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Trimethylsilyl cyanide addition to aldimines and its application in the synthesis of (*S*)-phenylglycine methyl ester

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Abstract—The addition of TMSCN to a variety of arylaldimines (Strecker reaction) in the presence of $LiClO_4$ or $BF_3{\cdot}Et_2O$ in acetonitrile has been studied. The reaction provided the addition products in very high yields. The method has been successfully utilized for the synthesis of (*S*)-phenylglycine methyl ester.

α-Amino acids are of great biological and economical importance due to their significance in chemistry and biology.[1] Substantial progress has been made towards the development of efficient methods for the preparation of these compounds.[2] The asymmetric Strecker reaction is one of the most important methods for the synthesis of enantiomerically pure α-amino acids.[3] A variety of chiral catalysts has been developed to achieve high asymmetric induction for addition of cyanide (usually as TMSCN) to imines.[4] Since simple imines are not very stable, *N*-benzyl and *N*-allyl imines or hydrazones have been used as substrates. However, *N*-tosyl imines have not been used as substrates for addition of TMSCN. The diastereoselective Strecker synthesis involving the addition of cyanide to chiral imines obtained from aldehydes and chiral auxiliaries such as α-methylbenzylamine,[5] (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane,[6] 1-amino-tetra-*O*-pivaloyl-β-D-galactopyranose,[7] α-phenylglycinol,[8] sulfinimines[9] and (*S*)-1-amino-2-methoxymethylindoline (SAMI)[10] have already been investigated. In all these cases, removal of the chiral auxiliaries needed harsh conditions. However, the use of (*S*)-(4-methoxyphenyl)ethylamine derived aldimines could have a significant role in the diastereoselective Strecker synthesis where the chiral auxiliary can be easily removed using ceric ammonium nitrate (CAN) or DDQ under mild conditions. To the best of our knowledge this has not been reported in the literature. In this letter, we report that the addition of TMSCN to *N*-tosylaldimines is catalyzed by $LiClO_4$ or $BF_3{\cdot}Et_2O$. We further report that (*S*)-1-(4-methoxyphenyl)ethylamine is an excellent chiral auxiliary for asymmetric Strecker synthesis.

N-Tosyl phenylaldimine was treated with TMSCN (1.1 mmol) in the presence of 10 mol% of $LiClO_4$ or $BF_3{\cdot}OEt_2$ in acetonitrile (5 mL) at room temperature. After completion of the reaction (checked by TLC), aqueous $NaHCO_3$ solution (1 mL) was added. Work-up and purification over silica gel gave the corresponding α-aminonitrile in high yield (Table 1, entry 1). In order to evaluate the scope and limitations of this method, the reaction was extended to a wide variety of *N*-tosyl arylaldimines, *N*-benzyl imines and *N*-aryl imines. In all cases, the yields were excellent (Table 1). The *N*-tosyl aldimines were synthesized by condensation of aldehydes and *p*-toluenesulfonamide in the presence of a cata- lytic amount of $BF_3{\cdot}Et_2O$. In the case of the imine derived from phenylhydrazine and benzaldehyde, the addition of TMSCN did not take place.

The utility of the above reaction was demonstrated by synthesizing a chiral α-amino acid. Chiral imine **1** was prepared by condensation of (*S*)-(+)-1-(4-methoxyphenyl)ethylamine and benzaldehyde in the presence of anhydrous Na_2SO_4 in MeOH at room temperature for 24 h. Treatment of **1** with TMSCN at room temperature in the presence of either $BF_3{\cdot}Et_2O$ or $LiClO_4$ provided a mixture of diastereomers **2** (major; R_f 0.46 in 10% EtOAc in petroleum ether) and **3** (minor; R_f 0.40 in 10% EtOAc in petroleum ether) in a ratio of 4:1 and

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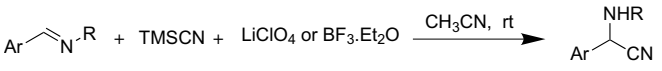
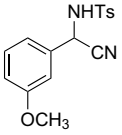
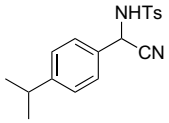
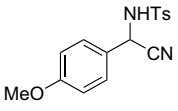
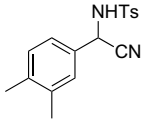
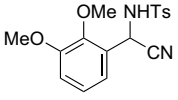
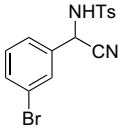
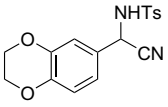
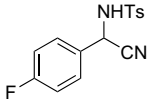
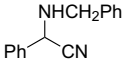
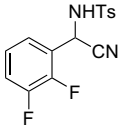
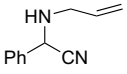
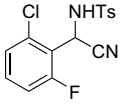
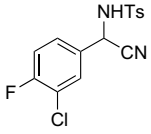
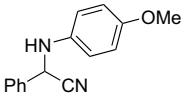
Table 1. Strecker reaction of a variety of aldimines in the presence of $LiClO_4$ or $BF_3{\cdot}OEt_2$[a]

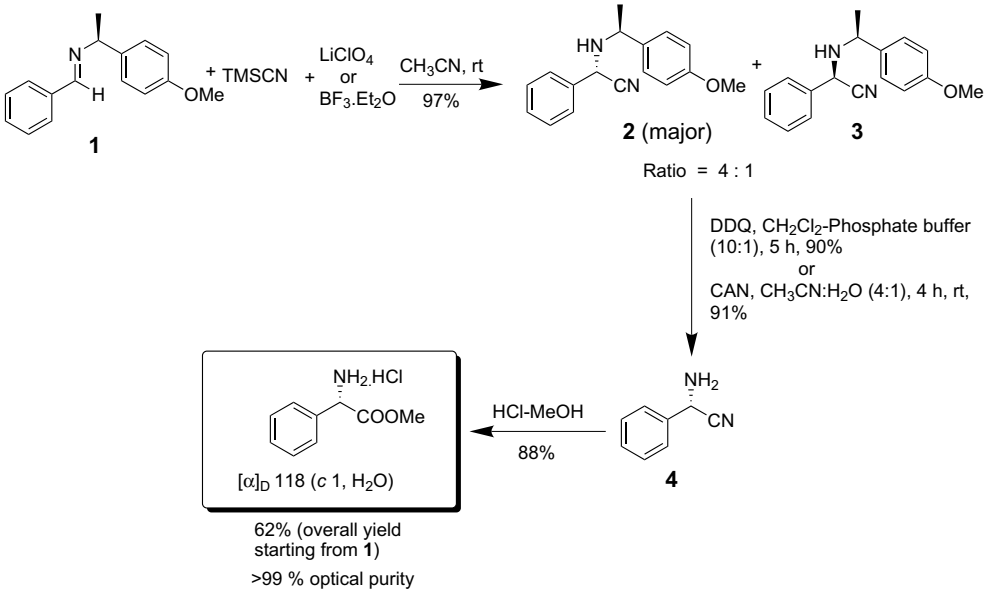


Entry	Product	$BF_3{\cdot}Et_2O$		$LiClO_4$		Entry	Product	$BF_3{\cdot}Et_2O$		$LiClO_4$	
		Time (h)	Yield[b] (%)	Time (h)	Yield[b] (%)			Time (h)	Yield[b] (%)	Time (h)	Yield[b] (%)
1		8	92	6	92	9		4	96	2	97
2		8	90	6	92	10		4	96	4	97
3		8	90	6	91	11		8	94	4	95
4		6	85	5	86	12		4	96	3	96
5		6	93	5	94	13		12	98	10	99
6		6	94	5	96	14		11	97	10	97
7		5	96	5	96	15		24	96	24	96
8		5	94	4	94	16		12	82	12	94

[a] In all cases 10 mol% of Lewis acid was used.
[b] Isolated yields after column chromatography.

in 97% yield (Scheme 1). Since these diastereomers showed good separation on TLC, they could be separated over silica gel by column chromatography. The major (*S*,*S*)-diastereomer **2** was treated with DDQ in DCM–phosphate buffer or CAN in CH_3CN–H_2O (4:1) to remove the chiral auxiliary. Thus, chiral aminonitrile **4** was obtained in 91% yield. This was treated with acidic methanol to provide (*S*)-phenylglycine methyl ester as its HCl salt in 88% yield and with >99% enantiopurity (Scheme 1).[11]

In summary, we have developed an efficient method for the TMSCN addition to aldimines in the presence of either $BF_3{\cdot}Et_2O$ or $LiClO_4$. We have further shown the



Scheme 1. Synthesis of (*S*)-phenylglycine methyl ester via the diastereoselective addition of TMSCN to chiral imine **1**.

application of the method in the synthesis of (*S*)-phenylglycine methyl ester in an efficient manner with high enantiopurity in an overall yield of 62%.

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