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Transition Metal-Catalyzed Synthesis and Reactivity of *N*-Alkenyl Aziridines

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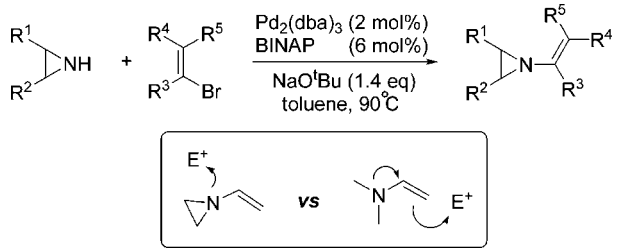
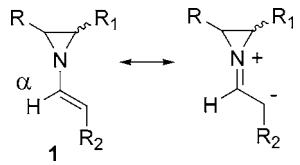
ABSTRACT



Straightforward methods for palladium-catalyzed alkenylation of aziridines with alkenyl halides and copper-catalyzed alkenylation of aziridines with alkenyl boronic acids have been developed. This methodology offers attractive alternatives to the known methods requiring activated alkenyl halides and acetylenes. A wide variety of *N*-alkenyl aziridines containing substituents other than electron-withdrawing substituents such as cyano groups and sulfones have been synthesized in good yields. Furthermore, these *N*-alkenyl aziridines exhibit quite a different reactivity from conventional enamines, as demonstrated by their reactivity.

Enamines derived from secondary amines are among the most versatile intermediates in organic synthesis.[1] Known as versatile enol synthons since the pioneering work of Stork,[2] enamines are typically prepared by reacting a given secondary amine with an appropriate aldehyde or ketone in a condensation process, often in the presence of an acid catalyst and a water scavenger.[3] This method is useful, but it also has several drawbacks such as lack of regioselectivity and low functional group tolerance. Other non-metal-catalyzed methods for the synthesis of *N*-alkenylamines are limited in scope due to the requirement for activated alkenyl halides. Furthermore, all examples known to date contain electron-withdrawing groups attached to the olefin moiety.[4] Our ongoing program in synthetic applications of aziridines required a general route to the enamines of type **1** (Scheme 1).

Scheme 1



1

The chemical shift of the α proton in enamines derived from simple amines is significantly upfield from the value recorded for the ethyleneimine-derived enamine, in agreement with the greater zwitterionic character in the ground state of the former.[5] One can therefore expect a deviation in

(1) Rappoport, Z. In *The Chemistry of Enamines*; Wiley & Sons: New York, 1994; Vol. 2.

(2) Stork, G.; Szmuszkovicz, J.; Terrell, R.; Brizzolara, A.; Landesman, H. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(3) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.

(4) For preparation of *N*-alkenylamines by nucleophilic substitution of alkenyl halogen by amine nucleophiles, see: (a) de Ancos, B.; Maestro, M. C.; Martin, M. R.; Farina, F. *Synthesis* **1988**, 136. (b) Cebulska, Z.; Laurent, A. J.; Laurent, E. G. *J. Fluor. Chem.* **1996**, *76*, 177. For reaction of ketene *S*,*N*-acetals with ethyleneimine to yield 3-anilino-3-(1-aziridinyl)-acrylnitriles, see: (c) Kumar, U.K.S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193. For aziridine addition to propiolates, see: (d) Expert, J.; Gelas-Mialhe, Y.; Vessiere, R. *J. Heterocycl. Chem.* **1985**, *22*, 1285. (e) Gelas-Mialhe, Y.; Touraud, E.; Vessiere, R. *Can. J. Chem.* **1982**, *60*, 2830. (f) Dolfini, J. E. *J. Org. Chem.* **1965**, *30*, 1298. For *N*-alkenyl aziridine synthesis via Peterson reaction, see: (g) Agawa, T.; Ishikawa, M.; Komatsu, M.; Ohshiro, Y. *Chem. Lett.* **1980**, 335. (h) Agawa, T.; Ishikawa, M.; Komatsu, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1205. For *N*-alkenyl aziridine synthesis by pyrolysis of Δ^2-triazolines, see: (i) Hassner, A.; Belinka, B. A.; Haber, M.; Munger, P. *Tetrahedron Lett.* **1981**, *22*, 1863.

(5) Buist, G. J.; Lucas, H. S. *J. Am. Chem. Soc.* **1957**, *79*, 6157.

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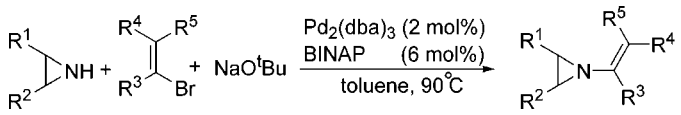
Table 1. Pd-Catalyzed N-Alkenylation of Aziridines



(1)

entry	R^1	R^2	alkenyl bromide	product	yield (%)
1	$-(CH_2)_4-$		α-bromostyrene	**1a**	22[a]
					69[b]
2	$-(CH_2)_4-$		β-bromostyrene (*E*/*Z* mixture)	(*E*)-**1b**	25[a]
					65[b]
3	Me	H	α-bromostyrene	**2a**	75[b]
4	Me	H	β-bromostyrene (*E*/*Z* mixture)	(*E*)-**2b**	67[c]
5	Me	H	*N*,*N*-dibenzyl-2-bromoallylamine	N/A[d]	
6	Me	H	2-bromo-1-decene	N/A[e]	
7	COOMe	H	α-bromostyrene	**3a**	65[b]
8	COOMe	H	β-bromostyrene (*E*/*Z* mixture)	(*E*)-**3b**	60[c]
9	(*R*)-Me	(*S*)-Ph	α-bromostyrene	**4a**	64[c]
10	(*R*)-Me	(*S*)-Ph	β-bromostyrene (*E*/*Z* mixture)	(*E*)-**4b**	68[c]
11	(*R*)-Me	(*S*)-Ph	1-bromo-2-methyl propene	**4c**	70[c]
12	(*R*)-Me	(*S*)-Ph	1-bromopropene	(*E*)-**4d**	65[c]
13	(*R*)-Me	(*S*)-Ph	2-bromo-2-butene	**4e**	85[c]
14	$CH_2{=}CHCH_2CH_2$-	PhCO−	α-bromostyrene	NR	
15	$CH_2{=}CHCH_2CH_2-$	PhCO−	2-bromopropene	N/A[e]	

[a] Purification on a silica gel column (4:1 hexanes/ethyl acetate). [b] Purification by Kugelrohr distillation. [c] Purification on alumina column (4:1 hexanes/ethyl acetate). [d] Unidentified byproducts/polymerization. [e] Decomposition of products.

chemistry of the aziridine-containing enamines compared to the conventional systems (Figure 1). We opted to investigate the N-nucleophilic character of these unusual intermediates, complementary to the more rigid bicyclic systems disclosed in our earlier work.[6]

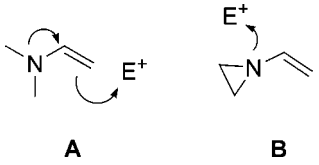


Figure 1.

Clearly, the use of an aziridine nucleophile as the secondary amine under standard conditions for enamine synthesis would lead to highly strained iminium intermediates, making the prospects of condensation chemistry problematic. We therefore turned to transition metal catalysis. The transition metal-catalyzed cross-coupling reaction of aryl halides with amines, known as the Buchwald−Hartwig reaction, has emerged as a powerful procedure for the creation of C−N bonds.[7,8] When a mixture of 7-azabicyclo-[4.1.0]heptane and α-bromostyrene was heated to 90 °C overnight in the presence of $Pd_2(dba)_3$, *rac*-BINAP, and NaO^{t}Bu (Table 1, entry 1),[9] a 22% yield of the enamine was obtained with no evidence for aziridine ring opening in the course of the reaction. The same reaction condition was applied to β-bromostyrene (supplied as a mixture of cis and trans isomers), which gave a similar yield as in the previous reaction (Table 1, entry 2). The product obtained had exclusively trans geometry. The relatively low yields are due to the sensitivity of the products to aziridine ring opening on silica gel and can be augmented by purification of the crude product using distillation. Thus, when the crude

(6) Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 14242.

(7) For recent reviews, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwtig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000. (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 133. (e) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(8) For intermolecular palladium-catalyzed cross-coupling of amines with alkenyl bromides, see: (a) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Commun*. **2002**, 2362. (b) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2004**, *10*, 494. For intramolecular palladium-catalyzed cross-coupling of alkenyl halide and β-lactam nitrogen, leading to a carbapenem skeleton, see: (c) Kozawa, Y.; Mori, M. *Tetrahedron Lett*. **2002**, *43*, 111. (d) Kozawa, Y.; Mori, M. *J. Org. Chem*. **2003**, *68*, 3064. For palladium-catalyzed cross-coupling of azoles with alkenyl bromides, see: (e) Lebedev, A. Y.; Izmer, V. V.; Kazyul'kin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett.* **2002**, *4*, 623.

(9) **General Procedure for Palladium-Catalyzed N-Alkenylation of Aziridines.** A flame-dried Schlenk flask under an argon atmosphere was charged with (±)-BINAP (6 mol %), Pd2(dba)3 (2 mol %), NaO^{t}Bu (1.4 equiv), and dry, degassed toluene. After the mixture was stirred at room temperature for about 10 min, the alkenyl bromide (1 equiv) and the aziridine (1.1 equiv) were added under argon, and the flask was immersed in an oil bath and heated to 90 °C with stirring until the starting alkenyl bromide had been completely consumed as judged by GC and TLC analysis. All reactions were generally complete after overnight stirring. The mixture was then allowed to cool to room temperature, diluted with hexanes, and filtered through Celite. The solvent was evaporated in vacuo, and the residue was redissolved in hexanes, filtered through Celite, concentrated under reduced pressure, and dried under high vacuum to remove any excess aziridine. This afforded a residue that consisted of the crude *N*-alkenyl aziridine, which was purified further by Kugelrohr distillation under high vacuum (dependent on the boiling point and amount of product obtained) or by column chromatography on alumina.

compounds were purified by Kugelrohr distillation (Table 1, entries 1 and 2), 69 and 65% respective yields were obtained. Likewise, 2-methyl aziridine led to enamines **2a** and (*E*)-**2b** in 75 and 67% yields, respectively (Table 1, entries 3 and 4). *N*,*N*-Dibenzyl-2-bromoallylamine and 2-bromo-1-decene[10] did not give any isolable products (Table 1, entries 5 and 6). Aziridine-2-carboxylic acid methyl ester gave the coupling products **3a** and (*E*)-**3b** in 65 and 60% yields, respectively (Table 1, entries 7 and 8). The reaction was extended to N−H aziridines containing aromatic rings.[11] (*2S*,*3R*)-3-methyl-2-phenylaziridine (**4**) was used in the N-alkenylation process with various alkenyl bromides to obtain aryl-containing *N*-alkenyl aziridines in good yields. For example, the aziridine **4** was reacted with α-bromostyrene as well as a mixture of *cis*- and *trans*-*β*-bromostyrene to give *N*-alkenyl aziridine **4a** and (*E*)-**4b** in 64 and 68% yields, respectively (Table 1, entries 9 and 10).[12] Nonaromatic alkenyl bromides provided the *N*-alkenyl aziridines in high yields (Table 1, entries 11−13). The (3-but-3-enyl-*trans*-aziridin-2-yl)phenylmethanone (**5**), synthesized according to literature procedure,[13] was found to be unreactive with α-bromostyrene (Table 1, entry 14). The reaction of **5** with 2-bromopropene under optimal reaction conditions, as well as with a higher loading of the palladium catalyst, did not lead to any conversion to *N*-alkenyl aziridine. Inseparable byproducts, thought to be the result of polymerization, were detected by NMR of the crude product along with unreacted starting material (Table 1, entry 15). The sluggish reactivity of **5** toward N-alkenylation of the aziridine nitrogen is likely due to chelation of the palladium center between the aziridine nitrogen and the carbonyl side chain oxygen (Figure 2), a process that is a likely impediment to catalysis.[14]

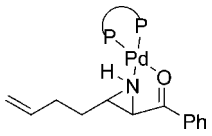
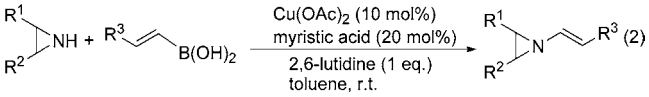


Figure 2.

Selected examples of the copper-based synthesis of *N*-aryl aziridines were reported by us earlier.[15,16] In the present case, the copper-catalyzed coupling of 7-azabicyclo[4.1.0]heptane with *trans*-2-tolylvinylboronic acid gave the *N*-alkenyl aziridine **1c** in 40% yield (Table 2, entry 1), and coupling of aziridine **4** with hexenyl vinyl boronic acid provided compound **4f** in 50% yield (Table 2, entry 2). The yields of the final products are lower using the copper-catalyzed procedure. However, the reactions with lower boiling alkenyl bromides do not proceed well with palladium. On the other hand, 2,4,6-trivinylcyclotriboroxane−pyridine complex, which serves as the boronic acid equivalent of vinyl bromide,[17] provided the *N*-vinyl product in 30% yield upon reaction with aziridine **4** (Table 2, entry 3). The coupling of 2,4,6-trivinylcyclotriboroxane−pyridine with aziridine **5** was unsuccessful even after prolonged reaction time (Table 2, entry 4).

Table 2. Cu-Catalyzed *N*-Alkenylation of Aziridines



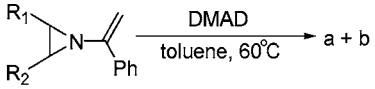
entry	R^1	R^2	R^3	product	yield (%)
1	$-(CH_2)_4-$		*p*-MeC_6H_4	**1c**	40
2	(*R*)-Me	(*S*)-Ph	^{n}Bu	**4f**	50
3	(*R*)-Me	(*S*)-Ph	*a*	**4g**	30
4	*b*		*a*	NR	

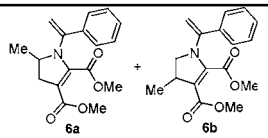
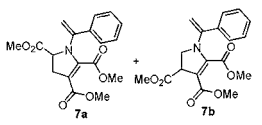
[a] 2,4,6-Trivinylcyclotriboroxane−pyridine was used as a boronic acid equivalent. [b] (3-But-3-enyl-trans-aziridin-2-yl)phenylmethanone was used as a substrate.

To test the extent of N-nucleophilicity and possible synthetic application of *N*-alkenyl aziridines, we explored their reactivity with electron-deficient acceptor molecules. When *N*-alkenyl aziridine **2a** was reacted with dimethylacetylene dicarboxylate (DMAD), the starting material disappeared within 24 h and a new product was generated in 80% yield.

Upon analysis of the g-COSY NMR, the product was assigned to a 1:1 mixture of regioisomeric pyrrolines obtained via formal [3 + 2] cycloaddition (Table 3, entry 1).[18] This reaction was also applied to *N*-alkenyl aziridines **3a**, **1a**, and

Table 3. *N*-Alkenyl Aziridine Reaction with DMAD



entry	N-alkenyl aziridine	products	yield (%)
1	**2a**	 **6a** + **6b**	80
2	**3a**	 **7a** + **7b**	65
3	**1a**	NR	-
4	*(E)*-**1b**	NR	-

(10) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(11) *S*,*3R*)-(+)-3-Methyl-2-phenylaziridine was synthesized according to published procedure; see: Galindo, A.; Orea, L. F.; Gnecco, D.; Enriquez, R. G.; Toscano, R. A.; Reynolds, W. F. *Tetrahedron: Asymmetry* **1997**, *8*, 2877.

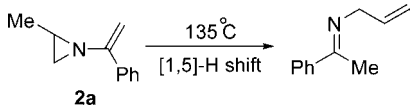
(12) For Pd-catalyzed isomerization of *cis*-olefins, see: Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627.

(13) Seko, S.; Tani, N. *Tetrahedron Lett.* **1998**, *39*, 8117.

(14) We have observed lack of reactivity of carbonyl-containing aziridines in other transition metal-catalyzed processes: Chen, G.; Yudin, A. K. Unpublished results.

(*E*)-**1b**. In the case of **3a**, the same type of reaction occurred as with **2a**, leading to two regioisomeric products in a 1:3 ratio and 65% yield (Table 3, entry 2). For the more sterically congested compounds **1a** and (*E*)-**1b**, no reaction occurred and the starting materials were recovered (Table 3, entries 3 and 4). Interestingly, a thermal [1,5] hydrogen shift was observed upon heating the *N*-alkenyl aziridine **2a** in the absence of DMAD at a higher temperature (Scheme 2).[19] Mechanistic investigation and synthetic application of these interesting reactions are in progress.

Scheme 2



2a

In summary, straightforward methods for palladium-catalyzed alkenylation of aziridines with alkenyl halides and Cu-catalyzed alkenylation of aziridines with alkenyl boronic acids are attractive alternatives to the known methods requiring activated alkenyl halides and acetylenes. A wide variety of *N*-alkenyl aziridines containing substituents other than electron-withdrawing groups such as cyano groups and sulfones have been synthesized in good yields. Furthermore, these *N*-alkenyl aziridines exhibit quite a different reactivity from conventional enamines. Future work will focus on expanding the scope of their applications in complex heterocycle construction.

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

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(15) For some recent examples of amination of aryl halides, see: (a) Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Chem. Commun*. **2004**, *17*, 1994. (b) Lu, Z.; Twilg, R. J.; Huang, S. D. *Tetrahedron Lett*. **2003**, *44*, 628. (c) Enguehard, C.; Allouchi, H.; Guieffer, A.; Buchwald, S. L. *J. Org. Chem*. **2003**, *68*, 4367. (d) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (e) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett*. **2002**, *58*, 7943. (f) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 581. (g) Clement, J. B.; Hayes, J. F.; Sheldrake, H. M.; Sheldrake, P. W.; Wells, A. S. *Synlett*, **2001**, *9*, 1423. (h) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron*, **2001**, *57*, 3891.

(16) Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem*. **2003**, *68*, 2045.

(17) Kerins, F.; O'Shea, D. F. *J. Org. Chem*. **2002**, *67*, 4968.

(18) Gaebert, C.; Mattay, J. *Tetrahedron* **1997**, *53*, 14297.

(19) For [1,5] hydrogen shifts in *C*-vinyl aziridines, see: Åhman, J.; Somfai, P. *Tetrahedron* **1999**, *55*, 11595.