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Ring Opening of Pymisyl-Protected Aziridines with Organocuprates**

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Dedicated to Professor Mikael Begtrup on the occasion of his 70th birthday

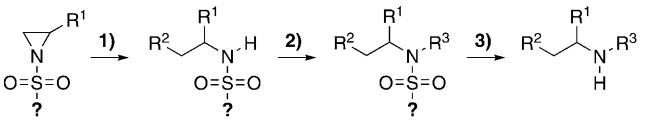
Abstract: The pyrimidine-2-sulfonyl (pymisyl) group is introduced as a new protecting group that can be used to activate aziridines towards ring opening. It is readily introduced and removed under mild conditions. Regioselective ring opening of pymisyl-protected 2-methyl-aziridine with organocuprates gives the corresponding sulfonamides in high yields, and the pymisyl group can subsequently be removed upon treatment with a thiolate. The versatility of this new nitrogen protecting group is illustrated with a new synthesis of Selegiline, a monoamine oxidase-B inhibitor marketed for the treatment of Parkinson's disease.

Keywords: nitrogen heterocycles · protecting groups · ring opening · small ring systems · synthetic methods

Introduction

The nucleophilic ring opening of aziridines has been studied intensively[1] and many different nucleophiles have been described, such as alcohols, amines, thiols, and stabilized carbanions. Perhaps the most challenging transformation is ring opening with nonstabilized carbon nucleophiles to form a new C–C bond. For this approach to be successful, the aziridine has to be activated by an electron-withdrawing substituent on the nitrogen. Different protecting groups have been utilized, among them diphenylphosphinyl[2] and *tert*-butoxycarbonyl (Boc),[3] but the tosyl (Ts) group has most often been employed due to its electron-withdrawing nature.[4–6] However, a major drawback with the Ts group is the harsh conditions necessary for deprotection, although progress has been made in developing milder protocols for its removal.[7] Other protecting groups have been used that can be removed under milder conditions, such as trimethylsilylethanesulfonyl (Ses)[8,9] and *tert*-butylsulfonyl (Bus).[10,11] The 2- and 4-nitrobenzenesulfonyl (nosyl, Ns) groups have been very well accepted by the synthetic community since their introduction by Fukuyama et al. in 1995.[12] Ns-protected amines are readily prepared using inexpensive, commercially available reagents, and Ns-sulfonamides are readily N-alkylated with alkyl halides or by using the Mitsunobu reaction.[13] The Ns group is stable to several different reagents (both acidic and basic) that cleave many other protecting groups, and can easily be removed in an orthogonal manner by the introduction of a thiol. A major drawback with the Ns group is the incompatibility with organometallic reagents, such as Grignards and organocuprates, due to the electrophilic nature of the nitro group. We were interested in addressing this shortcoming of the Ns group in connection with a research program directed towards the application of chiral aziridines in the synthesis of biologically active molecules. This hypothetical "Ns surrogate" would have to be applicable in the synthetic sequence outlined in Scheme 1.

The ability to successfully apply this approach with aryl cuprates would enable a very convergent way of preparing, for example, substituted phenethylamines, which is an important class of compounds with a very rich pharmacology.



Scheme 1. Proposed synthetic sequence for the targeted "Ns surrogate".

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[**] Pymisyl = pyrimidine-2-sulfonyl

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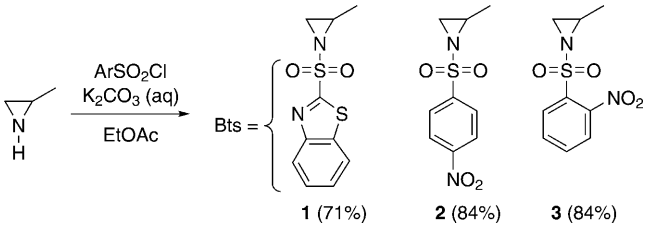
Results and Discussion

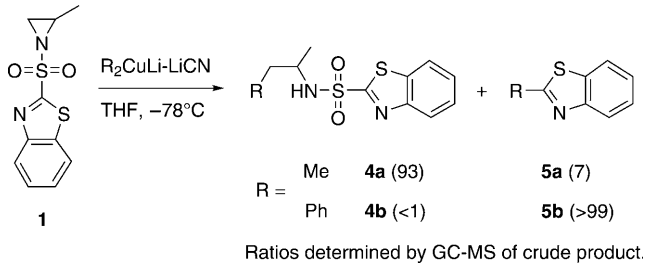
An initial survey of the literature indicated that the benzothiazole-2-sulfonyl group (Bts), introduced by Vedejs et al., would be a likely candidate as a replacement for Ns in organometallic reactions.[14] The Bts group can easily be introduced by using the corresponding sulfonyl chloride or pentafluorophenyl sulfonate ester,[15] and Bts-protected amines have been used as nucleophiles in the Mitsunobu reaction;[16] the Bts group can be removed with a thiol in analogy to the Ns group.[17] Furthermore, the Bts group has been shown to be stable under a range of different reaction conditions.[18]

Initially, the protected aziridines **1**–**3** (Scheme 2) were selected as test substrates for ring-opening reactions with organocuprates. The Ns-protected aziridines **2** and **3** were included to verify the presumed incompatibility with organometallic reagents. The N-sulfonylated aziridines were prepared in one step from commercially available (*rac*)-2-methylaziridine and the corresponding sulfonyl chlorides by adapting a literature procedure whereby the sulfonyl chloride was added to 2-methylaziridine in a two-phase mixture of ethyl acetate and aqueous potassium carbonate.[19] The Ns-protected aziridines **2** and **3** were treated with Me_2CuLi–LiCN and Ph_2CuLi–LiCN in THF at −78 °C. Not surprisingly, this led to very complex mixtures with extensive coloring of the reaction mixture, presumably through partial reduction of the nitro group, and **2** and **3** were not investigated any further.



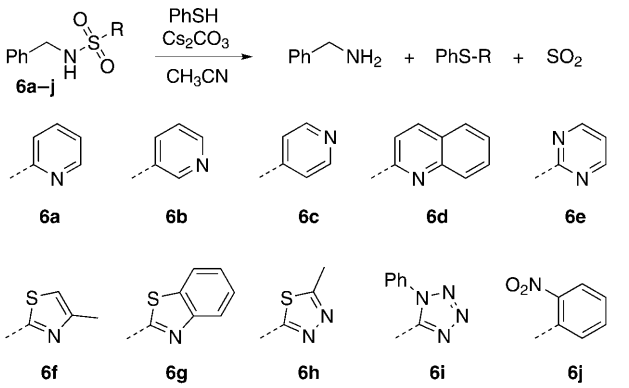
Scheme 2. Synthesis of *N*-sulfonyl-activated 2-methylaziridines.

The Bts-protected aziridine **1** reacted smoothly with Me_2CuLi–LiCN to give the desired Bts-protected 2-butanamine **4a** as the major product, accompanied by the formation of small amounts of **5a** (Scheme 3). However, the reaction with Ph_2CuLi–LiCN gave none of the expected Bts-protected amphetamine **4b**. Instead, 2-phenylbenzothiazole **5b**, which was presumably formed by nucleophilic attack on the 2-position of the benzothiazole core, was formed as the only detectable product. This result indicates a delicate balance between having a sulfonyl group with enough electrophilicity and stabilization for the assumed Meissenheimer-like intermediate to be deprotected by thiolates but, at the same time, be stable towards organocuprates. With this in mind, the search for an alternative sulfonyl group that could be removed by the action of thiolates, but at the same time be compatible with organocuprates, was initiated.



Scheme 3. Ring opening of Bts-protected 2-methylaziridine (**1**) with organocuprates.

Initially, the strategy was to access the corresponding *N*-benzyl-sulfonamides of new potential sulfonyl protecting groups to test whether the sulfonyl group could be removed with thiolates. Once this was established, we planned to move on to test the sulfonamide in the ring-opening reaction with organocuprates. Bearing in mind that the deprotection most likely occurs through a nucleophilic aromatic substitution addition–elimination mechanism (S_NAr), we focused on electron-deficient heteroaromatic sulfonyl groups containing the C=N unit because S_NAr is a common reaction pathway for the corresponding chlorides. Based on a literature search and on the availability of starting materials, the heterocyclic sulfonamides shown in Scheme 4 were selected; these included three pyridines, quinoline, thiazole, and pyrimidine. All were prepared by standard methods and the deprotection step was evaluated by treatment of the sulfonamides with thiophenol and cesium carbonate in acetonitrile at room temperature. If no deprotection took place at room temperature, the temperature was increased to 60 °C. The Bts and 2-Ns sulfonamides **6g** and **6j** were included for comparison.

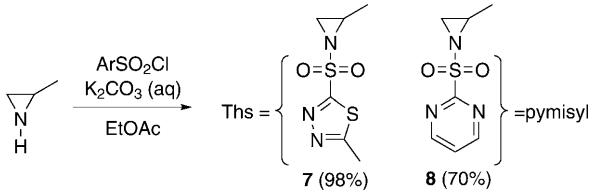


Substrate (**6a**–**j**)	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**
Relative rate of deprotection at RT	-	-	+	++	++	-	++	++	+++	++
pK_a value	10.4	10.1	9.6	10.2	9.3	9.6	8.7	8.2	7.2	10.1

Scheme 4. Evaluation of deprotection and acidity. The pK_a values measured are shown in brackets (pK_a for comparison: *N*-benzyl-4-nitrophenylsulfonamide (9.9), *N*-benzyl-benzenesulfonamide (10.8) and *N*-benzyl-4-methoxy-phenylsulfonamide (11.1)).

The 2- and 3-pyridine sulfonamides **6a** and **6b**, and the 2-thiazole sulfonamide **6f** were virtually unaffected by thiophenolate even at 60 °C, and the sulfonamides were recovered unchanged. Although it cannot be excluded that deprotection may occur under more forcing conditions, this was not pursued because a substitute for the Ns group would have to be readily deprotected under mild conditions to be attractive as a protecting group. The 2-pyrimidine **6e**, 1,3,4-thiadiazole **6h**, and tetrazole sulfonamide **6i** were all readily deprotected at room temperature in analogy to the Bts (**6g**) and Ns (**6j**) sulfonamides. Although no detailed kinetic study was performed, the relative rate of deprotection of the sulfonamides was established to be **6i** ≫ **6g** > **6d**, **6e**, **6h**, **6j** ≫ **6c**. Considering that both **6g** and **6h**[14] were deprotected at ambient temperature, it is somewhat puzzling that the thiazole sulfonamide **6f** failed to react even at 60 °C.

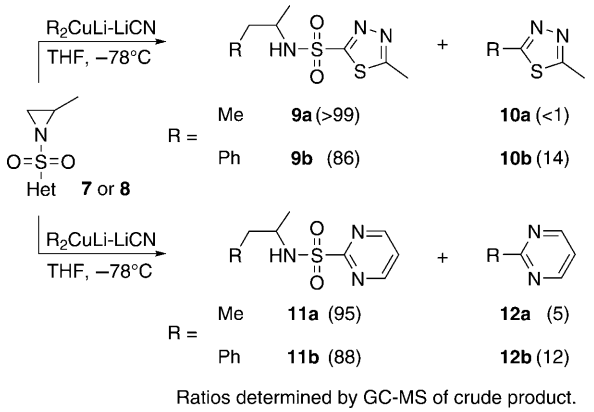
The acidity of the sulfonamides **6a**–**j** in water was also determined (Scheme 4). Nosylamides are sufficiently acidic to be useful in the Mitsunobu reaction, and any useful surrogate group should retain this important feature. All of the tested sulfonamides **6a**–**i** had a pK_a value that was lower or close to that of nosylamide **6j**. The large span in pK_a values, from *N*-benzyl-4-methoxyphenylsulfonamide (pK_a 11.1) to tetrazole sulfonamide **6i** (pK_a 7.2), is noteworthy. Four new candidates arose from the screening: **6d**, **6e**, **6h**, and **6i**. The relatively high cost of the precursor for **6d** and the low yield of the sulfonyl chloride needed for **6i**,[20] led us to continue with **6e** and **6h**. The sulfonyl-protected aziridines **7** and **8** were prepared by adding 1,3,4-thiadiazole-2-sulfonyl chloride (ThsCl) or pyrimidine-2-sulfonyl chloride (pymisyl chloride; generated in situ) to 2-methylaziridine in a two-phase mixture of ethyl acetate and aqueous potassium carbonate (Scheme 5). These sulfonyl chlorides have limited stability and can be substituted by the much more stable pentafluorophenyl sulfonate esters.[15]



Scheme 5. Synthesis of Ths- and pymisyl-activated 2-methylazirines **7** and **8**.

Attempts to use triethylamine or solid potassium carbonate in dichloromethane in the synthesis of **7** and **8** gave low yields of the N-sulfonylated aziridines, accompanied by by-products formed by chloride ion ring opening of the aziridine; which is a testimony to the high propensity of sulfonyl-activated aziridines to react with nucleophiles.

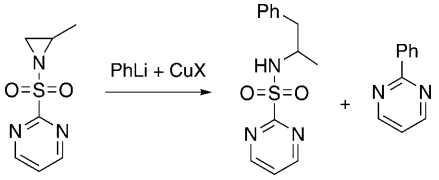
The activated aziridines **7** and **8** were reacted with Me_2CuLi–LiCN and Ph_2CuLi–LiCN (Scheme 6). The Ths-protected aziridine **7** reacted readily with both methyl and phenyl cuprates, giving a high ratio of ring opening to deprotection. Unfortunately, compound **7** proved to be unstable. Although it appeared to be stable in solution and towards moist silica, a clear, colorless solution of pure **7** darkened and tended to polymerize when concentrated in vacuo at 4 °C; when the material was stored in a freezer it eventually transformed into a dark red-brown resin. Thus, the Ths group was not investigated any further.



Scheme 6. Addition of organocuprates to **7** and **8**.

To our delight, the pymisyl-activated aziridin **8** was ring opened with both methyl and phenyl cuprates to give the desired pymisyl-protected amines. Furthermore, solid **8** was stable at room temperature for months, and was thus chosen for further investigations. To optimize the reaction, a series of phenylcuprates were screened (Table 1). The cuprate formed with $CuBr{\cdot}SMe_2$ suppressed deprotection, and **11b** was isolated in 83% yield; other phenylcuprates gave lower yields. It should be noted that, although no ring-opened 2-thionyl-containing product could be detected with 2-thienyl-Cu(CN)Li and PhLi, a small amount (ca. 5%) of thien-2-yl-2-pyrimidine was observed. The latter presumably results from transfer of the thiophene from the cuprate, which is normally considered to be an inert "dummy ligand".[21]

Table 1. Testing of different phenylcuprates. Ratio of products determined by GC-MS.

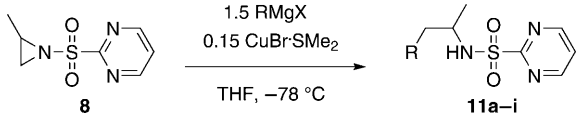


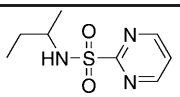
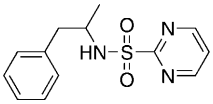
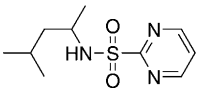
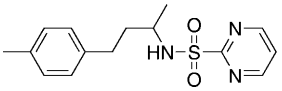
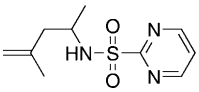
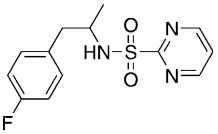
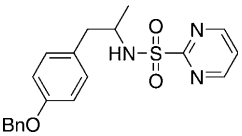
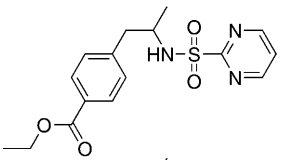
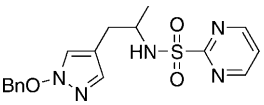
Entry	Cuprate	**11b** [%][a]	**12b** [%]	Other [%][b]
1	CuCN + 2PhLi	88 (50)	12	
2	CuCN + PhLi	60	< 1	40
3	CuCN·2LiCl + 2PhLi	79	≈ 1	20
4	$CuBr{\cdot}SMe_2$ + 2PhLi	> 99 (83)	< 1	
5	2-ThienylCu(CN)Li + PhLi	75 (56)	2 + 5[c]	23

[a] Isolated yield in parenthesis. [b] Unreacted **8** and chloride ring-opened products, exclusively or partly formed during workup from unreacted **8**. [c] Thien-2-yl-2-pyrimidine.

To broaden the scope of the reaction, Grignard reagents were also screened as nucleophiles because they are more easily handled than organolithium compounds. Functionalized Grignard reagents are widely available either commercially or by taking advantage of recent progress in halogen–magnesium exchange reactions of substituted aryl- and heteroaryl halides.[22] Furthermore, it has been shown that Grignard reagents react with N-activated aziridines in the presence of only catalytic amounts of copper salts.[4,23] A variety of Grignard reagents, both aliphatic and aromatic, were screened with 15 mol% $CuBr{\cdot}SMe_2$ and, in most cases, this provided the ring-opened sulfonamides in high yields as a single regioisomer (Table 2). Isopropylmagnesium chloride and 4-methylbenzylmagnesium chloride (Table 2, entries 3 and 4) gave low yields when 15 mol% $CuBr{\cdot}SMe_2$ was used. However, employing a stoichiometric amount of $CuBr{\cdot}SMe_2$ improved the yields substantially to 80% in both instances. Although $CuBr{\cdot}SMe_2$ fully suppressed the deprotection reaction with PhLi, very small amounts (ca. 2%) of the byproduct resulting from deprotection was observed with the Grignard reagents. Omission of $CuBr{\cdot}SMe_2$ resulted in the exclusive formation of 2-phenylpyrimidine at −78°C when **8** was treated with PhMgCl, whereas a 1:10 ratio of $CuBr{\cdot}SMe_2$ to Grignard reagent effectively directed the reaction towards ring opening, as seen from Table 2.

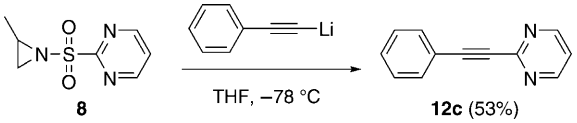
Table 2. $CuBr{\cdot}SMe_2$-catalyzed ring opening of **8** with Grignard reagents.



Entry	Product	11	Yield [%][a]
1		**11a**	96
2		**11b**	85 0[b]
3		**11c**	0 80[c]
4		**11d**	7 80[c]
5		**11e**	67
6		**11f**	84
7		**11g**	87
8		**11h**	82
9		**11i**	68

[a] Isolated yields after column chromatography. [b] No $CuBr{\cdot}SMe_2$ was added and 2-phenylpyrimidine **12b** was formed exclusively. [c] 150 mol% $CuBr{\cdot}SMe_2$ was used.

Phenylacetylidemagnesium chloride failed to deliver any of the desired product with either catalytic or stoichiometric amounts of $CuBr{\cdot}SMe_2$, and lithium phenylacetylide produced 2-(phenylethynyl)pyrimidine (**12c**) in 53% isolated yield, see Scheme 7. The failure of the pymisyl-protected aziridine to deliver any of the ring-opened product is contrasted by the successful ring opening of Ns-activated aziridines with lithium acetylides.[24] Nevertheless, this deprotection reaction might prove useful as a transition-metal-free synthesis of 2-substituted pyrimidines, which are otherwise typically accessed through cross-coupling of 2-halopyrimidines with palladium or nickel catalysts. In some cases the reaction gave small amounts (1–4%) of a byproduct resulting from the ring opening of the aziridine with chloride ions from the aqueous NH_4Cl used to quench the reactions, and this proved to be difficult to separate from the desired products by column chromatography. Thus, the reactions were quenched with an ammonium sulfate/ammonia mixture to avoid the formation of this byproduct in case unreacted **8** was present in the crude mixture.

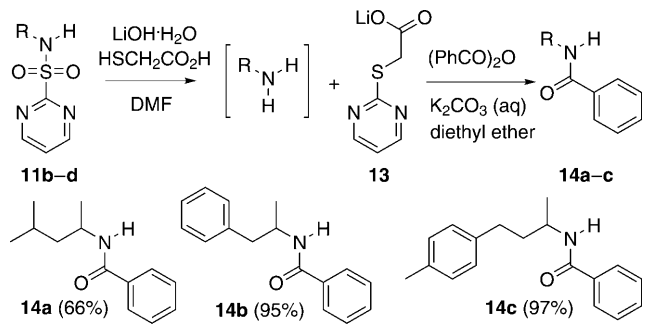


Scheme 7. Reaction of **8** with lithium phenylacetylide.

Overall, the reaction worked very well with both alkyl- and arylcuprates, and the pymisyl group initially satisfied the criteria for being an Ns group surrogate that could be applicable in organometallic chemistry. To show that the pymisyl group could be readily removed under conditions similar to those used to remove the Ns group, three of the products obtained in Table 2 were deprotected (Scheme 8).

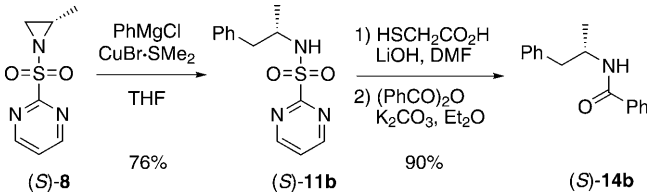
The free amines were converted directly into the corresponding benzamides by reaction with benzoic acid anhydride (one pot) because this greatly facilitated the isolation of the products. Using 2-mercaptoacetic acid instead of thiophenolate in the deprotection meant that the byproduct 2-(pyrimidin-2-ylthio)acetic acid (**13**) was easily removed by a simple aqueous alkaline workup, and the pure benzamides (**14a–c**) were isolated in 66–97% yield.

To investigate the stereochemical integrity of the chiral center during the cuprate addition and deprotection, we ac-



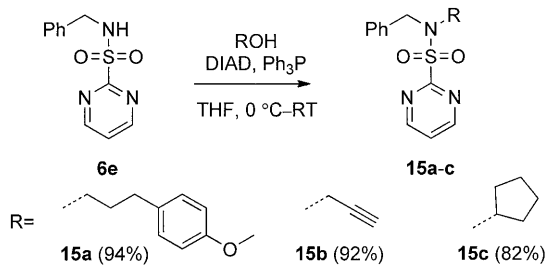
Scheme 8. Deprotection of the pymisyl group and direct conversion of amines into benzamides.

cessed (*S*)-**8** in enantiopure form from (*S*)-alaninol. We were able to show by chiral HPLC that ring opening with phenylmagnesium chloride, deprotection, and benzoylation proceeds without any detectable racemization, and that (*S*)-**14b** was obtained in optically pure form (Scheme 9).



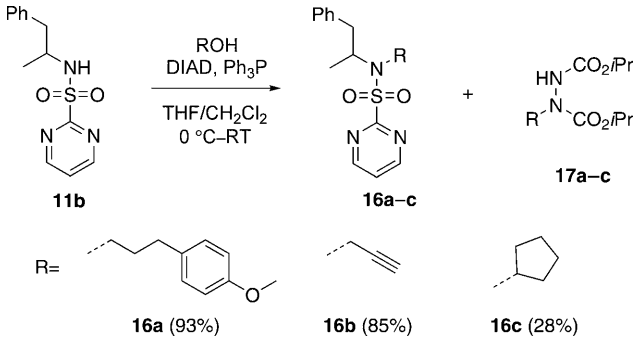
Scheme 9. Synthesis of (*S*)-**14b**. The stereochemical integrity is preserved during ring opening, acylation, and deprotection.

To fully function as an Ns group surrogate, N-substituted 2-pyrimidine sulfonamides should participate in the Mitsunobu reaction.[25] With a pK_a of 9.6, *N*-benzyl 2-pyrimidine sulfonamide (**6e**) compares favorably with the corresponding *N*-benzyl-2-Ns-sulfonamide (**6j**; pK_a = 10.1) and, indeed, compound **6e** underwent N-alkylation with alcohols under the conditions originally applied by Fukuyama et al. to Ns-sulfonamides,[12] in excellent yields (Scheme 10).



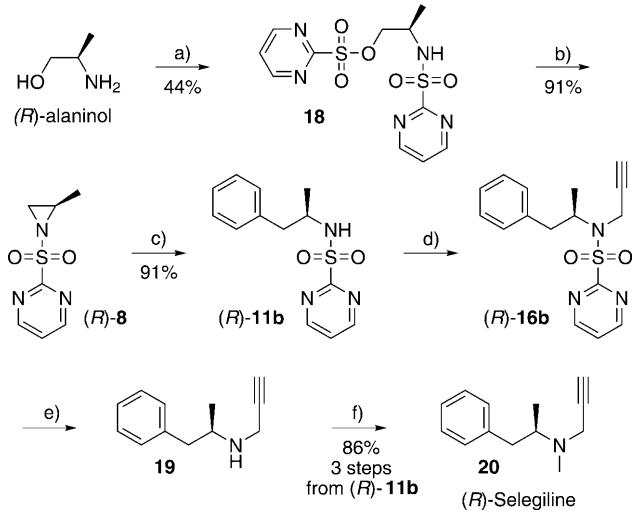
Scheme 10. Mitsunobu alkylation of **6e**. Reagents and conditions: Ph_3P (1.5 equiv), ROH (1.3 equiv), THF, then diisopropyl azodicarboxylate (DIAD; 1.5 equiv), 0 °C to RT.

When the same reaction conditions were applied to **11b** to validate a ring-opening/N-alkylation strategy using Mitsunobu conditions, the change in the steric bulk was found to have a large impact on the outcome of the reaction. The starting material **11b** was not fully consumed and substantial amounts of monoalkylated diisopropyl hydrazine-1,2-dicarboxylate **17a–c** was formed. Reversing the order of addition to preform the Ph_3P–DIAD betaine and raising the amounts of Ph_3P, DIAD, and ROH gave good yields of **16a** and **16b**, but when cyclopentanol was used, the main product was still **17c** (Scheme 11).



Scheme 11. Mitsunobu alkylation of **11b**. Reagents and conditions: Ph_3P (2 equiv), DIAD (2 equiv), CH_2Cl_2/THF, 30 min, 0 °C, then ROH (1.8 equiv), 0 °C to RT.

Having verified that the pymisyl group functions very well as a Ns group surrogate and is stable towards cuprates, we opted to demonstrate its utility in synthesis by developing a new approach to Selegiline—a monoamine oxidase-B inhibitor marketed for the treatment of Parkinson's disease.[26] Reacting (*R*)-alaninol with three equivalents of pymisyl chloride gave the bis-pymisyl-protected derivative **18** in 44% yield, as seen in Scheme 12. Subsequent cyclization yielded enantiomerically pure (*R*)-**8** in 91% yield. Ring opening with PhMgCl under the conditions detailed in



Scheme 12. Synthesis of Selegiline. Reagents and conditions: a) Pymisyl chloride (3.3 equiv), 4-dimethylaminopyridine (DMAP; 0.1 equiv), pyridine, CH_2Cl_2, −35 to 0 °C; b) K_2CO_3 (2 equiv), CH_3CN, CH_2Cl_2, RT, 25 min; c) PhMgCl (1.5 equiv), CuBr·SMe_2 (DMS) (0.15 equiv), THF, −78 °C; d and e) propargylic bromide (1.3 equiv), K_2CO_3, DMF, RT followed by 2-mercaptoacetic acid (2.5 equiv), LiOH·H_2O (5 equiv), DMF; f) $NaBH_3CN$ (1.6 equiv), formaldehyde (37%, 5 equiv), CH_3CN, 0 °C to RT, 20 min.

Table 2 provided the pymisyl-protected amphetamine (*R*)-**11b**. The final three steps were performed as follows: Alkylation with propargylic bromide, followed by deprotection with 2-mercaptoacetic acid in the same pot, gave secondary amine **19**. After aqueous workup, the methyl group on the nitrogen was introduced by reductive alkylation to give (*R*)-selegiline (**20**) in 86% yield over three steps from (*R*)-**11b**. This modular protocol is very flexible and high-yielding, allowing for easy manipulation of the selegiline structure.

The position of the ^{1}H and ^{13}C NMR signals and the specific rotation of our product **20** differed significantly from the data reported by Sudalai et al.[27,28] The product formed by using the current procedure had the same sign for the specific optical rotation, but its value was lower by a factor of eight, even though we could only detect a single enantiomer by chiral HPLC. We therefore carefully compared our data to those of an authentic sample of (*R*)-Selegeline[29] and found that the ^{1}H and ^{13}C NMR signals of the authentic product were in perfect agreement. Furthermore, the specific rotation of our product also matched that of the authentic sample. This leaves us with no doubt about the identity and purity of our product **20** (see the Supporting Information for further details). The reason for the large discrepancies between our data and those reported by Sudalai et al. is unclear.

Conclusion

The pymisyl sulfonyl group has been introduced as a new nitrogen protection group. The required sulfonyl chloride is readily prepared from inexpensive starting materials. The pymisyl group activates aziridines towards ring opening with organocuprates. The resulting sulfonamide can be alkylated with alkyl halides or alcohols by using the Mitsunobu protocol, and the pymisyl group can be removed under very mild conditions by using a thiolate. The versatility of this new protecting group was demonstrated in a convergent synthesis of Selegiline, which is a drug currently marketed for the treatment of Parkinson's disease. The sequence from the key intermediate (*R*)-**8**, the pymisyl-protected aziridine, proceeds very efficiently to give Selegiline in 78% yield over four steps.

Experimental Section

2-(2-Methylaziridin-1-ylsulfonyl)pyrimidine (**8**): Sodium hypochlorite (298 mL, 1.55 M, 0.462 mol) was slowly added to a mechanically stirred mixture of 2 M HCl (305 mL) and CH_2Cl_2 (400 mL) in a three-necked flask, keeping the internal temperature below −5 °C by intermittent cooling in an acetone–dry-ice bath. 2-Mercaptopyrimidine (15.7 g, 0.140 mol) was added as a solid in small portions to the yellow-greenish solution, keeping the temperature at −10 to −5 °C. After the addition was complete, stirring was continued for 10 min keeping the internal temperature at −10 to −5 °C (by then no remaining solid 2-mercaptopyrimidine (yellow) could be seen), then excess chlorine (indicated by a yellow-greenish color of the organic phase) was quenched by adding ice-cold 10% aqueous Na_2SO_3 (until KI/starch-paper no longer gave a positive reaction). The reaction mixture was then transferred to a precooled separating funnel and the organic layer was drained at a reasonable rate (faster than dropwise) into a vigorously stirred, two-phase mixture of 2-methylaziridine (8.85 mL, 0.125 mmol) in CH_2Cl_2 (100 mL) and 1 M K_2CO_3 (200 mL, 0.2 mol) at −5 to −2 °C. The aqueous layer in the separating funnel was extracted with cold (−20 °C) CH_2Cl_2 (40 mL) and the organic layer was added to the reaction mixture. After stirring for 30 min on an ice bath, the organic layer was washed with brine (100 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue (22.9 g) was purified by dry column vacuum chromatography on silica (EtOAc/heptane, 0:1→9:1) to afford the title compound **8** as a colorless solid after crystallization in the freezer (17.5 g, 70%). A small sample was recrystallized from EtOAc/hexane (40 °C). M.p. 55–56 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.98 (d, J = 4.8 Hz, 2H), 7.58 (t, J = 4.9 Hz, 1H), 3.21–3.09 (m, 1H), 2.94 (d, J = 6.9 Hz, 1H), 2.26 (d, J = 4.9 Hz, 1H), 1.42–1.34 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 158.8, 123.9, 37.3, 35.6, 16.8; elemental analysis calcd (%) for $C_7H_9N_3O_2S$ (199.1): C 42.20; H 4.55; N 21.09; found: C 42.43; H 4.41; N 21.35.

General procedure for CuBr·SMe$_2$-catalyzed ring opening of 8 with Grignard reagents: CuBr·SMe_2 (62 mg, 0.30 mmol) was added to a flame-dried Schlenk flask under nitrogen. THF was added and the slurry was stirred at RT for 15 min and then cooled to −55 °C (externally). The Grignard reagent (3.0 mmol) in THF was added dropwise by syringe and the mixture was stirred for 30–45 min at −50 °C and then cooled to −78 °C. 2-(2-Methylaziridin-1-ylsulfonyl)pyrimidine (397 mg, 2.0 mmol) in THF (3.5 mL) was added dropwise by syringe and the reaction mixture was stirred at −78 °C for 0.5–4 h. The reaction was quenched at −78 °C with saturated NH_4Cl (8 mL) and allowed to warm to RT in open air. The mixture was transferred to a 100 mL flask (using some THF, water and sat. aqueous NH_4Cl (4 mL)) and concentrated in vacuo to remove THF. CH_2Cl_2 (15–20 mL) was added and, if undissolved solid remained at this point, the mixture was filtered through Celite and the Celite was washed with CH_2Cl_2 and water. Otherwise the aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography afforded the pure sulfonamides.

Synthesis of (*R*)-Selegeline: (*R*)-2-(Pyrimidine-2-sulfonamido)propylpyrimidine-2-sulfonate (18): Sodium hypochlorite (72.1 mL, 1.83 M in H_2O, 132 mmol) was slowly added to a mechanically stirred mixture of 2-mercaptopyrimidine (4.48 g, 40 mmol) in 2 M HCl/1.5 M $CaCl_2$ (101 mL) and CH_2Cl_2 (130 mL) keeping the internal temperature at −10 to −7 °C with intermittent cooling in an acetone–dry-ice bath. After the addition was complete, stirring was continued for 15 min at −10 °C. Excess chlorine was quenched with cold 1 M Na_2SO_3 (10–12 mL) at −10 °C. The organic layer was separated through a Whatman phase separator 1 PS into a 250 mL two-necked flask cooled in a dry-ice–acetone bath with argon passing through the flask as a blanketing gas. A solution of (*R*)-alaninol (897 mg, 11.9 mmol), 4-dimethylaminopyridine (122 mg, 1 mmol), and pyridine (8.05 mL, 100 mmol) in anhydrous CH_2Cl_2 (5 mL) was slowly added below −35 °C (10 min). The reaction mixture was slowly allowed to warm to 0 °C (1.5 h) and then washed with 1 M $NaHSO_4$ (5×30 mL). The combined washings were extracted with CH_2Cl_2 (2×40 mL) and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was redissolved in CH_2Cl_2 and a small amount of CH_3CN and concentrated in vacuo with *i*PrOH (20–25 mL) until a white solid started to crystallize (ca. 18–20 g solvent). The mixture was cooled in an ice bath for 1 h and filtered. The white solid (2.19 g) was recrystallized from an EtOH/CH_3CN (19:1) mixture (ca. 32 mL) to afford **18** as a colorless solid (1.88 g, 44%). M.p. 122 °C (dec.: sample melts with gas formation and yellow coloration). $[\alpha]_D^{20}$ = +27.5 (*c* 1.04, CH_3CN); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.10 (d, J = 4.9 Hz, 2H), 9.00 (d, J = 4.8 Hz, 2H), 8.31 (d, J = 7.5 Hz, 1H), 7.91 (t, J = 4.9 Hz, 1H), 7.75 (t, J = 4.8 Hz, 1H), 4.34 (dd, J = 4.4, 8.9 Hz, 1H), 4.30 (dd, J = 4.1, 8.9 Hz, 1H), 3.90–3.75 (m, 1H), 3.31 (s, 3H), 1.13 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 165.8, 161.9, 159.4, 158.8, 125.2, 123.8, 75.6, 48.9, 17.2 ppm; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{13}N_5O_5S_2$: 360.0436 [*M*+H]; found: 306.0440.

(*R*)-2-(2-Methylaziridin-1-ylsulfonyl)pyrimidine ((*R*)-8): K_2CO_3 (2 M, 4 mL, 8 mmol) was added to a mixture of **18** (1.473 g, 4.1 mmol) in a CH_3CN/CH_2Cl_2 (1:1) mixture (32 mL) at RT. After stirring for 25 min at RT the mixture was diluted with CH_2Cl_2 (40 mL) and washed with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were washed with K_2CO_3 (0.5 M, 20 mL), KH_2PO_4 (0.25 M, 20 mL), and brine (25 mL); dried over Na_2SO_4; and concentrated in vacuo to afford (*R*)-**8** as an analytically pure, colorless oil (744 mg, 91%). $[\alpha]_D^{20} = -44.5$ (*c* 1.01, $CHCl_3$). Chiral HPLC analysis: only one peak at 21.3 min (>99% *ee*) was observed under the following conditions: Chiralcel OJ-H (0.46×25 cm) column; EtOH (0.1% Et_3N, 0.1% AcOH)/heptane (0.1% Et_3N, 0.1% AcOH), 35:65; flow: 0.7 mL min^{-1}; $\lambda = 280$ nm. Racemic sample: $t_R = 19.7$ ((*S*)-**8**) and 21.4 min ((*R*)-**8**).

(*R*)-*N*-(1-Phenylpropan-2-yl)pyrimidine-2-sulfonamide ((*R*)-14b): CuBr-DMS (113 mg, 0.54 mmol) was added to a flame-dried Schlenk flask under nitrogen. THF (22 mL) was added and the slurry was stirred at RT for 15 min and then cooled to −50 °C (externally). Phenylmagnesium chloride (3.13 mL, 1.72 M in THF, 5.38 mmol) was added dropwise and the mixture was stirred at −50 °C for 45 min. Compound (*R*)-**8** (0.715 g, 3.59 mmol) in THF (7 mL) was added dropwise by syringe at −78 °C and the reaction mixture was stirred for 1 h at −78 °C before being quenched with a saturated aqueous solution of NH_4Cl (16 mL) and allowed to warm to RT in open air. The mixture was transferred to a 250 mL flask using some THF, water and a saturated aqueous solution of NH_4Cl (8 mL), and concentrated in vacuo to remove the THF. The aqueous residue was extracted with CH_2Cl_2 (3×35 mL) and the combined layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica (EtOAc/heptane; 1:1 to 2:1) to afford (*R*)-**14b** as a colorless solid (907 mg, 88%). M.p. 88–89 °C. $[\alpha]_D^{20} = -9.6$ (*c* 1.01, $CHCl_3$).

(*R*)-*N*-(1-Phenylpropan-2-yl)prop-2-yn-1-amine (Des-methyl Selegiline) (19): A mixture of compound (*R*)-**14b** (279.5 mg, 1.008 mmol) and K_2CO_3 (278 mg, 2.0 mmol) in DMF (1.2 mL) was stirred at RT for 5 min. Propagylic bromide (140 μL, 1.30 mmol, 80% in toluene) was added and the mixture was stirred under argon until TLC ($CHCl_3/Et_2O$, 8:2) showed full conversion of (*R*)-**14b** (5 h). The mixture was diluted with DMF (1.8 mL) and 2-mercaptoacetic acid (174 μL, 2.50 mmol) and $LiOH{\cdot}H_2O$ (210 mg, 5.00 mmol) were added. The mixture was stirred under argon for 1 h at RT (by which time the mixture had turned into a gel making stirring impossible), then water (0.5 mL) was added to dissolve the gel and stirring was continued overnight (12 h). The mixture was partitioned between Et_2O (30 mL) and a 1:1 mixture of saturated aqueous solution of $NaHCO_3$ and water (20 mL). The aqueous layer was extracted with Et_2O (20 mL) and the combined organic layers were washed first with a mixture of sat. $NaHCO_3$ (5 mL) and 2×5% LiCl (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford **19** as a colorless oil containing trace amounts of DMF and toluene (185 mg, 106%). This material was used in the next step without further purification.

(*R*)-Selegiline (20): Compound **19** (180 mg, ca. 1 mmol) and formaldehyde (375 μL, 5 mmol, 37% in water) in CH_3CN (1.10 mL), cooled on an ice bath, was treated with sodium cyanoborohydride (105 mg, 1.60 mmol). The ice bath was removed after 2 min and the mixture was stirred at RT for 20 min. The reaction mixture was diluted with 0.1 M KOH (2 mL) and extracted with inhibitor-free Et_2O (5 mL then 2× 3 mL). The combined organic layers were dried over K_2CO_3 and concentrated in vacuo at 20 °C (product is volatile!). The residue was purified by column chromatography on silica (inhibitor-free Et_2O/PE, 1:1) to afford **20** as a colorless oil (164 mg, 86% from (*R*)-**11b**). $[\alpha]_D^{20} = -1.29$ (*c* 6.43, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$–7.24 (m, 2H), 7.22–7.15 (m, 3H), 3.44 (d, $J = 2.4$ Hz, 2H), 3.10–2.93 (m, 2H), 2.47–2.34 (m, 4H), 2.24 (t, $J = 2.4$ Hz, 1H), 0.97 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, relative to TMS): $\delta = 140.2$, 129.3, 128.3, 126.0, 80.3, 72.6, 59.5, 43.2, 39.8, 37.5, 15.1 ppm. Chiral HPLC analysis: only one peak at 5.6 min (>99% *ee*) was observed under the following conditions: LUX cellulose-1 (0.46×25 cm) column; 2-propanol (0.1% Et_3N, 0.1% AcOH)/heptane (0.1% Et_3N, 0.1% AcOH), 2:98; flow: 1.0 mL min^{-1}; $\lambda =$ 255 nm. Racemic sample: $t_R = 5.3$ ((*S*)-**20**), 5.6 min ((*R*)-**20**).

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