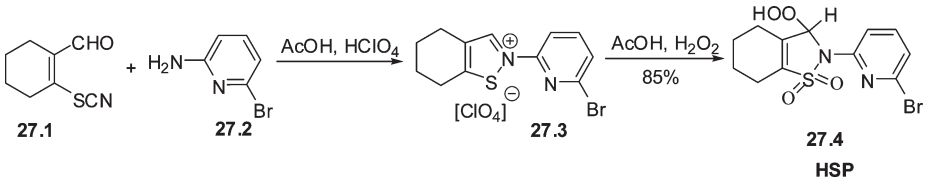


Figure 3. Potent inhibitor of hepatitis C virus.

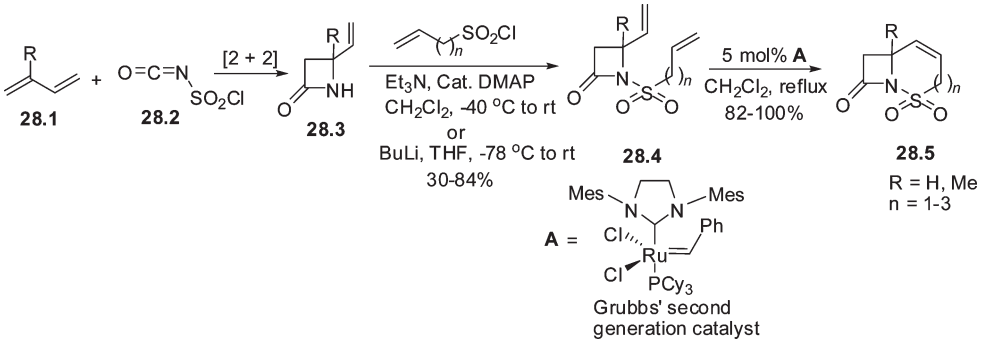
Scheme 26. Synthesis of Hydroperoxy Sultams



Scheme 27. Synthesis of Hydroperoxy Sultam by Oxidation of the Isothiazolium Salt with Hydrogen Peroxide



Scheme 28. Synthesis of β-Lactam-Fused Bicyclic Sultams Using Ring-Closing Metathesis (RCM) Reactions



subjected to the metathesis cascade transformation to yield the desired tricyclic sultam **32.5** (Scheme 32).

Hanson and co-workers disclosed the synthesis of norbornenyl sulfonamides **33.6** and **33.7** by RCM followed by Diels–Alder

dx.doi.org/10.1021/cr1003776 |*Chem. Rev.* 2011, 111, 7749–7773

reaction.[82] Sultams **33.4** and **33.5** underwent cycloaddition with cyclopentadiene under Lewis acid catalysis. These reactions proceeded with complete facial selectivity arising from an approach of the cyclopentadiene anti to the isopropyl group. The yield and endo/exo ratio obtained were strongly temperature-dependent. The endo adducts **33.6a** and **33.7a** were formed as the major diastereomers in each case. The exo isomers **33.6b** and **33.7b** were also formed, arising from the approach of the cyclopentadiene anti to the isopropyl group. It is important to note that it is impossible to separate **33.6a** and **33.6b** (R^1 = H) cleanly, but **33.7a** and **33.7b** can readily be separated by column chromatography (Scheme 33).

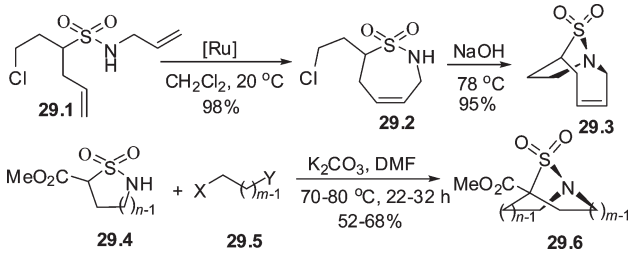
Their continued interest in the synthesis of sultams by Diels–Alder reactions[83] prompted Metz and co-workers to report[84,85] a stereoselective preparation of the tricyclic sultams **34.4** and **34.5** by thermal and high-pressure intramolecular Diels–Alder reaction of vinylsulfonamides **34.3** (Scheme 34), and Lee and co-workers synthesized tricyclic sultams by Diels–Alder reaction as well.[86]

Termin and co-workers reported[87] the stereo- and regiospecific formation of highly functionalized bridgehead-nitrogen tricyclic sultams **35.3a–c** by intramolecular nitrone-to-alkene cycloaddition reactions. The novelty of this synthesis is that three stereogenic centers are formed in a single step (Scheme 35).

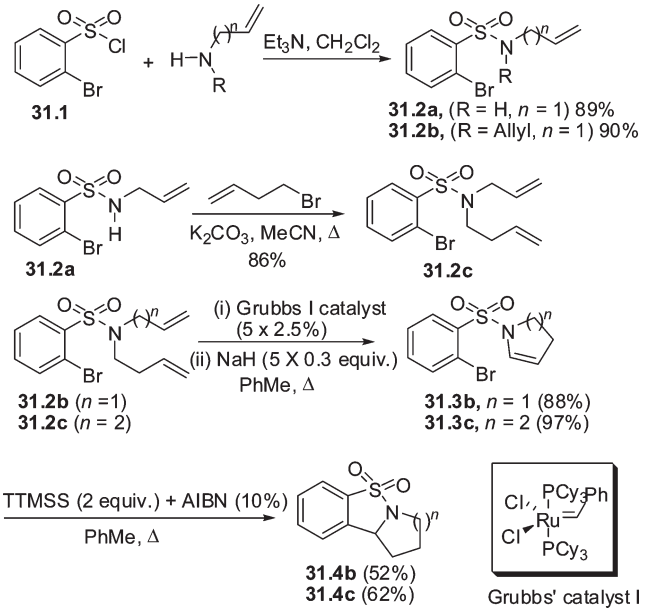
Steel and co-workers synthesized fused tricyclic sultams **36.3a–h** by ortho-lithiation of aryl sulfonamides **36.2a–h** in the presence of phosphoryl chloride.[88] The substrates **36.2a–h** were prepared in variable and unoptimized yields (33–80%) by metalation of the parent lactam **36.1** with *n*-BuLi and subsequent reaction with the appropriate sulfonyl chloride. Cyclization of both *N*-tosylpyrrolidinone **36.2b** and *N*-tosylpiperidinone **36.2c** were unsuccessful (entries 2 and 3). The 3-nitrophenylsulfonamide **36.2h** (entry 12) failed to provide any product. All the other sulfonamide analogues examined followed a similar profile, providing mainly the fused sultams accompanied by smaller quantities of the phosphonite and recovered starting materials, with the exception of the precursor to the 8-membered ring, which gave a higher proportion of the phosphonite (entry 4, Scheme 36). Attempts to enhance the yields through the use of alternative bases (BuLi, lithium bis(trimethylsilyl)amide (LHMDS)) and other additives (*N*,*N*′-dimethylpropyleneurea (DMPU) and hexamethylphosphoramide (HMPA)) as well as higher reaction temperatures provided no significant improvement.

de Meijere and co-workers developed a facile synthesis of tricyclic sultams by cycloisomerization of 4,9-diheterododecadienyne (**37.4**) followed by intramolecular [4 + 2]-cycloaddition.[89] Monoamination of 1,4-dibromobut-2-yne with **37.1** gave the monobromide **37.2** which on successive treatment with *n*-propylamine and 2-chloroethanesulfonyl chloride in the presence of triethylamine gave the sulfonamide **37.4** (78%). The palladium-catalyzed tricyclization of the dienyne **37.4** gave the thiadiazatricycles **37.5** and **37.6** in a ratio of 1:1 (Scheme 37). The poor regioselectivity is the main drawback of this reaction.

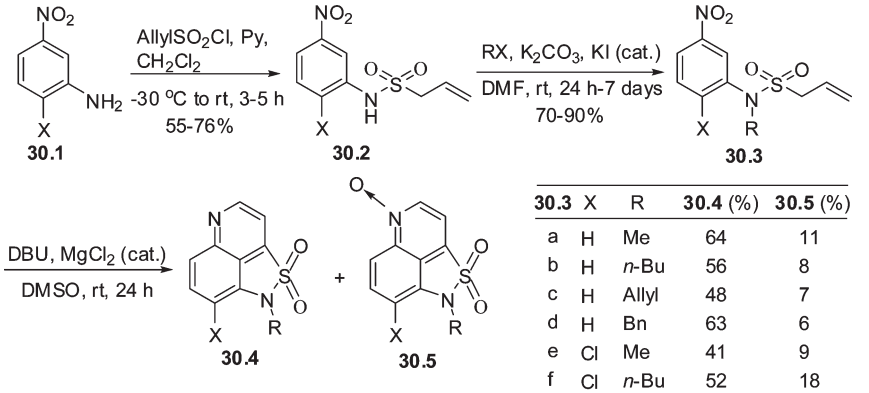
Scheme 29. Synthesis of Bicyclic Sultams with a Nitrogen at the Bridgehead and a Sulfur Atom in the Apex Position



Scheme 31. Synthesis of Tricyclic Sultams by a Cascade Ring-Closure Metathesis and Subsequent Radical Cyclization Reactions



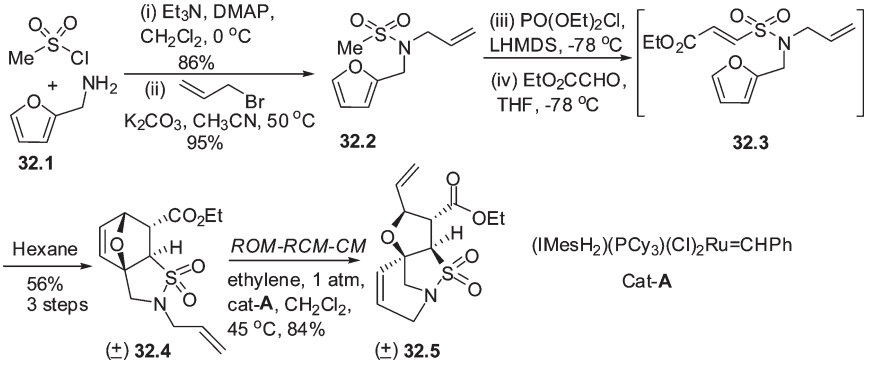
Scheme 30. Synthesis of Tricyclic Sultams by Tandem Ring-Closure Reactions



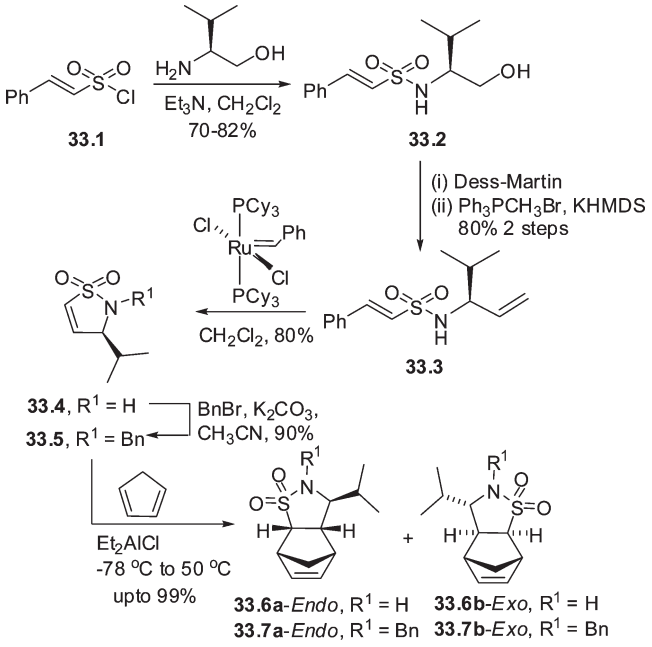
30.3	X	R	30.4 (%)	30.5 (%)
a	H	Me	64	11
b	H	*n*-Bu	56	8
c	H	Allyl	48	7
d	H	Bn	63	6
e	Cl	Me	41	9
f	Cl	*n*-Bu	52	18

dx.doi.org/10.1021/cr1003776 |*Chem. Rev.* 2011, 111, 7749–7773

Scheme 32. Metathesis Cascade Strategies (ROM−RCM−CM) for the Synthesis of Tricyclic Sultams



Scheme 33. Dual Metathesis Route for the Synthesis of Tricyclic Sultams



Demont and co-workers reported a tricyclic sultam ring system **38.5** for stable, potent, and orally bioavailable β-secretase 1 (BACE-1) inhibitors.[90] The synthesis of this ring system **38.5** used a high yielding (93%) intramolecular condensation of an α-sulfonamide ester (**38.3**) to a Vilsmeier−Haack adduct (**38.4**), which was subjected to decarboxylation and subsequent hydrogenation to give **38.5** (Scheme 38).

Lee et al. developed[21] a new synthetic route to the tricyclic sultam **39.3** employing an intramolecular sulfonamide dianion alkylation by treatment of the chlorosulfonamide **39.2** with diisopropylamine and *n*-BuLi at 50 °C followed by warming to 0 °C over 4 h (Scheme 39).

Miller et al. achieved the synthesis of the napthosultam **40.5** by two different routes.[91] In the first approach (**40.1** to **40.5**), the sultam ring was formed by direct addition of ammonia or benzylamine to the reaction mixture to form the nitrosulfonamide, which was then cyclized by heating with potassium carbonate. However, a problem of this method is that the nitrosulfonyl chloride intermediate **40.3** is shock-sensitive and highly explosive even at 42 °C.

In a revised synthetic route, cyclization of the nitrosulfonamide **40.2.2** to the required methylnaphthosultam **40.5** was carried out using a one-pot hydrogenation cyclization sequence. Reduction of **40.2.2** to the amine **40.2.3** was accomplished in quantitative yield under either standard hydrogen/catalyst or transfer hydrogenation conditions. The intermediate aminosulfonamide **40.2.3** was cyclized to the methylnaphthosultam **40.5** upon acidification with hydrochloric acid and heating under reflux for 3 h (Scheme 40).

Recently, a series of tricyclic sultams by Pd-catalyzed, ligand-free intramolecular cyclization have been synthesized in the authors' laboratory.[92] The required precursors **41.3a−d** for the synthesis of the tricyclic sultams **41.4a−d** were obtained in good to excellent yields by heating 2-halo-4-substituted benzylamines **41.2a,b** with *p*-toluenesulfonyl chloride or benzenesulfonyl chloride in pyridine at 80 °C for 4 h. The substituted benzylamines **41.2a,b** were in turn prepared in 90 and 84% yields, respectively, from the corresponding benzyl bromides **41.1a,b** by stirring with aqueous ammonia in ethanol at rt for 4 h. The intramolecular cyclization of the substrates **41.3a−d** was carried out in the presence of $Pd(PPh_3)_4$ in anhydrous DMF and tetra-*n*-butyl ammonium bromide (TBAB) as an additive with an organic base at 120 °C for 10 h under an inert atmosphere to give the tricyclic sultams **41.4a−d** in 80−85% yields (Scheme 41).

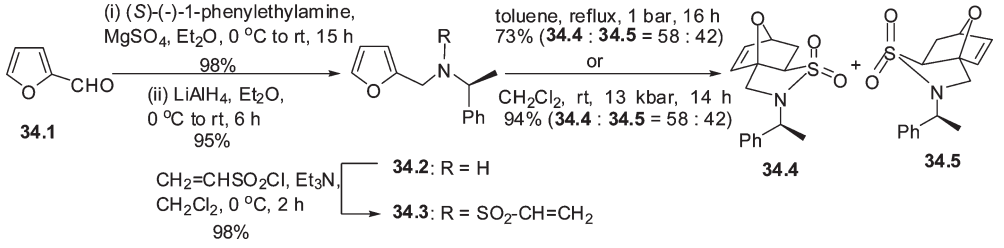
A synthesis of condensed sultams deriving from intramolecular 1,3-dipolar cycloadditions of nitrones was described by Yamamoto and co-workers.[93] The reaction of methyl L-prolinate hydrochloride [(*S*)-**42.1**] with ethenylsulfonyl chloride in the presence of triethylamine at room temperature gave methyl *N*-(ethenylsulfonyl)-L-prolinate (*S*)-**42.2** in 40% yield. A diisobutylaluminum hydride (DIBAL) reduction of (*S*)-**42.2** in toluene at −78 °C afforded *N*-ethenylsulfonyl-L-prolinal [(*S*)-**42.3**] in 32% yield. The nitrone (*S*)-**42.4** generated in situ from the reaction of (*S*)-**42.3** with phenylhydroxylamine in THF in the presence of calcium chloride at room temperature underwent an intramolecular 1,3-dipolar cycloaddition to give the tricyclic sultam (*S,R,S*)-**42.5** in 65% yield (Scheme 42).

4. TETRACYCLIC SULTAMS

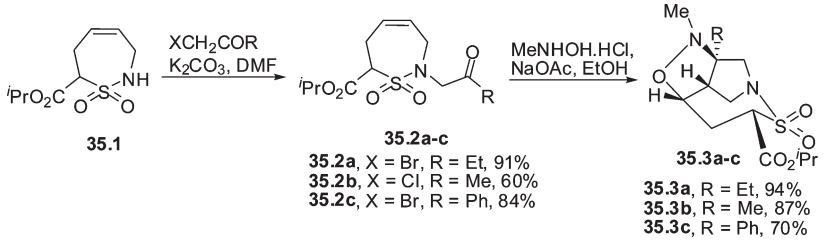
There are three reports on the synthesis of tetracyclic sultams. Recently Chemler's group has exploited a new methodology for the synthesis of tetracyclic sultams[94,95] by copper(II) acetate-promoted oxidative cyclization of arylsulfonyl-*o*-allylanilines. Compounds **43.1** on treatment with $Cu(OAc)_2$ (3 equiv) and Cs_2CO_3 in MeCN or DMF at 120 °C in a pressure tube

dx.doi.org/10.1021/cr1003776 |*Chem. Rev.* 2011, 111, 7749–7773

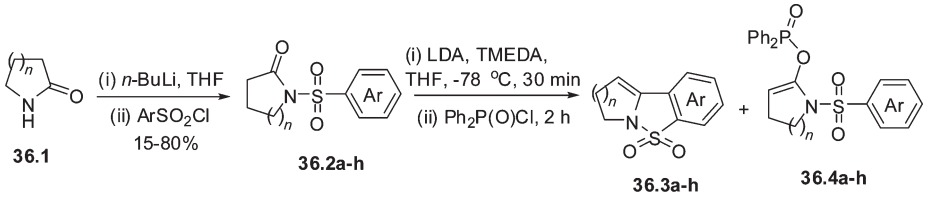
Scheme 34. Stereoselective Synthesis of Tricyclic Sultams by Thermal and High-Pressure Intramolecular Diels–Alder Reactions



Scheme 35. Synthesis of Tricyclic Sultams by Intramolecular Nitrone-to-Alkene Cycloaddition Reactions



Scheme 36. Formation of Tricyclic Sultams by Sequential Ortho-Lithiation, Cyclization and Elimination Reactions



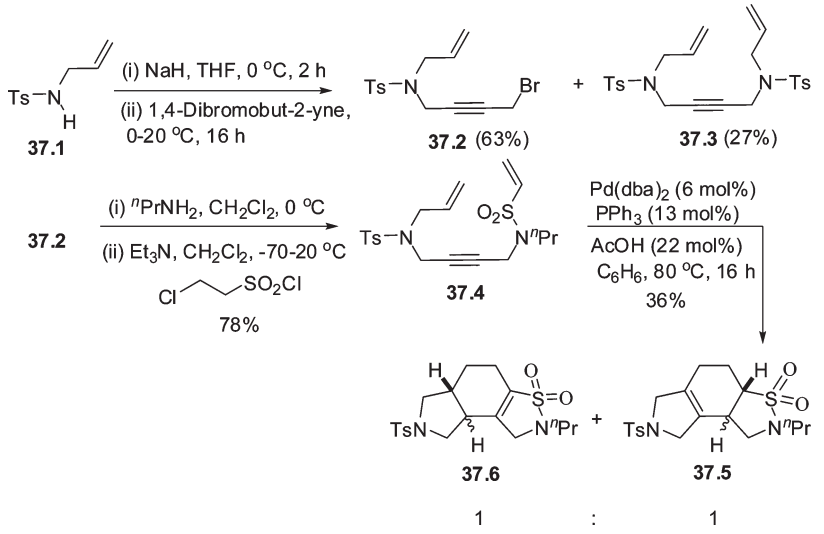
Entry	*n*	Ar		Yield **36.3** (%)	Yield **36.4** (%)	Recovered **36.2** (%)
1	3	4-Me-C_6H_4	**36.2a**	41	15	0-50
2	1	4-Me-C_6H_4	**36.2b**	0	0	43
3	2	4-Me-C_6H_4	**36.2c**	Trace	30	32
4	4	4-Me-C_6H_4	**36.2d**	18	24	0-16
5[a]	3	4-Me-C_6H_4	**36.2a**	44	14	0
6[b]	3	4-Me-C_6H_4	**36.2a**	11	0	15
7[c]	3	4-Me-C_6H_4	**36.2a**	0	0	100
8[d]	3	4-Me-C_6H_4	**36.2a**	0	73	0
9	3	1-Napthyl	**36.2e**	26	17	41
10	3	4-Br-C_6H_4	**36.2f**	46	0	0
11	3	4-MeO-C_6H_4	**36.2g**	32[e]	23	0
12	3	4-NO_2-C_6H_4	**36.2h**	0	0	50-100

underwent oxidative cyclization to give tetracyclic sultams **43.2**. The yields and selectivities vary considerably depending upon the electronic nature of the aryl substituent. In general, the reactions of electron-rich substrates proceed in good yields. meta-Substitution generally led to mixtures of regioisomeric products. Substrates with electron-withdrawing groups on the sulfonylated aromatic ring reacted more sluggishly, and DMF proved to be a better solvent than MeCN. Addition of DMSO (4 equiv) increased the yield of the reaction, sometimes with significant effect (Scheme 43).

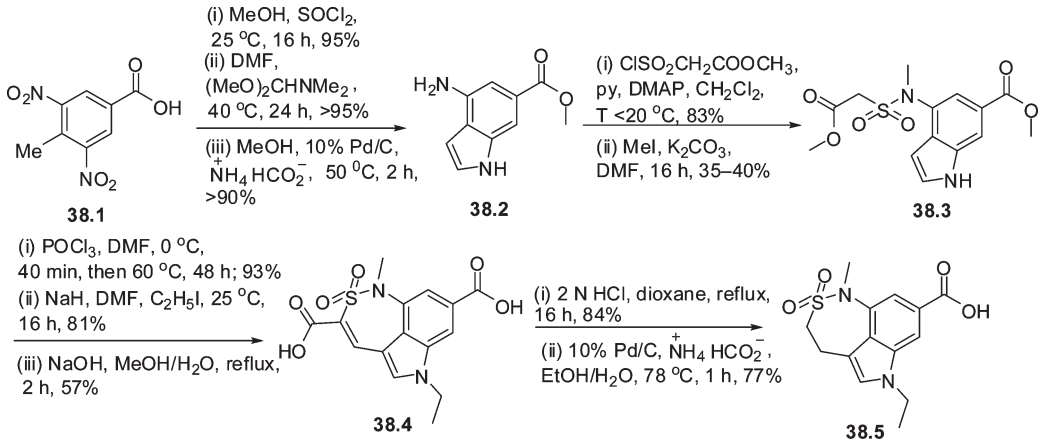
Potential mechanistic sequences (pathway a and pathway b) for the copper(II) acetate-promoted cyclization are described in Scheme 43a. One-electron oxidation of the nitrogen (**43.1** to **43.6**) followed by 5-exo-trig intramolecular ring closure generates **43.7**. Subsequent addition of the primary carbon-based radical onto the aromatic ring, followed by loss of a hydrogen

dx.doi.org/10.1021/cr1003776 |*Chem. Rev.* 2011, 111, 7749–7773

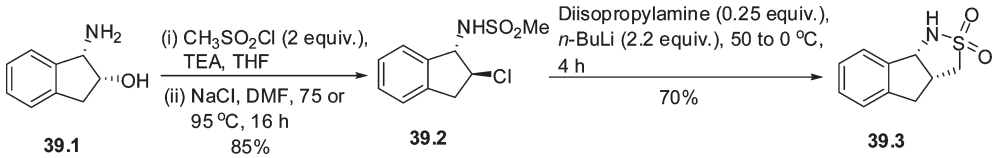
Scheme 37. Synthesis of Tricyclic Sultams via Cycloisomerizations Followed by [4 + 2]-Cycloaddition



Scheme 38. Synthesis of Tricyclic Sultams via Vilsmeier−Haack Adduct



Scheme 39. Synthesis of Tricyclic Sultams via Sulfonamide Dianion Alkylation



atom, would provide **43.2** (pathway a). An alternative mechanism would involve nitrogen−copper(II) bond formation (**43.3**) followed by intramolecular migratory insertion and subsequent addition to the aromatic ring, possibly in terms of a radical process (pathway b).

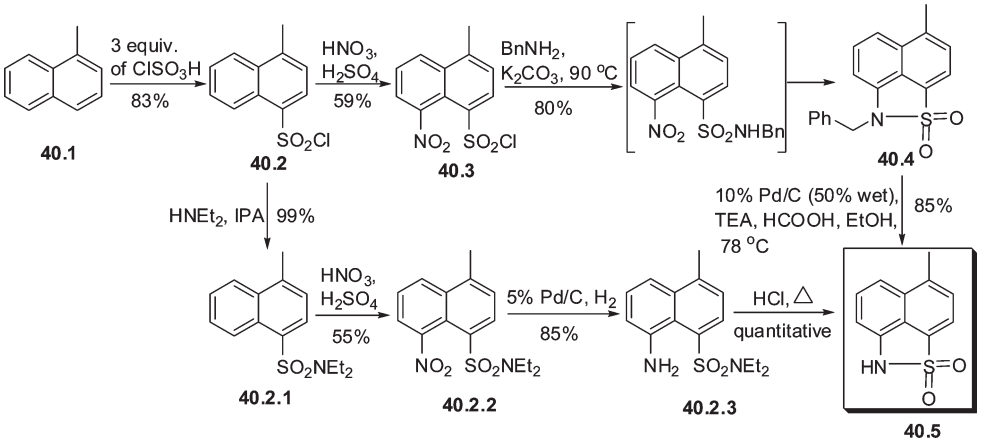
Landry and co-workers reported[96] the synthesis of the tetracyclic *N*-8-quinolinyl benzenesultam **44.5**, a novel nuclear factor kappa B (NF-κB) inhibitor. The synthesis was accomplished via diazotization-induced cyclization. The precursor **44.3** was prepared from **44.2** by reduction with $SnCl_2$. **44.2** was in turn prepared from 8-aminoquinoline (**44.1**) and 2-nitrobenzenesulfonyl chloride. Diazotization of **44.3** followed by in situ cyclization afforded the tetracyclic sultam **44.5** in 41% yield (Scheme 44).

5. PENTACYCLIC SULTAMS

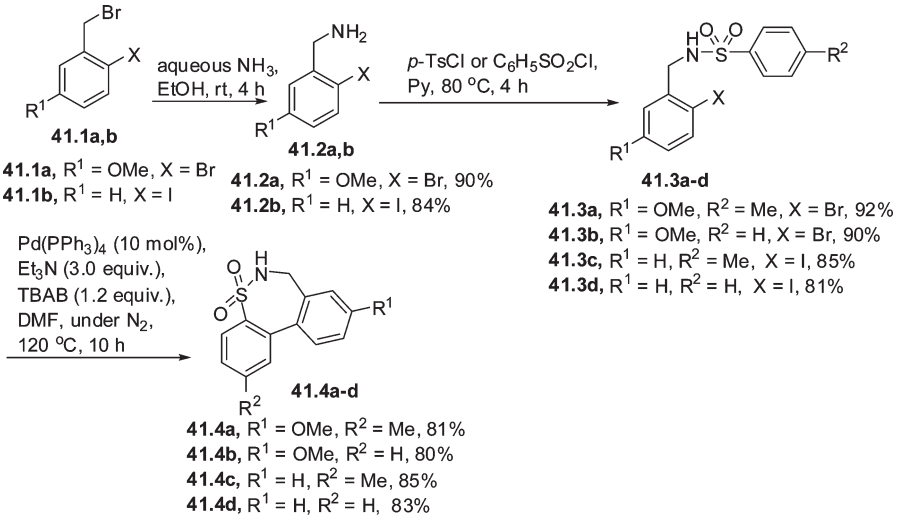
A recent literature survey revealed that there are no reports on the synthesis of pentacyclic sultams except for one from the author's laboratory, where they developed[97] a new synthetic route to pentacyclic sultams by ligand-free Pd-catalyzed, cross-coupling reaction. The required precursors **45.3a−f** were

dx.doi.org/10.1021/cr1003776 |*Chem. Rev.* 2011, 111, 7749–7773

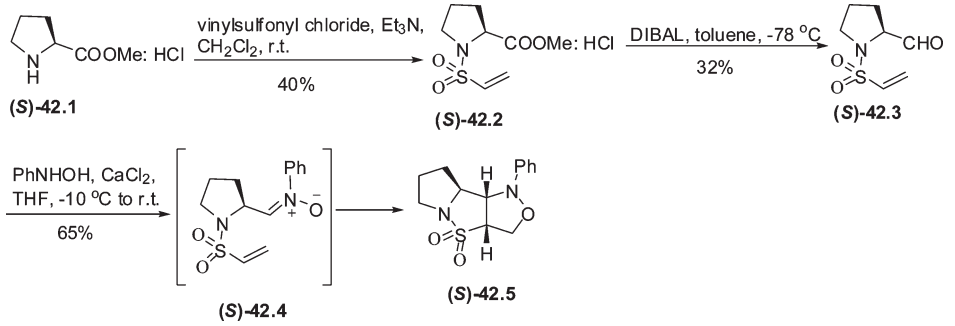
Scheme 40. Synthesis of Napthosultam



Scheme 41. Synthesis of Tricyclic Sultams by Palladium-Catalyzed Intramolecular Cyclization



Scheme 42. Synthesis of Enantiomerically Pure Tricyclic Sultams via Intramolecular 1,3-Dipolar Cycloaddition Reaction



synthesized in good to excellent yields by refluxing sulfonamides **45.1a**−**c** with either 2-bromobenzyl bromide (**45.2a**) or 2-bromo-5-methoxybenzyl bromide (**45.2b**) in anhydrous ethyl methyl ketone (EMK) in the presence of anhydrous potassium carbonate and a small amount of sodium iodide. The cross-coupling reactions of **45.3a**−**f** were carried out with Pd(OAc)$_2$ as catalyst in anhydrous *N*,*N*-dimethylformamide, with KOAc as base and TBAB as an additive at 120 °C for 10 h under a nitrogen atmosphere to give the pentacyclic sultams **45.4a**−**f** in 80−92% yields (Scheme 45). The structure of the sultam **45.4a**

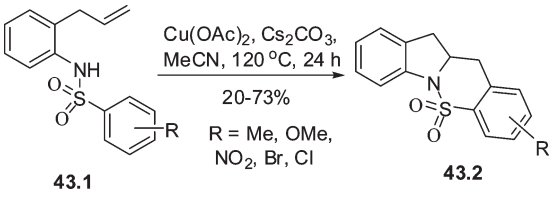
dx.doi.org/10.1021/cr1003776 |*Chem. Rev.* 2011, 111, 7749–7773

was unambiguously established from its single-crystal X-ray diffraction (XRD) data.

The reaction may probably proceed by an initial oxidative addition of the aryl bromide **45.3d** to Pd(0) to form an arylpalladium bromide intermediate **45.3d.1**.The cyclization may then occur by an electrophilic attack of the arylpalladium bromide **45.3d.1** at the electron-rich aromatic ring to give the monocyclized intermediate **45.3d.3** via the intermediate palladacycle **45.3d.2**.The monocyclized intermediate **45.3d.3** may repeat one more catalytic cycle to finally afford the bis-cyclized product **45.4d** via intermediate **45.3d.4** (Scheme 45a).

Coumarins and quinolones containing pentacyclic sultams have also been prepared by copper(II) acetate promoted oxidative cyclization.[98] When the sulfonamides **46.1a**−**h** were treated with $Cu(OAc)_2$ (3 equiv) and Cs_2CO_3 in MeCN at 120 °C in a sealed tube, the desired sultams **46.2a**−**h** were obtained in high yields (Scheme 46).

Scheme 43. Synthesis of Tetracyclic Sultams by Copper(II) Acetate-Promoted Oxidative Cyclization of Arylsulfonyl-*o*-allylanilines



6. SYNTHETIC APPLICATIONS OF FUSED SULTAMS

Over the past several years, fused sultams have emerged as valuable heterocyclic intermediates that offer scope for stereoselective tranformations. There have been several new developments in the synthesis of condensed sultams, which have also found application in the total synthesis of natural products.

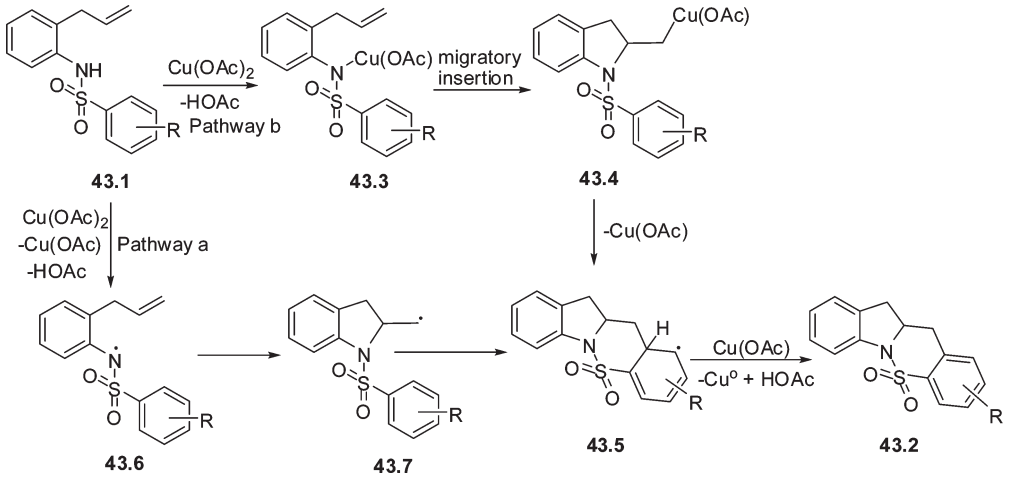
In 2004, Ley and co-workers developed[99] the total synthesis of the cytotoxic antitumor natural product epothilone C by coupling of the three fragments **1**, **2**, and **3** as shown in Figure 4. Among the three fragments, fragment **1** (**47.2**) was synthesized from a tricyclic sultam **47.1** (Scheme 47).

Davison et al. reported[100] the total synthesis of (−)-histrionicotoxin (**48.3**), (+)-histrionicotoxin (**48.4**), and (−)-histrionicotoxin 235A (**48.5**) by employing the tricyclic sultam **48.2** (Scheme 48).

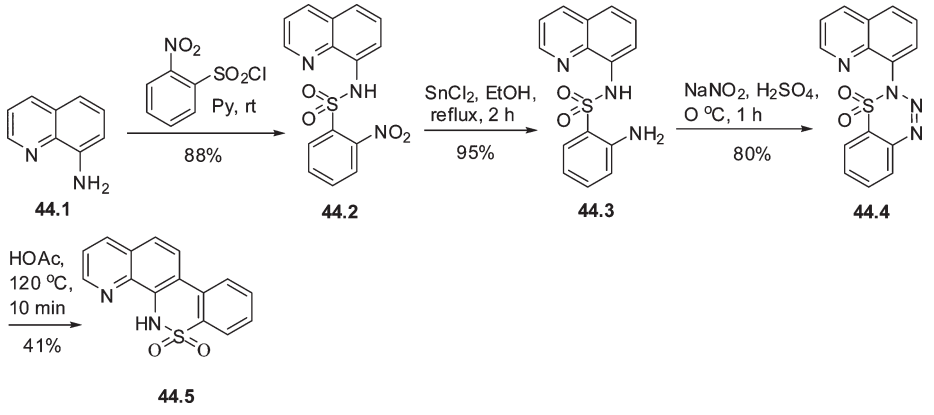
7. BIOLOGICAL ACTIVITIES OF FUSED SULTAMS

Sultams are an important class of drugs that display a vast array of biological activities like antibacterial, anticarbonic anhydrase,

Scheme 43a. Proposed Reaction Mechanism

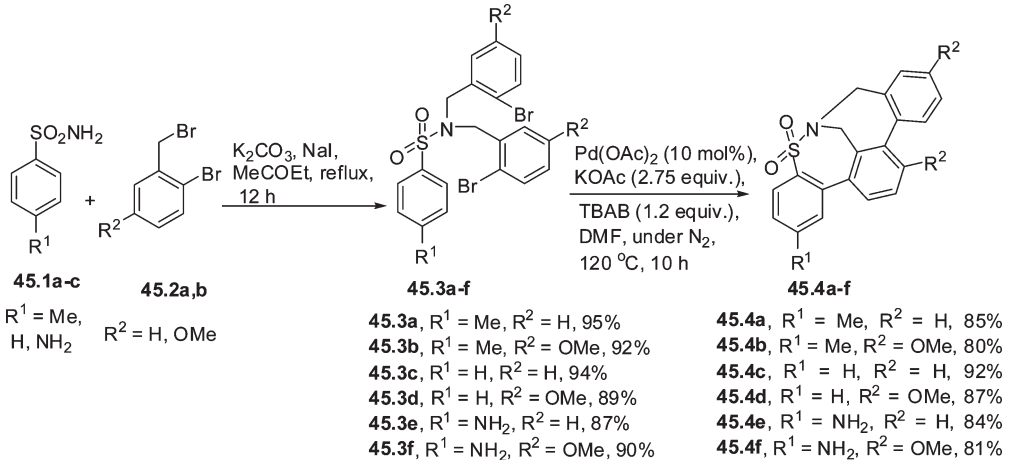


Scheme 44. Synthesis of *N*-8-Quinolinyl Benzenesultam via Triazine Intermediate

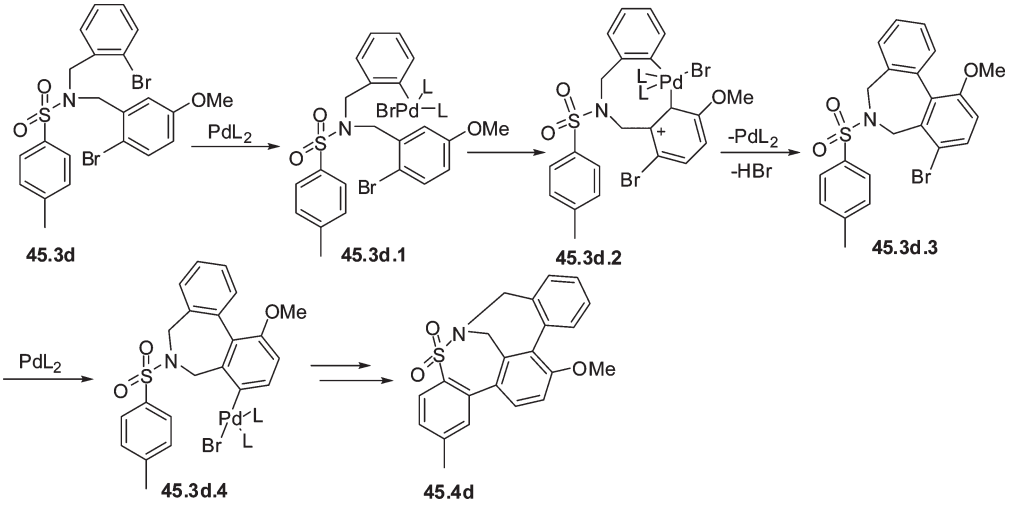


dx.doi.org/10.1021/cr1003776 |*Chem. Rev.* 2011, 111, 7749–7773

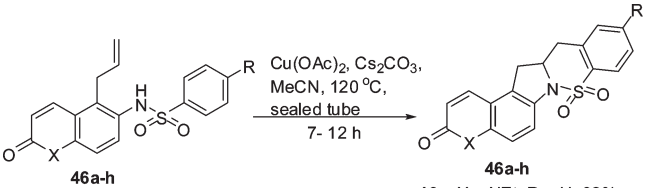
Scheme 45. Synthesis of Pentacyclic Sultams by Ligand-Free, Palladium-Catalyzed Intramolecular Cyclization



Scheme 45a. Proposed Reaction Mechanism



Scheme 46. Synthesis of Pentacyclic Sultams by Copper(II) Acetate-Promoted Oxidative Cyclization



46a, X = NEt, R = H, 82%
46b, X = NEt, R = Me, 85%
46c, X = NEt, R = OMe, 74%
46d, X = NMe, R = H, 79%
46e, X = NMe, R = Me, 80%
46f, X = NMe, R = OMe, 68%
46g, X = O, R = H, 75%
46h, X = O, R = Me, 78%

diuretic, hypoglycemic, etc. Oxicams (e.g., Ampiroxicam **49**)[101] are a large family of nonsteroidal anti-inflammatory agents. *N*-Alkylated saccharin derivatives act as agonists of 5-HT_{1A} receptors and have therefore found applications as neuroprotectants[102] or

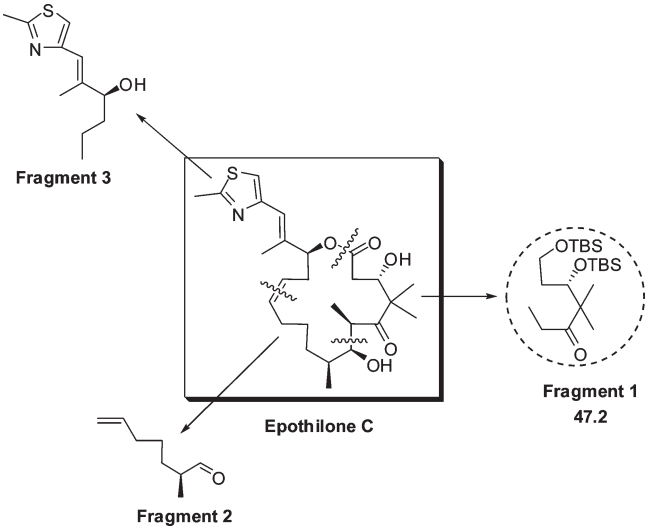


Figure 4. Three fragments of Epothilone C.

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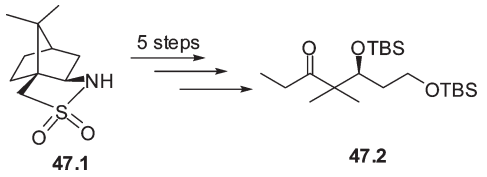
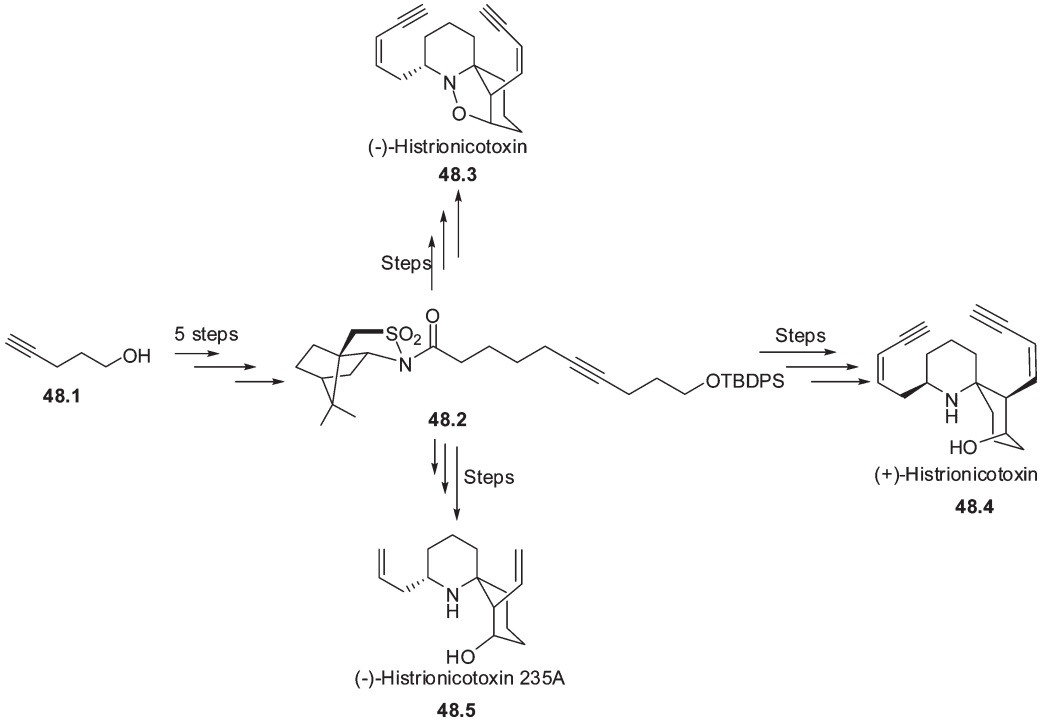
Scheme 47. Application of Sultam in the Total Synthesis of Epothilone C



anxiolytics (e.g., Ipsaspirone **50**).[103] They also selectively inhibit serine proteases (tryptase[104] or elastase[105]). Brinzolamides **51**[106] are very important for the treatment of glaucoma. Moreover, a number of benzofused sultams have recently surfaced that display potent activity including respiratory syncytial virus (RSV) inhibitors (**52**, **53**),[107] selective inhibitors of calpain I (**54**),[15] selective seven-transmembrane (7-TMR) G-protein coupled receptor (CXCR2) antagonists (**55**),[108] selective tumor necrosis factor inhibitors (**56**),[109] glucokinase activator (**57**),[110] hypoglycemic agent (**58**),[35]

Scheme 48. Application of Sultam in the Total Synthesis of (−)-Histrionicotoxin, (+)-Histrionicotoxin, and (−)-Histrionicotoxin 235A



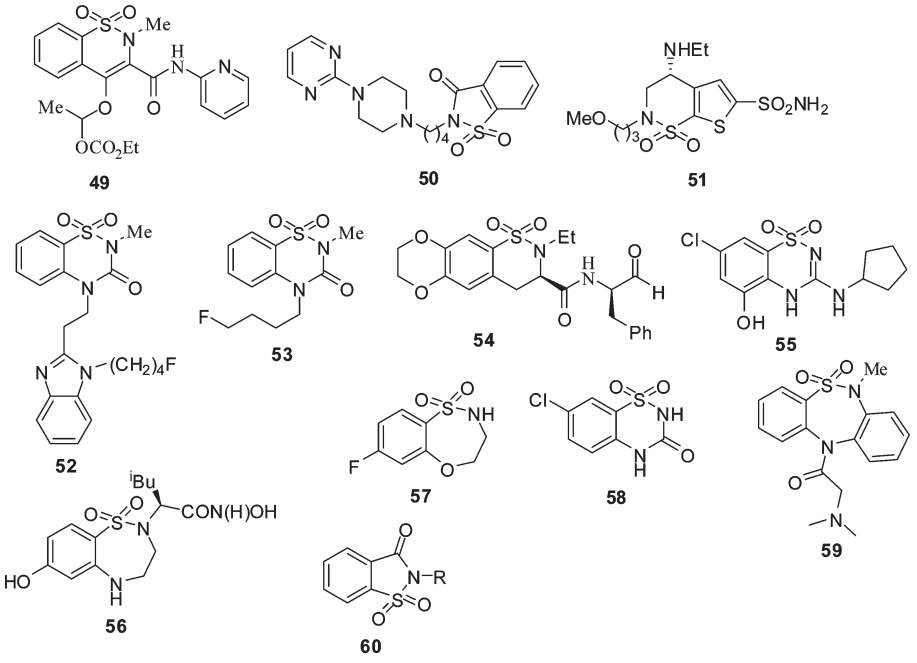


Figure 5. Biologically active sultams.

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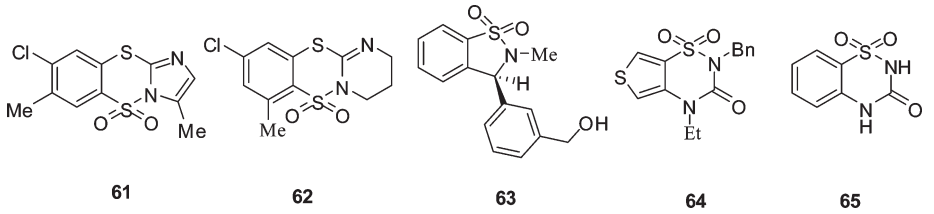

Figure 6. Anti-HIV active sultams.

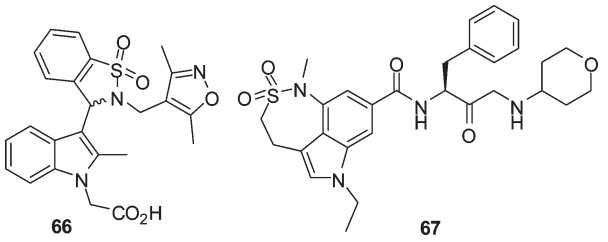

Figure 7. Selective antagonist of CRTh2 and BACE-1 inhibitor sultams.

antidepressant (**59**),[111] and 1,2-benzisothiazolinone-1,1-dioxides **60** (saccharin derivatives), which exhibit, among other properties, human leukocyte elastase inhibitory[112] and antifungal[113] activity (Figure 5). Here it is important to note that sultam thioureas are novel inhibitors of West Nile Virus (WNV) replication.[114]

In addition, the sultams of the invention are accordingly particularly useful in the treatment of infection by the human immunodeficiency virus (HIV) and also in the treatment of consequent pathological conditions associated with AIDS. For example, a number of benzodithiazine dioxides (**61**, **62**) and other fused sultams (**63**−**65**) display potential anti-HIV activity (Figure 6).[4,36,37,115]

Moreover, the 3-indolyl-condensed sultam **66** proved to be a selective antagonist of CRTh2 (cytokine release from Th2 cells), with a binding affinity of ∼9.2 μM (Figure 7).[116] The sultam **67** is the first example of a compound demonstrating that a tricyclic β-secretase (BACE-1) inhibitor without a hydroxyethylamine transition state mimetic and with fewer hydrogen-bond donors and acceptors can achieve excellent potency in cell-based assays (BACE-1 IC_{50} = 13 nM; Aβ40 IC_{50} = 48 nM) (Figure 7).[90] The tetracyclic *N*-8-quinolinyl benzosultam **44.5** exhibits a novel NF-κB inhibitor effect.[96] The benzodithiazines **4.3a**−**q** constitute a novel class of IN (a 32κDa viral enzyme) inhibitors.[46]

8. CONCLUSION

This review focuses on the recent (mainly the period 2000−2010) developments of condensed sultams. Emphasis has been given mainly to their syntheses, biological activities, and synthetic applications. Many fused sultams possess anti-HIV, antimicrobial, and antitumor activities. Condensed sultams are often used as chiral auxiliaries, protecting groups, and important intermediates in natural product synthesis. Hydroperoxy sultams are used as oxidizing agents. We hope that this review will be useful to those who have something to do with or interest in sultams.

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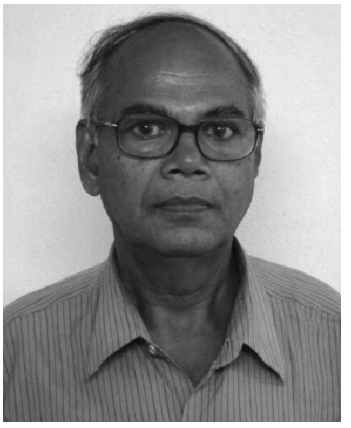

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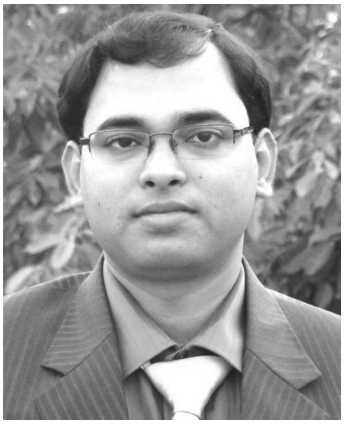

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