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A Suzuki cross-coupling route to substituted aziridines

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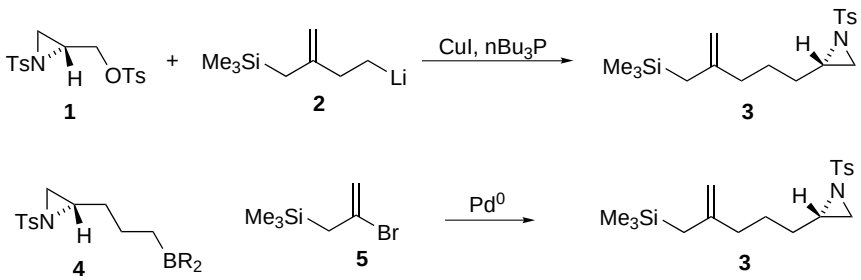
Abstract—We have shown that the Suzuki cross-coupling reaction of olefinic aziridines is an effective route for the synthesis of substituted aziridines. This is the first example of a palladium coupling reaction applied to an aziridine-containing molecule. This method is complementary to other methods of aziridine synthesis utilizing organocuprate reagents.

The Suzuki cross-coupling reaction provides an excellent method for coupling sp^3 hybridized carbons to sp^2 hybridized carbons (as well as sp^2 to sp^2). This reaction has been applied to the synthesis of a large variety of compounds.[1] Suzuki or similar types of reactions have not been carried out with an aziridine ring present in the molecule.[2,3] Such a process in the presence of an aziridine ring suggests a number of potential problems, such as reaction of the organometallic portion (e.g. **4**) with the aziridine ring,[4] palladium-catalyzed aziridine ring opening,[5] and hydrolysis of the aziridine ring under the basic reaction conditions (Scheme 1).

We were interested in preparing aziridine–allylsilanes such as **3** using our previously reported method involving the reaction of an organocuprate reagent (e.g. derived from **2**) with the aziridine **1**.[6] Unfortunately, the synthesis of the requisite organolithium reagent proved troublesome.[7] We thus began to explore the possibility of using a Suzuki coupling between the appropriately substituted aziridine (e.g. **4**) and an sp^2-bromide (e.g. **5**) to prepare the desired aziridines (**3**). This strategy could be very useful for the preparation of substituted aziridines, especially those in which the desired organometallic reagent (such as **2**) is not readily available or one in which the aziridine is not amenable to the type of ring opening reaction we have typically employed.[6]

The Suzuki cross-coupling reaction between an aliphatic partner and a sp^2-halide typically involves the conversion of the aliphatic partner to an organoborane via hydroboration. The appropriate olefin for hydroboration would be aziridine **9**. Olefin **9** was conveniently prepared from commercially available allylglycine (**6**). Treatment of amino acid **6** with MeOH/HCl followed by toluenesulfonyl chloride provided the diprotected amino acid **7**[8] in 80% yield from allylglycine. The ester was then reduced with $LiBH_4$ followed by a Mitsunobu ring closure to yield the target aziridine **9** (Scheme 2).[9]

Olefin **9** was then treated with 9-BBN followed by 2-bromopropene (**11**) and $PdCl_2(dppf)\cdot CH_2Cl_2$ under Suzuki cross-coupling conditions. We were pleased to



Scheme 1.

Keywords: aziridines; Suzuki reactions; coupling reactions; palladium and compounds.

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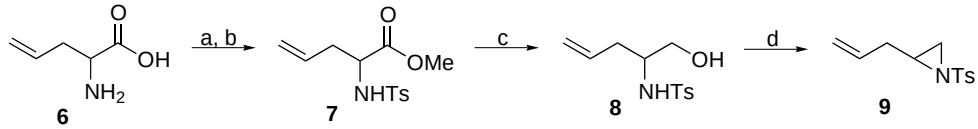
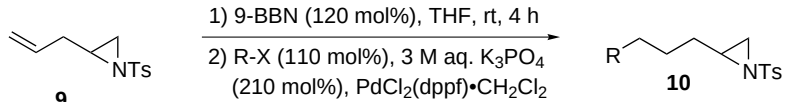
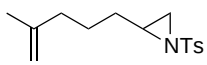
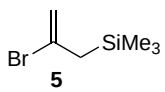
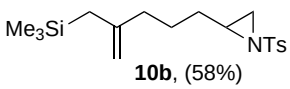
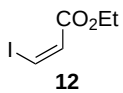
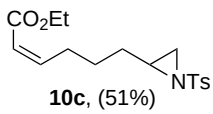
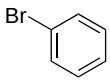
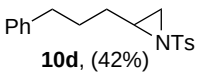
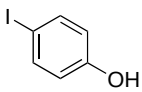
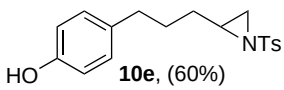
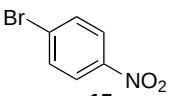
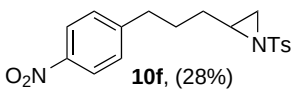
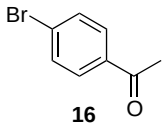
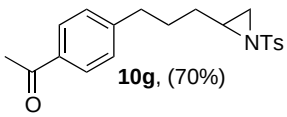
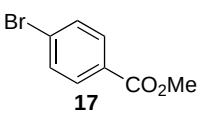
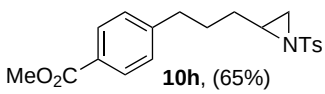


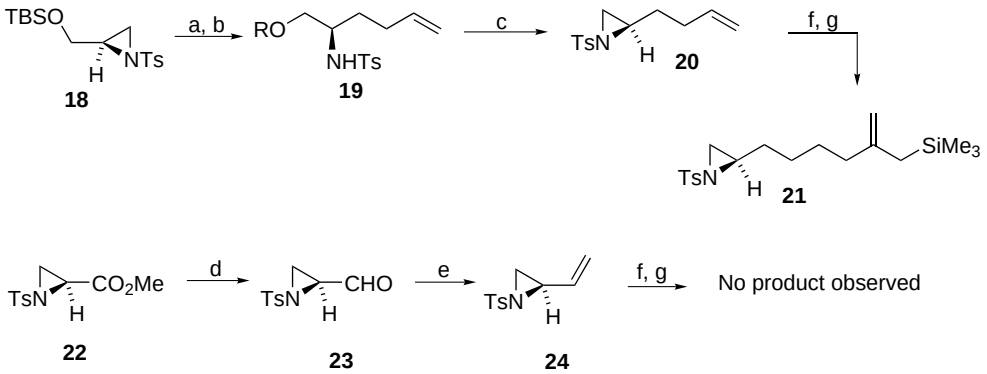
Scheme 2. (a) MeOH, AcCl (500 mol%), reflux, 24 h. (b) TsCl (110 mol%), Et_3N (250 mol%), CH_2Cl_2, rt, 24 h, 80% (two steps). (c) $NaBH_4$ (300 mol%), LiCl (300 mol%), EtOH:THF, 2:1, rt, 24 h, 80% (d) Ph_3P (110 mol%), DEAD (110 mol%), THF, rt, 16 h, 82%.

find that the coupling provided the desired coupling product in 47% yield (Table 1, entry 1). We have examined the coupling of **9** with a variety of vinylic and aryl halides (Table 1). The yields reported in Table 1 are of analytically pure material.[9] As hoped, the bromoallylsilane **5** was an excellent cross-coupling partner providing **10b** in 58% yield. Similar yields were obtained from a number of other aryl halides (**13**, **14**, **16**, **17**). The only exception being 4-nitro-bromobenzene, which afforded **10f** in only 28% yield. Some of the low yields observed in the cross-coupling reactions can be attributed to difficulties in purification. All of the cross-coupling products (to some extent) co-eluted with 9-BBN by-products from the reaction and required additional purification. We should note that for many of these examples the organolithium reagent that might be required to prepare aziridines **10a**–**h** from aziridine **1** would not be readily accessible. Thus, this method is an excellent complement to the addition of an organometallic reagent to an aziridine as a route to substituted aziridines (Scheme 3).

Table 1. Examples of Suzuki cross-coupling reactions of olefinic aziridines[9,10]



Entry	R-X	**Product** (yield)
1	 **11**	 **10a**, (47%)
2	 **5**	 **10b**, (58%)
3	 **12**	 **10c**, (51%)
4	 **13**	 **10d**, (42%)
5	 **14**	 **10e**, (60%)
6	 **15**	 **10f**, (28%)
7	 **16**	 **10g**, (70%)
8	 **17**	 **10h**, (65%)



Scheme 3. (a) AllylMgCl (300 mol%), CuCN (50 mol%), Et_2O:THF (1:1.5), −78 to 0°C, 45 h, R = Si(Me$_2$)*t*Bu, 75%. (b) *n*Bu$_4$NF (110 mol%), THF, 0°C, 1 h, R = H, 88%. (c) Ph_3P (110 mol%), DEAD (110 mol%), THF, 0°C to rt, 4 h, 93%. (d) DIBAL-H (160 mol%), CH_2Cl_2, −78°C, 3 h. (e) Ph_3PCH_2 (250 mol%), THF, −20°C, 1 h, 29% (two steps). (f) 9-BBN (120 mol%), THF, rt, 4 h. (g) **5** (110 mol%), 3 M aq. K_3PO_4 (210 mol%), $PdCl_2$(dppf)·CH_2Cl_2 (5 mol%), DMF, rt, 18 h, **21** (65%).

In an effort to extend this synthesis we prepared olefins **20** and **24**. Olefin **20** was readily prepared from the serine derived aziridine **18**.[6a] Reaction of **18** with allylmagnesium chloride/CuCN followed by removal of the silyl protecting group and Mitsunobu ring closure provided aziridine **20**[11] in excellent overall yield. Standard cross-coupling conditions using bromoallylsilane **5** provided substituted aziridine **21** in 65% yield.[9,10] We next turned our attention to olefin **24**. The known aziridine ester **22**[6a,12] can be reduced to aldehyde **23** by reaction with DIBAL-H. Wittig reaction of the aldehyde produces the vinyl aziridine **24**[13] in 29% yield over two steps. Unfortunately, hydroboration of **24**, followed by Suzuki coupling conditions did not provide any of the desired product. We have examined a number of variations of the Suzuki cross-coupling protocol and all were unsuccessful. No aziridine containing products were obtained, and we believe that the aziridinyl borane formed upon hydroboration of **24** is unstable.

In conclusion, we have shown that the Suzuki coupling reaction of olefinic aziridines proceeds quite well. This reaction should be useful for the preparation of a variety of substituted aziridines.

Acknowledgements

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7. While the desired organolithium reagent (**2**) has been prepared via a reductive lithiation of a phenylsulfide (see Manteca, I.; Ardeo, A.; Osante, I.; Lete, E.; Etxarri, B.; Arrasate, S.; Sotomayor, N. *Tetrahedron* **1998**, *54*, 12361–12378), we were hoping to carry out a metal halogen exchange between the corresponding iodide and *t*-BuLi. The synthesis of the alcohol needed for preparation of the iodide has been reported (see Ahmed-Schafield, A.; Mariano, P. S. *J. Org. Chem.* **1985**, *50*, 5667–5677). However, we were unable to convert this alcohol to the iodide using a number of different methods.
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9. All new products showed satisfactory ^1H, ^{13}C NMR and HRMS.
10. Typical procedure for the Suzuki cross-coupling reaction: The desired aziridinyl alkene (**9** or **20**, 1.1 mmol) was dissolved in dry THF (3.7 mL) and cooled to 0°C. A solution of 9-BBN (2.5 mL of a 0.5 M solution in THF) was added and the reaction was warmed to room temperature and stirred until no alkene remained (TLC, 20% EtOAc:hexanes, ca. 4 h). Distilled DMF (1.8 mL) was added followed by careful addition (H_2 evolution) of degassed aq. K_3PO_4 (3 M, 210 mol%). This was followed by a rapid addition of R-X (110 mol%, X = Br or I) and $PdCl_2$(dppf)·CH_2Cl_2 (5 mol%). The reaction was stirred overnight at room temperature. The solvent was removed in vacuo and the remaining DMF residue was partitioned

between Et_2O and saturated aq. $NaHCO_3$. The layers were separated and the aqueous layer was re-extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

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12. We prepared ester **22** in 92% yield by the Mitsunobu ring closure of methyl *N*-(4-methylphenyl)sulfonyl-(*S*)-serinate using Ph_3P (110 mol%) and DEAD (110 mol%) in THF at room temperature for 18 h. For other approaches, see: (a) Antunes, A. M. M.; Marto, S. J. L.; Branco, P. S.; Prabhakar, S.; Lobo, A. M. *Chem. Commun*. **2001**, 405–406; (b) Dauban, P.; Dodd, R. H. *Tetrahedron Lett*. **1998**, *39*, 5739–5742; (c) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309–6330.
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