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Metallated Aziridines for Cross-Coupling with Aryl and Alkenyl Halides via Palladium Catalysis

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Abstract

The palladium catalyzed coupling of an aziridinylzinc chloride intermediate with alkenyl and aryl halides has been demonstrated. The method provides products with retention of aziridine stereochemistry. The utility of the coupling procedure is illustrated in the synthesis of structures related to *L*-furanomycin.

Lithiated aziridines **1** (Scheme 1, Prot = SO₂R, CO₂R, alkyl) are useful intermediates for the preparation of functionalized aziridines **4**.¹ However, transition metal catalyzed coupling reactions involving **1–3** have not been reported to our knowledge. Prior work in our laboratory showed that stannylated aziridine **5** lacks sufficient reactivity while lithiated aziridine **6** produces complex reaction mixtures under palladium catalyzed conditions. Herein, we show that Negishi coupling can be achieved in good yields using the protected aziridinylzinc chloride **7** and an improved palladium catalyst.

Initial attempts to couple **7** with methyl 4-bromobenzoate using Pd(PPh₃)₄ (THF, 25 °C, 18 h) produced only traces of the desired product. The source of difficulties became clear when a control experiment was conducted under identical conditions, but without any palladium catalyst. Quenching the control with CH₃OD gave a complex mixture containing the deuterated aziridine **9** (37%) as the major component along with variable yields and ratios of imine **10** and the known acrolein imine **11** (ca. 10–30 % of **10** + **11** combined), and more consistently, the enol ether **12** (33%). Yet another product was sometimes isolated from this reaction, apparently resulting from a dimerization pathway, but this product was not formed reproducibly and the yield never exceeded 10%.^{3,4} Imines **10** and **11** are thought to arise from intramolecular ring opening of **7** to produce an intermediate **8**, with subsequent protonation or elimination of a benzyloxy group to form **10** or **11**, respectively.⁵ Because **10** was obtained without any significant deuterium incorporation after chromatographic purification, we suspect that the initial product of CH₃OD quenching is **8** with M = D, and that deuterium/proton exchange as well as conversion to **10** and **11** take place during workup. The origin of the enol ether **12** was also somewhat perplexing, but the reason for the apparent incorporation of methanol became more clear when freshly prepared **7** was quenched with CH₃OD at –78 °C. This afforded **9** and **12** without any of the other products

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Supporting Information Available: Experimental details and copies of ¹H NMR and ¹³C NMR spectra of representative compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(ca. 1:1 **9**:**12**, 75% combined yield after chromatography). Therefore, the other products (**10**, **11**, dimer) result from the thermal decomposition of **7** to **8**, while **9** and **12** reflect deuteration or methanolysis directly from **7** without prior decomposition.

Although details of the methanolysis step were not investigated, the conversion to **12** can be understood as an example of zinc-assisted leaving group displacement by CH₃OD to generate **13**, followed by 1,2-elimination. Prior examples of analogous displacement have been noted, but they are limited to simple structures such as XZnCH₂X (X = halide) and have not been investigated in depth.⁶ In the present example, we suggest that CH₃OD adds to **7** to generate a transient zincate intermediate, followed by deuterium transfer to nitrogen and internal methoxide transfer to carbon as the aziridine C-N bond is cleaved.

Fortunately, the complex background reactions resulting from the thermal decomposition of **7** at 25 °C could be suppressed by using the more reactive catalyst Pd₂(dba)₃/[(*t*Bu)₃PH]BF₄ in place of Pd(PPh₃)₄ in the Negishi coupling. This simple variation was so effective that none of the undesired products **9**–**12** were detected if sufficient time was allowed for complete conversion of **7** (ca. 3 h, rt). The scope of coupling was evaluated in several representative examples using a stoichiometry of 1 equiv **5**, 1.1 equiv *n*BuLi, 1.2 equiv ZnCl₂, 1.5 equiv halide, 2.5 mol % Pd₂(dba)₃ and 10 mol % [(*t*Bu)₃PH]BF₄ (Table 2).

The aromatic halides iodobenzene (entry 1) and methyl 4-bromobenzoate (entry 2) gave satisfactory yields of **15** and **17**, respectively. The alkenyl halides vinyl bromide (entry 3) or iodoacrylate **20** (entry 4) also afforded coupled products under the standard conditions. Similarly, iodoindole **22** reacted with **7** to produce the desired aziridine **23**, although in moderate yield.

To demonstrate the synthetic potential of aziridinylzinc chloride **7**, we have studied the conversion of aziridine **21** (Table 1, entry 4) into structures related to the antibacterial agent *L*-furanomycin **24** and the analogue **25** (Scheme 2).⁷

We planned to assemble the dihydrofuranyl moiety of **25** by manipulation of the appended acrylate of **21** via Grignard addition and intramolecular ring opening of the aziridine. Thus, **21** was treated with CH₃MgBr to afford the tertiary alcohol **26** and subsequent acid catalyzed aziridine cleavage gave **27** (52% from **21**). Reductive cleavage of the trityl protecting group of **27** with TFA/Et₃SiH₈ produced the corresponding amine, which was protected as the Boc derivative **28** (61% over the two steps). To avoid the risk of hydrogenating the double bond under H₂/Pd/C conditions, benzyl deprotection of **28** was accomplished using Na/NH₃ reduction to produce the alcohol **29** in 97% yield.⁹ Oxidation of the primary alcohol to the corresponding aldehyde using the Dess-Martin periodinane, followed by Pinnick oxidation gave the protected amino acid **30** (86%). The relative stereochemistry and substitution pattern of **30** was established by comparing NMR data with the enantiomeric structure used earlier as an intermediate in the synthesis of **25**.⁷ while the absolute configuration follows from the configuration of **5** and is confirmed by optical rotation comparison at the stage of **30**.^{1·7}

In summary, we have demonstrated that aziridinylzinc chloride **7** is a useful intermediate for palladium couplings with aryl and alkenyl halides. The thermal decomposition of **7**, resulting in complex background reactions, can be suppressed by using the more reactive catalyst Pd₂(dba)₃/[(*t*Bu)₃PH]BF₄. The synthetic utility of the coupling procedure was demonstrated by stereospecific synthesis of the protected dihydrofuranyl amino acid **30**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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3. The dimeric product is tentatively assigned structure **ii** based on NMR and MS data (see Supporting Information). By analogy to Hodgson's lithiated *N*-Bus aziridines (ref. 4), intermediate **i** may be formed by reaction of **7** with the carbene resulting from α -elimination, but elimination of the NTrM fragment to produce **ii** contrasts with the *N*-Bus aziridine where the aziridine C–N eliminates to give the symmetrical dimer. The *trans* stereochemistry of **ii** follows from $J_{2,3}$ = ca. 3 Hz and remains unexplained.

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Scheme 1.

Scheme 2.

Table 1

Scope of the Negishi Coupling Procedure^a

$ \begin{array}{c} \text{Tr} \\ \\ \text{Bu}_3\text{Sn} - \text{C} - \text{CH}_2 - \text{OBn} \\ \text{5} \end{array} \xrightarrow[3. \text{Pd}_2(\text{dba})_3 (2.5\%), \text{[(tBu)}_3\text{PH]BF}_4 (10.0\%), \text{R-X}]{1. n\text{BuLi, THF} \\ 2. \text{ZnCl}_2} \begin{array}{c} \text{Tr} \\ \\ \text{R} - \text{C} - \text{CH}_2 - \text{OBn} \end{array} $			
entry	R-X	product	% yield
1			65
2			75
3			64
4			80
5			48

^a Reaction conditions: 1 equiv **5**, 1.1 equiv *n*BuLi, THF, -60 to -20 °C; 1.2 equiv ZnCl₂, -78 °C; 1.5 equiv halide, 2.5 mol % Pd₂(dba)₃ and 10 mol % [(*t*Bu)₃PH]BF₄, 25 °C.