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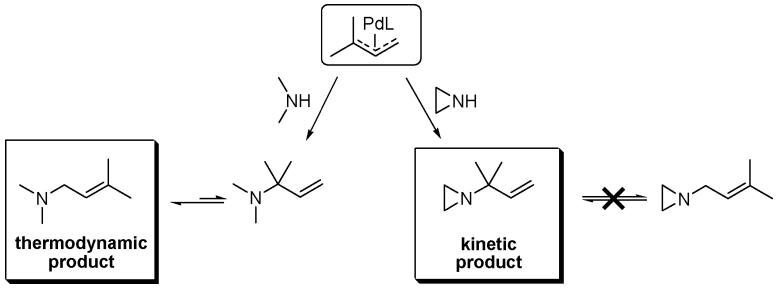

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New Insights into the Mechanism of Palladium-Catalyzed Allylic Amination

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Abstract: A comparative investigation into palladium-catalyzed allylic amination of unsubstituted aziridines and secondary amines has been carried out. The use of NH aziridines as nucleophiles favors formation of valuable branched products in the case of aliphatic allyl acetates. The regioselectivity of this reaction is opposite to that observed when other amines are used as nucleophiles. Our study provides evidence for the palladium-catalyzed isomerization of the branched (kinetic) product formed with common secondary amines into the thermodynamic (linear) product. In contrast, the branched allyl products obtained from unsubstituted aziridines do not undergo the isomerization process. Crossover experiments indicate that the isomerization of branched allylamines is bimolecular and is catalyzed by Pd^0. The reaction has significant solvent effect, giving the highest branched-to-linear ratios in THF. This finding can be explained by invoking the intermediacy of σ-complexes, which is consistent with NMR data. The apparent stability of branched allyl aziridines towards palladium-catalyzed isomerization is attributed to a combination of factors that stem from a higher degree of *s*-character of the aziridine nitrogen compared to other amines. The reaction allows for regio- and enantioselective incorporation of aziridine rings into appropriately functionalized building blocks. The resulting methodology addresses an important issue of forming quaternary carbon centers next to nitrogen. The new insights into the mechanism of palladium-catalyzed allylic amination obtained in this study should facilitate synthesis of complex heterocycles, design of new ligands to control branched-to-linear ratio, as well as absolute stereochemistry of allylamines.

Introduction

Installation of an aziridine functional group into organic molecules presents significant synthetic challenges. The aziridine ring in its simplest NH form does not benefit from a straightforward, one-step protocol similar to the abundant examples of oxygen atom transfer in epoxidation chemistry. Enantiomerically enriched aziridines have been available via transition metal catalysis since the early 1990s, but only in their *N*-protected forms where the substituent on nitrogen is typically difficult to remove. Conventional methods of making aziridines,[1,2] including reactions that utilize starting materials from the chiral pool, pose functional group compatibility issues. Therefore, *modification* of aziridine-containing starting materials can be viewed as a viable route for making more complex aziridine-containing molecules, especially if the ring installation is desired at a later stage of synthesis. At present, there are only a few reactions that fall into this category.[3] As a possible implementation of this strategy, we opted to explore routes from unsubstituted aziridines to their allylated derivatives as a potentially rich source of precursors to a wide range of allylamines. The allylamine functionality is found in many biologically active compounds.[4,5] Allylamines are also valuable synthetic intermediates for the preparation of α- and β-amino acids,[6a,b] alkaloids,[6c−g] and aza-carbohydrate derivatives.[6h,i] The allylamine group can be introduced by direct allylic amination of olefins or by nucleophilic substitution at the allylic position.[7] However, commonly used protocols that employ allyl alcohol starting materials, such as Mitsunobu chemistry, cannot be used for making allyl aziridines based on pK_a considerations,[8] whereas another commonly used route that utilizes epoxide ring opening/ring closure sequence is not divergent. In turn, allylation of unsubstituted aziridines using allyl bromides is complicated by overallylation and concomitant aziridine ring opening. Reductive amination, a typical solution to this problem in the

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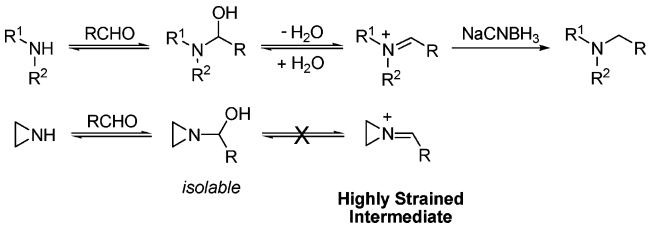

Figure 1. Reductive amination of secondary amines versus unsubstituted aziridines.

case of common secondary amines, is problematic with aziridines because the corresponding iminium ions are highly strained (Figure 1). Thus, transition metal catalyzed allylic amination of allyl alcohol derivatives[4,9] appears to be the most reasonable route toward *N*-allyl aziridines. In the course of our studies into the scope of this process, we uncovered a significant deviation in the behavior of aziridine nucleophiles from that of common secondary amines in allylic amination. The present study investigates the course of allylic amination with aziridines and provides a mechanistic basis for further development of related nitrogen transfer chemistry. In particular, our results suggest that the nature of amine can have a decisive effect on the regiochemistry of amination. Our study also underscores the facility with which simple aziridine-containing building blocks can be installed in complex environments for further elaboration.

Results

In the course of our recent studies in aziridine chemistry,[10] we found that unsubstituted aziridines undergo facile palladium-catalyzed allylic amination with allyl acetates and carbonates (eq 1).[10a] A wide range of allyl aziridines has been prepared using this procedure (Table 1).

Optimal reaction conditions were developed using cyclohexene imine (**1a**) and allyl acetate (**2a**) as model substrates (eq 2). With 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the source of palladium and 4 mol % PPh_3 as ligand, full conversion of **1a** to *N*-allyl cyclohexene imine (**3a**) was achieved in THF in 30 min with 1.2 equiv of **2a** (Table 2, entry 3). As expected, in the absence of ligand (Table 2, entry 2) the reaction did not proceed. The reaction also did not proceed if allyl alcohol was substituted for allyl acetate.[11] The reaction with allyl carbonates did continue to completion, although at a slower rate. The reaction worked equally well in THF (Table 2, entry 3), toluene (Table 2, entry 7), and MeCN (Table 2, entry 8) and with lower efficiency in diethyl ether (Table 2, entry 6) and hexanes (Table 2, entry 9). The reaction also worked with several other palladium sources (Table 2, entries 10−12). When the reaction was left longer than 30 min, an *O*-acyl *N,N′*-diallyl amino alcohol (*trans*-2-(diallylamino)cyclohexyl acetate, **7**) began to form, reducing the selectivity (Table 2, entry 4). Heating the reaction mixture or concentrating the solvent during workup increased the decomposition such that only traces of **3a** were isolated in these cases. When 2 equiv of **2a** were used and the reaction mixture was heated at 60 °C for 2 h, the decomposition was complete and no **3a** was seen by GC, allowing the bis-allylated product **7** to be isolated in 84% yield (Table 2, entry 5 and Table 1, entry 19). If *N*-benzyl cyclohexene imine was used in the reaction instead of **1a** (using the same conditions as Table 2, entry 3) no new products were observed. This indicates that the byproduct is not derived from a tetraalkyl aziridinium ion, as is the case in aziridine alkylation with alkyl halides.[1] Clearly, the decomposition results from a buildup of acetic acid over the course of the reaction. The acid-catalyzed opening of *N*-allyl cyclohexene imine by the acetate anion results in a secondary amine that is rapidly *N*-allylated. Addition of 2 equiv of K_2CO_3 to the reaction suppressed formation of the byproduct to such an extent that even after 72 h at 60 °C no ring-opened product was detected. K_2CO_3 was found to be superior to soluble amine bases such as Et_3N and DIPEA (2 equiv were used). The latter bases slowed, but did not prevent, decomposition.

When we attempted to recover **3a** (Table 1, entry 1), an isolated yield of 45% was achieved, although both conversion and selectivity were 100% by GC. The decrease in the isolated yield was attributed to the volatility of the allyl aziridine product (**3a**). Isolation of the allylic amination products of the reaction of **2a** with unsubstituted aziridines **1b** and **1c** was also complicated by the same issue. These volatile allyl aziridine products could be trapped by reaction with thiophenol, allowing recovery of the resultant 1,2-aminosulfide products in good yields (Table 1, entries 2 and 3). Allylic amination with aziridine **1d** required high catalyst loading (20 mol % Pd) and additional equivalents of **2a** to achieve complete conversion and isolation of the allyl aziridine product **3c** in 79% yield (Table 1, entry 4). The difficulties in achieving full conversion using aziridine **1d** were attributed to the increased steric environment around nitrogen. As well, the chelating ability of **1d** toward palladium between the aziridine nitrogen and the carbonyl side chain oxygen is a process that likely impedes catalysis.[12] Aziridine **1g** was by far the least reactive substrate used, providing only traces of *N*-allyl aziridine product when 4 equiv of **2a** and 20 mol % Pd are used and the reaction is heated at 40 °C for 72 h.

When monosubstituted allyl acetates were used in allylic amination reactions, the possibility of two regioisomeric products arose: the unsubstituted, or linear, isomer (**3**) and the substituted, or branched, isomer (**4**) (eq 1). When cinnamyl acetate (**2b**) was reacted with **1a**, the linear isomer (**3d**) was favored over the branched isomer (**4d**) (Table 1, entry 5). The $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/BINAP catalyst gave a 97% combined yield and produced the best product distribution with a 92:8 ratio favoring **3d**. In the case of PPh_3, the product distribution remained constant at 81:19 linear to branched, irrespective of the palladium source. Inclusion of the trifluoroacetate anion through the use of $Pd(CO_2CF_3)_2$ as the palladium source decreased the regioselectivity to 75:25. Sterically demanding phosphines such as $P(o\text{-Tol})_3$ and electron-deficient phosphines such as $P(C_6F_5)_3$ provided no conversion. Similar results were achieved when **1b** and **1c** were used, giving the linear allyl aziridine products **3e** and **3f** in 88 and 83% isolated yields, respectively (Table 1, entries 6 and 7). When 1,3-diphenyl allyl acetate (**2f**) was used, similar high yields were achieved (Table

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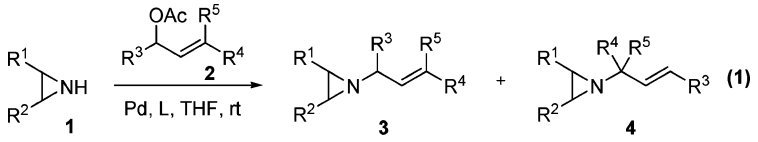
(12) We have observed a lack of reactivity of carbonyl-containing aziridines in other transition metal-catalyzed processes: Chen, G.; Yudin, A. K. 2004, The University of Toronto, Toronto, Canada, unpublished results.



1a R^1,R^2 = -$(CH_2)_4$-
1b R^1 = CH_3, R^2 = H
1c R^1 = CO_2Me, R^2 = H
1d R^1 = COPh, R^2 = -$(CH_2)_2CH{=}CH_2$
1e R^1 = Ph, R^2 = H
1f R^1 = Ph, R^2 = CH_3
1g R^1 = Ph, R^2 = COPh

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

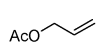
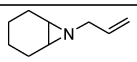
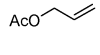
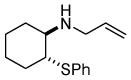
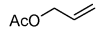
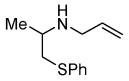
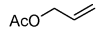
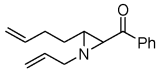
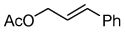
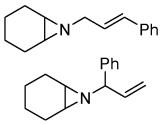
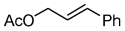
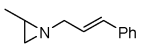
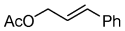
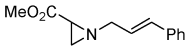
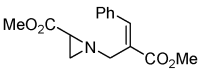
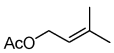
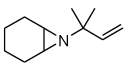
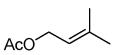
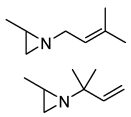
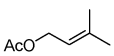
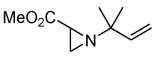
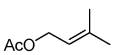
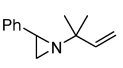
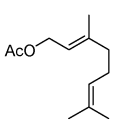
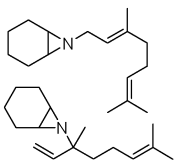
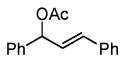
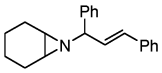
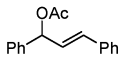
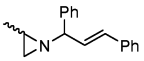
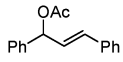
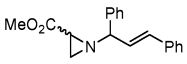
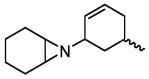
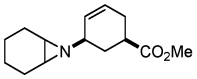
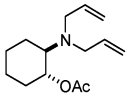
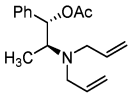
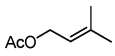
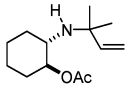
entry	allyl acetate		catalyst	product		isolated yield (%)
1[a]		**2a**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) PPh_3 (4 mol%)		**3a**	45[g]
2[b]		**2a**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) PPh_3 (4 mol%)		**5**	99
3[b]		**2a**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) PPh_3 (4 mol%)		**6**	64
4		**2a**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (10 mol%) BINAP (20 mol%)		**3c**	79
5		**2b**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3d** **4d**	99[e] (92:8)[f]
6		**2b**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3e**	88
7		**2b**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3f**	83
8		**2c**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3g**	84
9		**2d**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**4h**	89
10[b]		**2d**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3j** **4j**	90[e] (29:71)[f]
11		**2d**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) Xantphos (5 mol%)		**4k**	43[g]
12		**2d**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**4m**	72
13		**2e**	$Pd(CO_2CF_3)_2$ (5 mol%) PPh_3 (10 mol%)		**3n** **4n**	80[e] (12:88)[f]

Table 1 (Continued)

entry	allyl acetate		catalyst	product		isolated yield (%)
14		**2f**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3p**	97 (97% ee)
15		**2f**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3q**	97 (98% ee)[h]
16		**2f**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) PPh_3 (4 mol%)		**3r**	79
17		**2g**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3s**	70
18		**2h**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**3t**	80
19[d]		**2a**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) PPh_3 (4 mol%)		**7**	84
20[d]		**2a**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) PPh_3 (4 mol%)		**8**	65
21		**2d**	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%) BINAP (2 mol%)		**9**	79

[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 note b. [d] Reaction performed with 2 equiv of allyl acetate at 60 °C. [e] Combined yield. [f] Linear to branched ratio. [g] Isolated yield is low due to volatility of the product; GC analysis indicates that there is full conversion. [h] 0% de.

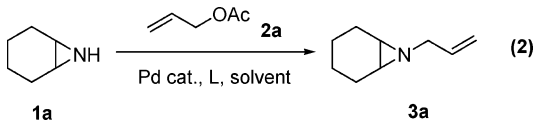


Table 2. Reaction of Cyclohexene Imine (**1a**) with 1.2 Equiv of Allyl Acetate (**2a**)

entry	palladium source (2 mol % Pd)	ligand (4mol %)	solvent	*T* (°C)	*t* (h)	conv (%)	selectivity (%)[a]
1	–	–	THF	rt	16	0	–
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	–	THF	rt	16	0	–
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	THF	rt	0.5	100	100
4	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	THF	rt	16	100	84
5	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	THF	60	2	100	0
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	Et_2O	rt	1	100	93
7	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	PhMe	rt	1	100	100
8	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	MeCN	rt	1	100	100
9	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	hexanes	rt	1	34	100
10	$Pd(PPh_3)_4$	–	THF	rt	0.5	100	100
11	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	THF	rt	0.5	100	100
12	$Pd(OAc)_2$	PPh_3	THF	rt	0.5	100	100
13	$Pd(PPh_3)_2Cl_2$	–	THF	rt	16	0	–

[a] Refers to the amount of *N*-allyl aziridine product vs the total amount of all products in the reaction observed by GC.

1, entries 14−16). This chemistry can be applied to the preparation of enantiomerically enriched aziridines[13] by enantioselective allylation. The use of (*R*)-BINAP as a ligand with aziridine **1a** afforded the corresponding *N*-allyl aziridine (**3p**) in 97% ee. Gratifyingly, **1b** afforded the corresponding *N*-allyl aziridine (**3q**) in 98% ee under similar reaction conditions. To our knowledge, these values are the highest achieved with BINAP in allylic amination, which usually gives low enantioselectivities.[14]

In the reaction of 1,1-dialkyl substituted allyl acetate **2d** (prenyl acetate) with **1a**, the branched isomer (**4h**) was unexpectedly found to be the only product, isolated in 89% yield (Table 1, entry 9). Although the reaction was sluggish with PPh_3 as a ligand, BINAP provided complete conversion within 6 h in THF at room temperature resulting in a regiochemical ratio of 8:92 (linear to branched). The use of 2-methylbut-3-en-2-yl acetate (**2j**), the isomer of **2d**, resulted in a similar regiochemical ratio (6:94) favoring the branched product (Figure 2). When the reaction with prenyl acetate (**2d**) was left for longer periods of time (up to 72 h), or heated at temperatures up to 60 °C, no linear product was ever observed. The only compound that was isolated under these reaction conditions was the product of ring-opening with acetic acid (Table 1, entry 21). To exclude the possibility of initial formation of linear product followed by its in situ conversion into the isolated branched aziridine, we

(13) (a) Lee, W. K.; Ha, H.-J. *Aldrichimica Acta* **2003**, *36*, 57−63. (b) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichimica Acta* **2003**, *36*, 39−50.
(14) Kodama, H.; Taiji, T.; Ohta, T.; Furukawa, I. *Synlett* **2001**, 385−387.

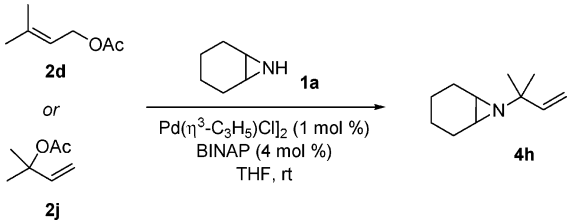


Figure 2. Formation of branched allyl aziridine **4h** from isomeric allyl acetates.

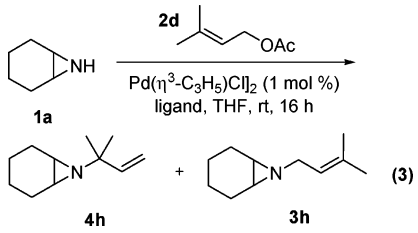


Table 3. Variation of Ligand and Dependance of Regiochemistry

entry	ligand	bite angle (deg)[a]	conv (%)	regioselectivity (linear/branched)
1	PPh_3	−	15	10/90
2	$P(OEt)_3$	−	100	8/92
3	dppe	82.6	82	15/85
4	dppp	91.6	92	14/86
5	BINAP	92.8	100	8/92
6	(*S*)-Tol-BINAP	−	100	11/89
7	dppb	97.1	100	6/94
8	dppf	98.7	100	15/85
9	(*S*,*S*)-DIOP	100.0	100	7/93
10	Xantphos	104.6	100	4/96

[a] Average P−M−P angles calculated from crystal structures retrieved from the CSD.[15]

synthesized *N*-prenyl cyclohexene imine (7-(3-methylbut-2-enyl)-7-aza-bicyclo[4.1.0]heptane, **3h**) by alkylation of cyclohexene imine with prenyl bromide. The aziridine **3h** was subjected to typical reaction conditions. No branched product was observed, indicating that linear-to-branched interconversion does not operate under the reaction conditions.

We examined whether changes in the steric environment around palladium would have any effect on the observed regioselectivity of allylic amination with aziridines. Different phosphine ligands were employed in the reaction to assess whether there was an effect on regiochemistry. A number of different bidentate ligands with varying bite angles[15] were used in the reaction of cyclohexene imine (**1a**) with prenyl acetate (**2d**) (Table 3). All the ligands employed favored the branched product in similar ratios, ranging from 15:85 to 4:96 with Xantphos. The latter provided the highest regioselectivity (Table 3, entry 10).

A significant solvent effect was observed in the reaction between **1a** and **2d**. A high regioselectivity of 8:92 favoring the branched product was observed in THF with BINAP as the ligand (Table 4, entry 1). When the solvent was changed to toluene, acetonitrile, or dichloromethane, the reaction regioselectivity disappeared (Table 4, entries 2−4). In the cases of toluene and acetonitrile the linear-to-branched ratio was close to 1:1, while in the case of dichloromethane, the linear isomer predominated by about 6:4. In all these cases there was more

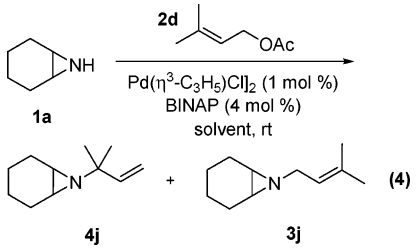


Table 4. Effect of Solvent on Conversion and Regiochemistry

entry	solvent	dielectric constant[a]	time (h)	conv (%)	regioselectivity (linear/branched)
1	THF	7.6	6	100	8/92
2	PhMe		14	49	46/54
3	MeCN	38	14	49	45/55
4	CH_2Cl_2	8.9	14	31	61/39
5	$CHCl_3$	4.8	24	0	−

[a] See ref 16.

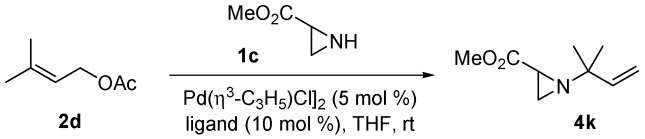


Table 5. Effect of Various Ligands on the Reaction with **1c**

entry	palladium source	ligand	time (h)	conv (%)	regioselectivity (linear/branched)
1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	BINAP	24	65	3/97
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	dppf	21	39	3/97
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Xantphos	8	100	1/99
4	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	dppe	21	0	−
5	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	dppb	21	0	−
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	(*S*,*S*)-DIOP	21	0	−
7	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	$P(OEt)_3$	21	0	−
8	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	PPh_3	21	0	−
9	$Pd(CO_2CF_3)_2$	PPh_3	21	0	−
10	$Pd(CO_2CF_3)_2$	BINAP	21	0	−

than a 4-fold decrease in the reaction rate. In the case of chloroform the reaction did not proceed (Table 4, entry 5).

Methyl aziridine (**1b**), methyl aziridine-2-carboxylate (**1c**) and phenyl aziridine (**1e**) also produced the branched allyl aziridine product when reacted with **2d** in THF (Table 1, entries 10−12). The reaction between **1b** and **2d** produced an allyl aziridine that was too volatile to be directly isolated. Addition of thiophenol into the reaction mixture after the initial allylic amination was complete allowed the ring-opened 1,2-aminosulfide product to be isolated in 90% yield favoring the branched isomer in a ratio of 71:29 (Table 1, entry 10).[17] In the case of **1c**, the usual reaction conditions using the BINAP ligand gave only 6% conversion. When the amount of palladium catalyst was increased to 5 mol %, the conversion increased, but was still only 65% (Table 5, entry 1). A number of different conditions and phosphine ligands were attempted with this substrate (Table 5). Most of the conditions that were tried failed to give any conversion (Table 5, entries 4−10). Only with the bidentate Xantphos ligand did the reaction reach full conversion

(15) Dierkes, P.; van Leeuwen, P. *J. Chem. Soc., Dalton Trans.* **1999**, 1519−1529.

(16) Riddick, J. A.; Bunger, W. B. *Organic Solvents: Physical Properties and Methods of Purification*, 3rd ed.; Techniques of Organic Chemistry; Wiley-Interscience: New York, 1970; Vol. II.

(17) We believe that the lower regioselectivity in this case results from some isomerization of the ring-opened product as the ring-opening step is performed in the presence of Pd catalyst (one-pot procedure).

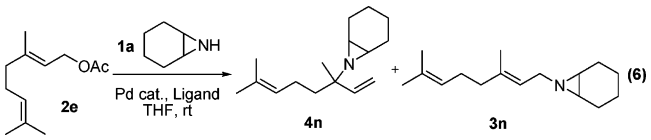


Table 6. Reaction of **1a** with **2e** in THF

entry	palladium source	mol %	ligand[a]	time (h)	conv (%)	selectivity (%)[b]	regioselectivity (linear/branched)
1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	5	BINAP	12	99	56	19/81
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	5	PPh_3	72	100	52	17/83
3	$Pd(CO_2CF_3)_2$	5	PPh_3	32	100	76	12/88
4	$Pd(CO_2CF_3)_2$	1	PPh_3	48	79	65	12/88
5	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	1	$P(OEt)_3$	48	100	54	29/71
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	1	dppb	16	100	41	19/81
7	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	1	dppe	48	69	37	25/75
8	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	1	$CyPPh_2$	48	79	22	3/97
9	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	1	$(p\text{-MeO-}C_6H_4)_3P$	16	3	9	16/84
10	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	1	$P(o\text{-Tol})_3$	48	0	–	–

[a] 2:1 ligand to Pd for monodentate ligands, 1:1 ligand to Pd for bidentate ligands. [b] Refers to the amount of *N*-allyl aziridine product vs the total amount of all products in the reaction observed by GC.

in 8 h, while the regioselectivity still favored the branched isomer (Table 5, entry 3). Optimization of the reaction enabled a 43% yield of **4m** using 2.5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 5 mol % Xantphos (Table 1, entry 11). The low yield of **4m** was attributed to the volatility of the product, which made its isolation difficult.

The use of geranyl acetate (**2e**) in the reaction with **1a** also produced the branched product **4n** as the major isomer (Table 6) in THF. The reaction was more sluggish than the prenyl acetate (**2d**) reaction, and higher catalyst loadings were required to achieve full conversion. As with cinnamyl acetate (**2b**), $P(o\text{-Tol})_3$ did not provide any conversion (Table 6, entry 10). Full conversion and good selectivities were achieved with $P(OEt)_3$ or PPh_3 with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the palladium source (Table 6, entries 5 and 2, respectively) after fairly long reaction times (48 and 72 h, respectively). BINAP was found to be the best ligand in combination with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. This combination provided a linear-to-branched ratio of 19:81 and full conversion within 12 h. However, the reaction with geranyl acetate was found to produce significant amounts of volatile byproducts that reduced the selectivity to around 50%. These products were found to be the result of a background reaction of **2e** with Pd^0, not the previously observed acetate ring-opening of the *N*-allyl aziridine products. The selectivity of the reaction suffered as a result of the concurrent production of myrcene, (*E*)-ocimene, and (*Z*)-ocimene via competing β-hydride elimination.[18] The selectivity was improved with a 1:4 $Pd(CO_2CF_3)_2/PPh_3$ catalyst that provided a linear-to-branched ratio of 12:88 (Table 6, entry 4). By increasing the amount of catalyst, the reaction time was decreased and full conversion was achieved with a selectivity of 76% (Table 6, entry 3). Finally, when the reaction was performed with a slight excess of **2e** (1.2 equiv), a combined yield of 80% was achieved after 32 h (Table 1, entry 13).

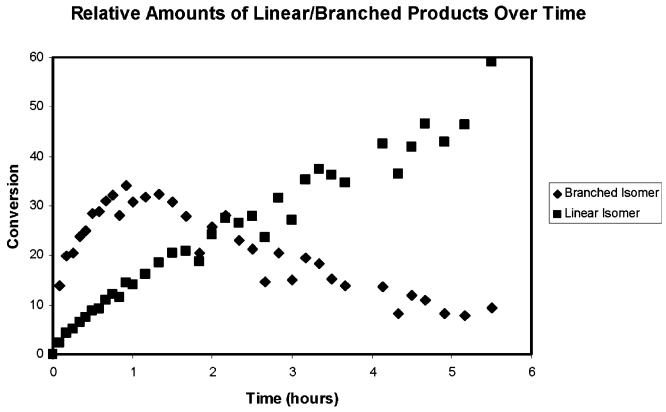
To determine the stereochemical course of the reaction, allylic amination with the syn-isomer of methyl 5-acetoxycyclohex-3-enecarboxylate (**2h**) was performed.[19] This substrate simplified product analysis since the resultant π-allyl complex has a symmetrical structure. The reaction of **2h** and **1a** with 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 2 mol % BINAP in THF at room temperature gave the allyl aziridine product (**3t**) in 80% isolated yield after 16 h (Table 1, entry 18). The syn-stereochemistry was assigned to allyl aziridine (**3t**) by NMR analysis (see Supporting Information). This result shows that the stereochemistry present in the starting allyl acetate is retained. Verbenol acetate (**2k**) failed to react with **1a** under a variety of different conditions, including high temperatures, long reaction times, and use of both mono- and bidentate phosphine ligands.

The unusual regiochemical outcome of the reaction between unsubstituted aziridines and prenyl type systems prompted us to examine other amine nucleophiles (Table 7). When we performed the allylic amination reaction between piperidine and prenyl acetate (**2d**), only the linear isomer was detected after 16 h (Table 7, entry 2). As with other secondary amines such as morpholine, 1,2,3,4-tetrahydroisoquinoline, and *N*-methylaniline (entries 3−5, respectively), only the linear allylamine products were isolated. Likewise, the use of benzylamine (Table 7, entry 6) resulted in exclusive formation of the linear product as a mixture of mono- and dialkylated compounds. Sterically encumbered amines such as 2,2,6,6-tetramethylpiperidine (entry 7) and *cis*-2,6-dimethylpiperidine (entry 8) did not react, even when the reaction was heated to 60 °C.

Subsequent examination of the reaction between piperidine and prenyl acetate (**2d**) by GC analysis indicated the initial buildup of the branched product (**10**) followed by its decrease as the linear product (**11**) began to form (Figure 3). The amount of **10** peaked at around 1 h and then began to decrease. By 2 h, **11** was the major isomer present in the reaction mixture. The ratio of the isomers changed throughout the reaction as the percentage of **11** in relation to **10** steadily increased. *This data indicates that the linear and branched isomers are able to equilibrate in the cases of amines other than aziridines.* If 2 equiv of potassium carbonate or 1 equiv of Proton Sponge are

(18) Reaction of geranyl acetate with 5 mol % $Pd(PPh_3)_4$ in THF at 60 °C gives full conversion to the background products in 6 h. See also the following references: (a) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151−11152. (b) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1−2.

(19) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730−4743. (b) Granberg, K. L.; Backvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858−6863. (c) Granberg, K. L.; Backvall, J. E. *J. Am. Chem. Soc.* **1994**, *116*, 10853−10853.



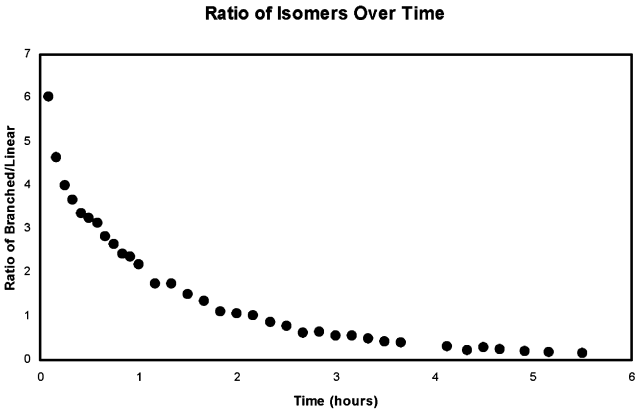
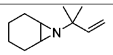
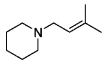
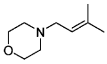
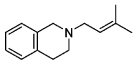
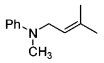
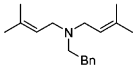


Figure 3. Conversion/time diagram for the reaction of prenyl acetate (**2d**) with piperidine.

Table 7. Reaction of Different Amines with Prenyl Acetate (**2d**) under Standard Conditions[a]

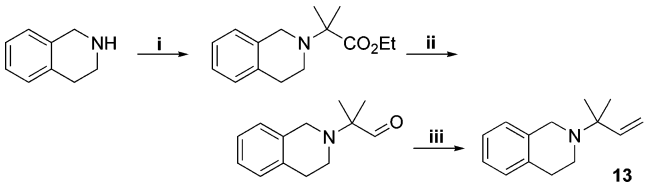
entry	amine	pK_{aH}	conv. (%)	predominant regioisomer	product	
1		8.04[b]	100	branched		**4h**
2		11.12[c]	100	linear		**11**
3		8.33[c]	100	linear		**12**
4		9.66	100	linear		**14**
5		4.84[c]	53	linear		**15**
6		9.33	100	linear		**16**
7		11.07[c]	0[d]	-	-	
8		11.07[c]	0[d]	-	-	

[a] 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol % BINAP, THF, rt. [b] pK_{aH} of ethylene imine from ref 73. [c] Values taken from "Dissociation Constants of Organic Acids and Bases", in *CRC Handbook of Chemistry and Physics*, Internet Version 2005; David R. Lide, Ed., http://www.hbcpnetbase.com; CRC Press: Boca Raton, FL, 2005. [d] Reaction did not proceed even upon heating at 60 °C.

added to the reaction between piperidine and **2d**, there is no change in the regioselectivity at the end of the reaction; the linear regioisomer remains the dominant product.

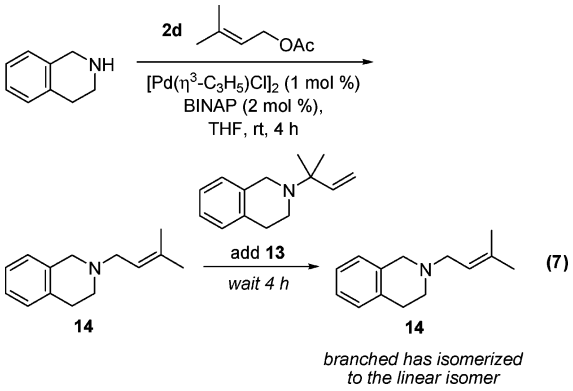
1,2,3,4-Tetrahydroisoquinoline behaved analogously to piperidine, initially producing the branched isomer (**13**), which then isomerized to the linear isomer (**14**) with either $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/BINAP or $Pd(PPh_3)_4$ in THF. To investigate the isomerization, the branched amine of 1,2,3,4-tetrahydroisoquinoline (**13**) was synthesized by a three-step procedure (Scheme 1) without the use of any palladium reagents. The ability of **13** to isomerize to **14** was then tested. First, 1,2,3,4-tetrahydroisoquinoline was allowed to react with prenyl acetate (**2d**) with 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 2 mol % BINAP in THF. Within 4 h the reaction equilibrated to linear isomer **14**, and only traces of branched isomer were detected by GC. The branched isomer

Scheme 1. Synthesis of Branched Amine **13**



i) $BrC(CH_3)_2CO_2Et$, Et_3N, 80°C, 8 h, **76%**, ii) DIBAL-H, PhMe, -78°C, 2 h, **81%**, iii) $MePPh_3Br$, NaHMDS, THF, rt, 16 h, **51%**

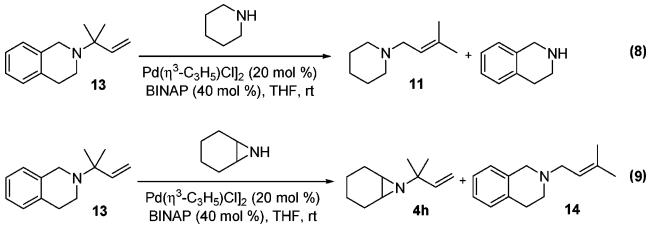
13 was added to the reaction mixture leading to its isomerization, such that linear isomer **14** predominated (eq 7).



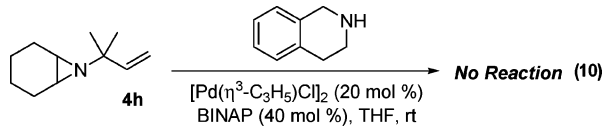
Branched amine **13** was then subjected to different reaction conditions to determine which components of the catalytic system were necessary for branched-to-linear interconversion. When 1 equiv of TFA was added to **13** in THF, no isomerization was observed over 72 h at room temperature. Reaction of **13** with 10 mol % of either $Pd(OAc)_2$ or $Pd(PPh_3)_4$ in THF also gave no isomerization over 72 h. Additionally, reaction of **13** with 1 equiv of TFA and 10 mol % of $Pd(PPh_3)_4$ in THF gave no isomerization over 72 h. Finally, reaction of **13** with 1 equiv of prenyl acetate (**2d**) and 10 mol % of $Pd(PPh_3)_4$ in THF gave no isomerization over 72 h.

Crossover experiments were performed between **13** and piperidine or cyclohexene imine (**1a**). When **13** was mixed with 1 equiv of piperidine using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/BINAP as the catalyst, **13** disappeared such that almost none remained after 4 h at room temperature. Both the branched (**10**) and linear (**11**) piperidine crossover products were detected, with only **11** present after 4 h (eq 8). Similarly, when **13** was mixed with 1 equiv of cyclohexene imine (**1a**) under the same conditions,

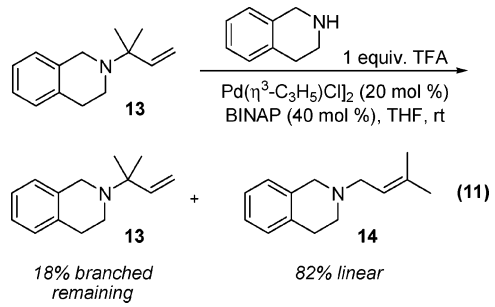
crossover occurred and a small amount of branched aziridine (**4h**) was detected (14% crossover). No linear aziridine was detected. None of the original branched amine **13** remained; instead, the linear amine (**14**) was detected, indicating that isomerization of the starting material was occurring under these conditions (eq 9).



The ability of branched amine **13** to act as an electrophile prompted us to examine whether branched aziridine **4h** would react in a similar way. When **4h** was mixed with 1 equiv of 1,2,3,4-tetrahydroisoquinoline using [Pd(η^3-C_3H_5)Cl]$_2$/BINAP as the catalyst, no reaction was observed over 72 h at room temperature (eq 10).



The fact that crossover was occurring prompted us to once again attempt to isomerize **13**. Using [Pd(η^3-C_3H_5)Cl]$_2$/BINAP as the catalyst in THF, we added 1 equiv of TFA and 1,2,3,4-tetrahydroisoquinoline to **13**. After 16 h at room temperature, 18% of **13** and 82% of **14** remained , indicating that isomerization did occur (eq 11).



Discussion

We have investigated the palladium-catalyzed allylic amination reaction using unsubstituted aziridines as nucleophiles. The process allows for the asymmetric allylic amination of unsubstituted aziridines with high enantioselectivities in the case of cinnamyl systems and creates the possibility of introducing aziridine moieties into functionalized environments with high levels of regioselectivity and high isolated yields. Our investigations into the allylic amination of unsubstituted aziridines have revealed some interesting trends with respect to the regiochemistry of the products. In the case of cinnamyl substrates, the linear allyl aziridines are the main products. In these cases, the resulting regiochemistry of the product is as expected, producing the same regioisomer that is observed when other alkylamines are used in palladium-catalyzed allylic amination. In the reaction of 1,1-dialkyl-substituted allyl acetates such as prenyl and geranyl acetate, the branched isomer was unexpectedly found to be the major product. This result is unusual as other classes of nitrogen nucleophiles including primary[20a] and secondary alkylamines,[20b] azide,[20c,d] and amides[20e] all favor the linear allylamine products under similar palladium-catalyzed conditions. Indeed, when we reacted a variety of secondary amines with prenyl acetate we only isolated linear products (Table 7). This interesting dichotomy warranted mechanistic investigation.

The vast majority of palladium systems produce the linear product as the major regioisomer.[4] This is in contrast to metals such as iridium,[21a−d] rhodium,[21e−g] molybdenum,[21h−j] and ruthenium,[21k] which favor the branched product. There are only a few other examples of palladium-catalyzed allylic aminations of terminal allyl esters or carbonates resulting in predominant formation of the branched isomers.[22] These examples employ special ligands to switch the regioselectivity. They differ from our example in that in our case the same catalyst-ligand system produces different regioisomeric products depending on whether a common amine or aziridine nucleophile is used. The steric environment around palladium appears to have no effect on the regiochemical outcome of the reaction with unsubstituted aziridines. Although a number of bidentate phosphines were tried with a range of bite angles, the branched-to-linear ratio remained constant at around 9:1 (Table 3).

The possibility that a switch in the nature of the key bond-forming step was operating with an unsubstituted aziridine nucleophile led us to examine the stereochemical course of the reaction. In palladium-catalyzed allylic substitution, the attack by the nucleophile can occur externally by anti-addition to the π-allyl complex or internally by reductive elimination (Figure 4). Hard nucleophiles such as Grignard,[23a] organozinc,[23b] organotin,[23c−e] organoaluminum,[23b] silyl aluminum,[23f] disilane,[23g] organoboranes (under Ni^0 catalysis),[23h,i] carbon monoxide,[23d,j] and certain hydride reagents[23k] are known to react internally resulting in inversion of stereochemistry. Amine nucleophiles are known to react externally resulting in overall retention of stereochemistry (double inversion).[24] The use of allyl acetate **2h** allowed the stereochemical course of the reaction with unsubstituted aziridines to be determined. The syn-isomer, observed in the allylic amination reaction, provides direct evidence that the unsubstituted aziridine attacks the palladium complex in an external fashion. This relative stereochemistry is identical to what is observed with other amine nucleophiles. Moreover, when verbenol acetate (**2k**) was used as the substrate,

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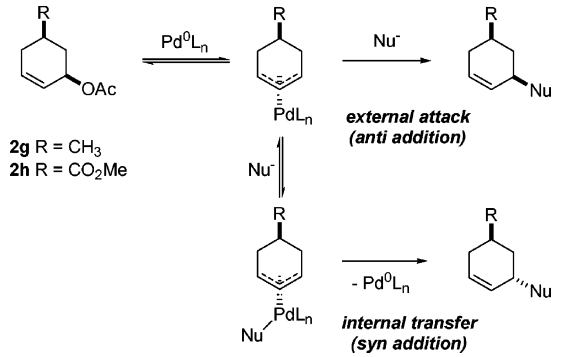

Figure 4. Internal versus external transfer in cyclic allyl acetate substrates.

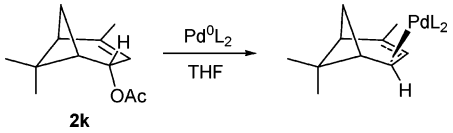

Figure 5. Ionization of (*S*)-*cis*-verbenol acetate (**2k**).

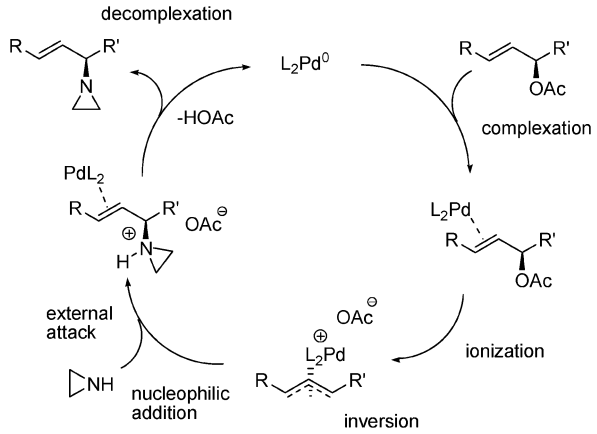

Figure 6. Mechanism of allylic amination with unsubstituted aziridines.

no reaction took place. This is consistent with the gem-dimethyl group blocking the exo-face of attack (Figure 5) and provides further evidence that the attack is external. Thus, one may conclude that the nucleophilic attack operates by the classical mechanism of allylic amination in the case of aziridine nucleophiles as depicted in Figure 6.

In the rhodium-catalyzed allylic substitution, the regioselectivity is determined by the position of the leaving group.[25] Memory effects are also known to operate in some situations during palladium-catalyzed allylic substitution.[26] We examined whether a similar effect was operating with aziridine nucleophiles in the case of palladium. When isomeric acetates **2d** or **2j** are used in the allylic amination reaction with an unsubstituted

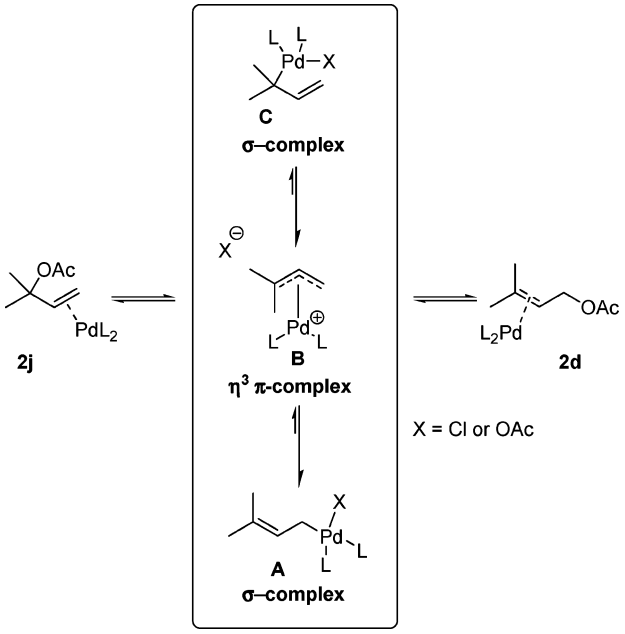

Figure 7. Interconversion of isomeric allyl acetates.

aziridine such as **1a**, the branched allyl aziridine product predominates in about the same regiochemical ratio. This shows that the position of the leaving group has no bearing on the regiochemical outcome of allylic amination with aziridines. The fact that either of the isomeric acetates results in the same product ratio indicates that both isomeric allyl acetates (Figure 7, **2d** and **2j**) operate through the same intermediate, an η^3 π-complex (**B**).

Once the allyl aziridine product (**4h**) is produced, it appears to be stable toward isomerization. Over the course of the reaction, the branched-to-linear ratio remains constant. The ratio is not affected if the reaction mixture is left for extended periods of time or if the reaction mixture is heated. Indeed, the linear isomer is a trisubstituted olefin and should be of lower energy than the disubstituted product. When the linear aziridine **3h** was subjected to typical reaction conditions, no branched product was observed. Therefore, there is no interconversion between the branched and linear allyl aziridines under any of the conditions we tried.

This behavior is in contrast to that observed with the allylamine products when secondary amines such as piperidine are used in the reaction. The observation of an initial branched product in the reaction between piperidine and **2d**, followed by its disappearance while the amount of linear isomer increases, indicates that the allylamine isomers are able to equilibrate. Therefore, in the case of aziridines and other secondary amines the kinetic product is the branched isomer. However, in the case of other amines the branched product converts to the linear isomer, while in the case of aziridines this equilibration apparently does not occur (Figure 8).

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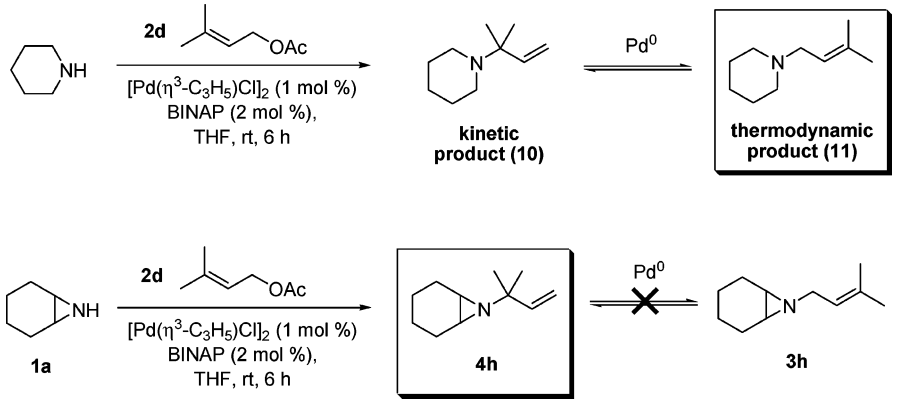

Figure 8. Differences in experimentally observed products in the course of allylic amination chemistry.

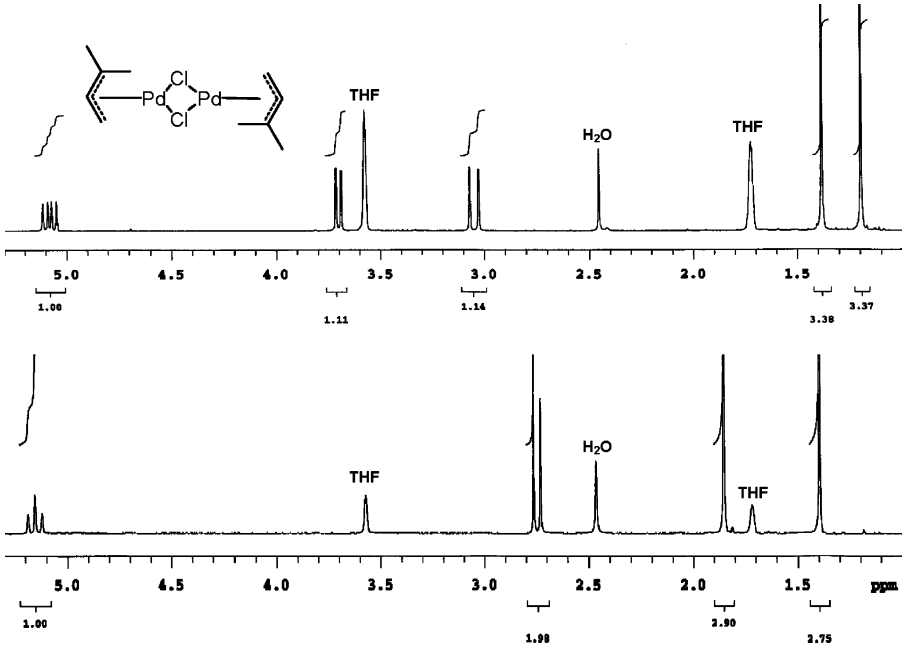

Figure 9. ^{1}H NMR in d^8-THF. (Top) $[Pd(\eta^3\text{-}C_5H_9)Cl]_2$. (Bottom) $[Pd(\eta^3\text{-}C_5H_9)Cl]_2$ with 4 equiv of PPh_3.

What is the reason for the observed kinetic selectivity? The mechanism of allylic substitution is classically shown as proceeding through an η^3 π-complex. However, this complex is in equilibrium with the σ-complexes as shown in Figure 7.[27] The extent of the equilibrium depends on many factors, including temperature, solvent, metal, ligand, and counterion. It is known that in THF the allyl palladium species exists as a σ-complex with counterion coordinated to the metal to a much greater extent than in other more polar solvents.[28] The presence of chloride, added as part of the Pd source ($[Pd(\eta^3\text{-}C_3H_5)Cl]_2$), is also known to induce the formation of neutral σ-complexes.[29] ^{1}H NMR experiments using the prenyl palladium chloride dimer ($[Pd(\eta^3\text{-}C_5H_9)Cl]_2$) and PPh_3 reveal formation of a σ-complex in d^8-THF (Figure 9).[28a,30] Attack by the nucleophile likely proceeds through S_N2'-type attack at the more substituted allyl position to produce the branched product. The loss of selectivity observed when different solvents are used (Table 4) is attributed to the differing equilibrium existing between the η^3 π-complex and σ-complexes in solvents of different polarities. Therefore, in these cases there is a loss of kinetic selectivity.

One can propose several different pathways through which the isomerization of branched amines may occur. One possibility is that the branched products isomerize in the presence of either AcOH or Pd^{II} that accumulates in the reaction medium.[31] However, **13** was shown to be stable to both TFA and catalytic $Pd(OAc)_2$.[32] Another possibility is that the branched product is subsequently allylated via a palladium catalyst, producing a diallylated species that could re-ionize back to an allylamine. No evidence for this mechanism was observed since in the presence of both prenyl acetate and Pd^0 no isomerization of **13** took place.

The most likely mechanistic explanation for the isomerization seems to be by a Pd^0-catalyzed process. This could arise by

(27) Some σ-allyl palladium complexes have been structurally characterized: (a) Kollmar, M.; Helmchen, G. *Organometallics* **2002**, *21*, 4771−4775. (b) Braunstein, P.; Naud, F.; Dedieu, A.; Rohmer, M.-M.; DeCian, A.; Rettig, S. *Organometallics* **2001**, *20*, 2966−2981.

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(32) Phosphines are known to reduce $Pd(OAc)_2$ to Pd^0. See the following references: (a) Amatore, C.; Carre, E.; Jutand, A.; Mbarki, M. A. *Organometallics* **1995**, *14*, 1818−1826. (b) Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241−3249.

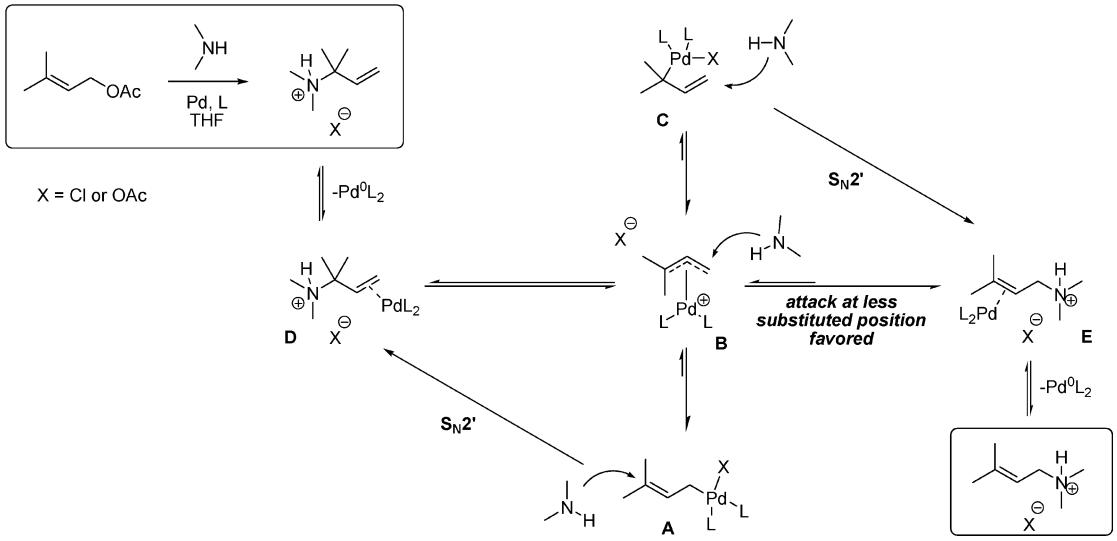

Figure 10. Rationale behind allylamine isomerization.

two possible paths: oxidative addition or re-ionization. Oxidative addition into a C−N bond has been observed in the Suzuki cross-coupling of aryltrimethylammonium salts[33a] and 1-aryltriazenes.[33b] In these cases, Ni^0 catalysts are required for the reaction to proceed, whereas palladium catalysts are unsuccessful.[33a] These observations make oxidative addition an unlikely pathway. An alternative, more likely mechanism involves the re-ionization of the allyl aziridine product to generate an allyl palladium electrophile and an amine. The reversibility of the C−N bond-forming step has been observed in allylic amination when carbon nucleophiles were used in the palladium-catalyzed reaction of allylic ammonium halides.[34] However, reaction of **13** with Pd^0 in THF failed to produce any isomerization. Our experiments show that allylamine isomerization requires very particular conditions. While the reaction of 1,2,3,4-tetrahydroisoquinoline with prenyl acetate resulted in fully isomerized product within 4 h, subjecting independently prepared branched amine **13** to Pd^0 and ligand resulted in no isomerization. However, **13** did isomerize to linear product **14** when added to the reaction contents of the original allylic amination (eq 11).

The fact that crossover of the prenyl moiety was observed from branched amine **13** to other amines such as piperidine indicated that the mechanism for isomerization is bimolecular. The crossover experiments also clearly demonstrate the differing abilities of branched *N*-allylamines and *N*-allyl aziridines to act as electrophile precursors under the reaction conditions. The branched amine **13** was able to transfer its prenyl unit to both piperidine and cyclohexene imine (**1a**). In the case of piperidine there was complete crossover and the product fully isomerized to the linear isomer. Therefore, the crossover conditions contained all the components necessary for isomerization. In these experiments both a nucleophile (the amine or aziridine) and an acid, generated from the palladium precursor, were additionally present. When isomerization of **13** was again attempted with Pd^0, acid, and 1,2,3,4-tetrahydroisoquinoline, the isomerization to **14** was observed. To summarize, all three components (Pd^0 catalyst, acid, and nucleophile) are required for isomerization. This information leads us to propose a rationale for the observed branched-to-linear interconversion (Figure 10).

In THF, the reaction produces protonated branched amine as the kinetic product by an S_N2' reaction with an allyl palladium σ-complex. Recomplexation of Pd^0 to the product alkene enables ionization to either the η^3 π-complex **B** or σ-complex **A**, which are also in equilibrium (Figure 10). It is the generation of these electrophilic components that enables crossover reactions to occur. Attack of a nucleophile on the more prevalent σ-complex **A** simply regenerates branched allylamine. However, reaction at the η^3 π-complex **B** should favor attack at the less substituted carbon, resulting in formation of the linear product. The reaction through σ-complex **C** is unlikely. Due to the increased steric hindrance around palladium in **C** compared to **A**, **C** is likely to be a very small component in the equilibrium. The strength of the palladium/olefin interaction in complex **D** is higher than that in complex **E** due to increased degree of substitution in **E**.[35] As a consequence, ionization of complex **D** should be more facile than complex **E**. Therefore, the dynamic process outlined in Figure 10 will steadily increase the amounts of the linear product. With aziridine the formation of either **A** or **B** does not take place, which accounts for the observed lack of branched-to-linear isomerization in the case of *N*-allyl aziridines. We considered the possibility that protonation of the allylamine product was required for the isomerization. We reasoned that the lower basicity of aziridines relative to that of amines (Table 7) would result in a lower equilibrium concentration of protonated amine. Therefore, no isomerization would take place. The lower basicity of aziridines results from bond strain which increases the s-character of the nitrogen lone pair. For instance, ethylene imine has a pK_{aH} (8.04[36]) that is closer to an sp^2 nitrogen atom in an imine (diphenyl imine $pK_{aH} = 7.2$) than to an sp^3 nitrogen atom in an amine (piperidine $pK_{aH} = 11.12$). Further investigation of amines revealed that pK_a is not likely

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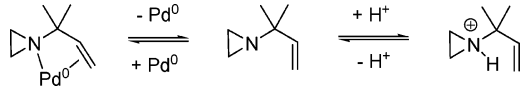

Figure 11. Allyl aziridine coordinated to palladium.

to be *the sole* factor contributing to the observed behavior (Table 7). A variety of different amines were employed in the reaction, having pK_{aH} values both higher and lower than ethylene imine. In all cases in which amines where used as nucleophiles the only isomer that was isolated was the linear product.

The amination of allyl acetates produces 1 equiv of acetic acid. In the absence of base and with full conversion of the aziridine starting material the acid was expected to form an aziridinium salt with the allyl aziridine products. In an attempt to prevent the unwanted aziridine ring opening with acetic acid, we employed potassium carbonate as the acid scavenger, which led to a significant decrease in the reaction rate (by almost half). A possible reason for this unexpected decrease in the reaction efficiency is coordination of the allyl aziridine products to palladium, sequestering some of the catalyst out of the catalytic cycle and thus slowing the rate of conversion (Figure 11).[37] Evidence for allyl aziridine/palladium interaction comes from lack of crossover when allyl aziridine is mixed with 1,2,3,4-tetrahydroisoquinoline and palladium.[38] Protonation of the aziridine nitrogen should prevent coordination to the metal.

In closing, significant deviation in behavior of aziridine nucleophiles in palladium-catalyzed allylic amination allows facile synthesis of useful branched amines that are difficult to obtain using other techniques. It appears that the origin of this behavior can be traced back to lack of isomerization of the initially produced branched product, whereas in the case of other amine nucleophiles a pathway for interconversion exists. The higher s-character of the aziridine nitrogen and, hence, its lower basicity reduce the relative amount of the protonated species that is necessary for isomerization to take place. The quantitative crossover experiments clearly confirm this relative lack of nucleophilicity. These experiments also demonstrate that even when protonated aziridine species **is** present, it is far less capable of reacting with Pd^0 than the common amine-derived allylated species. This lack of reactivity is a result of the stronger C−N bond due to, once again, higher s-character of the aziridine nitrogen.

Conclusions

In summary, we have investigated the palladium-catalyzed allylic amination reaction using unsubstituted aziridines. The observed regioselectivity favors valuable branched products in the cases of aliphatic allyl acetates, underscoring the decisive effect of the amine on the course of allylic amination. This observed switch in regiochemistry results only from the structural differences between amines and aziridines. Our investigations uncovered isomerization of allylated amines under palladium catalysis. This observation is significant for palladium catalysis as it suggests a possible explanation for low enantioselectivities typically observed with common amines as well as points to avenues for kinetic resolution.[39]

Experimental Section

General Procedures. Anhydrous acetonitrile, dichloromethane, diethyl ether, and toluene were obtained using the method described by Grubbs.[40] Tetrahydrofuran (THF) was distilled from sodium benzophenone under argon. Acetone was stored over 4 Å molecular sieves. Column chromatography was carried out using Silicycle 230−400 mesh silica gel or aluminum oxide, neutral, Brockman type 1. Analytical thin-layer chromatography (TLC) was performed on Macherey Nagel precoated glass-backed TLC plates (SIL G/UV254, 0.25 mm) and visualized by UV lamp (254 nm), iodine and potassium permanganate stain. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300, VRX-S (Unity) 400 or Unity 500 spectrometer. All unsubstituted aziridines **1a**−**g** were either purchased from commercial sources or synthesized by literature methods. All allyl acetates **2a**−**k** were synthesized by the literature method from their respective allyl alcohols.

Representative Procedure for the Preparation of Allyl Aziridines by Pd-Catalyzed Allylic Amination: 7-Allyl-7-aza-bicyclo[4.1.0]-heptane (3a). In a 15 × 100 mm screw cap test tube, equipped with septum and magnetic stir bar, were placed $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mg, 0.0137 mmol), PPh_3 (14 mg, 0.0547 mmol), K_2CO_3 (379 mg, 2.74 mmol), and dry THF (2 mL). Allyl acetate (**2a**) (148 μL, 1.37 mmol) and **1a** (133 mg, 1.37 mmol) were added via syringe, and the solution was stirred under a stream of argon at room temperature for 30 min, when GC analysis showed no cyclohexene imine (**1a**) remaining. Water (4 mL) was added, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 2 mL). The combined organic layers were concentrated in vacuo, and the residue was purified by flash chromatography (R_f 0.35, SiO_2, 9:1 hexanes/EtOAc) to yield *N*-allyl cyclohexene imine (**3a**) (85 mg, 0.62 mmol, 45%) as a clear liquid.

7-Allyl-7-aza-bicyclo[4.1.0]heptane (*N*-Allyl Cyclohexene Imine, 3a): Clear liquid, 45% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.91 (ddt, J = 17.3, 10.4, 5.3 Hz, 1H), 5.22 (ddd, J = 17.3, 3.7, 1.8 Hz, 1H), 5.08 (ddd, J = 10.4, 3.5, 1.5 Hz, 1H), 2.85 (dt, J = 5.3, 1.5 Hz, 2H), 1.86−1.71 (m, 4H), 1.50−1.48 (m, 2H), 1.39−1.13 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.1, 115.7, 63.4, 38.3, 24.7, 20.8. ESI: *m*/*z* (%) 138 ($M^+ + 1$); EI-MS: *m*/*z* (%) 136 ($M^+ - 1$, 100), 123 (46), 108 (47), 96 (42), 84 (67); HR-MS: calcd for $C_9H_{15}N$, 137.1204; obsd, 137.1202.

(*N*-Allyl-3-(but-3-enyl)aziridin-2-yl)(phenyl)methanone (3c): Clear oil, 83% yield. Peaks have been assigned by analysis of 2D NMR data: COSY, HSQC, and CIGAR. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02−7.99 (m, 2H, *ortho*-aromatics), 7.61−7.56 (m, 1H, *para*-aromatic), 7.51−7.46 (m, 2H, *meta*-aromatics), 5.90−5.76 (m, 2H, −C***H***=CH_2), 5.15−4.95 (m, 4H, −CH=C***H*****$_2$**), 3.39 (d, J = 2.9 Hz, 1H, −C***H***COPh), 3.36 (dd, J = 5.7 Hz, 1H, NC***H*****$_2$**CH=CH_2), 3.25 (dd, J = 14.3, 6.0 Hz, 1H, NC***H*****$_2$**CH=CH_2), 2.47 (m, 1H, −CH_2C***H***−), 2.33−2.12 (m, 2H, CH_2=CHC***H*****$_2$**CH_2−), 1.74−1.55 (m, 2H, CH_2=$CHCH_2$C***H*****$_2$**−); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 195.7 (**C**=O), 138.5 (*ipso*-aromatic), 137.9 (−CH_2CH_2***C***H=CH_2), 135.6 (NCH_2***C***H=CH_2), 133.4 (*para*-aromatic), 128.8 (*meta*-aromatics), 128.4 (*ortho*-aromatics), 117.1 (NCH_2CH=***C***H_2), 115.4 (−CH_2CH_2CH=***C***H_2), 54.1 (N***C***H_2CH=CH_2), 47.5 (−CH_2***C***H−), 43.9 (-***C***HCOPh), 32.5 (CH_2=$CHCH_2$***C***H_2−), 31.7 (CH_2=CH***C***H_2CH_2−). Rotamer peaks: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.08−5.96 (m, 0.25H), 5.30−5.24 (m, 0.25H), 3.50−3.44 (m, 0.25H), 3.20−3.14 (m, 0.25H), 2.79 (d, J = 2.8 Hz, 0.25H), 2.59 (m, 0.25H), 2.00−1.91 (m, 0.2H), 1.84−1.76 (m, 0.2H); ^{13}C NMR ($CDCl_3$, 125

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(38) The reverse is not the case: there is crossover when NH aziridine **1a** is added to allylated branched 1,2,3,4-tetrahydroisoquinoline (**13**).

(39) For recent use of Ir-catalyzed kinetic resolution of allyl acetates, see: Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628−1629.

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MHz): δ 196.6, 137.3, 137.2, 135.4, 133.2, 128.7, 128.4, 116.6, 115.9, 54.6, 47.8, 47.3, 31.7, 25.6. ESI: *m*/*z* (%) 242 ($M^+ + 1$); EI-MS: *m*/*z* (%) 241 (M^+, 6), 200 (13), 186 (73), 136 (70), 105 (100), 91 (22), 77 (68), 67 (17); HR-MS: calcd for $C_{16}H_{19}NO$, 241.1466; obsd, 241.1468.

7-Cinnamyl-7-aza-bicyclo[4.1.0]heptane (3d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38−7.35 (m, 2H), 7.31−7.26 (m, 2H), 7.19 (m, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.29 (dt, *J* = 15.8, 5.6 Hz, 1H), 3.00 (dd, *J* = 5.6, 1.5 Hz, 2H), 1.90−1.71 (m, 4H), 1.57−1.53 (m, 2H), 1.44−1.32 (m, 2H), 1.26−1.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.5, 130.8, 128.6, 127.7, 127.3, 126.4, 62.8, 38.3, 24.6, 20.7. ESI: *m*/*z* (%) 214 ($M^+ + 1$, 100), 117 (60); EI-MS: *m*/*z* (%) 213 (M^+, 24), 117 (46), 96 (100), 69 (54); HR-MS: calcd for $C_{15}H_{19}N$, 213.1517; obsd, 213.1511.

7-(1-Phenylallyl)-7-aza-bicyclo[4.1.0]heptane (4d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.36 (m, 2H), 7.33−7.27 (m, 2H), 7.24−7.18 (m, 1H), 5.97 (ddd, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.19 (ddd, *J* = 17.1, 1.8, 1.3 Hz, 1H), 5.05 (ddd, *J* = 10.2, 1.8, 1.0 Hz, 1H), 2.89 (d, *J* = 6.6 Hz, 1H), 1.87−1.53 (m, 6H), 1.49−1.37 (m, 2H), 1.24−1.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.5, 140.6, 128.2, 127.4, 126.9, 114.6, 77.2, 38.1, 38.0, 24.7, 24.6, 20.7, 20.6. ESI: *m*/*z* (%) 214 ($M^+ + 1$, 100) + 117 (30).

1-Cinnamyl-2-methylaziridine (3e): Clear oil, 84% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (d, *J* = 7.0 Hz, 2H), 7.30−7.25 (m, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 16.2, 5.7 Hz, 1H), 2.98 (dddd, *J* = 15.0, 14.4, 5.7, 1.5 Hz, 2H), 1.52 (d, *J* = 3.7 Hz, 1H), 1.43−1.36 (m, 1H), 1.26 (d, *J* = 6.3 Hz 1H), 1.20 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.2, 131.0, 128.5, 127.3, 127.2, 126.3, 62.7, 34.6, 34.4, 18.4. ESI: *m*/*z* (%) 174 ($M^+ + 1$, 30), 117 (100); EI-MS: *m*/*z* (%) 173 (M^+, 18), 130 (15), 117 (68), 104 (18), 91 (32), 77 (13), 56 (100); HR-MS: calcd for $C_{12}H_{15}N$, 173.1204; obsd, 173.1206.

Methyl 1-Cinnamylaziridine-2-carboxylate (3f): Clear oil, 88% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 16.1 Hz, 1H), 6.31 (dt, *J* = 16.1, 6.0 Hz, 1H), 3.73 (s, 3H), 3.19 (ddd, *J* = 13.7, 6.0, 1.3 Hz, 1H), 3.06 (ddd, *J* = 13.7, 6.0, 1.3 Hz, 1H), 2.23 (d, *J* = 3.3 Hz, 1H), 2.17 (dd, *J* = 6.4, 3.3 Hz, 1H), 1.69 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 136.8, 132.6, 128.7, 127.8, 126.5, 125.7, 62.4, 52.4, 37.3, 34.5. ESI: *m*/*z* (%) 218 ($M^+ + 1$, 20), 117 (100); EI-MS: *m*/*z* (%) 217 (M^+, 7), 158 (59), 130 (74), 117 (100), 91 (42); HR-MS: calcd for $C_{13}H_{15}NO_2$, 217.1102; obsd, 217.1101.

(*E*)-Methyl 1-(2-(Methoxycarbonyl)-3-phenylallyl)aziridine-2-carboxylate (3g): Clear oil, 84% yield. Compound isolated as an inseparable mix of regioisomers. Major regioisomer: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.42−7.35 (m, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 3.42 (d, *J* = 12.3 Hz, 2H), 3.29 (d, *J* = 12.3 Hz, 2H), 2.41 (m, 1H), 2.22 (m, 1H), 1.95 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 168.3, 143.8, 134.8, 130.1, 129.2, 128.5, 72.2, 55.0, 52.1, 52.0, 37.1, 34.8. Minor regioisomer, mix of diasteriomers: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.23 (m, 1H), 6.40 (s, 0.2H), 6.32 (s, 0.2H), 3.66 (s, 0.6H), 3.62 (s, 0.6H), 2.32 (m, 0.2H), 2.26−2.24 (m, 0.2H), 1.82 (d, 0.2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 166.4, 141.3, 140.0, 128.4, 127.7, 127.7, 126.5, 60.3, 51.8, 37.2, 35.4, 20.9, 14.2. ESI: *m*/*z* (%) 276 ($M^+ + 1$, 100), 175 (80); EI-MS: *m*/*z* (%) 275 (M^+, 9), 244 (12), 216 (92), 188 (100), 156 (20), 115 (85); HR-MS: calcd for $C_{15}H_{17}NO_4$, 275.1157; obsd, 275.1150.

7-(3-Methylbut-2-enyl)-7-aza-bicyclo[4.1.0]heptane (3h): In a flame-dried 50-mL one-neck round-bottom flask, equipped with magnetic stir bar and septum, were placed **1a** (200 μL, 1.95 mmol), K_2CO_3 (540 mg, 3.90 mmol), and dry acetone (20 mL). Prenyl bromide (227 μL, 1.95 mmol) was slowly added to the solution via syringe at room temperature. The resulting solution was stirred under a stream of nitrogen at room temperature for 30 min, when GC analysis showed no remaining cyclohexene imine (**1a**). Solvent was removed in vacuo, and the resultant yellow oil was purified by flash chromatography (R_f 0.56, SiO_2, 8:2 hexanes/EtOAc) to yield **3h** (145 mg, 0.88 mmol, 45%) as a clear oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.29 (m, 1H), 2.82 (d, *J* = 6.4 Hz, 2H), 1.85−1.71 (m, 4H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.58 (s, 3H), 1.48−1.47 (m, 2H), 1.40−1.29 (m, 2H), 1.20−1.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 132.9, 122.5, 58.8, 38.0, 25.8, 24.6, 20.6, 18.2. ESI: *m*/*z* (%) 166 ($M^+ + 1$).

7-(1,1-Dimethylallyl)-7-aza-bicyclo[4.1.0]heptane (4h): Clear liquid, 89% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.63 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.07−5.00 (m, 2H), 1.71−1.66 (m, 4H), 1.41−1.26 (m, 6H), 1.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.2, 113.7, 56.6, 34.9, 31.8, 30.2, 25.7, 25.3, 22.9, 20.8, 14.3. ESI: *m*/*z* (%) 166 ($M^+ + 1$, 100), 98 (40); EI-MS: *m*/*z* (%) 165 (M^+, 2), 150 (27), 96 (100), 84 (67), 69 (87); HR-MS: calcd for $C_{11}H_{19}N$, 165.1517; obsd, 165.1517.

Methyl 1-(3-Methylbut-2-enyl)aziridine-2-carboxylate (3k): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.32 (t, *J* = Hz, 1H), 3.72 (s, 3H), 3.03 (dd, *J* = 13.2, 6.9 Hz, 1H), 2.91 (dd, *J* = 13.2, 6.9 Hz, 1H), 2.16 (d, *J* = 2.8 Hz, 1H), 2.10 (d, *J* = 6.4, 2.8 Hz, 1H), 1.62 (d, *J* = 6.4 Hz, 1H), 1.73 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.6, 135.5 120.5, 57.9, 52.3, 36.9, 34.3, 25.9, 18.3. EI-MS: *m*/*z* (%) 170 ($M^+ + 1$, 1) 168 (1), 154 (31), 110 (61), 83 (23), 69 (100), 55 (29); HR-MS: calcd for $C_9H_{16}NO_2$, 170.1181; obsd, 170.1176.

Methyl 1-(2-Methylbut-3-en-2-yl)aziridine-2-carboxylate (4k): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.56 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.17 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.11 (dd, *J* = 17.4, 1.2 Hz, 1H), 3.72 (s, 3H), 2.24 (dd, *J* = 6.3, 2.9 Hz, 1H), 1.98 (dd, 2.9, 1.2 Hz, 1H), 1.79 (dd, 6.3, 1.2 Hz, 1H), 1.21 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, 139.7, 116.1, 57.0, 52.1, 30.8, 27.7, 25.8, 25.4; ESI: *m*/*z* (%) 170 ($M^+ + 1$, 80), 102 (100); ESI(QStar) calcd for $C_9H_{16}NO_2$, 170.1175; obsd, 170.1170.

1-(2-Methylbut-3-en-2-yl)-2-phenylaziridine (4m): Clear oil, 72% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30−7.22 (m, 4H), 7.20−7.14 (m, 1H), 5.68 (dd, *J* = 17.3, 11.1 Hz, 1H), 5.12 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.10 (dd, *J* = 11.1, 1.5 Hz, 1H), 2.56 (dd, *J* = 6.4, 3.1 Hz, 1H), 1.85 (dd, *J* = 6.4, 1.0 Hz, 1H), 1.62 (dd, *J* = 3.1, 1.0 Hz, 1H), 1.20 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.5, 141.2, 128.3, 126.7, 126.6, 115.0, 56.9, 33.9, 30.5, 26.0, 25.7. ESI: *m*/*z* (%) 188 ($M^+ + 1$, 100), 120 (75); EI-MS: *m*/*z* (%) 186 ($M^+ - 1$, 2), 146 (8), 118 (94), 91 (100); HR-MS: calcd for $C_{13}H_{16}N$, 186.1282; obsd, 186.1286.

(*E*)-7-(3,7-Dimethylocta-2,6-dienyl)-7-aza-bicyclo[4.1.0]heptane (3n): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.33−5.29 (m, 1H), 5.08−5.13 (m, 1H), 2.85 (d, *J* = 6.3 Hz, 2H), 2.17−1.99 (m, 4H), 1.85−1.72 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H), 1.57 (s, 3H), 1.50−1.49 (m, 2H), 1.40−1.26 (m, 2H), 1.20−1.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.7, 131.6, 124.4, 122.4, 58.8, 39.8, 38.2, 26.7, 25.9, 24.8, 20.8, 17.9, 16.8. ESI: *m*/*z* (%) 234 ($M^+ + 1$, 100), 98 (8); EI-MS: *m*/*z* (%) 233 (M^+, 3), 218 (5), 190 (3), 164 (8), 150 (8), 136 (6), 121 (4), 110 (11), 96 (100), 81 (14), 69 (39), 55 (7); HR-MS: calcd for $C_{16}H_{27}N$, 233.2143; obsd, 233.2147.

7-(3,7-Dimethylocta-1,6-dien-3-yl)-7-aza-bicyclo[4.1.0]heptane (4n): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.55 (dd, *J* = 11.0, 17.6 Hz, 1H), 5.15−5.09 (m, 1H), 5.09 (dd, *J* = 1.8, 11.0 Hz, 1H), 5.03 (dd, *J* = 1.8, 17.6 Hz, 1H), 2.08−1.99 (m, 4H), 1.70−1.65 (m, 7H), 1.60 (s, 3H), 1.52−1.43 (m, 2H), 1.43−1.34 (m, 2H), 1.19−1.06 (m, 2H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.5, 131.2, 125.4, 115.1, 59.2, 41.8, 30.1, 29.7, 25.9, 25.3, 25.2, 23.1, 21.3, 20.9, 20.8, 17.8. ESI: *m*/*z* (%) 234 ($M^+ + 1$, 100), 98 (20); EI-MS: *m*/*z* (%) 233 (M^+, 11), 218 (12), 190 (27), 164 (11), 150 (100), 136 (29), 121 (18), 108 (24), 96 (93), 81 (45), 69 (82), 55 (27); HR-MS: calcd for $C_{16}H_{27}N$, 233.2143; obsd, 233.2149.

7-(1,3-Diphenylallyl)-7-aza-bicyclo[4.1.0]heptane (3p): White solid, 97% yield (mp of racemate = 79.5−81.0 °C), 97% ee as measured by HPLC (AD column, 1 mL/min, 99:1 hexanes/*i*-PrOH, *t* = 4.5 and 5.0 min. 97% ee − 4.5 min enantiomer, using (*R*)-BINAP). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (d, *J* = 6.9 Hz, 2H), 7.39−7.17 (m, 8H),

6.57 (d, $J = 15.8$ Hz, 1H), 6.35 (dd, $J = 15.8$, 7.0 Hz, 1H), 3.08 (d, $J = 7.0$ Hz, 1H), 1.94−1.58 (m, 6H), 1.50−1.40 (m, 2H), 1.26−1.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.8, 137.4, 132.4, 129.8, 128.6, 128.4, 127.6, 127.5, 127.1, 126.7, 76.8, 38.3, 38.3, 24.9, 24.8, 20.9, 20.8. ESI: *m*/*z* (%) 193 (100), 115 (10); EI-MS: *m*/*z* (%) 289 (M^+, 7), 207 (41), 193 (100), 178 (27), 115 (89), 96 (68); HR-MS: calcd for $C_{21}H_{23}N$, 289.1830; obsd, 289.1824.

1-(1,3-Diphenylallyl)-2-methylaziridine (3q): White solid, 97% yield (mp 39−40 °C, racemate is a clear oil), 98% ee as measured by HPLC (AD column, 1 mL/min, 95:5 hexanes/*i*-PrOH, $t = 5.0$, 6.3, 6.9, and 7.2 min. 98% ee − 5.0 and 6.3 min enantiomers, using (*R*)-BINAP). Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46−7.18 (m, 20H), 6.66 (d, $J = 16.0$ Hz, 1H), 6.55 (d, $J = 16.0$ Hz, 1H), 6.39 (t, $J = 16.2$ Hz, 1H), 6.39 (dd, $J = 16.0$, 2.8 Hz, 1H), 3.05 (dd, 2H), 1.70 (d, $J = 3.2$ Hz, 1H), 1.68−1.61 (m, 1H), 1.59 (d, $J = 5.3$ Hz, 1H), 1.56−1.52 (m, 2H), 1.41 (d, $J = 6.3$ Hz, 1H), 1.30 (d, $J = 5.6$ Hz, 3H), 1.19 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 142.0, 137.1, 137.0, 131.8, 131.6, 130.1, 129.8, 128.5, 128.5, 128.4, 128.4, 127.6, 127.5, 127.4, 127.3, 127.3, 127.2, 126.5, 126.5, 76.8, 76.7, 35.4, 35.0, 34.5, 34.4, 18.5, 18.2. ESI: *m*/*z* (%) 193 (100), 115 (45); EI-MS: *m*/*z* (%) 249 (M^+, 19), 207 (43), 193 (100), 178 (35), 115 (76); HR-MS: calcd for $C_{18}H_{19}N$, 249.1517; obsd, 249.1499.

(*E*)-Methyl 1-(1,3-diphenylallyl)aziridine-2-carboxylate (3r): White solid, 79% yield. Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52−7.21 (m, 17H), 6.64 (d, $J = 15.8$ Hz, 1H), 6.62 (d, $J = 15.8$ Hz, 0.75H), 6.46 (dd, $J = 15.8$, 7.3 Hz, 0.75H), 6.44 (dd, $J = 16.0$, 7.0 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 2H), 3.20 (d, $J = 7.0$ Hz, 2H), 2.40 (d, $J = 3.1$ Hz, 1H), 2.38 (d, $J = 3.2$ Hz, 0.75H), 2.28 (d, $J = 3.1$ Hz, 1H), 2.26 (d, $J = 3.2$ Hz, 0.75H), 1.93 (d, $J = 6.6$ Hz, 0.75H), 1.78 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 170.9, 141.0, 140.9, 136.7, 136.6, 130.9, 130.9, 130.6, 130.4, 128.7, 128.6, 127.8, 127.73, 127.68, 127.61, 127.2, 126.6, 126.6, 76.5, 76.4, 52.3, 52.2, 37.9, 37.2, 34.9, 34.2. ESI: *m*/*z* (%) 193 (100), 115 (15); EI-MS: *m*/*z* (%) 293 (M^+, 12), 292 ($M^+ - 1$, 23), 234 (63), 193 (94), 178 (31), 115 (100), 91 (48); HR-MS: calcd for $C_{19}H_{18}NO_2$, 292.1337; obsd, 292.1339.

7-(5-Methylcyclohex-2-enyl)-7-aza-bicyclo[4.1.0]heptane (3s): Clear oil, 70% yield. Isolated as an 82:18 mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.80−5.67 (m, 1H), 5.63 (dm, 1H), 2.05−1.99 (m, 1H), 1.92−1.71 (m, 6H), 1.70−1.57 (m, 2H), 1.55 (m, 2H), 1.41−1.24 (m, 3H), 1.21−1.08 (m, 2H), 0.97 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 129.1, 128.4, 67.3, 38.0, 37.4, 36.8, 34.4, 28.2, 25.0, 24.9, 22.4, 20.8, 20.7. Spectroscopic data assigned to the minor diastereomer: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.9, 127.6, 63.7, 37.2, 36.6, 33.8, 25.2, 24.8, 24.7, 21.4, 20.9. ESI: *m*/*z* (%) 192 ($M^+ + 1$); EI-MS: *m*/*z* (%) 191 (M^+, 9), 149 (8), 96 (100), 69 (51), 55 (16); HR-MS: calcd for $C_{13}H_{21}N$, 191.1674; obsd, 191.1675.

(*Z*)-Methyl-5-(7-aza-bicyclo[4.1.0]heptan-7-yl)cyclohex-3-enecarboxylate (3t): Clear oil, 80% yield. See Supporting Information for peak assignments. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.76−5.73 (m, 1H), 5.67 (dm, $J = 10.1$ Hz, 1H), 3.68 (s, 3H), 2.56−2.49 (m, 1H), 2.29−2.25 (m, 2H), 2.21 (dm, $J = 12.4$ Hz, 1H), 1.96−1.93 (m, 1H), 1.81−1.75 (m, 4H), 1.69 (dt, $J = 12.7$, 10.4, 1H), 1.59 (m, 2H), 1.38−1.31 (m, 2H), 1.19−1.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.5, 129.3, 126.5, 66.2, 51.7, 38.8, 37.5, 36.8, 31.8, 28.0, 24.8, 20.6, 20.5. ESI: *m*/*z* (%) 236 ($M^+ + 1$, 100); EI-MS: *m*/*z* (%) 236 ($M^+ + 1$, 8), 96 (100), 79 (28), 69 (41), 55 (10); HR-MS: calcd for $C_{14}H_{21}NO_2$, 235.1572; obsd, 235.1567.

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Supporting Information Available: Full 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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