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Synthesis of Chiral *N*-Sulfonyl and *N*-Phosphinoyl α-Halo Aldimine Precursors

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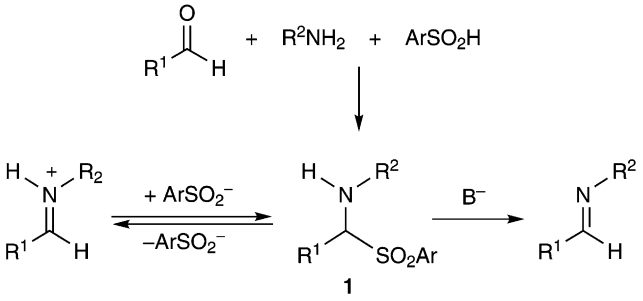
Abstract: α-Halogenated aldimines have emerged as an important class of synthetic intermediates. The stability and reactivity of α-halo aldimines can vary greatly depending on the nitrogen protecting group. A general synthesis of stable, chiral α-halo-*N*-sulfonyl and *N*-phosphinoyl aldimine precursors is presented (42–96% yield). The corresponding α-halo aldimines can be isolated upon treatment with a mild base. Enantioenriched α-chloro aldehydes can be employed to afford aldimine precursors with no erosion of optical purity. Both the enantioenriched aldimine precursor and the isolated aldimine can react with an alkynyllithium nucleophile to give *trans*-β-chloroamine products with excellent *dr*. Ring closure affords the enantioenriched *trans*-aziridine, demonstrating the potential for this approach in complex molecule synthesis.

Keywords: diastereoselectivity; halogenation; multicomponent reactions; nitrogen heterocycles; synthetic methods

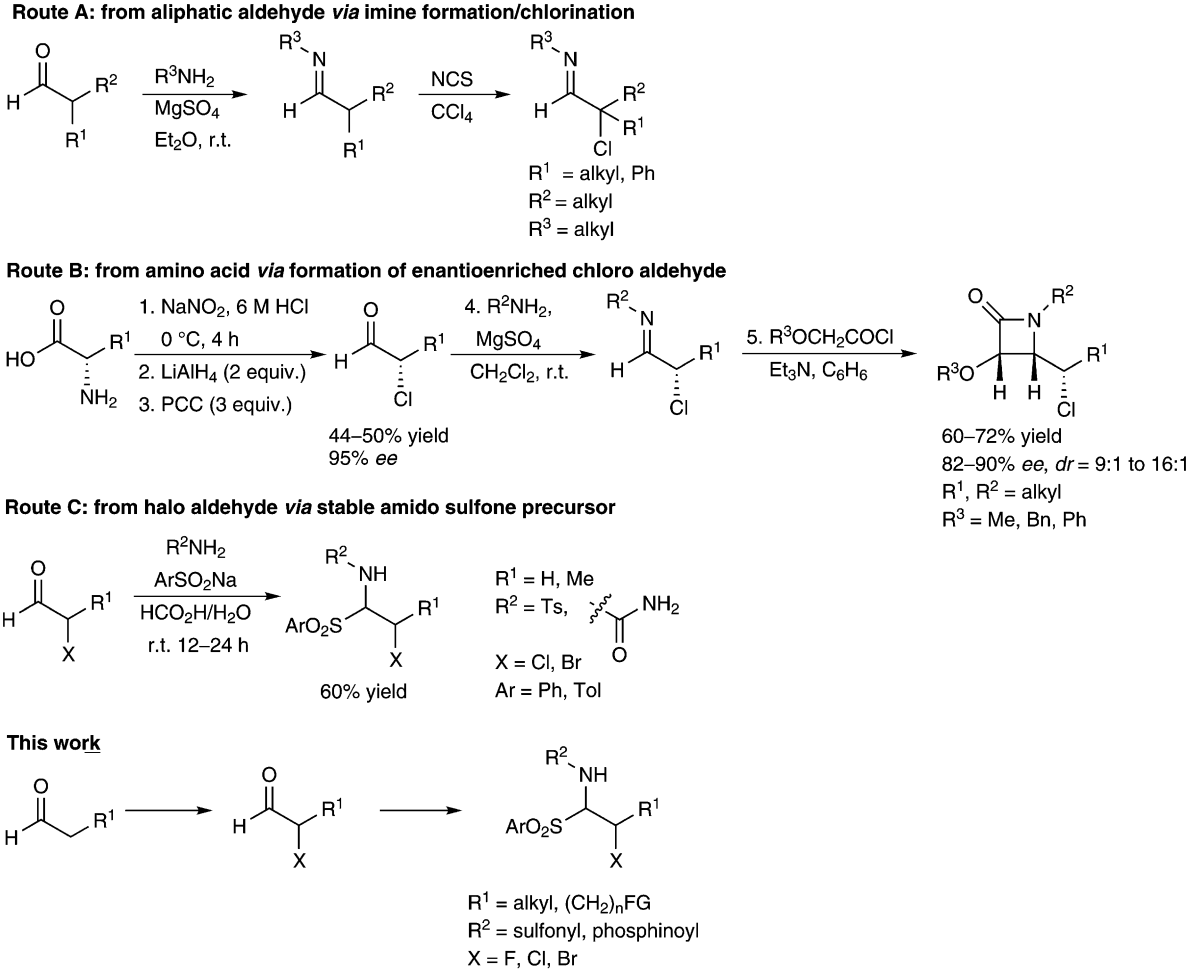
Introduction

Enantioenriched nitrogen-containing molecules are ubiquitous in natural products and other biologically active scaffolds. As a result, the stereoselective formation of nitrogen-bound carbon centers continues to be an important area in methods development.[1] A common approach to access this structural motif is nucleophilic addition of organometallic reagents to C=N double bonds with α-stereogenic centers.[2] Although the *N*-alkyl- and *N*-arylimine precursors to these additions are straightforward to prepare and store, they often suffer from low reactivity towards nucleophiles. Alternatively, imines bearing electron-withdrawing groups such as *N*-acyl,[3] *N*-sulfonyl,[4] *N*-sulfinyl,[5] and *N*-phosphinoyl,[6] exhibit enhanced reactivity. While imines prepared from aromatic aldehydes and primary amine derivatives bearing an electron-withdrawing group on the nitrogen are reasonably stable, aliphatic aldimines undergo a facile hydrolysis or self-condensation *via* tautomerization to the corresponding enamines. Consequently, aliphatic aldimines with α-hydrogens are often generated and trapped to circumvent these decomposition pathways.[4] One exception to this pronounced instability is sulfinyl imines, which exhibit enhanced stability relative to their sulfonyl counterparts.

Based on the early work of Engerts and Strating,[7] α-amido sulfones have gained much attention as stable, storable aldimine precursors in synthesis.[8] The preparation of α-amido sulfone derivatives (**1**) involves a three-component reaction of a suitable carbamate or sulfonamide, aldehyde, and sodium sulfinate under acidic conditions (Scheme 1).[7b,c,8] Later studies showed that the corresponding aldimine could be isolated upon treatment of the amido sulfone **1** with a mild base.[9] More recently, Chemla and co-



Scheme 1. Formation of α-amido sulfone **1**.



Scheme 2. Previous routes to α-halogenated aldimines.

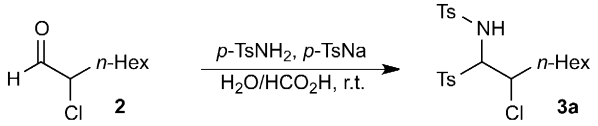
workers have utilized this two-step method to generate *N*-sulfonyl aldimines from enolizable, aliphatic aldehydes.[10] It is noteworthy that bisulfite adducts have been used in a similar manner to store unstable aldehydes.[11]

α-Halogenated aldimines have been known for quite some time and represent a useful class of intermediates for the synthesis of aza-heterocycles including aziridines, azetidines, and β-lactams.[12] Several methods for their syntheses are outlined in Scheme 2. De Kimpe and co-workers pioneered studies on the synthesis and reactivity of *N*-alkyl-α-chloro aldimines.[13] Their approach involved the condensation of α,α-disubstituted acetaldehydes with primary amines and subsequent chlorination of the resulting aldimine with *N*-chlorosuccinimide (Route A).[13a] This method was extended to include *N*-tosyl derivatives.[14] Enolizable *N*-alkyl-α-chloro aldimines (R^1 or $R^2 = H$) necessitated an alternate approach from α-chloro aldehydes to circumvent the formation of dichlorinated side products.[13a] De Kimpe has also explored the generation of enantioenriched, *N*-alkyl-α-chloro aldimines bearing an α-hydrogen *en route* to stereodefined β-lactams (Route B).[15] The β-lactam products were afforded with 82–90% *ee*, showing minimal erosion of optical purity in a multi-step sequence from readily available amino acids.

One drawback to the direct synthesis of more activated α-chloro aldimines with an electron-withdrawing group on the nitrogen is the instability of the formed aldimine. Hayashi and co-workers have demonstrated the first examples of stable *N*-tosyl-α-chloro aldimine precursors (Scheme 2, Route C).[16] This amido sulfone, derived from chloro acetaldehyde, can be employed in one-pot reactions in which the aldimine is formed *in situ*. However, other substituted α-chloro aldehydes were not studied. We are aware of only one other example of conversion of amido sulfone precursors to α-halo aldimines derived from urea with a limited scope (Scheme 2, Route C).[17]

Despite key advancements in accessing α-halogenated aldimines and their broad applications, syntheses of α-halo-*N*-sulfonyl aldimines containing a hydrogen at the α-stereogenic center are lacking. With this in

Table 1. Optimization of the synthesis of *N*-tosyl sulfone **3a**.[a]



Entry	Conditions	Time	Yield [%]
1	a	12 h	31
2	a	24 h	40
3	a	72 h	54
4	a	120 h	80
5	***b***	***72 h***	***85***
6	b	120 h	86

[a] *Condtions a:* 3 mL of H_2O:HCO_2H (1:1) were employed per mmol of chloro aldehyde (0.33 M). *Condtions b:* 1.5 mL of H_2O:HCO_2H (1:1) were employed per mmol of chloro aldehyde (0.67 M).

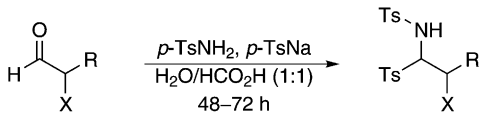
mind, we set out to prepare stable amido sulfone precursors to these aldimines. In particular, we aimed to explore whether a practical approach to storable, enantioenriched α-chloro aldimine precursors of type **1** could be achieved. We also demonstrate their utility in the addition of two types of organometallic nucleophiles to the aldimines to afford useful enantioenriched building blocks.

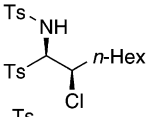
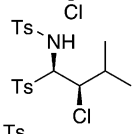
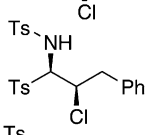
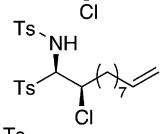
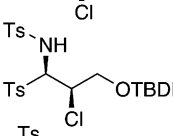
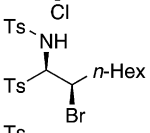
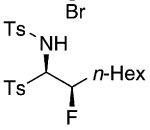
Results and Discussion

Initially, we examined the reaction of 2-chlorooctanal, *p*-toluenesulfonamide, and *p*-toluenesulfinic acid sodium salt hydrate in aqueous formic acid. Conducting the reaction under conditions used for non-halogenated aldehydes by Chemla and co-workers[10] resulted in poor conversions (Table 1, entries 1 and 2). Significantly longer reaction times (3 and 5 days) furnished the α-amido sulfone product **3a** with increased yield (up to 80%, entries 3 and 4). We were pleased to find that employing more concentrated reaction conditions (0.33 M to 0.67 M with respect to the aldehyde) further improved the yield to 85% and reduced the reaction time to 72 h (entry 5). As shown in entry 6, a longer reaction time did not increase the yield and, therefore, we used the conditions in entry 5 to proceed with our studies.

The optimized reaction conditions in Table 1 (entry 5) were applied to a variety of aliphatic α-chloro aldehydes (Table 2). Both a terminal olefin and a silyl protected β-hydroxy group were tolerated under the reaction conditions (entries 4 and 5). The α-amido sulfone products were afforded in good to excellent yields (64–90%). Of significance, these imine precursors can be generated on a multi-gram scale in comparable yields. For example, when the reaction in entry 2 was conducted under aqueous conditions using *p*-toluenesulfonamide on a 15-mmol scale, the α-amido sulfone product was obtained in 75% yield. Both α-bromo and α-fluoro aldehydes also were amenable to the method (entries 6 and 7).

Table 2. Synthesis of α-halo-*N*-tosyl aldimine precursors under aqueous conditions.



Entry	X	R	Product		Yield[a]	(*dr*)[b]
1	Cl	*n*-hexyl		**3a**	85%	(4:1)
2	Cl	*i*-propyl		**3b**	75%	(>20:1)[c]
3	Cl	benzyl		**3c**	88%	(4:1)
4	Cl			**3d**	90%	(12:1)
5	Cl			**3e**	64%	(>20:1)[d]
6	Br	*n*-hexyl		**3f**	83%	(4:1)
7	F	*n*-hexyl		**3g**	65%	(10:1)

[a] 1.5 mL of H_2O:HCO_2H (1:1) were employed per mmol of chloro aldehyde (0.67 M) using *p*-$TolSO_2Na$. Ts = *para*-toluenesulfonyl.
[b] The *dr* was determined by analysis of ^1H NMR spectra.
[c] Reaction conducted on a 15-mmol scale
[d] Major diastereomer determined to be *syn* by X-ray analysis.

With synthetic methods in place to prepare the α-chloro-*N*-tosyl aldimine precursors, we focused on determination of their stereochemistry. As illustrated in Figure 1, the relative stereochemistry of **3e** was determined to be *syn* as ascertained by X-ray analysis. The high level of diastereoselectivity seen in the formation of **3e** (Table 2, entry 5) can be attributed to a favorable hydrogen bonding interaction between the α-chloro moiety and the protonated *N*-sulfonyl imine. Petrini and co-workers have observed similar stereochemical outcomes in their synthesis of α-amido sul-

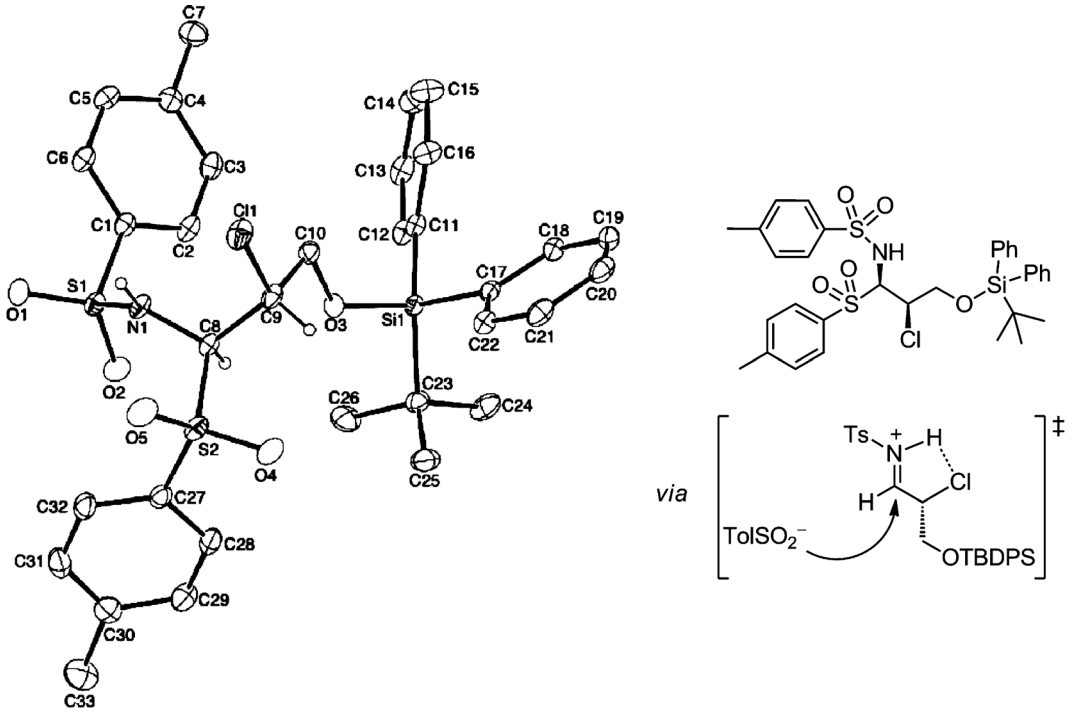
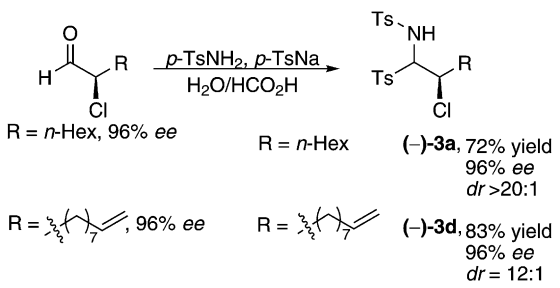


Figure 1. X-ray crystal structure of amido sulfone **3e** and proposed transitions state to account for observed stereochemistry.

fones from chiral α-alkoxy and α-amidoalkyl aldehydes.[18] In a series of computational studies, they found that the preferred conformation of the *N*-acylium ion intermediate was stabilized by an electrostatic interaction between the NH and the α-alkoxy or α-amido group in a similar fashion to that shown in Figure 1.

Several elegant processes have been developed to synthesize enantioenriched α-chloro aldehydes.[19] To demonstrate the synthetic utility of our method, we examined the compatibility of enantioenriched α-chloro aldehydes with the aqueous reaction conditions. Gratifyingly, employing (*R*)-2-chlorooctanal[19b] of 96% *ee* provided amido sulfone (−)-**3a** with no erosion of *ee* (Scheme 3). Interestingly, in contrast to the reaction using the racemic aldehyde (Table 2, entry 1), the product was generated with >20:1 *dr* (Scheme 3). A single diastereomer was also isolated



Scheme 3. Formation of enantioenriched amido sulfones.

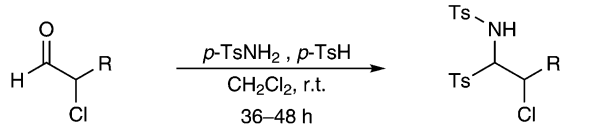
when (*S*)-2-chlorooctanal was used. Similarly, amido sulfone (−)-**3d** was furnished with 96% *ee*.

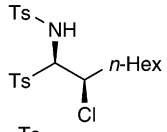
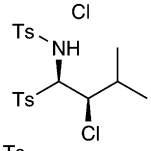
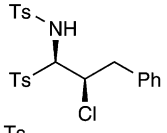
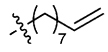
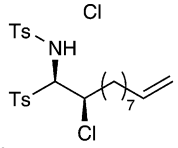
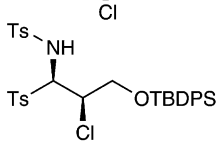
For substrates prone to a small equilibrium constant in favor of the iminium ion over sulfone **1** in water (Scheme 1), we envisioned a second set of conditions in organic solvents.[20] When dichloromethane was used as a solvent, comparable or improved yields were achieved in most cases (Table 3). Unfortunately, enantioenriched α-chloro aldehydes suffered considerable erosion of *ee* using this method. A crucial difference between the aqueous and dichloromethane reaction conditions is that under the aqueous conditions, the α-chloro aldehydes are insoluble and, therefore, less susceptable to racemization. In dichloromethane, the reactions are homogeneous and it is likely that the *p*-$TolSO_2^-$ promotes racemization.

It is worth noting that the corresponding *N*-tosyl-α-chloro aldimine can be isolated in excellent yield upon treatment of α-amido sulfone **3a** with a mild base (Scheme 4).[9,10] Aldimine **4** is stable at room temperature for several hours for use in subsequent reactions. Unfortunately, aldimines derived from more functionalized precursors such as **3c** and **3e** are very unstable, showing significant amounts of hydrolysis within an hour.

We next surveyed the substrate scope with respect to the protecting group on nitrogen. As illustrated in Table 4, a variety of *N*-sulfonyl sulfone derivatives can be synthesized in moderate to good yield (entries 1–4). Sulfonyl protecting groups[21] that are removed under mild conditions, such as Bs, Nos, and 2-

Table 3. Synthesis of α-chloro *N*-tosyl aldimine precursors in organic solvent.

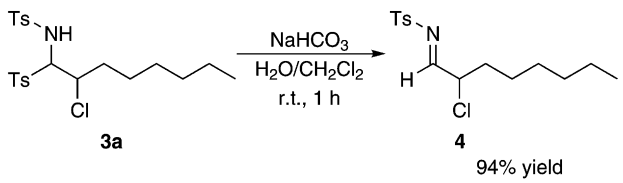


Entry	R	Product		Yield[a]	(dr)[b]
1	*n*-hexyl		**3a**	67%	(2:1)
2	*i*-propyl		**3b**	83%	(>20:1)
3	benzyl		**3c**	90%	(3:1)
4			**3d**	96%	(4:1)
5			**3e**	53%	(>20:1)

[a] Reaction conducted in CH_2Cl_2 under a nitrogen atmosphere using *p*-TolSO_2H.
[b] The *dr* was determined by analysis of ^{1}H NMR spectra.

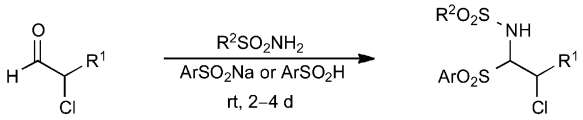
thienyl,[22] were good substrates for this transformation. The sulfinic acid moiety can also be modified, further demonstrating the tunability of the precursors for one-pot/tandem reaction design (entry 5).

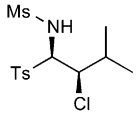
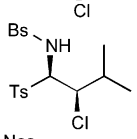
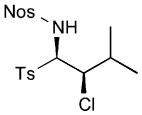
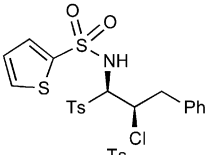
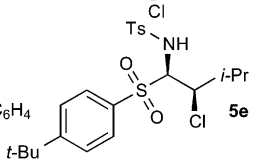
N-Phosphinoyl imines have emerged as a useful class of electrophiles in organic synthesis.[6,23] However, we are not aware of any examples of *N*-phosphinoyl imines containing an α-halo group. The advantage of phosphinamides is that the phosphinoyl group can be removed under fairly mild reaction conditions. We examined the reaction of diphenylphosphinamide with 2-chloroisovaleraldehyde and *p*-toluenesulfinic acid. Phosphinamido sulfone **6a** was furnished in 61% yield as a single diastereomer (Scheme 5). Other simple alkyl-substituted α-chloro aldehydes were suitable in the reaction.



Scheme 4. α-Chloro aldimine formation.

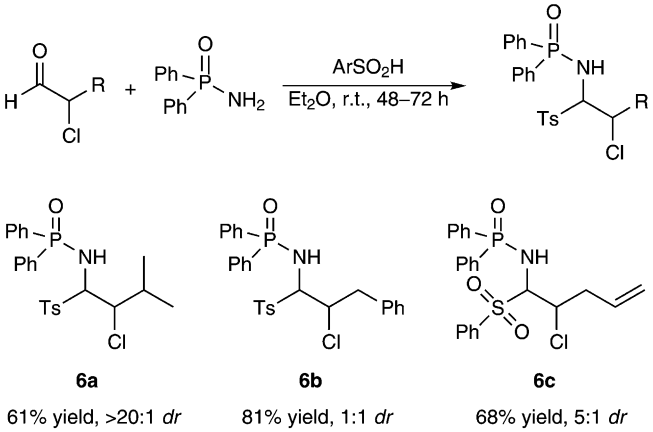
Table 4. Synthesis of other α-chloro-*N*-sulfonyl aldimine precursors.



entry	R^1	R^2	Ar	product		% yield (dr)[a]
1	*i*-Pr	Me	*p*-Tol		**5a**	82 (>20:1)[b]
2	*i*-Pr	*p*-BrC_6H_4	*p*-Tol		**5b**	66 (>20:1)[c]
3	*i*-Pr	*p*-$NO_2C_6H_4$	*p*-Tol		**5c**	42 (>20:1)[b]
4	Bn	2-(thienyl)	*p*-Tol		**5d**	72 (12:1)[b]
5	*i*-Pr	*p*-Tol	*p*-*t*-BuC_6H_4		**5e**	70 (>20:1)[c]

[a] The *dr* was determined by analysis of ^{1}H NMR spectra. Ms = methanesulfonyl, Bs = *para*-bromobenzenesulfonyl, Nos = *para*-nitrobenzenesulfonyl.
[b] 1.5 mL of H_2O:HCO_2H (1:1) were employed per mmol of chloro aldehyde (0.67 M) using *p*-TolSO_2Na.
[c] Reaction conducted in CH_2Cl_2 under a nitrogen atmosphere using *p*-TolSO_2H.

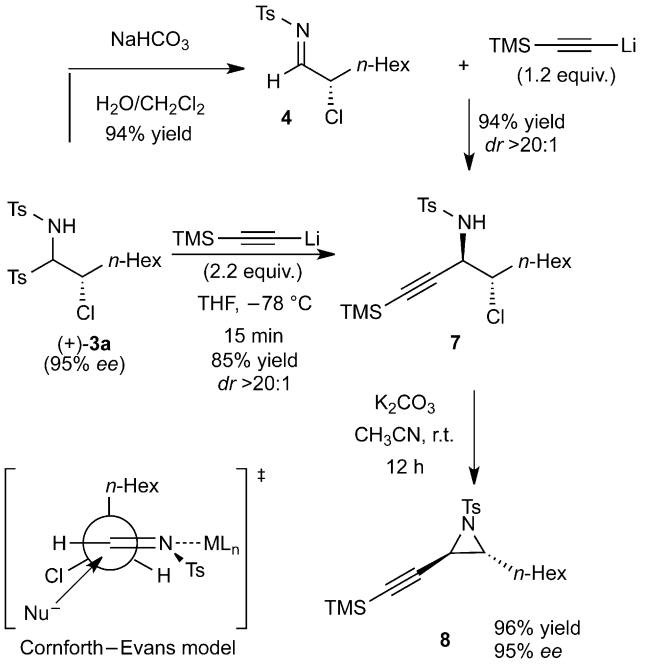
To demonstrate the synthetic utility of our α-chloro aldimines, we next identified several applications of the α-chloro aldimine precursors. Stereodefined alkynylaziridines are valuable scaffolds and several



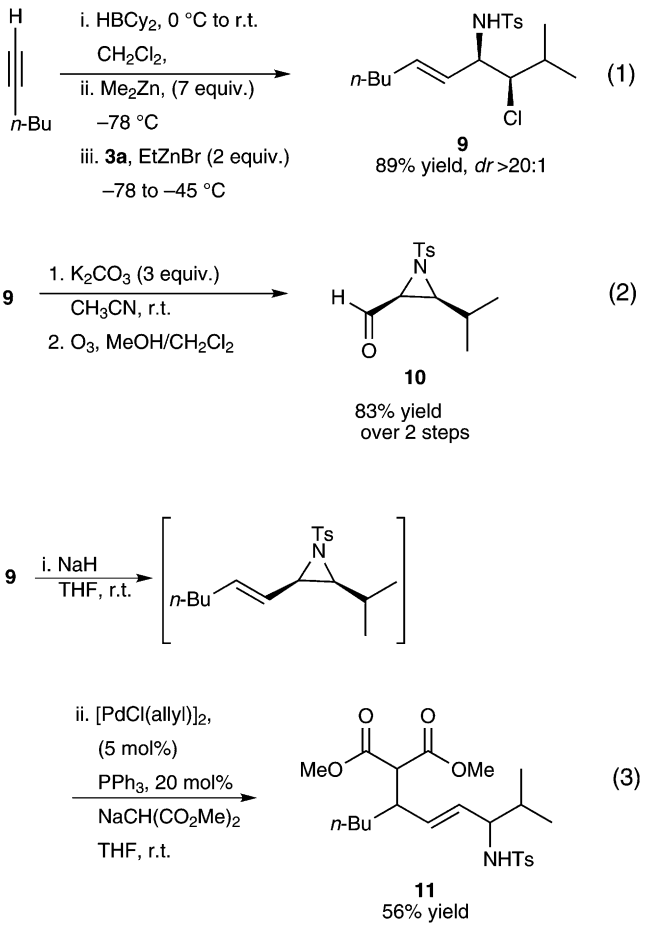
Scheme 5. Synthesis of *N*-phosphinoyl aldimine precursors

excellent methods for their synthesis have been developed.[24] We conceived a complementary, one-pot reaction in which an excess of the organometallic reagent could be used to generate the aldimine *in situ*. Towards this end, enantioenriched amido sulfone (+)-**3a** was reacted with excess lithium TMS-acetylide[25] to give β-chloroamine **7** in 85% yield as a single diastereomer (Scheme 6). Subsequent ring closure under mild conditions provided *trans*-aziridine **8** with 95% *ee* in 96% yield. Alternatively, aldimine **4** was isolated after treatment with $NaHCO_3$ (94% yield) and reacted with 1.2 equivalents of lithium TMS-acetylide to give **7** in comparable yield and *dr*. The relative stereochemistry was confirmed by examination of the aziridine H-1/H-2 coupling constant (J = 4.5 Hz). The high *anti*-selectivity of the addition step can be rationalized by the Cornforth–Evans stereoinduction models.[26] Other models have also been proposed for additions to α-halogenated carbonyl derivatives.[27] It is worth noting that Hilmersson and coworkers have recently disclosed a new method for the deprotection of tosyl amides under mild reaction conditions.[28] These conditions were shown to be compatible with aziridine substrates. Highly functionalized aziridine **8** can potentially be used to prepare aziridine-2-carboxylic acid derivatives. These important building blocks have been widely applied in the synthesis of amino acid and peptide derivatives.[29]

Recently we have been interested in the addition of organometallic nucleophiles to chiral aldehydes and ketones with substituents on the α- or β-carbons that traditionally do not coordinate to metals and therefore undergo Felkin addition.[30] In this work, we demonstrated that α- and β-silyloxy aldehydes and α-silyloxy ketones undergo chelation-controlled addition of a wide range of organozinc nucleophiles in the presence of alkylzinc halides and sulfonates, RZnX and $RZnOSO_2R^F$.[31] With this work in mind, we investigated several other applications of our α-halo aldimine precursors (Scheme 7). We have recently disclosed a new one-pot route to yield *syn*-β-chloro allylic amines such as **9** with excellent *dr* favoring the unprecidented *chelation-controlled* product [Eq. (1)].[32] Allylic amines constitute an important class of intermediates in synthesis.[33] In the current work, we sought to explore the utility of the highly functionalized *syn*-β-chloro allylic amine products in multi-step and tandem reactions. Chloroamine **9** was used in a two-step sequence to generate *cis*-aziridine-2-carboxaldehyde **10** in 83% yield *via* ring closure followed by ozonolysis [Eq. (2)]. Stereodefined aziridine-2-carbonyl derivatives are known to undergo directed nucleophilic additions using organometallic reagents with high diastereoselectivity.[34] Furthermore, chloroamine **9** was applied in a tandem ring closure/palladium-catalyzed allylic substitution reaction [Eq. (3)].



Scheme 6. Synthesis of enantioenriched *trans*-alkynylaziridines



Scheme 7. Applications of *syn*-β-chloro allylic amines.

Allylic amine **11** was obtained as a single regioisomer and a mixture of diastereomers (*dr*~10:1).

Conclusions

In summary, facile routes to chiral *N*-sulfonyl-α-halo aldimine precursors have been developed. Additionally, we have expanded the scope of this method to include *N*-phosphinoyl-α-chloro aldimine adducts. We have demonstrated that enantioenriched α-chloro aldehydes are compatible with aqueous reaction conditions, giving rise to α-amido sulfone products with no erosion of *ee*. These stable precursors can be utilized in one-pot aldimine formation/diastereoselective addition reactions to access *trans*-alkynylaziridines, *cis*-aziridine-2-carboxaldehyde derivatives, and γ-functionalized allylic amines.

Experimental Section

General Procedure for the Formation of *N*-Sulfonyl Aldimine Precursors Under Aqueous Conditions

To a 10-mL round-bottom flask was added α-chloro aldehyde (1.5 mmol) followed by deionized water (1.2 mL), *p*-toluenesulfonamide (171 mg, 1 mmol), and *p*-toluenesulfinic acid sodium salt monohydrate (267 mg, 1.5 mmol). Formic acid (1.2 mL) was subsequently added, and the reaction mixture was stirred at room temperature for 72 h. The resulting solid was filtered through a sintered glass funnel. The solid was washed thoroughly with water (3×10 mL) and hexanes (5×10 mL). The solid was then collected, dissolved in CH_2Cl_2 (25 mL) and filtered through celite. The filtrate was concentrated and dried under vacuum for several hours. Most products can be used in subsequent reactions without further purification. Products of higher purity can be obtained by recrystallization from EtOAc/hexanes.

General Procedure for the Formation of *N*-Sulfonyl Aldimine Precursors in Dichloromethane

A dry 10-mL round-bottom flask, which was purged with nitrogen, was charged with *p*-toluenesulfonamide (171 mg, 1 mmol), *p*-toluenesulfinic acid (187 mg, 1.2 mmol), α-chloro aldehyde (1.5 mmol) and CH_2Cl_2 (4 mL). $MgSO_4$ was added to the flask and the reaction mixture was allowed to stir at room temperature until complete as determined by TLC (24–48 h). The mixture was diluted with CH_2Cl_2 (20 mL), filtered through celite, and concentrated under vacuum. The solid product was collected onto a sintered glass filter and washed sequentially with hexanes (5×10 mL) to remove the excess aldehyde. Most products can be used in subsequent reactions without further purification. Products of higher purity can be obtained by recrystallization from EtOAc/hexanes.

General Procedure for the Formation of *N*-Phosphinoyl Aldimine Precursors

A dry 10-mL round-bottom flask, which was purged with nitrogen, was charged with diphenylphosphinamide (217 mg, 1 mmol), *p*-toluenesulfinic acid (234 mg, 1. mmol), α-chloro aldehyde (1.5 mmol) and dry Et_2O (6 mL). The reaction mixture was allowed to stir at room temperature until complete as determined by TLC (72 h), upon which the solid product precipitated out of the solution. The solid product was collected onto a sintered glass filter and washed sequentially with Et_2O to remove the excess aldehyde. Most products can be used in subsequent reactions without further purification. Products of higher purity can be obtained by recrystallization from EtOAc/hexanes.

Supporting Information

Supporting Information for this article, including reaction procedures, compound characterization and NMR spectra, is available. CCDC 882573 contains the crystallographic data for compound **3e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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