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Investigation of a Flexible Enantiospecific Approach to Aziridines

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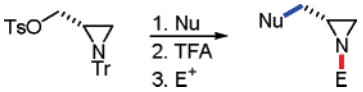
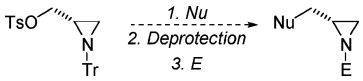


A flexible approach to functionalized and enantioenriched aziridines has been developed from an intermediate aziridinylmethyl tosylate. This protocol features a Cu-catalyzed Grignard substitution reaction that allows a range of functionalized organic fragments to be incorporated. Moreover, a convenient one-pot procedure is outlined that allows the trityl group to be exchanged for a range of common *N*-protecting groups.

Aziridines are extremely useful building blocks in organic synthesis because of their ability to function as reactive electrophilic substrates.[1] They undergo a large number of nucleophilic ring-opening processes, often with excellent control of regio- and stereoselectivity. Accordingly, a great many methods have been developed for the preparation of these compounds in enantioenriched form, including asymmetric catalytic aziridination,[2] kinetic resolution,[3] stereoselective aziridine functionalization,[4] and enantiospecific synthesis from α-amino acids.[5] Recent work in this department has focused on the exploitation of aziridines in [3 + 3] annulation processes for the stereoselective synthesis of piperidines.[6] A prerequisite of this methodology is the availability of enantiopure aziridine starting materials; however, our substrates to-date have been limited to those that are accessible from commercial α-amino acid sources. Accordingly, we sought to develop a flexible route to enantiopure 2-substituted aziridines that would allow a range of groups to be incorporated from a single late-stage intermediate, while providing a means for flexibility in *N*-protecting group incorporation.

A survey of the literature revealed some useful manifestations of this general concept. Specifically, De Kimpe demonstrated that *N*-Ts aziridinylmethyl bromides underwent smooth substitution with Li_2CuCNR_2 and R_2CuLi (R = Me, Bu),[7] while Bergmeier demonstrated that enantiopure Ts-protected aziridinylmethyl tosylates underwent substitution with dialkylcuprates via a ring opening-cyclization mechanism.[8] This study also highlighted that the reaction was unsuccessful for Ph- and vinylmetal species and that the products could be prone to further addition. Sweeney et al. showed that similar chemistry could be carried out using diphenylphosphoryl- (Dpp) in place of Ts-groups. Furthermore, the employment of Grignard reagents provided the opportunity to use substoichiometric quantitites of Cu-salts.[9] These studies also confirmed that the substitution proceeded via initial ring opening of the aziridine. Finally, De Kimpe has demonstrated that dialkylcuprates react with *N*-alkyl aziridinylmethyl bromides, although 2−3 equiv of the cuprate are required and only alkyl- and Ph-groups may be transferred.[10] In this case, direct substitution is more likely although this was not confirmed. For the purposes of employing this strategy as a general method to access enantiopure functionalized aziridines for further elaboration, we wanted to establish a general protocol that allowed the use of functionalized organometallic species. Furthermore, we opted to utilize a trityl protecting group in order to discourage competing ring opening processes and to facilitate the introduction of various activating groups at the aziridine *N*-atom at a late stage (Scheme 1).

SCHEME 1. Functionalization of Enantiopure Tr-Protected Aziridine



Our studies began by developing a practical synthesis of enantiopure tosylate **2**. Accordingly, **1** was prepared in four steps from commercial (*S*)-serine methyl ester hydrochloride according to literature procedures[11] and converted into tosylate **2** under standard conditions in high yield (Scheme 2).

With the key aziridine intermediate in hand, we turned our attention to the Cu-catalyzed alkylation chemistry (Table 1).

As outlined in entries 1 and 2, alkyl Grignard reagents **3** and **4** substituted in high yield as expected, although the yield

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(1) For reviews on aziridine chemistry see: (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (d) Yudin, A. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH.: Weinheim, Germany, 2006.
(2) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.
(3) Kim, S. K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952.
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(5) Craig, D.; Berry, M. B. *Synlett* **1992**, 41.
(6) (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596. (b) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286. (c) Moran, W. J.; Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2003**, *5*, 3427. (d) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207. (e) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett* **2005**, *7*, 2993. (f) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089. (g) Provoost, O. Y.; Hedley, S. J.; Hazelwood, A. J.; Harrity, J. P. A. *Tetrahedron Lett.* **2006**, *47*, 331.
(7) D'hooghe, M.; Kerkaert, I.; Rottiers, M.; De Kimpe, N. *Tetrahedron* **2004**, *60*, 3637.
(8) (a) Bergmeier, S. C.; Punit, P. S. *J. Org. Chem.* **1997**, *62*, 2671. (b) Lapinsky, D. J.; Bergmeier, S. C. *Tetrahedron Lett.* **2001**, *42*, 8583.
(9) Sweeney, J. B.; Cantrill, A. A. *Tetrahedron* **2003**, *59*, 3677.
(10) (a) D'hooghe, M.; De Kimpe, N. *Synlett* **2004**, 271. (b) D'hooghe, M.; Rottiers, M.; Jolie, R.; De Kimpe, N. *Synlett* **2005**, 931.
(11) (a) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309. (b) Bosche, U.; Nubbermeyer, U. *Tetrahedron* **1999**, *55*, 6883.

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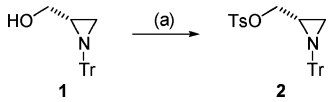
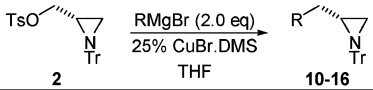
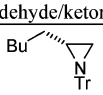
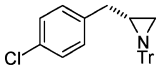
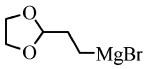
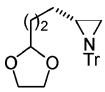
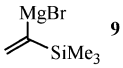
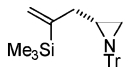
SCHEME 2. Synthesis of Tr-Protected Aziridine Intermediate[a]



[a] Reagents and conditions: (a) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 16 h; 92%.

TABLE 1. Cu-Catalyzed Alkylation Reactions

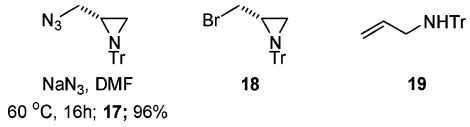


entry	Grignard[a]	aldehyde/ketone	yield
1	BuMgBr **3**		**10;** 86%
2	CH_2=$CH(CH_2)_2MgBr$ **4**		**11;** 79%
3	CH_2=$CHCH_2MgBr$ **5**		**12;** 36%
4	PhMgBr **6**		**13;** 90%
5	*p*-ClC_6H_4MgBr **7**		**14;** 65%
6	 **8**		**15;** 81%[b]
7	 **9**		**16;** 82%

[a] Conditions: Grignard was added to a THF solution of aziridine and Cu-catalyst at − 78 °C and the reaction warmed to room temperature before stirring for 16 h. [b] 50 mol % of CuBr·DMS employed in this case. DMS: dimethyl sulfide.

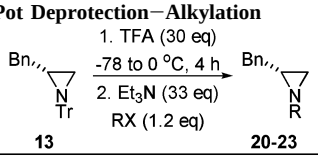
dropped somewhat when employing allylmagnesium bromide **5** (entry 3). The incorporation of aryl groups proceeded smoothly (entries 4 and 5) as did more functionalized reagents **8** and **9** (entries 6 and 7).

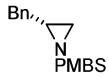
Some additional noteworthy observations made during this study were the following: (1) The potential for heteroatom centered displacements was demonstrated by the incorporation of azide. Specifically, **17** was formed in excellent yield upon heating **2** with NaN_3 in DMF. (2) Addition of butyl- and allylmagnesium bromide to **2** in the absence of Cu-catalyst resulted in recovery of starting material. In contrast, around 50% conversion of **2** to **15** was observed upon addition of the Büchi Grignard **8** (16 h; as judged by 250 MHz ^{1}H NMR spectroscopy).[12] (3) The corresponding aziridinylmethyl bromide **18** appears to be significantly less reactive than the tosylate **2**. Cu-catalyzed addition of the Büchi Grignard **8** provided a 23% yield of **15** after 16 h with the majority of remaining material consisting of starting aziridine **18**. Moreover, reaction of allylmagnesium bromide with **18** resulted in reductive ring opening to the allylamine **19** (76%) and none of the desired product **12**.[13]



We next turned our attention to the conversion of the *N*-Tr moiety into alternative protecting groups that activate the aziridine to ring opening reactions. The traditional two-step deprotection−protection protocol could give rise to volatility problems when low molecular weight substrates were employed so we sought a one-pot procedure that would allow a range of activating groups to be introduced at nitrogen. We carried out our investigations on substrate **13** and our results are highlighted in Table 2.

TABLE 2. One-Pot Deprotection−Alkylation



entry	RX	aziridine	yield
1	TsCl		**20;** 81%
2	*p*-$MeOC_6H_4SO_2Cl$		**21;** 79%
3	CbzCl		**22;** 85%
4	DppCl		**23;** 65%

Removal of the trityl group was carried out using standard TFA deprotection conditions[14] whereupon the solution was basified by addition of triethylamine. The addition of TsCl then allowed **20** to be isolated in high yield (entry 1). Moreover, chiral HPLC analysis for **20** indicated >99% ee and optical rotation data showed this compound to have (*R*)-configuration[15] confirming that the Grignard substitution had taken place through direct displacement to give the aziridine with retention of absolute configuration. In the context of the reactions outlined in Table 1, these data provide evidence for direct substitution rather than addition at the aziridine followed by cyclization. Finally, addition of appropriate reagents for *p*-methoxybenzenesulfonyl- (PMBS), Cbz-, and Dpp-protection proceeded smoothly to give the corresponding products **20**−**23** in good yield (entries 2−4). Notably, in the reaction indicated in entry 1, we found that the acid quench could be carried out with less expensive NH_4OH (22 equiv). Subsequent addition of Et_3N (3 equiv) and TsCl (1.2 equiv) provided **20** in 72% yield.

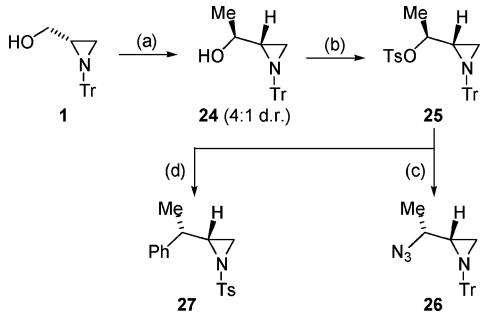
(12) The Büchi Grignard reagent **8** has been proposed to exist as a dialkylmagnesium species that can undergo transformations more typical of an organocuprate. For example, **8** can undergo conjugate addition to enones in the absence of Cu-catalysts: Sworin, M; Neumann, W. L. *Tetrahedron Lett.* **1987**, *28*, 3217.

(13) Elimination appears to be promoted by allyl Grignard, indeed, **19** was also observed as the major byproduct when the tosylate **2** was employed (Table 1, entry 3). These observations mirror those made by De Kimpe and co-workers in their studies.[10b]

(14) Righi, P.; Scardovi, N.; Marotta, E.; ten Holte, P.; Zwanenburg, B. *Org. Lett.* **2002**, *4*, 497.

(15) Optical rotation data for (*S*)-**20** ($[\alpha]^{25}_D$ +17.8 (*c* 1.82, $CHCl_3$)) shows the opposite sign to that observed in our sample: $[\alpha]^{22}_D$ −20.0 (*c* 1.00, $CHCl_3$). Alonso, A. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455.

SCHEME 3. Synthesis and Functionalization of Tr-Protected Aziridine 21[a]



[a] Reagents and conditions: (a) (i) Swern. (ii) MeLi, THF, −78 °C to rt, 1 h; 87% over two steps. (b) TsCl, Et_3N, cat. DMAP, 4 d; 81%. (c) NaN_3, DMF, 60 °C, 16 h; 72%. (d) (i) PhMgBr, 25% CuBr·DMS, THF, −78 °C to rt, 16 h. (ii) TFA, $CHCl_3$, MeOH (3:1), −78 °C to rt, 4 h. (iii) Et_3N, TsCl, 16 h; 54% over three steps.

In an effort to develop the chemistry to include more heavily substituted systems, we investigated the synthesis and alkylation of a secondary tosylate analogue **25**. As outlined in Scheme 3, oxidation of **1** followed by addition of MeLi provided a 4:1 mixture of diastereomeric alcohols **24** that were tosylated in good yield. A diastereomerically enriched (20:1 dr) sample of **25** was generated by recrystallization from hexane/ethyl acetate. Azide substitution of **25** took place in good yield and with clean inversion to provide **26**. Moreover, Cu-catalyzed substitution with PhMgBr was also successful; however, the nonpolar nature of the product resulted in inefficient chromatographic purification. We therefore subjected the crude material to the one-pot deprotection−protection protocol and were pleased to isolate **27** in 54% yield over the three steps.[16]

In summary, we report a simple and practical route to a range of enantioenriched aziridines through the Cu-catalyzed substitution of a readily available aziridinylmethyl tosylate **2**. Moreover, we have developed a one-pot procedure for the conversion of the product *N*-trityl aziridines to a range of more activated substrates that could be further employed as electrophilic reagents.

Experimental Section

(*S*)-(1-Tritylaziridin-2-yl)methyl 4-Methylbenzenesulfonate (2). To a solution of (*S*)-(1-tritylaziridin-2-yl)-methanol (**1**, 1.94 g, 6.15 mmol, 1 equiv)[11b] in CH_2Cl_2 (31 mL) were added triethylamine (0.94 mL, 6.77 mmol, 1.1 equiv), tosyl chloride (1.30 g, 6.77 mmol, 1.1 equiv), and DMAP (0.08 g, 0.62 mmol, 0.1 equiv) at 0 °C. The solution was left to warm to rt overnight, washed with $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo to provide **2** as a pale yellow solid (2.65 g, 92%). Mp 82−84 °C. $[\alpha]^{23}_D$ −33.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.04 (1H, d, J = 6.0 Hz), 1.43 (1H, m), 1.62 (1H, d, J = 2.5 Hz), 2.39 (3H, s), 4.06 (1H, dd, J = 10.5, 5.5 Hz), 4.32 (1H, dd, J = 10.5, 5.5 Hz), 7.14−7.68 (19H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.1, 25.5, 30.5, 72.5, 73.8, 126.8, 127.5, 127.9, 129.3, 129.9, 133.2, 144.0, 144.7; FTIR (film, υ_{max} cm^{-1}) 3057 (w), 1597 (s), 1490 (s), 1480 (s) 1365 (m); HRMS (EI) *m*/z (M^+) calcd for $C_{29}H_{27}NO_3S$ 469.1712, found 469.1708.

Representative Procedure for Cu-Catalyzed Grignard Substitution: (*R*)-2-Pentyl-1-tritylaziridine (10). To a solution of **2** (0.1 g, 0.213 mmol, 1 equiv) and CuBr·DMS (11 mg, 0.05 mmol, 0.25 equiv) in THF (1.3 mL) was added freshly prepared butylmagnesium bromide solution in THF (titrated to 0.55 M, 0.77 mL, 0.426 mmol, 2 equiv) at −78 °C. The resulting solution was stirred at −78 °C for 15 min and allowed to warm to rt overnight. The reaction mixture was quenched with water, poured onto brine, and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (5:1, petroleum ether:EtOAc) provided **10** as a clear oil (65 mg, 86%). $[\alpha]^{22}_D$ −19.4 (*c* 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 6.5 Hz), 1.02 (1H, d, J = 6.0 Hz), 1.10−1.25 (8H, m), 1.55 (1H, d, J = 3.5 Hz), 1.87 (1H, m), 7.19−7.51 (15H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0, 22.6, 26.6, 26.7, 31.8, 32.8, 33.0, 72.1, 126.5, 127.3, 129.6, 145.0; FTIR (film, υ_{max} cm^{-1}) 3056 (w), 2927 (w), 1596 (s), 1489 (s), 1447 (m); HRMS (EI) *m*/z (M^+) calcd for $C_{26}H_{29}N$ 355.2300, found 355.2288.

Synthesis of (*S*)-2-(Azidomethyl)-1-tritylaziridine (17). To a solution of **2** (0.25 g, 0.532 mmol, 1 equiv) in DMF (1.8 mL) was added sodium azide (0.17 g, 2.66 mmol, 5 equiv) at rt. The solution was heated to 60 °C and left overnight. Upon cooling, diethyl ether was added to the solution and the reaction was quenched with brine. The organic extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (5:1 petroleum ether:EtOAc) provided **17** as a pale yellow oil (0.175 g, 97%). $[\alpha]^{23}_D$ −12.0 (*c* 1.67, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17 (1H, d, J = 6.0 Hz), 1.48 (1H, m), 1.82 (1H, d, J = 3.0 Hz), 3.48 (2H, d, J = 5.0 Hz), 7.16−7.35 (9 H, m), 7.52 (6 H, d, J = 7.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 25.5, 31.6, 53.6, 74.0, 126.8, 127.6, 129.4, 144.2; FTIR (film, υ_{max} cm^{-1}) 3057 (w) 2923 (m), 2852 (m), 2096 (s), 1596 (m), 1487 (m); HRMS (EI) *m*/*z* (M^+) calcd for $C_{22}H_{20}N_4$ 340.1688, found 340.1685.

Representative Procedure for the Deprotection and Reprotection of Tritylaziridines. (*R*)-2-Benzyl-1-tosylaziridine (20).[15] To a solution of **13** (0.1 g, 0.27 mmol, 1 equiv) in a mixture of chloroform (1.5 mL) and methanol (0.5 mL) was added trifluoroacetic acid (0.616 mL, 7.99 mmol, 30 equiv) at −78 °C. The solution was stirred at −78 °C for 15 min then allowed to warm to 0 °C for 4 h upon which triethylamine (1.23 mL, 8.79 mmol, 33 equiv) was added to the solution at 0 °C. After 10 min, a solution of tosyl chloride (61 mg, 0.32 mmol, 1.2 equiv) in chloroform (0.5 mL) was added via cannula and the mixture was stirred overnight at 0 °C. $NaHCO_3$ solution was added and the solution was extracted with chloroform. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo and the product purified by flash chromatography (5:1 petroleum ether:EtOAc) to provide **20** as a colorless solid (63 mg, 81%). Mp 92−94 °C. $[\alpha]^{22}_D$ −20.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.15 (1H, d, J = 4.5 Hz), 2.42 (3H, s), 2.67 (1H, dd, J = 15.0, 7.0 Hz) 2.72 (1H, d, J = 7.0 Hz), 2.80 (1H, d, J = 15.0, 5.0 Hz), 2.89−3.00 (1H, m), 7.01−7.18 (5H, m), 7.20 (2H, d, J = 8.0 Hz), 7.67 (2H, d, J = 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.6, 32.8, 37.5, 41.2, 126.5, 127.9, 128.4, 128.7, 129.6, 134.9, 137.0, 144.3.

Acknowledgment. We are grateful to the EPSRC and Eli Lilly and Company Ltd for financial support.

Supporting Information Available: Experimental procedures, ^{1}H /^{13}C NMR spectra for selected compounds, and X-ray data for compounds **25**, **26**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7023637

(16) The stereochemistry of compounds **25**, **26**, and **27** has been elucidated by X-ray crystallography. CCDC 659299, CCDC 659300, and CCDC 661089 contain the supplementary crystallographic data for **25**, **26**, and **27**, respectively. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax (+44) 1223−336-033; or request@ccdc.cam.ac.uk).