Unusual Selectivity of Unprotected Aziridines in Palladium-Catalyzed Allylic Amination Enables Facile Preparation of Branched Aziridines

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The allylamine functionality is found in a wide range of biologically active compounds.[1,2] Allylamines are also valuable synthetic intermediates for the preparation of α- and β-amino acids,[3a] alkaloids,[3b−e] and aza-carbohydrate derivatives.[3f,g] The allylamine functionality can be introduced by nucleophilic substitution at the allylic position or by direct allylic amination of olefins.[4] The transition metal-catalyzed allylic amination of allyl alcohol derivatives is particularly attractive because the C−N bond can be installed with high regio- and stereoselectivity.[1,5]

Unprotected aziridines have not been extensively used in transition metal-catalyzed reactions.[6] Recent results from our lab suggest that aziridines tolerate a range of oxidative conditions and participate in transition metal-catalyzed coupling chemistry.[7] The present paper details the unusual behavior of aziridines in allylic amination and underscores the facility with which simple aziridine-containing building blocks can be installed in complex environments for further elaboration.
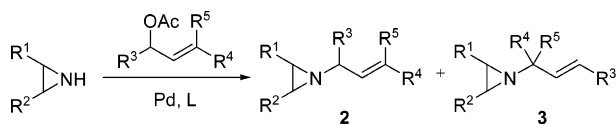
1a R^1,R^2: -(CH$_2$)$_4$-; **1b** R^1: CH$_3$, R^2: H; **1c** R^1: COPh, R^2: -(CH$_2$)$_2$CH=CH$_2$

Because conventional methods of making aziridines[8] often pose functional group compatibility issues, modification of aziridine-containing starting materials should be a viable means for making highly functionalized nitrogen-containing molecules. At present, there are only a few reactions that fall into this category.[9] Our interest in synthetic applications of *N*-allyl aziridines suggested alkylation of unprotected aziridines with allyl halides as a possible entry into this class of compounds. However, due to *N,N′*-diallyl aziridinium ion formation and subsequent ring-opening by the halide ion, low selectivity was observed. We subsequently found that unprotected aziridines undergo facile palladium-catalyzed allylic amination with allyl acetates and carbonates. The optimal reaction conditions were found using cyclohexene imine and allyl acetate as model substrates. With 1 mol % of [Pd(η^3-C$_3$H$_5$)Cl]$_2$ as the source of palladium and 4 mol % PPh$_3$ as a ligand, full conversion of cyclohexene imine to *N*-allyl cyclohexene imine was achieved in THF in 30 min. Allyl carbonates gave full conversion, although at a slower rate. We noticed that if the reaction was left longer than 30 min, formation of the *O*-acyl *N,N′*-diallyl amino alcohol byproduct (**6**) took place, presumably through ring-opening by acetic acid (Table 1, entry 12). This byproduct formation was suppressed by the addition of 2 equiv of K$_2$CO$_3$ or by the use of allyl carbonates.

In the reaction of prenyl acetate with cyclohexene imine, the branched isomer (**3e**) was unexpectedly found to be the only detectable product, isolated in 89% yield. Although the reaction
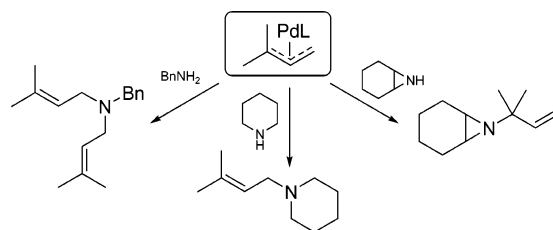

Figure 1. Dependence of the regiochemistry of products in allylic amination as a function of amine (1 mol % [Pd(η^3-C$_3$H$_5$)Cl]$_2$ and 2 mol % BINAP in THF, room temperature).

was sluggish with PPh$_3$ as a ligand, BINAP provided complete conversion within 6 h in THF at room temperature (Figure 1). This result is particularly interesting because there appears to be only one other example of the palladium-catalyzed allylic amination of a terminal allyl ester or carbonate resulting in predominant formation of the branched isomer.[10] Other classes of nitrogen nucleophiles including primary[11a] and secondary alkylamines,[11b] azide,[11c,d] and amides[11e] all favor the linear allylamine product under similar palladium-catalyzed conditions. When we performed the reaction between piperidine and prenyl acetate, only the linear isomer was detected. Likewise, the use of benzylamine resulted in exclusive formation of the linear product as a mixture of mono- and dialkylated compounds. To exclude the possibility of initial formation of linear product followed by its in situ conversion into the isolated branched aziridine, we synthesized 7-(3-methylbut-2-enyl)-7-aza-bicyclo[4.1.0]heptane (**10**) which was subjected to typical reaction conditions. No branched product was observed, indicating that linear to branched interconversion does not operate under our conditions, which points to the unusual behavior of aziridine nucleophiles in allylic amination.

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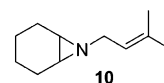
Geranyl acetate also led to the branched isomer (**3g**) as the major product. However, the reaction was sluggish relative to the case of prenyl acetate, and higher catalyst loading was required to achieve full conversion. When [Pd(η^3-C$_3$H$_5$)Cl]$_2$ was used as the source of palladium, BINAP, P(OEt)$_3$, and PPh$_3$ gave full conversions and good regioselectivities while P(*o*-Tol)$_3$ did not induce any reaction. Significant amounts of volatile byproducts reduced the selectivity to around 50% in the best case. These products resulted from a background reaction between geranyl acetate and Pd(0) that produced a mixture of myrcene, (*E*)-ocimene, and (*Z*)-ocimene via competing β-hydride elimination.[12,13] Fortuitously, this elimination was suppressed with a 1:4 Pd(CO$_2$CF$_3$)$_2$/PPh$_3$ catalyst that provided a linear to branched ratio of 12:88 and full conversion within 48 h. The competing β-hydride elimination was not an issue for prenyl

Table 1. Synthesis of N-Allyl Aziridines by Palladium-Catalyzed Allylic Amination

Entry	Allyl Acetate	Product	Isolated Yield (%)
1[a]	AcO⌇	**2a**	45
2[b]	AcO⌇	**4**	99
3[c]	AcO⌇	**2k**	64
4	AcO⌇	**2b**	79
5	AcO⌇Ph	**2c** / **3c**	99[e] (92:8)[f]
6	AcO⌇Ph	**2d**	83
7	AcO⌇	**3e**	89
8[c]	AcO⌇	**2f** / **3f**	90[e] (29:71)[f]
9	AcO⌇	**2g** / **3g**	80[e] (12:88)[f]
10	OAc, Ph⌇Ph	**2h**	97 (97% ee)
11	OAc, Ph⌇Ph	**2j**	97 (98% ee)[g]
12[d]	AcO⌇	**6**	84

[a] Reaction performed with 2 equiv of K_2CO_3. [b] Isolated after addition of 1 equiv of PhSH to in situ prepared allyl aziridine in MeCN. [c] Volatile products isolated after reaction with PhSH as per footnote b. [d] Reaction performed with 2 equiv of allyl acetate. [e] Combined yield. [f] Linear to branched ratio. [g] 0% de.

acetate. The reaction between cinnamyl acetate and cyclohexene imine favored the linear isomer (**2c**). The [Pd(η^3-C₃H₅)Cl]₂/BINAP catalyst gave a 97% combined yield and produced the best product distribution with a 92:8 ratio. This is the same regioselectivity that is expected when alkylamines are used in the Pd-catalyzed allylic amination.[14]

The N-allyl aziridines synthesized by this protocol can be transformed into functionalized branched amines by established ring-opening protocols. For instance, to access the N-allyl trans-diamine (**7**), N-cinnamyl cyclohexene imine was opened with aniline in 85% yield by our previously developed ring-opening chemistry using a catalytic amount of $B(C_6F_5)_3$.[6]

Preliminary results indicate that this chemistry can be applied to the preparation of enantiomerically enriched aziridines[15] via enantioselective allylation. The use of (R)-BINAP as a ligand afforded the N-allyl aziridine **2j** in 98% ee. Under similar reaction conditions, cyclohexene imine afforded the corresponding N-allyl aziridine (**2h**) in 97% ee.

In summary, we have uncovered the first example of palladium-catalyzed allylic amination reaction using unprotected aziridines. The observed regioselectivity favors valuable branched products in the cases of aliphatic acetates, underscoring the decisive effect of the amine on the course of allylic amination. The reasons for these unusual regioselectivity patterns are the subject of ongoing investigations. The process allows for the asymmetric allylic amination of unprotected aziridines with high enantioselectivities and creates a possibility to introduce aziridine moieties into functionalized environments with high levels of regio- and enantioselectivities, and high isolated yields.

Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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