JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

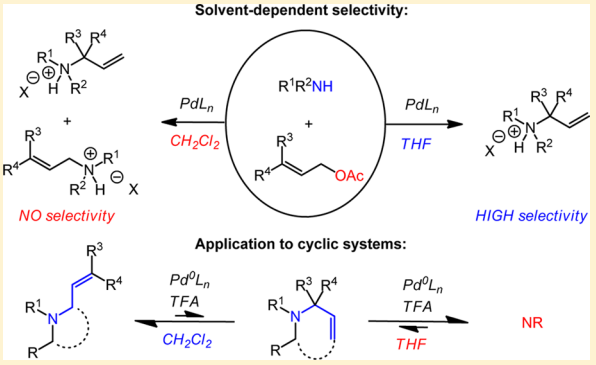
Achieving Control over the Branched/Linear Selectivity in Palladium-Catalyzed Allylic Amination

Igor Dubovyk, Iain D. G. Watson, and Andrei K. Yudin*

Davenport Research Laboratories, Department of Chemistry, The University of Toronto, 80 St George Street, Toronto, Canada M5S 3H6

Supporting Information

ABSTRACT: Palladium-catalyzed reaction of unsymmetrical allylic electrophiles with amines gives rise to regioisomeric allylic amines. We have found that linear products result from the thermodynamically controlled isomerization of the initially formed branched products. The isomerization is promoted by protic acid and active palladium catalyst. The use of base shuts down the isomerization pathway and allows for the preparation and isolation of branched allylic amines. Solvent plays a key role in achieving high kinetic regioselectivity and in controlling the rate of isomerization. The isomerization can be combined with ring-closing metathesis to afford the synthesis of exocyclic allylic amines from their endocyclic precursors.



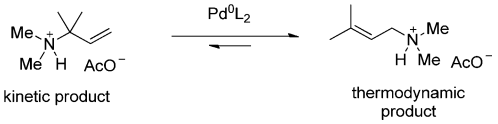
INTRODUCTION

Controlling regioselectivity has been an important goal in transition-metal-catalyzed allylic substitution.[1,2] Branched allylic amines have attracted particular interest due to the frequent occurrence of these structural fragments among natural products and pharmaceuticals. In addition, branched allylic amines are valuable building blocks in chemical synthesis.[3] The challenge of branched selectivity has been approached using metals such as iridium[4] and rhodium.[5] The corresponding catalysts allow for the selective formation of branched products from the corresponding amines and allylic acetates or carbonates. The use of palladium catalysts in the amination of allylic acetates and carbonates typically leads to the formation of the more thermodynamically stable linear products.[1]

Branched product formation with palladium has been observed and reported in the literature since 1981. Åkermark and co-workers were the first to describe amination of crotyl- and prenylpalladium chloride complexes to be reversible, suggesting that the linear product was formed as a result of isomerization of the kinetic branched product (Scheme 1).[6]

The original explanation suggested σ-complexes as reactive species, but subsequent studies provided no evidence supporting this claim.[7] Hou,[8a] Hayashi,[8b] and Faller[8c] hypothesized that certain bidentate ligands direct amines to the more substituted site on the palladium π-allyl complex, which ultimately results in the irreversible formation of branched products. In addition to catalyst modifications, there were also instances when the reactants themselves were biased to give high branched selectivities. Thus, Trost and co-workers have shown that ring size could be used to control selectivity in intramolecular allylic amination.[9] Branched 2-vinylpyrrolidines form kinetically faster and are more thermodynamically stable than the corresponding linear allylic tetrahydroazepines. Certain substituents on the allylic substrates such as trifluoromethyl group may also favor the formation of branched isomers.[10] Our own investigations in allylic amination started with a finding that, unlike typical branched allylic amines, branched allylic aziridines are stable against branched-to-linear (b/l) isomerization. Despite the fact that the origins of this stability are still not well understood, it became clear that the regioselectivity can be controlled by the selection of an appropriate nucleophile.[11] Subsequently, Hartwig and co-workers found that hydrazine and hydroxylamine derivatives can also be used to form the corresponding branched products.[12] We later discovered that a wider range of amines can be allylated with high b/l ratios *provided that the pathway for the proton-driven isomerization of the branched allylic amine to the linear isomer is shut down.*[13] The present contribution documents the scope of this process and its mechanistic foundation. In the course of our studies aimed at delineating the role of base additives, we have stumbled upon a curious effect of THF in this chemistry, which further highlights

Scheme 1

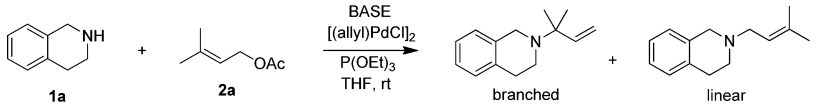


kinetic product — thermodynamic product

Received: December 10, 2012
Published: January 18, 2013

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

Table 1. Optimization of Base Additives



1a 2a branched linear

entry	base	equiv	time, h	GC conv (%)	regioselectivity (b/l)
1			24	100	0:100
2	tetrahydroisoquinoline	3	24	100	1:99
3	2,6-di-*tert*-butylpyridine	1	24	20	-
4	pyridine	1	24	100	1:99
5	Hunig's base	1	24	100	1:99
6	*N*-methylmorpholine	1	24	100	1:3
7	Et_3N	1	24	100	2:1
8	Et_3N	1	96	50	2:1
9	Et_3N	1	96	50	2:1
10	DABCO	1	24	100	2:1
11	TMEDA	1	24	100	2:1
12	^{t}BuOK	1	24	15	2:1
13	K_2CO_3	2	24	100	-
14	NaH	2	24	100	-
15	Bu_4NOH	1	24	100	-
16	DBU	1	24	100	19:1
17	DBN	1	24	91	19:1
18	phosphazene base P_1-^{t}Bu-tris(tetramethylene)	1	24	100	19:1

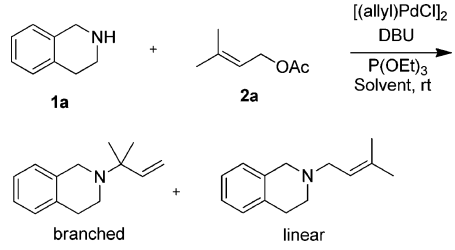
palladium's versatility. This effect also allowed us to optimize reaction conditions for a rearrangement of cyclic allylic amines.

RESULTS

In the course of our studies in the area of palladium-catalyzed allylic amination, we discovered that the presence of base can alter the regioselectivity of this reaction, channeling it toward the branched products. At the outset, we noted that during the amination of prenyl acetate with 2 equiv of piperidine, 1 equiv of this amine acted as the base, giving piperidinium acetate salt precipitate and the corresponding branched allylated product (4:1 branched/linear selectivity). This effect was limited to piperidine and relied on the removal of acid from the reaction mixture by precipitation. Starting with an equimolar mixture of **1a** and prenyl acetate gave full conversion with the corresponding linear allylic amine as the major product (Table 1, entry 1), which indicates that the presence of base in solution is critical to achieving high branched selectivity.[11b] With 2 equiv of **1a** (Table 1), the corresponding linear product was formed exclusively (Table 1, entry 2), whereas 2,6-di-*tert*-butylpyridine, a commonly used proton scavenger,[14] gave a very low conversion (Table 1, entry 3). We carried out an extensive search for base additives that could lead to high branched selectivity without concomitant base allylation. Pyridine and Hunig's base (Table 1, entries 4 and 5) had almost no effect on the reaction. These additives preferentially gave the linear product, whereas *N*-methylmorpholine gave linear product with 3:1 selectivity (Table 1, entry 6). Other bases such as triethylamine, DABCO, TMEDA, and ^{t}BuOK (Table 1, entries 7−12) gave the branched product with a low 2:1 selectivity even when a 10-fold excess of base was used. The reactions with inorganic bases such as K_2CO_3, NaH, and Bu_4NOH (Table 1, entries 13−15) produced very little allylic amine product because of the background reaction with the acetate. Finally, DBU (Table 1, entry 16) was found to give the branched product with a 19:1 selectivity. DBU has a pK_{aH} of 16.6 in THF, which is substantially higher than that of other organic bases[15] such as triethylamine (pK_{aH} 12.5). DBN and P_1-^{t}Bu-tris(tetramethylene)phosphazine (Table 1, entries 17 and 18) showed the same selectivity for the branched product as did DBU, although with DBN the reaction took longer to reach completion, whereas with P_1-^{t}Bu-tris(tetramethylene)-phosphazine the reaction was not as clean, probably due to the decomposition of this base. Optimal conditions were developed using **1a** (1 equivalent) and prenyl acetate (1 equivalent). Full conversion was reached after 17 h using 1 mol % of $[(\eta^3$-allyl)PdCl$]_2$ as the source of palladium, 4 mol % of P(OEt)$_3$ as the ligand, and 1 equiv of DBU as the base (Table 1, entry 16).

Our system was found to exhibit a strong solvent effect.[16] Table 2 shows that the branched products are favored in THF, whereas the selectivity drops substantially in less polar solvents such as dichloromethane. While 2-methyl-THF (Table 2, entry 3) was found to provide similar selectivity to the reaction in THF, 2,5-dimethyl-THF (Table 2, entry 4) showed a decrease in the b/l selectivity. The reaction in less polar THP displayed a

Table 2. Solvent Effects on Regioselectivity in Palladium-Catalyzed Allylic Amination

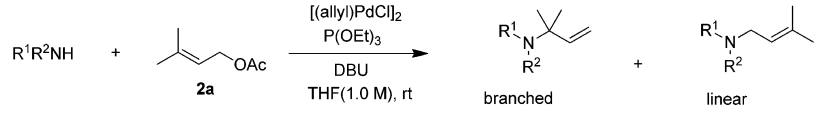


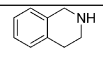
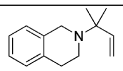
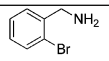
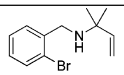
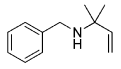
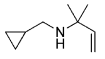
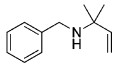
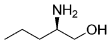
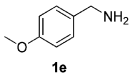
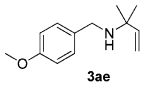
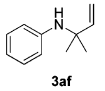
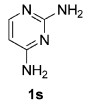
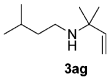
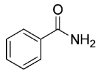
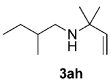
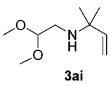
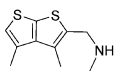
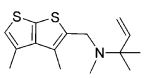
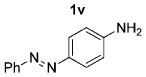
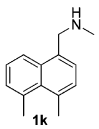
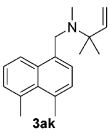
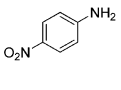
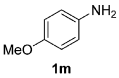
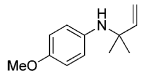
1a 2a branched linear

entry	solvent	b/l
1	THF	95:5
2	CH_2Cl_2	1:1
3	2-methyl-THF	96:4
4	2,5-dimethyl-THF	78:22
5	THP	85:15

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

Table 3. Substrate Scope of Amination of Prenyl Acetate



entry	amine	product	%yield (b/l)[a]	entry	amine	product	%yield (b/l)[a]
1	 1a	 3aa	92[d] (19:1)	15	 1o	 3ao	85 (19:1)
2	 1b	 3ab	80[d] (99:1)	16	 3ad		-[b]
3	 1c	 3ac	81[b,c,d] (19:1)	17	 1p	-	-[b]
4	 1d	 3ad	90[d] (9:1)	18	 1q	-	-[b]
5	 1e	 3ae	85[b,d] (19:1)	19	 1r	-	-[b]
6	 1f	 3af	71[b,d] (4:1)	20	 1s	-	-[b]
7	 1g	 3ag	80[b,d] (9:1)	21	 1t	-	-[b]
8	 1h	 3ah	87[b,d] (19:1)	22	 1u	-	-[b]
9	 1i	 3ai	87[b,d] (99:1)	23	 1v	-	-[b]
10	 1j	 3aj	61[b,d] (4:1)	24	 1w	-	-[b]
11	 1k	 3ak	76[b,d] (9:1)	25	 1x	-	-[b]
12	 1l	-	-[b]	26		-	-[b]
13	 1m	 3am	71[b] (24:1)	27	 1z	-	-[b]
14	1n	3an	54[b] (12:1)				

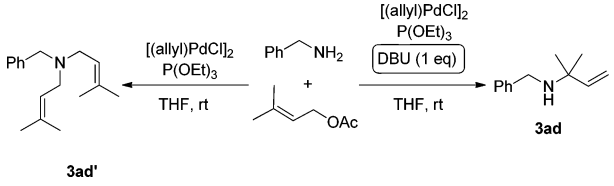
[a]Isolated yields of branched products. b/l obtained by GC. [b]The reaction was carried out at 50 °C. [c]NMR yield. The product could only be purified by distillation and was contaminated with $P(OEt)_3$. [d]These entries have been previously reported in our communication.[13]

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

preference for the branched product,[17] albeit with lower selectivity (Table 2, entry 5).

Table 3 shows the scope of reactivity of secondary as well as primary amines with prenyl acetate. Primary amines exhibited different reactivity depending on whether or not DBU was present in the system. With no DBU added, the allylation of benzylamine with prenyl acetate gave mixtures of linear mono- and bis-allylated products, whereas with DBU present, only the monoallylated branched product **3ad** (Table 3, entry 4) was observed even when a 2-fold excess of prenyl acetate was used (Scheme 2). Most other amines showed high regioselectivity in

Scheme 2

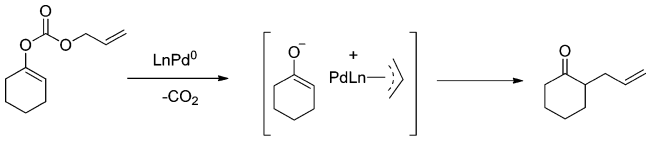


the presence of DBU, except for aniline (Table 3, entry 6). The use of an electron-defficient $P(OEt)_3$ as a ligand made the reaction tolerant to functional groups such as aryl bromide (Table 3, entry 15). Switching to more electron-poor amines (Table 3, entries 17−27) resulted in full recovery of prenyl acetate even at 50 °C. Surprisingly, amine **1q** gave no conversion.

We examined the lack of overallylation with primary amines (Table 3). It transpired that substituents next to the nitrogen atom produced a profound effect on the reaction outcome. Thus, sterically congested *cis*-2,6-dimethyl piperidine **1l** (Table 3, entry 12) showed no conversion even at 50 °C. Neither was any conversion observed when the branched allylic amine **3ad** (Table 3, entry 16) was resubjected to the reaction conditions in the presence of DBU. The fact that without DBU primary amines can produce bis-allylated products such as **3ad′**, while amines with substituents next to nitrogen are completely unreactive, suggests that the kinetic branched product has to undergo isomerization before another allylation can occur (Scheme 3). When the monoallylated branched product cannot isomerize, it is too hindered to react with another molecule of prenyl acetate leading to the monosubstituted branched product (Scheme 3).

We later decided to explore the reactivity of allylic carbonates. Allyl enol carbonates were previously explored by Stoltz[18] and Trost[19] toward allylation of enolates. The formation of stable palladium enolates took place upon extrusion of CO_2 from the carbonate (Scheme 4). The

Scheme 4



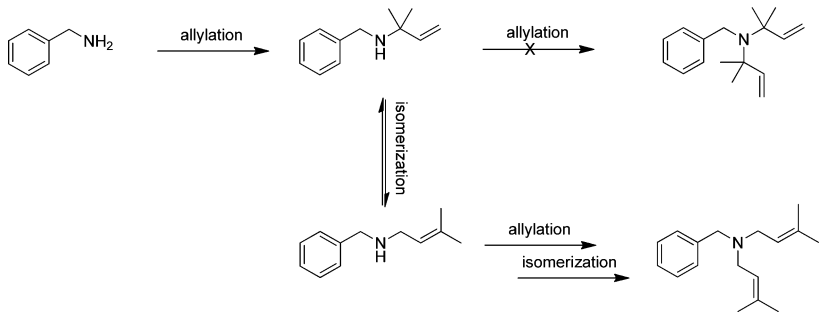
formation of CO_2 and palladium enolate is the driving force for the decarboxylation step. When we replaced prenyl acetate **2a** with the corresponding carbonate, there was no change in selectivity for the branched product. Similarly, when no DBU was used, only the linear product was observed. One explanation for this result is that ethyl carbonic acid that forms in situ does not rapidly decompose into ethanol and water, but rather remains in solution long enough to promote product protonation and the b/l isomerization in the absence of DBU (Scheme 5). Alternatively, if ethyl carbonic acid does decompose to release CO_2, ethanol could activate the branched allylic amine to ionization via hydrogen bonding. This latter system has been described by Zhang in palladium-catalyzed allylation of ketones with allylic amines in protic solvents.[20]

While we were able to control regioselectivity with prenyl acetate, achieving high levels of selectivity with disubstituted substrates was not as straightforward. The reaction outcome strongly depended on the nature of the ligand (Table 4) and the substituent R^3 on the acetate (Table 5). When hex-2-enylacetate **2d** was reacted with amine **1a** in the presence of DBU and $P(OEt)_3$, a 1:4 b/l ratio was detected (Table 4, entry 1). This is in contrast to the reaction between **1a** and prenyl acetate **2a**, where $P(OEt)_3$ afforded 19:1 branched selectivity under the same reaction conditions. In order to test whether the inferior selectivity with **2d** was kinetic in origin, we monitored the reaction progress using GC. In the presence of DBU and $P(OEt)_3$, the b/l ratio of 1:4 remained constant throughout the experiment, indicating that isomerization is not occurring under these conditions. This finding suggests that the presence of DBU only prevents the erosion of the initial regioselectivity, whereas the electronic effects of the allylic acetate determine this selectivity.

Replacing $P(OEt)_3$ with other ligands showed a strong variation in selectivity (Table 4). The bidentate ligands (Table 4, entries 3−7) gave the linear product almost exclusively. Most monodentate ligands also favored the linear product, although with lower selectivity. The highest selectivity for the branched product was obtained with (*o*-biphenyl)dicyclohexyl phosphine[21] (Table 4, entry 16).

The reactions with *trans*-hex-2-enylacetate **2d** were very slow, and therefore, crotyl acetate **2b** was used instead. (*o*-Biphenyl)dicyclohexylphosphine significantly improved the

Scheme 3



dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

Scheme 5

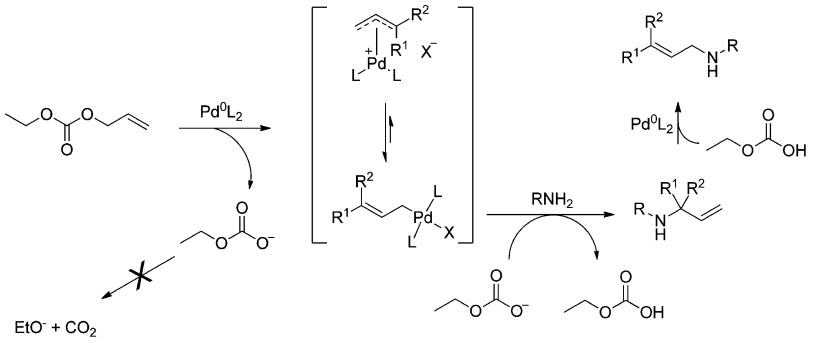
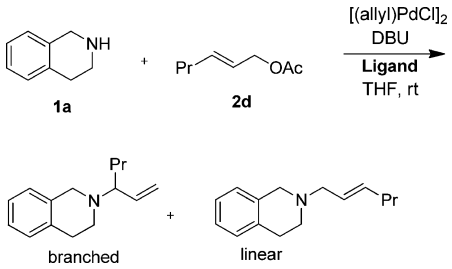


Table 4. Ligand Screening for Amination of Disubstituted Allylic Acetates[a]



entry	ligand	% conversion	b/l
1	$P(OEt)_3$	100	1:4
2	$P(OEt)_3$	100	0:1[b]
3	(*rac*-BINAP)	100	1:32
4	dppf	100	1:19
5	(*S*,*S*)-DIOP	100	1:24
6	Xantphos	100	1:24
7	dppp	100	1:24
8	$P(OPh)_3$	0	-
9	PPh_3	100	1:3
10	$Pd(PPh_3)_4$	100	1:4
11	Ph_2P(Ph-oxazoline)	100	1:19
12	$CyPPh_2$	100	1:3
13	PCy_3	0	-
14	$(^tBu)_2P$(*o*-biphenyl)	100	1:6
15	P^tBu_3	40 (2 days)	2:1
16	Cy_2P(*o*-biphenyl)	80 (2 days)	2:1

[a]Allyl acetate (1 equiv), nucleophile (1 equiv), DBU (1 equiv), [(π-allyl)PdCl]$_2$ 1 mol %, monodentates 4 mol %, midentates 2 mol %, THF 0.5 M, 24 h. [b]No DBU was used.

selectivity, giving greater than 99:1 b/l ratio for this challenging allylic acetate (Table 5, entry 6). $P(OEt)_3$, the ligand of choice for the trisubstituted substrates, gave inferior 6:1 b/l selectivity with **2b** (Table 5, entry 2). When the methyl group on the crotyl substituent was replaced with a phenyl substituent, however, the conjugated linear product predominated over the branched regioisomer with a 2.5:1 selectivity (Table 5, entry 5).

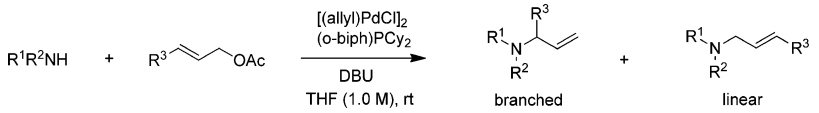
We had mentioned earlier that the nature of the reaction solvent was crucial in establishing high branched regioselectivity (Table 2). In addition to this kinetic effect of THF, we also discovered the solvent influence on the rate of branched to linear isomerization. Thus, the product isomerization in the presence of DBU in THF was slow, and only 30% of product isomerized after one week. In contrast, with DBU in CH_2Cl_2, branched allylic amines fully isomerized to form linear products within 4 days. Inspired by such observations, we envisioned this isomerization to be enabling in paving access to cyclic amines by skeletal isomerizations of allylic amine scaffolds.[22]

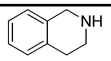
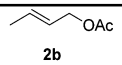
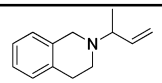
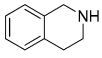
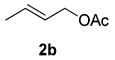
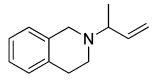
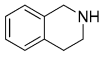
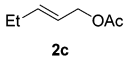
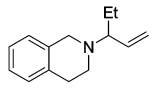
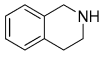
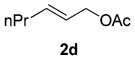
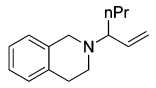
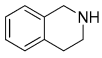
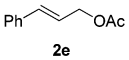
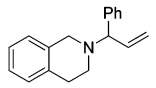
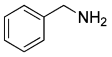
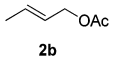
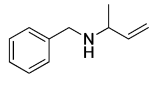
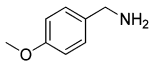
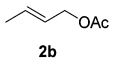
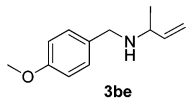
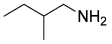
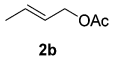
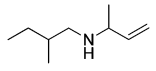
Table 6 shows the condition optimization for the isomerization-driven ring construction. We were encouraged that in dichloromethane 50% of tetrahydroazepine **4a** was converted to the corresponding 2-prenylpyrrolidine **5a** after 8 h (Table 6, entry 2). One equivalent of TFA was employed to activate the amine. Interestingly, the addition of morpholine (10 mol %) gave further boost and pushed the reaction to completion (Table 6, entry 3). With no ligand present, the rearrangement of **4a** did not occur (Table 6, entry 4). In addition, uncatalyzed olefin isomerization was not observed when either **4a** or **5a** was used as the starting material. Switching the solvent to THF with or without the addition of morpholine gave no conversion (Table 6, entries 1 and 5). Reaction with only 5 mol % of TFA gave no conversion with or without morpholine added. This methodology can be strategically applied to late-stage modifications of complex amines by using amine-containing fragments simultaneously as nucleophiles and as leaving group precursors. Once combined with olefin ring closing metathesis, the methodology was shown to find application in combinatorial chemistry.[23]

Originally, morpholine was added with the intention to help form the active catalyst from allyl palladium precursor. Nucleophilic morpholine attacks the π-allyl ligand on palladium(II) leading to the formation of *N*-allylmorpholine and a catalytically active palladium(0) complex.[24] However, the reaction did reach 50% conversion in the absence of morpholine, which suggests that morpholine is not essential for catalyst activation. For instance, a fraction of starting tertiary cyclic allylic amine can reduce allylpalladium(II) complex in a similar fashion, forming a quaternary amine as a result. Another possibility is that morpholine acts as a nucleophilic catalyst in the reaction. To test if this was the case, morpholine was replaced with *N*-methylmorpholine. Such modification gave full conversion (Table 6, entry 8), ruling out the catalytic role of morpholine. In addition, morpholine-containing intermediates have never been isolated or observed spectroscopically during our studies. Alternatively, the combination of morpholine and TFA likely forms a buffer, in which morpholinium trifluoroacetate acts as an active acid to allow for the controlled protonation of the starting tetrahydroazepine. Such careful protonation is necessary to avoid the undesirable protonation of palladium catalyst or the ligand. Indeed, even in the presence of morpholine, the reaction fails when a phosphite ligand is replaced by a more basic phosphine (Table 6, entry 9). The substrate scope is shown in Table 7. All of the starting materials were prepared using metathesis protocols and other standard reactions.[25]

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

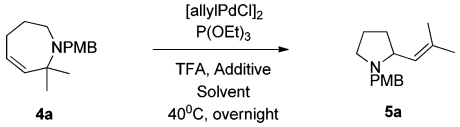
Table 5. Substrate Scope of Amination with Trans-Disubstituted Allylic Acetates



entry	amine	acetate	product	%yield (b/l)[a]
1	 1a	 2b	 3ba	82[d] (13:1)
2	 1a	 2b	 3ba	100[c,e] (6:1)
3	 1a	 2c	 3ca	83 (6:1)
4	 1a	 2d	 3da	80[c,d] (2:1)
5	 1a	 2e	 3ea	66 (1:2.6)
6	 1d	 2b	 3bd	84[b,d] (99:1)
7	 1e	 2b	 3be	82[b,d] (19:1)
8	 1h	 2b	 3bh	81[b,d] (9:1)

[a]Combined isolated yields of mixtures. b/l obtained by GC. [b]The reaction was carried out at 50 °C. [c]Conversion determined by GC. [d]These results have been previously reported in our communication.[13] [e]The reaction was performed with $P(OEt)_3$ instead of (*o*-biphenyl)PCy_2.

Table 6. Condition Screening for the Aza-allylic Rearrangement



entry	ligand	solvent	additive (10 mol %)	% conv[a]
1	$P(OEt)_3$	THF	-	0
2	$P(OEt)_3$	CH_2Cl_2	-	50
3	$P(OEt)_3$	CH_2Cl_2	morpholine	100
4	-	CH_2Cl_2	morpholine	0
5	$P(OEt)_3$	THF	morpholine	0
6	$P(OEt)_3$	CH_2Cl_2	-	0[b]
7	$P(OEt)_3$	CH_2Cl_2	morpholine	0[b]
8	$P(OEt)_3$	CH_2Cl_2	*N*-methylmorpholine	100
9	Trost ligand	CH_2Cl_2	morpholine	0

[a]Conversion was monitored by ^1H NMR. [b]5 mol % acid was used.

DISCUSSION

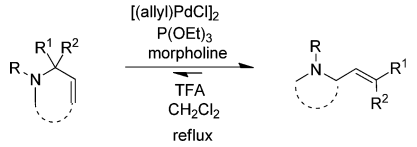
We have achieved control over regioselectivity in palladium-catalyzed allylic amination by suppressing the proton-assisted b/l isomerization, which is responsible for the observed linear selectivity. This selectivity is thermodynamic in nature and can be reversed in the presence of DBU. In addition to controlling the b/l isomerization with base, there are factors that influence the kinetic formation of branched products.

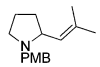
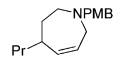
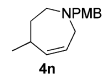
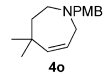
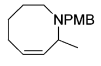
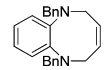
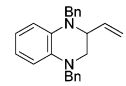
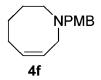
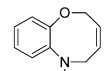
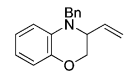
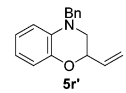
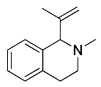
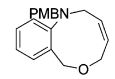
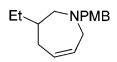
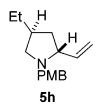
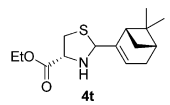
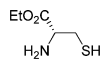
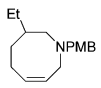
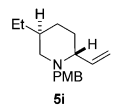
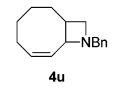
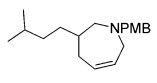
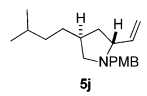
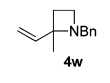
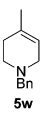
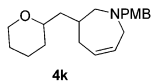
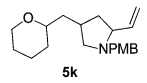
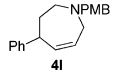
Kinetic Solvent Effects. Solvent is a key parameter that is responsible for the observed kinetic regioselectivity in allylic amination. As can be seen from Table 2, the formation of the branched product is kinetically favored in THF, whereas in other solvents lower or no selectivity is observed. To explain the formation of both branched and linear products, the presence of both π- and σ-metal complexes may be considered. π-Complexes are known to be in equilibrium with their σ-isomers,[26] and the extent of this equilibrium depends on the nature of the metal, ligand, solvent, and counteranion.[27]

Computational studies performed previously[28] on prenyl η^3-allylpalladium complexes showed that the difference in the activation barriers for the attack at the tertiary and primary carbons is less than 1 kcal/mol, which is too small of a difference to account for the observed branched kinetic selectivity based on the η^3-allyl complex alone. Despite the fact that the computational study did not take into account the

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

Table 7. Reaction Scope of the Aza-allylic Rearrangement



entry	reactant	product	yield	entry	reactant	product	yield
1	 **4a**	 **5a**	97[d]	13	 **4m**	S.M.	-[b]
2	 **4b**	S.M.	-	14	 **4n**	S.M.	-[b]
3	 **4c**	 **5c**	94[d] (*E*/*Z*=3.6 :1)	15	 **4o**	S.M.	-[b]
4	 **4d**	 **5d**	92[d] (*E*/*Z*=4.6 :1)	16	 **4p**	S.M.	-[b]
5	 **4e**	 **5e**	93[d]	17	 **4q**	 **5q**	78[d]
6	 **4f**	 **5f**	97[d]	18	 **4r**	 **5r**  **5r'**	83[d] (1:1)
7	 **4g**	S.M.	-	19	 **4s**	S.M.	-[b]
8	 **4h**	 **5h**	53[b,d] (2:1)	20	 **4t**	 **5t**	-[b]
9	 **4i**	 **5i**	71[d] (3:1)	21	 **4u**	S.M.	-[b]
10	 **4j**	 **5j**	50[b,d] (2:1)	22	 **4w**	 **5w**	96[c,d]
11	 **4k**	 **5k**	68[b,d] (1:1)				
12	 **4l**	S.M.	-[b,d]				

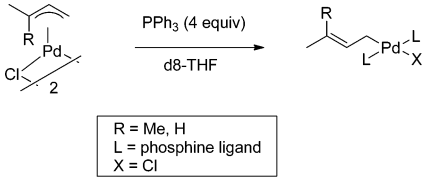
[a]Isolated yields. Pd-catalyst/ligand/morpholine/substrate/TFA = 1/4/10/40/40 in CH_2Cl_2 (0.5 M) reflux, overnight. [b]Pd-catalyst/ligand/morpholine/substrate/TFA = 1/4/10/20/20 in DCE (0.5 M) reflux overnight. [c]Pd catalyst/ligand/morpholine/substrate/TFA = 1/4/10/100/100 in CH_2Cl_2 (0.2 M) rt, overnight. [d]These results have been previously reported in our communication.[22]

nature of solvent and PH_3 ligands were used for simplification, this result suggests a possibility of another catalytically relevant palladium intermediate, which would account for high branched selectivity.[29]

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

The dependence of regioselectivity on the nature of the solvent (Table 2) prompted us to examine the solvent effect on the equilibrium between allylpalladium intermediates. When prenylpalladium chloride dimer was mixed with PPh_3 in THF-d_8, the corresponding σ-complex was the only species observed by NMR (Scheme 6).[11a,30] This observation, combined with

Scheme 6



the fact that high branched selectivity is only observed in THF, led us to examine whether the involvement of palladium σ-allyl intermediate in THF was a possible reason for the high branched selectivity.

Table 2 shows a correlation between the solvent nucleophilicity and branched selectivity in allylic amination. One can conclude that THF alters the reactivity of allyl palladium intermediates.[31] Such behavior would explain the selectivity trend in other ethereal solvents. When THF is replaced by 2,5-dimethylmethyl-THF, the oxygen center becomes less nucleophilic (Table 2, entry 4), and the selectivity for the branched product drops. A similar result was observed with the less coordinating THP. To estimate the minimum amount of THF that is sufficient to favor branched products, we monitored branched selectivity in THF/CH_2Cl_2 mixtures of different composition (Figure 1). In the presence of $P(OEt)_3$, it

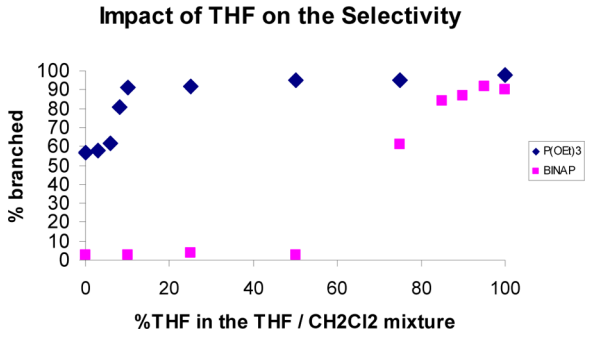


Figure 1. Impact of THF on selectivity in the presence of $P(OEt)_3$ and BINAP ligands.

takes as low as 10% THF in solution to maintain branched selectivity of 9:1. On the other hand, with BINAP, almost 90% THF is required to give rise to the branched product. The results of this study support the notion that THF is able to compete for palladium as a ligand. We believe that by coordinating to palladium, THF can promote the η^3 to η^1 isomerization, thus altering the b/l selectivity of the reaction.[32] Since bidentate ligands stabilize π-allyl complexes much better than monodentate ligands, it is not surprising that with BINAP at least 90% of THF in dichloromethane is required in order to reach the selectivity observed with $P(OEt)_3$. The fact that THF cannot be used in substoichiometric quantities to dictate the selectivity does not necessarily revoke the possibility of coordination of THF to palladium. Such large amounts of THF may be needed because compared to phosphines, acetate, or chloride THF is a weak ligand, and high concentrations of it are required to make it competitive in terms of binding.[33]

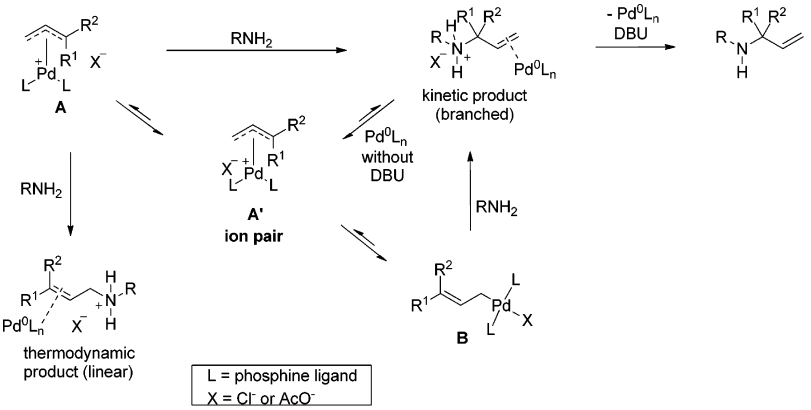
Upon conducting a more detailed study, however, we observed exclusive σ-complex formation in dichloromethane, in which there is no kinetic selectivity at all. This finding suggests that there is no correlation between the abundance of the σ-complex in solution and branched selectivity. Therefore, the presence of the σ-complex cannot alone explain the observed branched selectivity. Even though the π-complex is the minor of the two allyl-palladium intermediates in solution, it is expected to be more reactive, by virtue of it being charged.[34] This ionic nature of the π-complex makes its reactivity strongly dependent on the polarity of the solvent. Given that dichloromethane has a higher dielectric constant than THF,[35] it is conceivable that dichloromethane can preferentially make the relevant cationic π-complex more reactive by increasing the extent of its ion pair dissociation. The nucleophilic attack on this charged intermediate would then give poor kinetic regioselectivity, which is consistent with our results, and predicted by computations. On the other hand, in THF the ionic π-complex exists as a tighter ion pair and, therefore, is expected to be less reactive when compared to the π-complex in dichloromethane.[36]

Scheme 7 shows possible palladium intermediates that may explain the observed kinetic selectivity. Intermediate **B** can convert into **A** through an intimate ion pair **A′**, which upon dissociation would form a solvent separated ion pair **A**. Amine attack on intermediate **A** is expected to yield both branched and linear products because the termini of the π-complex are not well differentiated.[28] On the other hand, intermediate **B** is susceptible to a nucleophilic attack proceeding in an S_N2' fashion at the more substituted terminus, which would lead to the branched allylic amine. In dichloromethane, the interconversion between **A** and **A′** is expected to be fast comparing to the nucleophilic attack on **B**. Since intermediate **A** is charged, and is therefore more reactive toward nucleophiles than **B**, the reaction is more likely to proceed through **A**. Given the negligible difference in activation energy between the attacks on either terminus of **A**, the resulting reaction outcome in dichloromethane suggests that both branched and linear products in fact come from **A**. On the other hand, in THF, even though the attack on the intermediate **A** is still faster than that on **B**, the interconversion between **A** and **A′** must be slow compared to the nucleophilic attack on **B**. In the presence of DBU, the charged newly formed branched kinetic product is irreversibly deprotonated to form the neutral kinetic product, which is unable to re-enter the catalytic cycle. In the absence of DBU the protonated branched product re-enters the catalytic cycle to form complex **A′**. Therefore, the solvent dictates kinetic regioselectivity by controlling the accessibility of the dissociated charged cationic π-allyl complex.

Thermodynamic Solvent Effect. In addition to the ability of the solvent to control kinetic regioselectivity by controlling the rate of dissociation of reactive palladium intermediates, solvent can also affect the extent of isomerization by modulating the relative strength of acid in solution. The fact that in the presence of DBU in THF only 30% of the branched product isomerizes to give the corresponding linear product after one week, whereas under the same conditions in dichloromethane full isomerization is observed after only 4 days, and, likewise, the fact that aza-allylic rearrangement proceeds in dichloromethane, but not in THF, both suggest that the relative acid strength of $DBUH^+OAc^-$ and

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

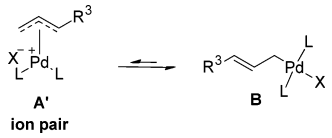
Scheme 7



morpholinium trifluoroacetate, respectively, is higher in dichloromethane than in THF. In THF each acid may exist as an ion pair shielded by the solvent cage, which prevents it from achieving the proton transfer to the allylic amine. On the other hand, in dichloromethane, ion-pair dissociation and the proton transfer occur to a much greater extent.[37]

Kinetic Ligand Effect. Table 4 shows the effect of different ligands on kinetic selectivity of amination of a *trans*-disubstituted allylic acetate in THF. The results indicate that in the presence of DBU all of the bidentate ligands preferentially favor the formation of the linear regioisomer, whereas the corresponding branched product was given preference with bulky monodentate ligands. Whereas it is still unclear why all bidentate ligands favor high kinetic linear selectivity, the trend with monodentate ligands can be explained by examining the corresponding palladium intermediates shown in Scheme 8.

Scheme 8



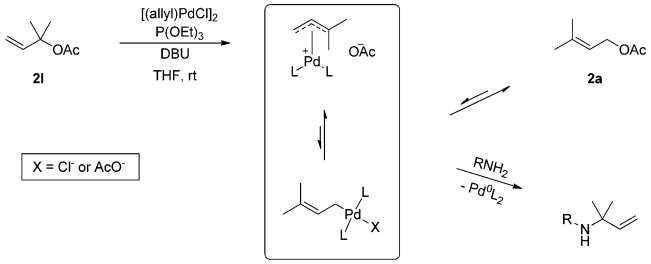
Bulky monodentate ligands are more likely to arrange themselves in the *trans*-fashion favoring the σ-complex, the attack on which is expected to give high branched selectivity. Bidentate ligands, on the other hand, can only arrange themselves in the *cis*-fashion, which would make the formation of the σ-complex improbable, and the reaction would likely proceed through the π-complex. Even though computations mentioned earlier predict that the attack on a π-complex should give both regioisomers with equal distribution, such computations have not been performed with bidentate ligands, and, therefore, do not exclude the possibility that with bidentate ligands the attack on the less-substituted terminus of the π-complex is preferred.

This ligand effect is much more pronounced with disubstituted allylic acetates than it is with the prenyl acetate. This is because in the π-complex derived from prenyl acetate one of the methyl substituents will always be placed in the *anti*-position imposing additional energy cost due to the 1,3-allylic strain. In contrast, the π-complex derived from a disubstituted acetate can avoid such cost by placing its largest substituent in the *syn* position. As a result, the formation of a π-complex is more feasible with disubstituted acetates, and therefore the nature of the ligand becomes an important factor in imposing selectivity (Table 5, entries 1 and 2).

In addition, the size of the substituent R^3 on a disubstituted allylic acetate (Scheme 8) also has some impact on the regioselectivity. Table 5 shows that as R^3 becomes larger than R^3 = Me, the regioselectivity drops and finally becomes reversed when R^3 = Ph (Table 5, entries 1, 3, 4, and 5). Additionally, the rate of reaction also slows down. Both of these factors suggest that when R^3 becomes large, the rate of attack on the σ-complex becomes smaller, while the rate of attack on the π-complex becomes more significant and eventually overrides the effects of the ligand.

Original Position of the Leaving Group. Testing our system for the presence of the memory effect has supported the involvement of the π-allyl complex. When acetate **2a** was replaced with its isomer **2l**, no change in selectivity took place. When the reaction of **2l** was monitored by GC, the formation of the acetate **2a** was observed (Scheme 9). Furthermore, without the nucleophile, acetate **2l** isomerized into prenyl acetate **2a**.[38]

Scheme 9

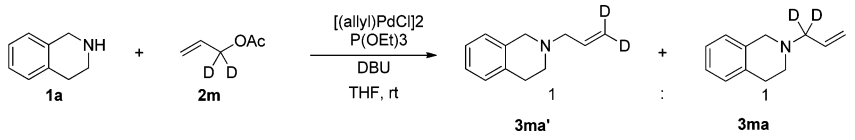


In addition, when the deuterated allyl acetate was used, our system showed deuterium scrambling in the product (Scheme 10). This observation is indicative of the absence of a memory effect that is known to occur with carbon-based nucleophiles.[39] The absence of the memory effect suggests that there is a common intermediate and is consistent with the presence of a symmetrical π-complex, which again supports the fact that the π-complex is involved even though it is not observed spectroscopically.

Driving Force in the Isomerization of Cyclic Allylic Amines. We have turned back to our test substrate in attempts to figure out which of the two factors (the size of the ring or the

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

Scheme 10



substitution on the alkene) was tipping the balance in favor of the product. Subjecting tetrahydroazepines **4c** and **4e** to the reaction conditions yielded the corresponding 2-vinylic pyrrolidines with di- and monosubstituted alkenes, respectively, in high yields (Table 7, entries 3 and 5). Similar yields were observed when analogous hexahydroazocines **4d** and **4f** were used in place of tetrahydroazepines (Table 7, entries 4 and 6). In cases where disubstituted olefins were obtained, *trans*-isomers predominated. The fact that products containing the less-substituted alkenes formed in high yields suggests that the rearrangement is primarily driven by the stability of the ring. The preference to yield the more stable ring also overrides the formation of a conjugated alkene, as can be seen from the attempted ring-expansion of a tetrahydroisoquinoline **4g** (Table 7, entry 7).

Steric Effects in the Isomerization of Cyclic Allylic Amines. We became interested in whether it is be possible to control the diastereoselectivity of the rearrangement. To test this, we subjected substituted seven- and eight-membered precursors (Table 7, entries 8−11) to allylpalladium chloride and $P(OEt)_3$ in dichloromethane in the presence of morpholine and TFA. None of the subjected allylic amines gave the rearranged products except for **4i**, which rearranged to the corresponding piperidine **5i** in good yield with a 3:1 selectivity for the *trans*-isomer. When dichloromethane was replaced with dichloroethane and the reaction temperature was increased, tetrahydroazepines **4h**, **4j**, and **4k** (Table 7, entries 8, 10, and 11) gave the corresponding ring-contracted products in modest yields with very low selectivity for the *trans*-product. Such poor selectivities are probably thermodynamic in nature, and reflect the difference in relative stability between the *trans*- and the *cis*-isomers. Moreover, the resulting chiral centers are not contiguous, and are less likely to affect each other. Tetrahydroazepines **4l**, **4m**, and **4n** with substituents in the 4-positions (Table 7, entries 12−14) were designed such that in case the rearrangement did occur, the products would contain two contiguous chiral centers. Unfortunately, none of these substrates underwent the rearrangement, probably due to the excessive steric interactions between the substituents that are placed in close proximity during cyclization. Likewise, **4o** and **4p** gave no rearranged product, most likely for the same reason (Table 7, entries 15 and 16).

Electronic Effects in the Isomerization of Cyclic Allylic Amines. Another class of substrates that were subjected to the rearrangement reaction contained an extra heteroatom (Table 7, entries 2 and 17−20). When subjected to the reaction conditions, tetrahydrodiazocine **4q** gave the corresponding tetrahydroquinoxaline **5q** in good yield (Table 7, entry 17). Similarly, dihydrooxazocine **4r** gave the expected dihydrobenzooxazine **5r** along with its isomer **5r′**, which was formed from the ionization of the phenol ether (Table 7, entry 18). Phenoxide is a good leaving group and has been utilized as a leaving group in allylic alkylation.[40] There is no control over chemoselectivity of this system, and both products form in an equimolar ratio. Interestingly, the homologated version of this substrate, **4s**, showed no conversion to the expected tetrahydrobenzooxazepine (Table 7, entry 19). This is most likely due to the reduced basicity of **4s**, which lacks the electron-donating alkoxy substituent on the aromatic ring. As a result, the effective concentration of the protonated aniline **4s** in the already buffered system is quite low. Substrate **4r** is more electron rich, which explains why products **5r** and **5r′** are formed in high yield. Similarly, amide **4b** did not undergo the rearrangement due to its low bacisity, when compared to **4a**. Heterocycle **4t** underwent full hydrolysis under the reaction conditions due to the presence of the acid-sensitive carbanol-amine functionality (Table 7, entry 20).

Stereoelectronic Effects in the Isomerization of Cyclic Allylic Amines. Finally, stereoelectronic effects were found to be very significant when we considered the rearrangement of bicyclic allylic amines. Vinyl azetidine **4w** rearranged to give tetrahydropyridine **5w** (Table 7, entry 22). We became interested in whether we could use strain to drive the rearrangement of two rings simultaneously in a fused bicyclic system. To test this, we prepared bicycle **4u** (Table 7, entry 21) and subjected it to the reaction conditions. Surprisingly, it did not show any conversion even in DCE at reflux. Such a difference in behavior between the simple vinyl azetidine **4w** and bicycle **4u** can be attributed to the limited ability of the latter to achieve the reactive conformation, with π-system and the C−N bond being placed orthogonal to one another either during ionization or ring-closure steps. Such condition is necessary to ensure the favorable overlap between the π-orbital of the alkene and the σ^* orbital of the C−N bond.

■ CONCLUSIONS

In summary, we have investigated the factors that control regioselectivity in palladium-catalyzed allylic amination. We have shown that the branched regioselectivity can be first set by choice of the appropriate solvent and ligand that determine the extent of equilibrium between the competing η^1 and η^3 allyl palladium intermediates. Mixed solvent studies showed that the highest regioselectivity was observed in THF in the presence of $P(OEt)_3$. This branched selectivity can be further maintained by preventing acid-promoted isomerization by using DBU. In addition, solvent was shown to have a thermodynamic effect on the reaction regioselectivity by either favoring or slowing down the branched-to-linear isomerization. This thermodynamic effect of solvent formed the basis for developing the rearrangement of cyclic amines. In addition to the solvent effects and basicity effects, steric as well as stereoelectronic effects dictated the feasibility of the aza-allylic ring rearrangements.

■ EXPERIMENTAL SECTION

General Procedure A for the Preparation of Allylic Acetates. In a flame-dried, 250 mL, one-neck, round-bottom flask, equipped with a magnetic stir bar, were placed allylic alcohol (98.4 mmol), triethylamine (35 mL, 250 mmol), and dry dichloromethane (75 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.60 g, 4.92 mmol) was added. The flask was cooled in an ice bath, and acetic anhydride (23.5

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

mL, 250 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight, when GC analysis showed no remaining starting material. The reaction mixture was washed with saturated $NaHCO_3$ (2 × 100 mL). The combined organic fractions were then washed with brine (100 mL) and dried over Na_2SO_4. Solvent was removed in vacuo, and crude product was obtained as slightly yellow oil, which was subjected to Kugelrohr distillation to yield the corresponding allylic acetate as a clear oil.

*Prenyl Acetate (**2a**).*[41] Procedure A. GC retention time of **2a**: T = 6.7 min. Yield = 88%, 11.96 g. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.35 (t, J = 6.3 Hz, 1H), 4.57 (d, J = 6.3 Hz, 2H), 2.05 (s, 3H), 1.76 (s, 3H), 1.71 (s, 3H).

*Crotyl Acetate (Mixture of Trans and Cis) (**2b**).*[42] Procedure A. GC retention time of **2b**: T = 3.65 min. Yield = 63%, 8.7 g. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.86−5.72 (m, 1H), 5.65−5.54 (m, 1H), 4.50(d, J = 6.3 Hz, 2H), 2.06 (s, 3H), 1.72 (d, J = 7.9 Hz, 3H).

*(E)-Pent-2-enyl Acetate (**2c**).*[43] Procedure A. GC retention time of **2c**: T = 6.5 min. Yield = 51%, 6.93 g. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.89−5.78 (m, 1H), 5.56 (dt, J = 15.3, 6.5 Hz, 1H), 4.5 (d, 6.5 Hz, 2H), 2.11−2.04 (m, 2H), 2.06 (s, 3H), 1.01 (t, J = 7.5 Hz, 3H).

*(E)-Hex-2-enyl Acetate (**2d**).*[44] Procedure A. GC retention time of **2d**: T = 8.8 min. Yield = 88%, 10.47 g. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.81−5.72 (m, 1H), δ 5.61−5.53 (m, 1H), 4.51(d, J = 6.5 Hz, 2H), 2.06 (s, 3H), 2.04 (q, J = 6.4 Hz, 2H), 1.46−1.37 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

*2-Methylbut-3-en-2-yl Acetate (**2l**).*[45] Procedure A. GC retention time of **2l**: T = 3.2 min. Yield = 23%, 3.13 g. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.06 (dd, J = 17.5, 10.9 Hz, 1H), 5.17 (d, J = 17.5 Hz, 1H), 5.07 (d, J = 10.9 Hz, 1H), 1,99 (s, 3H), 1.52 (s, 6H).

*Ethyl 3-Methylbut-2-enyl Carbonate (**2a′**).*[46] Procedure A. GC retention time of **2a′**: T = 10.6 min. Yield = 55%, 9.23 g. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.38 (t, J = 7.3 Hz, 1H), 4.62 (d, J = 7.3 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.76 (s, 3H), 1.73 (s, 3H), 1.30 (q, J = 7.1 Hz, 3H).

*Cinnamyl Acetate (**2e**).*[47] Procedure A. Solvent was removed in vacuo, and the residue was purified by flash chromatography (R_f = 0.57, SiO_2, 9:1 hexanes/ethyl acetate) to yield **2e** (8.67g, 37.4 mmol, 76%) as a clear liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.26 (m, 5H), 6.60 (d, J = 15.9 Hz, 1H), 6.29 (dt, J = 15.9, 6.4 Hz, 1H), 4.73 (d, J = 6.4 Hz, 2H), 2.10 (s, 3H).

*1,1-Dideuteroallyl Alcohol (**2n**).*[48] In a flame-dried, 100 mL, one-neck, round-bottom flask, equipped with septum and magnetic stir bar, were placed $LiAlH_4$ (1.0 g, 23.8 mmol) and 50 mL of anhydrous ether. The solution was cooled to −8 °C, acryloyl chloride was added dropwise, and the reaction was allowed to stir for 4 h. Then the reaction was quenched with 1.3 mL of water, NaOH (1.3 mL, 4 N), and 1.3 mL of water, extracted with ether, and dried over sodium sulfate. The crude solution was concentrated and distilled on a Kugehlrohr apparatus at room temperature at 0.9 mmHg to yield 1,1-dideuteroallyl alcohol **2n** (1.14 g, 19 mmol, 80%) as a clear liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ5.99 (dd, J = 17.2, 10.4 Hz, 1H), 5.28 (dd, J = 17.2, 1.4 Hz, 1H), 5.15 (dd, J = 10.4, 1.5 Hz, 1H), 2.26 (s, 1H).

*1,1-Dideuteroallyl Acetate (**2m**).*[49] In a flame-dried, 50 mL, one-neck, round-bottom flask, equipped with a magnetic stir bar, were placed 2,2-dideuteroallyl alcohol **2n** (1.21g, 20.13 mmol), triethylamine (6.68 mL, 50.32 mmol), and dry dichloromethane (20 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.125 g, 1.02 mmol) was added. The flask was cooled in an ice bath, and acetic anhydride (4.7 mL, 50.32 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated $NaHCO_3$ (2 × 100 mL). The combined organic fractions were then washed with brine (50 mL) and dried (Na_2SO_4). Solution was concentrated and distilled on Kugehlrohr at room temperature at 0.9 mmHg to yield 1,1-dideuteroallyl acetate **2m** (0.551 g, 5.4 mmol, 27%) as a clear liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ5.92 (dd, J = 17.2, 10.4 Hz, 1H), 5.32 (dd, J = 17.2, 1.5 Hz, 1H), 5.24 (dd, J = 10.4, 1.5 Hz, 1H), 2.08 (s, 1H).

General Procedure B for the Preparation of Allylic Amines. In a 17 × 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). $P(OEt)_3$ (9 μL, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate **2a** (0.19 mL, 1.37 mmol), and an amine (1.37 mmol) were added via syringe, and the solution was stirred under argon at room temperature for 20 h until GC analysis showed no remaining prenyl acetate **2a**. Water (4 mL) was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash chromatography.

General Procedure C for the Preparation of Allylic Amines. Same as general procedure B, except that the reaction is heated to 50 °C for 20 h.

*2-(2-Methylbut-3-en-2-yl)-1,2,3,4-tetrahydroisoquinoline (**3aa**).*[11a] Procedure B. GC retention time of **3aa**: T = 18.2 min (R_f = 0.28, SiO_2, 4:1 hexanes/ethyl acetate) to yield **3aa** (253 mg, 1.26 mmol, 92%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08−7.06 (m, 3H), 7.02−7.00 (m, 1H), 5.95 (dd, J = 17.9, 10.8 Hz, 1H), 5.11 (dd, J = 17.9, 1.5 Hz, 1H), 5.08 (dd, J = 10.8, 1.5 Hz, 1H), 3.76 (s, 2H), 2.84 (t, J = 5.6 Hz, 2H), 2.76 (t, J = 5.6 Hz, 2H), 1.23 (s, 6H).

*1-(2-Methylbutyl-3-en-2-yl)piperidine (**3ab**).*[50] Procedure B. GC retention time of **3ab**: T = 10.0 min. The crude residue was distilled under reduced pressure to yield **3ab** (838 mg, 5.48 mmol, 80%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.95 (dd, J = 17.9, 10.8 Hz, 1H), 5.11 (dd, J = 17.9, 1.5 Hz, 1H), 5.08 (dd, J = 10.8, 1.5 Hz, 1H), 2.48 (t, J = 5.0 Hz 4H), 1.61−1.51 (m, 4H), 1.43 (q, J = 5.3 Hz 2H), 1.12 (s, 6H).

*N-(Cyclopropylmethyl)-2-methylbut-3-en-2-amine (**3ac**).*[13] Procedure C. GC retention time of **3ac**: T = 7.8 min. The crude residue was distilled under reduced pressure to yield **3ac** (152 mg, 1.1 mmol, 81%) as a clear oil contaminated with 10% of $P(OEt)_3$ that codistills at 85 °C at 0.9 mmHg. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (dd, J = 17.9, 10.8 Hz, 1H), 5.02 (dd, J = 17.9, 1.5 Hz, 1H), 4.97 (dd, J = 10.8, 1.5 Hz, 1H), 2.32 (d, J = 6.7 Hz 2H), 1.64 (s, 1H), 1.16 (s, 6H), 0.85−1.0 (m, 1H), 0.46 (ddd J = 10.0, 5.9, 4.4 Hz 2H), 0.42−0.50 (m, 2H).

*N-Benzyl-2-methylbut-3-en-2-amine (**3ad**).*[51] Procedure B. GC retention time of **3ae**: T = 14.4 min. The crude residue was purified by flash chromatography (R_f = 0.56, SiO_2, 1:1 CH_2Cl_2/methanol) to yield **3ad** (216 mg, 1.23 mmol, 90%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35−7.22 (m, 5H), 5.84 (dd, J = 17.9, 10.8 Hz, 1H), 5.14 (dd, J = 17.9, 1.5 Hz, 1H), 5.08 (dd, J = 10.8, 1.5 Hz, 1H), 3.65 (s, 2H), 1.25 (s, 6H).

*N-(4-Methoxybenzyl)-2-methylbut-3-en-2-amine (**3ae**).*[13] Procedure C. GC retention time of **3ae**: T = 17.9 min. The crude residue was purified by flash chromatography (R_f = 0.31, SiO_2, 19:1 CH_2Cl_2/MeOH) to yield **3ae** (238 mg, 1.16 mmol, 85%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, J = 8.8, 2H), 6.84 (d, J = 8.8, 2H), 5.84 (dd, J = 17.9, 10.6 Hz, 1H), 5.11 (dd, J = 5.6, 1.2 Hz, 1H), 5.08−5.06 (m, 1H), 3.78 (s, 3H), 3.57 (s, 2H), 1.23 (s, 6H).

*N-(2-Methylbut-3-en-2-yl)benzenamine (**3af**).*[13] Procedure C. GC retention time of **3af**: T = 13.7 min. The crude residue was purified by flash chromatography (R_f = 0.41, SiO_2, 9:1 hexanes/ethyl acetate) to yield **3af** (156 mg, 0.97 mmol, 71%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (dd, J = 8.8, 7.0 2H), 6.70−6.69 (m, 1H), 6.68 (d, J = 7.0 Hz 2H), 6.00 (dd, J = 17.4, 10.6 Hz, 1H), 5.20 (dd, J = 17.4, 1.2 Hz, 1H), 5.08 (dd, J = 10.6, 1.2 Hz, 1H), 1.38 (s, 6H).

*N-Isopentyl-2-methylbut-3-en-2-amine (**3ag**).*[13] Procedure C. GC retention time of **3ag**: T = 8.5 min. The crude residue was purified by flash chromatography (R_f = 0.21, SiO_2, 19:1 CH_2Cl_2/MeOH) to yield **3ag** (170 mg, 1.10 mmol, 80%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.77 (dd, J = 17.9, 10.3 Hz, 1H), 5.05−5.03 (m, 1H), 4.99 (dd, J = 5.7, 1.2 1H), 2.48 (t, J = 7.6 Hz, 2H), 1.68−1.52 (m, 1H), 1.34 (q, J = 7.3 Hz, 2H), 1.17 (s, 6H), 0.88 (d, J = 6.5 Hz, 6H).

*2-Methyl-N-(2-methylbutyl)but-3-en-2-amine (**3ah**).*[13] Procedure C. GC retention time of **3ah**: T = 8.4 min. The crude residue was purified by flash chromatography (R_f = 0.18, SiO_2, 19:1 CH_2Cl_2/MeOH) to yield **3ah** (185 mg, 1.19 mmol, 87%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.77 (dd, J = 17.9, 10.3 Hz, 1H), 5.03

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

(dd, J = 17.9, 1.1 Hz, 1H), 4.99 (dd, J = 10.3, 1.1 Hz, 1H), 2.40 (dd, J = 11.2, 5.6 Hz, 1H), 2.24 (dd, J = 10.9, 6.8 Hz, 1H), 1.48−1.34 (m, 3H), 1.17 (s, 6H), 0.91−0.86 (m, 6H).

*N-(2,2-Dimethoxyethyl)-2-methylbut-3-en-2-amine (**3ai**).*[13] Procedure C. GC retention time of **3ai**: T = 10.7 min. The crude residue was purified by flash chromatography (R_f = 0.21, SiO_2, 19:1 CH_2Cl_2/MeOH) to yield **3ai** (206 mg, 1.19 mmol, 87%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.76 (dd, J = 17.9, 10.6 Hz, 1H), 5.06 (dd, J = 16.4, 1.1 Hz, 1H), 5.00 (dd, J = 10.6, 1.1 Hz, 1H), 4.40 (t, J = 5.6 Hz, 1H), 3.37 (s, 6H), 2.61 (d, J = 5.6 Hz, 2H), 1.35 (s, 1H), 1.17 (s, 6H).

*N-((3,4-Dimethylthieno[2,3-b]thiophene-2-yl)methyl)-N,2-dimethylbut-3-en-2-amine (**3aj**).*[13] Procedure C. GC retention time of **3aj**: T = 29.0 min. The crude residue was purified by flash chromatography (Rf = 0.21, SiO_2, 98:2 pentane/ether) to yield **3aj** (233 mg, 0.84 mmol, 61%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.80 (s, 1H), 5.98 (dd, J = 17.6, 10.5 Hz, 1H), 5.11 (dd, J = 17.6, 1.3 Hz, 1H), 5.07 (dd, J = 10.6, 1.3 Hz, 1H), 3.65 (s, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 2.24 (s, 3H), 1.21 (s, 6H).

*(1,1-Dimethylallyl)-(4,5-dimethylnaphthalen-1-ylmethyl)-methylamine (**3ak**).*[13] Procedure C. The crude residue was purified by flash chromatography (R_f = 0.59 in hexanes, SiO_2, graduate elution from hexanes to 98:2 hexanes/ethyl acetate) to yield **3ak** (291 mg, 1.04 mmol, 76%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.35−7.15 (m, 3H), 6.08 (dd, J = 17.6, 10.9 Hz, 1H), 5.13 (dd, J = 17.6, 1.3 Hz, 1H), 5.08 (dd, J = 10.9, 1.3 Hz, 1H), 3.91 (s, 2H), 2.91 (s, 3H), 2.89 (s, 3H), 2.10 (s, 3H), 1.28 (s, 6H).

*4-Methoxy-N-(2-methylbut-3-en-2-yl)aniline (**3am**).* Procedure B. GC retention time of **3am**: T = 17.0 min. The crude residue was purified by flash chromatography (R_f = 0.63 in SiO_2, 4:1 hexanes/ethyl acetate) to yield **3am** (190 mg, 1.0 mmol, 73%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.70 (s, 4 H), 5.99 (dd, J = 17.5, 10.7 Hz, 1H), 5.12 (d, J = 17.5 Hz, 1H), 5.05 (dd, J = 10.7, 1.1 Hz, 1H), 3.69 (s, 3H), 3.28 (s, NH), 1.30 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.8, 146.5, 140.1, 118.9, 114.0, 112.2, 55.4, 54.9, 28.0. HRMS [TOF ESI+]: calcd for $C_{12}H_{18}NO$ 192.1382, found 192.1382.

*N-(2,3-Dimethoxybenzyl)-2-methylbut-3-en-2-amine (**3an**).* Procedure B. GC retention time of **3an**: T = 19.1 min. The crude residue was purified by flash chromatography (R_f = 0.28 in SiO_2, 3:97 MeOH/ether) to yield **3an** (173 mg, 0.73 mmol, 54%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.00 (dd, J = 7.9, 7.7 Hz, 1H), 6.92 (dd, J = 7.7, 1.6 Hz, 1H), 6.81 (dd, J = 7.9, 1.6 Hz, 1H), 5.87 (dd, J = 17.5, 10.7 Hz, 1H), 5.11 (dd, J = 17.6, 1.3 Hz, 1H), 5.08 (dd, J = 10.7, 1.3 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.63 (s, 2H), 1.24 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ152.7, 147.4, 146.4, 135.1, 124.2, 122.1, 112.2, 111.3, 60.9, 55.8, 54.7, 42.7, 27.1. HRMS [TOF ESI+]: calcd for $C_{14}H_{22}NO_2$ 236.1645, found 236.1656.

*N-(2-Bromobenzyl)-2-methylbut-3-en-2-amine (**3ao**).* Procedure C. GC retention time of **3ao**: T = 17.8 min. The crude residue was purified by flash chromatography (R_f = 0.27 in SiO_2,19:1 CH_2Cl_2/MeOH) to yield **3ao** (281 mg, 1.1 mmol, 81%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (dd, J = 7.9, 1.1 Hz, 1H), 7.45 (dd, J = 7.6, 1.4 Hz, 1H), 7.26 (dt, J = 7.4, 1.1 Hz, 1H), 7.08 (dt, J = 7.8, 1.4 Hz, 1H), 5.88 (dd, J = 17.6, 10.7 Hz, 1H), 5.13 (dd, J = 17.6, 1.2 Hz, 1H), 5.10 (dd, J = 10.7, 1.2 Hz, 1H), 3.70 (s, 2H), 1.26 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.1, 140.4, 132.7, 130.6, 128.5, 127.7, 124.0, 112.5, 54.9, 47.7, 27.1. HRMS [TOF EI+]: calcd for $C_{12}H_{17}BrN$ 253.0466, found 253.0470.

General Procedure D for the Preparation of Allylic Amines. In a 17 × 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). (2-Biphenyl)dicyclohexylphosphine (19 mg, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), allylic acetate (1.37 mmol), and an amine (1.37 mmol) were added via syringe, and the solution was stirred under argon at room temperature for 20 h until GC analysis showed no remaining allylic acetate. Water (4 mL) was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash chromatography.

General Procedure E for the Preparation of Allylic Amines. Same as general procedure D, except that the reaction was carried out at 50 °C for 20 h.

*2-(But-3-en-2-yl)-1,2,3,4-tetrahydroisoquinoline (**3ba**).*[52] Procedure D. GC retention time of **3ba**: T = 17.1 min. The crude residue was purified by flash chromatography (R_f = 0.41, SiO_2, 9:1 hexanes/ethyl acetate) to yield **3ba** (210 mg, 1.12 mmol, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10−7.05 (m, 3H), 7.01−6.99 (m, 1H), 5.88 (ddd, J = 17.6, 10.4, 7.6 Hz, 1H), 5.16 (d, J = 17.6 Hz, 1H), 5.14 (d, J = 10.4 1H), 3.74 (d, J = 14.8 Hz 1H), 3.68 (d, J = 14.8 Hz 1H), 3.19−3.15 (m, 1H), 2.90−2.81 (m, 3H), 2.74−2.62 (m, 1H), 1.26 (d, J = 6.6 Hz, 3H).

*1,2,3,4-Tetrahydro-2-(pent-1-en-3-yl)isoquinoline (**3ca**).* Procedure D. The reaction was monitored by ^{1}H NMR. The crude residue was purified by flash chromatography (R_f = 0.32 in SiO_2, 4:1 hexanes/ethyl acetate) to yield **3ca** (228 mg, 1.44 mmol, 83%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11−7.07 (m, 3H), 7.02−6.99 (m, 1H), 5.75 (ddd, J = 17.1, 10.3, 8.2 Hz, 1H), 5.22 (dd, J = 10.3, 2.0 Hz, 1H), 5.14 (dd, J = 17.1, 2.0 Hz, 1H), 3.76 (d, J = 14.9 Hz 1H), 3.68 (d, J = 14.9 Hz 1H), 2.94−2.80 (m, 4H), 2.70−2.64 (m, 1H), 1.86−1.72 (m, 1H), 1.61−1.47 (m, 1H), 0.91 (t, J = 7.4 Hz 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ137.5, 135.4, 134.6, 128.6, 126.6, 125.8, 125.4, 117.6, 69.6, 52.8, 46.8, 29.5, 24.7, 10.8. HRMS [TOF EI+]: calcd for $C_{14}H_{19}N$ 201.1517, found 201.1512.

*1,2,3,4-Tetrahydro-2-(1-phenylallyl)isoquinoline (**3ea**) and 2-Cinnamyl-1,2,3,4-tetrahydroisoquinoline (**3ea′**).* Procedure D. The reaction was monitored by ^{1}H NMR. The crude residue was purified by flash chromatography (R_f = 0.69 and 0.24 in SiO_2, respectively, 19:1 hexanes/EtOAc) to yield **3ea** and **3ea′** (453 mg, 0.9 mmol, 66%) as a clear oil and an orange solid, respectively.

3ea. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40−7.28 (m, 5H), 7.11−7.08 (m, 3H), 6.98−6.96 (m, 1H), 6.02 (ddd, J = 17.6, 10.7, 8.8 Hz, 1H), 5.29 (dd, J = 17.1, 1.5 Hz, 1H), 5.15 (dd, J = 10.1, 1.6 Hz, 1H), 3.86 (d, J = 8.8 Hz, 1H), 3.75 (d, J = 15.2 Hz, 1H), 3.54 (d, J = 15.7 Hz, 1H), 2.88−2.84 (m, 2H), 2.74−2.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ141.7, 139.7, 134.7, 134.2, 128.2, 127.4, 126.8, 126.4, 125.6, 125.1, 115.9, 74.0, 54.1, 47.9, 28.7. HRMS [TOF EI+]: calcd for $C_{18}H_{19}N$ 249.1517, found 249.1511.

3ea′. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.30 (m, 5H), 7.12−7.11 (m, 3H), 7.03−7.01 (m, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.37 (dt, J = 15.9, 6.6 Hz, 1H), 3.68 (s, 2H), 3.34 (d, J = 6.31 Hz, 2H), 2.94 (t, J = 5.8 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ136.5, 134.3, 133.8, 132.4, 128.2, 127.1, 126.5, 126.2, 125.9, 125.7, 125.2, 60.4, 55.7, 50.4, 28.7. HRMS [TOF EI+]: calcd for $C_{18}H_{19}N$ 249.1517, found 249.1513.

*N-Benzylbut-3-en-2-amine (**3bd**).*[53] Procedure D. The reaction was monitored by ^{1}H NMR. The crude residue was purified by flash chromatography (R_f = 0.41, SiO_2, 9:1 hexanes/ethyl acetate) to yield **3bd** (184 mg, 1.15 mmol, 84%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32−7.30(m, 5H), 5.73 (ddd, J = 17.6, 10.3, 7.9 Hz 1H), 5.14 (d, J = 17.6 Hz 1H) 5.09 (d, J = 10.3 Hz 1H), 3.81 (d, J = 13.0 Hz 1H), 3.69 (d, J = 12.9 Hz 1H), 3.28−3.18 (m, 1H), 1.18 (d, J = 6.5 Hz, 3H).

*N-(4-Methoxybenzyl)but-3-en-2-amine (**3be**).*[54] Procedure E. GC retention time of **3be**: T = 17.0 min. The crude residue was purified by flash chromatography (R_f = 0.40, SiO_2, 19:1 CH_2Cl_2/MeOH) to yield **3be** (217 mg, 1.12 mmol, 82%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, J = 8.8, 2H), 6.84 (d, J = 8.8, 2H), 5.71 (ddd, J = 17.6, 10.0, 7.6 Hz, 1H), 5.11 (dd, J = 17.6, 1.2 Hz, 1H), 5.07 (dd, J = 10.0, 1.2 Hz, 1H), 3.79 (s, 3H), 3.77 (d, J = 12.9 Hz 1H), 3.61 (d, 12.9 Hz, 1H), 3.26−3.15 (m, 1H), 1.34 (s, 1H), 1.16 (d, J = 6.4 Hz 3H).

*N-(2-Methylbutyl)but-3-en-2-amine, a Mix of Diastereomers (**3bh**).*[13] Procedure E. GC retention time of **3bh**: T = 8.5 min. The crude residue was purified by flash chromatography (R_f = 0.18, SiO_2, 19:1 CH_2Cl_2/MeOH) to yield **3bh** (157 mg, 1.1 mmol, 81%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.69 (ddd, J = 17.6, 10.3, 2.6 Hz, 1H), 5.09 (dm, J = 17.3, 1H), 5.03 (dm, J = 10.3 Hz, 1H), 3.19−3.10 (m, 1H), 2.50 (ddd, J = 17.6, 11.4, 6.2 Hz, 1H), 2.33 (ddd, J =

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

17.6, 11.4, 6.2 Hz, 1H), 1.57−1.35 (m, 3H), 1.16 (d, J = 6.5 Hz, 3H), 0.92−0.85 (m, 6H).

*2-(1,1-Dideuteroallyl)-1,2,3,4-tetrahydroisoquinoline (**3ma**) and 2-(3,3-Dideuteroallyl)-1,2,3,4-tetrahydroisoquinoline (**3ma′**).* In a 17 × 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mg, 0.0069 mmol) and dry THF (0.6 mL). $P(OEt)_3$ (5 μL, 0.0274 mmol), DBU (0.080 mL, 0.53 mmol), 1,1-dideuteroallyl acetate **2m** (51 mg, 0.50 mmol), and 1,2,3,4-tetrahydroisoquinoline (0.062 g, 0.50 mmol) were added via syringe and the solution was stirred under argon at room temperature for 17 h; when NMR analysis showed no remaining1,1-dideuteroallyl acetate **2m**. Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash chromatography (R_f = 0.41 in SiO_2, 4:1 hexanes/EtOAc) to yield a 1:1 mixture of **3ma** and **3ma′**.

3ma and **3ma′**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11−7.09 (m, 3), 7.01−6.99 (m, 1H), 5.95 (m, 1H), 5.25 (dd, J = 17.2, 1.9 Hz, 1H), 5.19 (dd, J = 10.2, 2.0 Hz, 1H), 3.62 (s, 2H), 3.17 (d, J = 6.5 Hz, 2H), 2.90 (t, J = 5.9 Hz, 2H), 2.74 (td, J = 5.9, 1.9 Hz, 2H). HRMS [TOF ESI+]: calcd for $C_{12}H_{14}ND_2$ 176.1408, found 176.1401.

*Prenylpalladium Chloride Dimer (**6**).*[11a] Palladium chloride (0.933g, 5.3 mmol) and lithium chloride (0.45g, 13.4 mmol) were weighed into a 50 mL round-bottom flask equipped with a stir bar. The mixture was diluted with water (1.5 mL) and methanol (13 mL). The reaction flask was purged with nitrogen gas, and prenyl chloride (18.1 mmol, 1.6 mL) was added to the reaction solution. CO gas was bubbled through the solution for 2 h when the yellow precipitate appeared. The solution was poured into water, extracted with chloroform, dried over sodium sulfate, and concentrated. The product was recrystallized out of chloroform and methanol to give 567 mg (1.3 mmol) of yellow solid in 48% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.08 (dd, J = 12.6, 7.3 Hz, 2H), 3.85 (dd, J = 7.3, 1.3 Hz, 2H), 3.09 (dd, J = 12.6, 1.3 Hz, 2H), 1.44 (s, 6H), 1.24 (s, 6H).

*σ-Palladium Prenyl Complex in THF (**7**).* In the glovebox, prenylpalladium chloride dimer (1 equiv) and triphenylphosphine (4 equiv) were added to the 8 in. NMR tube. The contents were dissolved in deuterated THF, and the solution was submitted to NMR. ^{1}H NMR (THF-d_8, 400 MHz): δ 5.16 (t, J = 10.0 Hz, 1H), 2.75 (d, J = 10.0 Hz, 2H), 1.86 (s, 3H), 1.40 (s, 3H).

*σ-Palladium Prenyl Complex in CH_2Cl_2 (**8**).* In the glovebox, prenylpalladium chloride dimer (1 equiv) and triphenylphosphine (4 equiv) were added to the 8 in. NMR tube. The contents were dissolved in deuterated dichloromethane, and the solution was submitted to NMR. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 5.11 (t, J = 9.9 Hz, 1H), 2.74 (d, J = 9.9 Hz, 2H), 1.79 (s, 3H), 1.35 (s, 3H).

*Crotylpalladium Chloride Dimer (**9**).*[55] Palladium chloride (88 mg, 0.5 mmol) and sodium chloride (58 g, 1.0 mmol) were weighed into a 17 × 60 mm screw cap vial equipped with a stir bar. The mixture was diluted with water (0.20 mL) and methanol (1.2 mL). The reaction flask was purged with nitrogen gas, and crotyl chloride (1.34 mmol, 0.13 mL) was added to the reaction solution. CO gas was bubbled through the solution for 1.2 h when the yellow precipitate appeared. The solution was poured in water, extracted with chloroform, dried over sodium sulfate, and concentrated. The product was recrystallized out of chloroform and methanol to give 66 mg (0.17 mmol) of yellow solid in 67% yield. ^{1}H NMR (THF-d_8, 300 MHz): δ 5.31 (ddd, J = 22.8, 11.4, 6.7 Hz, 2H), 3.87−3.77 (m, 2H), 3.73 (d, J = 6.7 Hz, 2H), 2.72 (d, J = 11.8 Hz, 2H), 1.27 (d, J = 6.3 Hz, 6H).

*σ-Palladium Crotyl Complex in THF (**10**).* In the glovebox crotylpalladium chloride dimer and triphenyl phosphine were added to the 8 in. NMR tube. The contents were dissolved in deuterated THF and the solution was submitted to NMR. ^{1}H NMR (THF-d_8, 300 MHz): δ 5.37 (dt, J = 12.7, 9.3 Hz, 1H), 4.39−4.28 (m, 1H), 2.71 (d, J = 9.3 Hz, 2H), 1.74 (d, J = 6.3 Hz, 3H).

Solvent Studies. In a 17 × 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). $P(OEt)_3$ (9 μL, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate (0.19 mL, 1.37 mmol), and 1,2,3,4-tetrahydroisoquinoline (0.17 mL, 1.37 mmol) were added via syringe, and the solution was stirred under argon at room temperature for 17 h. Biphenyl (0.685 mmol, 105 mg) was added to the reaction mixture, after which the reaction was allowed to stir for additional 5 min to allow biphenyl to dissolve. A saturated solution of sodium bisulfite (4 mL) was added, and the resulting mixture was extracted with dichloromethane (3 × 2 mL). A sample from organic layer was passed through a small Celite and silica plug with 3 mL of HPLC grade acetonitrile, and 0.2 mL of the resulting solution was analyzed by GC using the method described above. (GC retention time of branched product: T = 18.2 min, linear: T = 18.2 min). The procedure was repeated using 0.035, 0.065, 0.100, 0.130, 0.350, 0.650, 1.00, and 1.3 mL of anhydrous dichloromethane in THF keeping the reaction volume at 1.3 mL. The reaction was then repeated using BINAP (0.274 mmol, 17 mg) ligand in 0, 0.130, 0.350, 0.650, 1.00, 1.1, 1.2, and 1.3 mL of anhydrous dichloromethane in THF keeping the reaction volume at 1.3 mL.

Preparation of Substrates for the Aza-allylic Rearrangement. *1-(4-Methoxybenzyl)-7,7-dimethyl-3,4-dihydro-1H-azepin-2(7H)-one (**4b**).*[22] In the glovebox Hoveyda−Grubbs II catalyst (0.007 mmol, 4.5 mg) was weighed out in a flame-dried scintillation vial equipped with a stir bar. The vial was removed from the glovebox, and the complex was dissolved in 15 mL of anhydrous dichloromethane. *N*-(4-Methoxybenzyl)-*N*-(2-methylbut-3-en-2-yl)pent-4-enamide (0.35 mmol, 0.100g) was then added dropwise to the reaction solution, and the reaction mixture was allowed to stir under reflux for 2 days. The reaction mixture was then washed with brine, extracted with dichloromethane, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (Hex/EtOAc = 1:1, R_f = 0.59) to yield **4b** (0.23 mmol, 58 mg, 65%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.73 (dt, J = 12.0, 4.5 Hz, 1H), 5.40 (dt, J = 11.9, 2.0 Hz, 1H), 4.76 (s, 2H), 3.78 (s, 3H), 2.97−2.81 (m, 2H), 2.47−2.35 (m, 2H), 1.45 (s, 6H).

General Procedure F for the Reduction of Lactams. In a flame-dried scintillation vial equipped with a stir bar was weighed lithium aluminum hydride (1.0 equiv). The powder was mixed with anhydrous THF to make a 0.5 M solution, and the reaction mixture was allowed to cool to 0 °C. After that, anhydrous aluminum chloride (0.28 equiv) was transferred in small portions to the reaction vial under a flow of nitrogen. The reaction mixture was allowed to stir at 0 °C for additional 15 min after which 0.5 M solution of lactam (0.45 equiv) in anhydrous THF was added dropwise to the reaction mixture. The reaction vial was sealed with a cap and was allowed to stir at 50 °C overnight. After that the reaction mixture was cooled down to 0 °C followed by the addition of distilled water, 10% NaOH(aq), and distilled water again. The resulting mixture was filtered through Celite and the filtrate was diluted with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography.

General Procedure G for the Reduction of Lactams. Same as general procedure F, except that the reaction was allowed to warm to room temperature instead of 50 °C.

*1-(4-Methoxybenzyl)-7,7-dimethyl-2,3,4,7-tetrahydro-1H-azepine (**4a**).*[22] Procedure F. The crude product was purified by flash chromatography (Hex/EtOAc = 1:1, R_f = 0.32) to yield **4a** (0.36 mmol, 87.2 mg, 79%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (d, J = 8.6 Hz, 2H), 6.85 (dt, J = 8.6, 2.4 Hz, 2H), 5.57 (dt, J = 11.4, 6.4 Hz, 1H), 5.33 (dt, J = 11.4, 1.1 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 2H), 2.79 (t, J = 6.1 Hz, 2H), 2.29 (ddd, J = 13.3, 6.6, 1.1 Hz, 2H), 1.49−1.40 (m, 2H), 1.28 (s, 6H).

*1-(4-Methoxybenzyl)-7-methyl-2,3,4,7-tetrahydro-1H-azepine (**4c**).*[22] Procedure F. Yield = 80%, 196 mg. R_f = 0.32 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.88−5.81 (m, 1H), 5.50 (ddd, J = 10.9, 5.4, 1.9 Hz, 1H), 3.78 (s, 3H), 3.61 (d, J = 14.0 Hz, 1H), 3.54 (d, J = 13.0 Hz, 1H), 3.04 (ddd, J = 14.1, 5.0, 3.9 Hz, 1H), 2.83 (ddd, J = 13.9, 10.1, 3.5 Hz, 1H), 2.37−2.28 (m, 1H), 2.22 (dtd, J = 10.1, 7.1, 3.0 Hz, 1H), 1.75−1.61 (m, 1H), 1.45−1.37 (m, 1H), 1.25 (d, J = 7.1 Hz, 3H).

*(Z)-1-(4-Methoxybenzyl)-8-methyl-1,2,3,4,5,8-hexahydroazocine (**4d**).*[22] Procedure G. Yield = 90%, 84.3 mg. R_f = 0.32 (SiO_2, hex/

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 5.60 (dtd, J = 9.6, 8.0, 1.6 Hz, 1H), 5.26 (ddd, J = 10.9, 7.1, 1.6 Hz, 1H), 3.70 (s, 3H), 3.62 (d, J = 13.2 Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H), 2.74−2.62 (m, 1H), 2.62−2.46 (m, 2H), 1.95 (ddd, J = 12.7, 8.1, 4.1 Hz, 1H), 1.72−1.56 (m, 2H), 1.42−1.20 (m, 2H), 1.14 (d, J = 6.7 Hz, 3H).

*1-(4-Methoxybenzyl)-2,3,4,7-tetrahydro-1H-azepine (**4e**).*[22] Procedure F. Yield = 54%, 43.2 mg. R_f = 0.37 (SiO_2, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.98−5.80 (m, 1H), 5.63 (dtt, J = 10.9, 5.4, 1.2 Hz, 1H), 3.78 (s, 3H), 3.58 (s, 2H), 3.15 (d, J = 5.4 Hz, 2H), 2.88−2.78 (m, 2H), 2.23 (ddd, J = 11.5, 5.8, 1.2 Hz, 2H), 1.66 (dt, J = 11.5, 5.7 Hz, 2H).

*(Z)-1-(4-Methoxybenzyl)-5,6,7,8-tetrahydroazocin-2(1H)-one (**4f**).*[22] Procedure F. Yield = 48%, 91 mg. R_f = 0.59 (SiO_2, EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.97 (dt, J = 12.5, 5.2 Hz, 1H), 5.81 (dt, J = 12.6, 1.6 Hz, 1H), 4.58 (s, broad, 2H), 3.76 (s, 3H), 3.44 (s, broad, 2H), 2.24 (s, broad, 2H), 1.58 (s, broad, 4H).

*3-Ethyl-1-(4-methoxybenzyl)-2,3,4,7-tetrahydro-1H-azepine (**4h**).*[22] Procedure G. Yield = 62%, 31.4 mg. R_f = 0.34 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.90−5.77 (m, 1H), 5.61 (dtd, J = 7.4, 5.2, 2.2 Hz, 1H), 3.79 (s, 3H), 3.58 (s, 2H), 3.13 (d, J = 5.0 Hz, 2H), 2.87 (dd, J = 12.7, 3.9 Hz, 1H), 2.47 (dd, J = 12.7, 9.6 Hz, 1H), 2.20 (ddd, J = 15.2, 7.3, 2.3 Hz, 1H), 2.07 (tdd, J = 15.5, 4.0, 1.9 Hz, 1H), 1.68 (dtt, J = 12.8, 6.2, 3.1 Hz, 1H), 1.25−1.14 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H).

*(Z)-3-Ethyl-1-(4-methoxybenzyl)-1,2,3,4,5,8-hexahydroazocine (**4i**).*[22] Procedure G. Yield = 37%, 16 mg. R_f = 0.20 (SiO_2, hex/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.74 (ddd, J = 10.9, 9.3, 8.0 Hz, 1H), 5.49 (dt, J = 11.1, 5.5 Hz, 1H), 3.80 (s, 3H), 3.57 (d, J = 13.1 Hz, 1H), 3.46 (d, J = 13.1 Hz, 1H), 3.18 (dd, J = 15.9, 5.0 Hz, 1H), 3.06 (dd, J = 15.6, 5.9 Hz, 1H), 2.99−2.85 (m, 1H), 2.58 (dd, J = 12.6, 9.0 Hz, 1H), 2.47−2.38 (m, 1H), 2.23−2.11 (m, 1H), 1.80−1.58 (m, 2H), 1.19 (dq, J = 14.3, 7.3 Hz, 2H), 0.85 (t, J = 7.4 Hz, 3H).

*3-Isopentyl-1-(4-methoxybenzyl)-2,3,4,7-tetrahydro-1H-azepine (**4j**).*[22] Procedure G. Yield = 64%, 33.5 mg. R_f = 0.45 (SiO_2, hex/EtOAc = 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.83 (ddd, J = 11.6, 7.5, 4.3 Hz, 1H), 5.61 (dtd, J = 7.4, 5.2, 2.2 Hz, 1H), 3.79 (s, 3H), 3.57 (s, 2H), 3.13 (d, J = 5.1 Hz, 2H), 2.85 (dd, J = 12.7, 3.8 Hz, 1H), 2.47 (dd, J = 12.7, 9.5 Hz, 1H), 2.19 (ddd, J = 15.3, 7.3, 2.0 Hz, 1H), 2.11−2.03 (m, 1H), 1.79−1.63 (m, 1H), 1.52−1.37 (m, 1H), 1.20−1.02 (m, 4H), 0.84 (dd, J = 6.6, 1.8 Hz, 6H).

*1-(4-Methoxybenzyl)-3-((tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,7-tetrahydro-1H-azepine (**4k**).*[22] Procedure G. Yield = 60%, 28.9 mg. R_f = 0.23 (SiO_2, hex/EtOAc = 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.87−5.77 (m, 1H), 5.62 (dtd, J = 6.8, 5.3, 1.6 Hz, 1H), 3.96−3.87 (m, 1H), 3.80 (s, 3H), 3.58 (d, J = 13.0 Hz, 1H), 3.54 (d, J = 13.0 Hz, 1H), 3.27 (td, J = 11.4, 2.7 Hz, 1H), 3.23−3.17 (m, 1H), 3.13 (dd, J = 15.6, 5.2 Hz, 1H), 3.09−3.00 (m, 1H), 2.82 (dd, J = 12.9, 3.4 Hz, 1H), 2.53 (dd, J = 12.9, 8.5 Hz, 1H), 2.24−2.15 (m, 1H), 2.15−1.95 (m, 2H), 1.76 (dd, J = 12.7, 2.1 Hz, 1H), 1.59−1.08 (m, 9H).

*1-(4-Methoxybenzyl)-4-phenyl-2,3,4,7-tetrahydro-1H-azepine (**4l**).*[22] Procedure G. Yield = 30%, 32 mg. R_f = 0.44 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35−7.23 (m, 6H), 7.21 (dd, J = 6.8, 1.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.95−5.82 (m, 1H), 5.70 (dtd, J = 11.1, 5.4, 2.5 Hz, 1H), 3.79 (s, 3H), 3.71 (d, J = 11.5 Hz, 1H), 3.62 (s, 2H), 3.24 (d, J = 5.2 Hz, 2H), 3.01−2.87 (m, 1H), 2.82−2.73 (m, 1H), 2.07 (dtd, J = 14.2, 10.3, 3.9 Hz, 1H), 1.81 (dddd, J = 11.1, 5.5, 3.9, 2.9 Hz, 1H).

*1-(4-Methoxybenzyl)-4-propyl-2,3,4,7-tetrahydro-1H-azepine (**4m**).* Procedure F. Yield = 21%, 25 mg. R_f = 0.44 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, J = 9.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.70 (dd, J = 11.3, 3.4 Hz, 1H), 5.64−5.56 (m, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.13 (d, J = 5.3 Hz, 2H), 2.99 (dt, J = 12.9, 4.4 Hz, 1H), 2.77−2.60 (m, 1H), 2.40−2.36 (m, 1H), 1.61−1.47 (m, 2H), 1.47−1.24 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 139.4, 131.5, 130.3, 127.9, 113.7, 60.2, 56.8, 55.4, 53.3, 38.9, 38.8, 32.0, 20.5, 14.4. HRMS [TOF ESI+]: calcd for $C_{17}H_{26}NO$ 260.2014, found 260.2008.

*1-(4-Methoxybenzyl)-4-methyl-2,3,4,7-tetrahydro-1H-azepine (**4n**).* Procedure G. Yield = 14%, 12 mg. R_f = 0.44 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, J = 8.7 Hz, 2H), 6.87−6.83 (m, 2H), 5.69−5.60 (m, 1H), 5.57 (ddd, J = 11.1, 5.4, 2.2 Hz, 1H), 3.80 (s, 3H), 3.57 (d, J = 2.2 Hz, 2H), 3.14 (d, J = 5.3 Hz, 2H), 3.01−2.93 (m, 1H), 2.74−2.67 (m, 1H), 2.55−2.51 (m, 1H), 1.69−1.60 (m, 1H), 1.55−1.50 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 140.4, 130.3, 127.6, 113.6, 60.2, 56.6, 55.4, 53.4, 34.4, 33.9, 22.6. HRMS [TOF ESI+]: calcd for $C_{15}H_{21}NO$ 232.1685, found 232.1695.

*1-(4-Methoxybenzyl)-4,4-dimethyl-2,3,4,7-tetrahydro-1H-azepine (**4o**).* Procedure F. Yield = 79%, 44 mg. R_f = 0.44 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, J = 9.2 Hz, 2H), 6.99−6.71 (m, 2H), 5.51 (d, J = 11.6 Hz, 1H), 5.42 (dt, J = 11.6, 5.2 Hz, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.11 (d, J = 4.5 Hz, 2H), 2.86−2.60 (m, 2H), 1.71−1.49 (m, 2H), 1.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 142.7, 131.6, 130.2, 125.3, 113.7, 61.2, 55.4, 52.9, 52.7, 39.5, 36.6, 29.8. HRMS [TOF ESI+]: calcd for $C_{16}H_{23}NO$ 246.1856, found 246.1852.

*1-(4-Methoxybenzyl)-5-methyl-2,3,4,7-tetrahydro-1H-azepine (**4p**).* Procedure F. Yield = 41%, 36 mg. R_f = 0.44 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.09 (m, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.54−5.25 (m, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.07 (d, J = 5.9 Hz, 2H), 2.90−2.72 (m, 2H), 2.24−2.10 (m, 2H), 1.76 (s, 3H), 1.71−1.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 143.2, 131.3, 130.4, 122.8, 113.7, 60.4, 58.8, 55.4, 52.8, 33.7, 26.2, 25.2. HRMS [TOF ESI+] calcd for $C_{15}H_{21}NO$ 232.1685, found 232.1693.

*(Z)-9-Benzyl-9-azabicyclo[6.2.0]dec-6-ene (**4u**).* Procedure F. Yield = 82%, 419 mg. R_f = 0.70 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52−6.98 (m, 5H), 5.67−5.35 (m, 1H), 5.24 (d, J = 11.2 Hz, 1H), 4.05 (d, J = 7.9 Hz, 1H), 3.72 (d, J = 12.8 Hz, 1H), 3.57 (d, J = 12.8 Hz, 1H), 3.21 (dd, J = 10.0, 5.9 Hz, 1H), 3.21 (dd, J = 10.0, 5.9 Hz, 1H), 3.02 (dd, J = 7.1, 4.0 Hz, 1H), 2.70−2.44 (m, 1H), 2.25−1.12 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 129.9, 129.6, 129.0, 128.9, 128.3, 128.2, 127.0, 65.8, 62.0, 59.3, 39.3, 32.3, 29.5, 28.2, 27.0. HRMS [TOF ESI+]: calcd for $C_{16}H_{22}N$ 228.1752, found 228.1759.

*1-Benzyl-4-methyl-4-vinylazetidine (**4w**).*[56] Procedure H. Yield = 33%, 160 mg. R_f = 0.69 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.12 (m, 5H), 6.05 (dd, J = 17.4, 10.7 Hz, 1H), 5.19 (d, J = 17.4 Hz, 1H), 5.07 (d, J = 10.6 Hz, 1H), 3.58 (d, J = 13.1 Hz, 1H), 3.48 (d, J = 13.1 Hz, 1H), 3.22−3.08 (m, 2H), 2.22−2.07 (m, 1H), 1.91 (ddd, J = 10.3, 8.0, 4.9 Hz, 1H), 1.33 (s, 3H).

*2-Methyl-1-(prop-1-en-2-yl)-1,2,3,4-tetrahydroisoquinoline (**4g**).* 3,4-Dihydroisoquinoline (15.2 mmol, 2.0g) was dissolved in acetone (60 mL), after which methyl iodide (45.6 mmol, 2.85 mL) was added. The reaction was allowed to stir for 10 min, after which the newly formed precipitate was filtered and dried. The resulting iminium salt was suspended in 125 mL of anhydrous THF. The solution was cooled to −78 °C, and isopropenylmagnesium bromide was added in one portion. The reaction was allowed to warm to room temperature and was allowed to stir overnight. The reaction was then carefully quenched with aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give **4g** in 98%, 2.79g without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14−7.09 (m, 4H), 5.09 (s, 2H), 3.68 (s, 1H), 3.19−3.10 (m, 1H), 3.10−2.98 (m, 1H), 2.69 (d, J = 15.1 Hz, 1H), 2.49 (ddd, J = 15.2, 9.9, 3.1 Hz, 1H), 2.33 (s, 3H), 1.49 (d, J = 1.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.2, 136.1, 135.2, 128.6, 126.8, 126.2, 125.9, 116.0, 74.1, 52.5, 44.2, 29.8, 17.2. HRMS [TOF ESI+]: calcd for $C_{13}H_{18}N$ 188.1439, found 188.1442.

*(Z)-1,6-Dibenzyl-1,2,5,6-tetrahydrobenzo[b][1,4]diazocine (**4q**).*[22] Procedure F. Yield =32%, 147 mg. R_f = 0.83 (SiO_2, dichloromethane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38−7.12 (m, 10H), 6.98 (dd, J = 5.9, 3.6 Hz, 2H), 6.82 (dd, J = 5.9, 3.6 Hz, 2H), 4.34 (s, 4H), 3.85 (d, J = 3.1 Hz, 2H).

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

*(Z)-6-Benzyl-5,6-dihydro-2H-benzo[b][1,4]oxazocine (**4r**) and (Z)-6-Benzyl-3,4,5,6-tetrahydro-2H-benzo[b][1,4]oxazocine (**4r′**)*.[22] Procedure F. Yield = 46%, 62 mg. Ratio of **4r**:**4r′** = 4:1. R_f = 0.83 (SiO_2, dichloromethane). **4r**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40−7.18 (m, 5H), 7.02−6.89 (m, 2H), 6.80−6.67 (m, 2H), 5.87−5.66 (m, 2H), 4.79−4.72 (m, 2H), 4.51 (s, 2H), 4.17 (s, 2H). **4r′**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40−7.18 (m, 5H), 6.88−6.82 (m, 2H), 6.62 (dd, J = 11.8, 4.6 Hz, 2H), 4.47 (s, 2H), 4.21−4.15 (m. 2H), 3.79−3.70 (m, 2H), 1.87 (dt, J = 11.8, 5.7 Hz, 2H), 1.76 (ddd, J = 8.0, 6.7, 3.0 Hz, 2H).

*(Z)-1-(4-Methoxybenzyl)-1,2,5,7-tetrahydrobenzo[c][1,5]-oxazonine (**4s**)*. Procedure F. Yield = 68%, 120 mg. R_f = 0.90 (SiO_2, dichloromethane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51−7.17 (m, 7H), 7.10 (d, J = 7.9 Hz, 1H), 6.97 (t, J = 7.3 Hz, 1H), 5.48−5.18 (m, 2H), 4.66 (s, 2H), 4.32 (d, J = 2.9 Hz, 2H), 3.79 (d, J = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.6, 139.6, 132.5, 132.2, 129.5, 129.1, 128.4, 127.2, 122.4, 119.8, 69.5, 68.7, 58.8, 54.0. HRMS [TOF ESI+]: calcd for $C_{18}H_{20}NO$ 266.1545, found 266.1534.

*(4R)-Ethyl 2-((1S,5R)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-thiazolidine-4-carboxylate (**4t**)*. (*R*)-Myrtenal (2.6 mmol, 0.45 mL) was mixed with cysteine ethyl ester (2.6 mmol, 0.385 g) in dichloromethane in the presence of 4 Å molecular sieves overnight. The reaction was filtered, and the filtrate was concentrated and purified on SiO_2. Yield = 81%, 593 mg. R_f = 0.30 (SiO_2, hex/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 300 MHz) major diastereomer: δ 5.70 (s, 1H), 5.05 (s, 1H), 4.30−4.23 (m, 2H), 3.87−3.75 (m, 1H), 3.32 (dd, J = 10.2, 6.8 Hz, 1H), 2.87−2.77 (m, 1H), 2.51−2.15 (m, 6H), 2.15−2.04 (m, 1H), 1.39−1.22 (m, 6H), 0.84 (d, J = 5.8 Hz, 3H); minor diastereomer: δ 5.59 (dd, J = 2.9, 1.4 Hz, 1H), 5.21 (d, J = 1.0 Hz, 1H), 4.30−4.23 (m, 2H), 4.16 (dd, J = 7.1, 5.3 Hz, 1H), 3.21 (dd, J = 10.6, 7.2 Hz, 1H), 3.10 (dd, J = 10.6, 5.1 Hz, 1H), 2.51−2.15 (m, 6H), 2.15−2.04 (m, 1H), 1.39−1.22 (m, 6H), 0.84 (d, J = 5.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) both diastereomers: δ 172.0, 171.2, 146.0, 143.5, 121.7, 118.6, 73.5, 71.9, 65.3, 64.5, 61.6, 61.5, 42.2, 40.9, 38.3, 37.3, 31.5, 31.1, 26.1, 26.0, 21.3, 21.0, 14.2. HRMS [TOF ESI+]: calcd for $C_{15}H_{24}NO_2S$ 282.1528, found 282.1536.

Preparation of Cyclic Allylic Amines by Pd-Catalyzed Rearrangement. *General Procedure H for the Rearrangement of Cyclic Amines.* In the glovebox into a flame-dried vial equipped with a stir bar was weighed allylpalladium chloride dimer (2.5 mol %). Outside of the glovebox, the complex was dissolved in anhydrous dichloromethane. To the reaction mixture were added triethyl phosphite (10 mol %) and morpholine (25 mol %), and the mixture was allowed to stir for 5 min. A 0.4 M solution of cyclic allylic amine (1.0 equiv) in anhydrous dichloromethane was added to the reaction mixture, followed by the addition of trifluoroacetic acid (1.0 equiv). The reaction vial was sealed and allowed to stir under reflux for 10 h. The reaction mixture was cooled to room temperature, washed with saturated solution of sodium bicarbonate, extracted with dichloromethane, dried with sodium sulfate, and concentrated. The crude material was purified on flash chromatography.

General Procedure I for the Rearrangement of Cyclic Amines. Similar to procedure H, except that the reaction is carried out at 60 °C in dichloroethane with 50 mol % of morpholine.

*1-(4-Methoxybenzyl)-2-(2-methylprop-1-en-1-yl)pyrrolidine (**5a**)*.[22] Procedure H. The crude material was purified on flash chromatography (Hex/EtOAc = 9:1, R_f = 0.36) to give **5a** (0.39 mmol, 96 mg, 97%) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.26 (d, J = 9.1 Hz, 1H), 4.00 (d, J = 12.9 Hz, 2H), 3.79 (s, 3H), 3.26 (d, J = 12.6 Hz, 2H), 3.28−3.24 (m, 1H), 3.11−3.00 (m, 1H), 2.40−2.19 (m, 1H), 2.02−1.81 (m, 2H), 1.78 (s, 3H), 1.68 (s, 3H), 1.80−1.58 (m, 2H).

*(E)-1-(4-Methoxybenzyl)-2-(prop-1-en-1-yl)pyrrolidine (**5c**)*.[22] Procedure H. Yield = 94%, 87 mg. R_f = 0.36 (SiO_2, hex/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.63 (dq, J = 15.1, 6.4 Hz, 1H), 5.41 (ddd, J = 15.2, 8.4, 1.4 Hz, 1H), 5.41 (ddd, J = 15.2, 8.4, 1.4 Hz, 1H), 3.97 (d, J = 12.8 Hz, 1H), 3.79 (s, 3H), 3.01 (d, J = 12.9 Hz, 1H), 2.94−2.86 (m, 1H), 2.70 (dd, J = 16.1, 8.2 Hz, 1H), 2.06 (dd, J = 16.1, 8.2 Hz, 1H), 1.96−1.84 (m, 1H), 1.72 (dd, J = 6.4, 1.6 Hz, 3H), 1.80−1.55 (m, 3H).

*(E)-1-(4-Methoxybenzyl)-2-(prop-1-en-1-yl)piperidine (**5d**)*.[22] Procedure H. Yield = 92%, 65.3 mg. R_f = 0.39 (SiO_2, hex/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.60 (dq, J = 12.7, 6.2 Hz, 1H), 5.50−5.44 (m, 1H), 3.99 (d, J = 13.4 Hz, 1H), 3.79 (s, 3H), 2.99 (d, J = 13.5 Hz, 1H), 2.77 (dd, J = 11.6, 3.1 Hz, 1H), 2.66−2.51 (m, 1H), 1.91−1.77 (m, 1H), 1.70 (d, J = 6.0 Hz, 3H), 1.67−1.23 (m, 6H).

*1-(4-Methoxybenzyl)-2-vinylpyrrolidine (**5e**)*.[9] Procedure H. Yield = 93%, 80.8 mg. R_f = 0.51 (SiO_2, hex/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.08−5.83 (m, 1H), 5.39−5.34 (m, 2), 4.14 (d, J = 13.1 Hz, 1H), 3.79 (s, 3H), 3.59 (d, J = 13.1 Hz, 1H), 3.37−3.30 (m, 1H), 3.28−3.18 (m, 1H), 2.71−2.56 (m, 1H), 2.17−1.75 (m, 4H).

*1-(4-Methoxybenzyl)-2-vinylpiperidine (**5f**)*.[57] Procedure H. Yield = 97%, 90.2 mg. R_f = 0.51 (SiO_2, hex/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.89 (ddd, J = 17.4, 10.2, 8.6 Hz, 1H), 5.35−5.15 (m, 1H), 5.10 (dd, J = 10.2, 1.7 Hz, 1H), 3.97 (d, J = 13.4 Hz, 1H), 3.79 (s, 3H), 3.03 (d, J = 13.4 Hz, 1H), 2.80 (dt, J = 11.4, 3.0 Hz, 1H), 1.87 (td, J = 11.2, 2.5 Hz, 1H), 1.74−1.58 (m, 2H), 1.58−1.39 (m, 3H), 1.34−1.22 (m, 1H).

*anti-4-Ethyl-1-(4-methoxybenzyl)-2-vinylpyrrolidine (**5h**)*.[22] Procedure I. Yield = 53%, 16.6 mg. R_f = 0.31 (SiO_2, hex/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.87−5.70 (m, 1H), 5.18 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 3.93 (d, J = 12.8 Hz, 1H), 3.80 (s, 3H), 3.06−2.98 (m, 2H), 2.88−2.77 (m, 1H), 2.09−1.97 (m, 1H), 1.87−1.79 (m. 1H), 1.73 (t, J = 9.1 Hz, 1H), 1.62−1.54 (m, 1H), 1.31 (dtd, J = 14.5, 7.3, 1.8 Hz, 2H), 0.83 (t, J = 7.4 Hz, 3H).

*anti-5-Ethyl-1-(4-methoxybenzyl)-2-vinylpiperidine (**5i**)*.[22] Procedure H. Yield = 71%, 11.4 mg. R_f = 0.66 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.85 (ddd, J = 17.5, 10.1, 8.6 Hz, 1H), 5.20 (dd, J = 17.3, 1.7 Hz, 1H), 5.10 (dd, J = 10.2, 1.7 Hz, 1H), 4.00 (d, J = 13.5 Hz, 1H), 3.80 (s, 3H), 3.01 (d, J = 13.5 Hz, 1H), 2.81 (ddd, J = 11.1, 3.2, 2.0 Hz, 1H), 2.56 (dd, J = 8.6, 3.2 Hz, 1H), 1.86−1.71 (m, 1H), 1.66−1.61 (m, 2H), 1.50−1.44 (m, 2H), 1.19−1.03 (m, 2H), 0.87 (dd, J = 12.8, 3.9), 0.80 (t, J = 7.5 Hz, 3H).

*anti-4-Isopentyl-1-(4-methoxybenzyl)-2-vinylpyrrolidine (**5j**)*.[22] Procedure I. Yield = 50%, 11.2 mg. R_f = 0.24 (SiO_2, hex/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (dd, J = 8.6, 2.9 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.86−5.68 (m, 1H), 5.18 (dddd, J = 17.1, 5.7, 1.9, 0.6 Hz, 1H), 5.10 (dd, J = 10.1, 1.9 Hz, 1H), 3.92 (dd, J = 13.0, 3.5 Hz, 1H), 3.80 (s, 3H), 3.18−3.02 (m, 1H), 2.99 (d, J = 13.0 Hz, 1H), 2.09−2.01 (m, 1H), 1.60−1.53 (m, 1H), 1.52−1.40 (m, 1H), 1.38−1.23 (m, 4H), 1.13−1.05 (m, 2H), 0.85−0.83 (m, 3H), 0.83−0.81 (m, 3H).

*1-(4-Methoxybenzyl)-4-((tetrahydro-2H-pyran-2-yl)methyl)-2-vinylpyrrolidine (**5k**)*.[22] Procedure I. Yield = 68%, 19.7 mg. R_f = 0.42 (SiO_2, hex/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (dd, J = 8.7, 2.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.88−5.67 (m, 1H), 5.18 (ddd, J = 17.1, 8.0, 1.9 Hz, 1H), 3.92 (d, J = 12.8 Hz, 1H), 3.93−3.88 (m, 1H), 3.80 (d, J = 1.0 Hz, 1H), 3.34 (td, J = 11.4, 2.7 Hz, 1H), 3.18−2.99 (m, 2H), 2.94−2.81 (m, 1H), 2.63 (dd, J = 9.6, 4.2 Hz, 1H) (minor), 2.38 (t, J = 9.1 Hz, 1H), 2.34−2.21 (m, 1H) (minor), 2.09 (ddd, J = 12.3, 8.1, 6.2 Hz, 1H) (minor), 1.90−1.72 (m, 4H), 1.68−1.13 (m, 13H), 0.93−0.82 (m, 1H).

*1,4-Dibenzyl-2-vinyl-1,2,3,4-tetrahydroquinoxaline (**5q**)*.[22] Procedure H. Yield = 78%, 96 mg. R_f = 0.27 (SiO_2, hex/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.28 (m, 10H), 6.62−6.46 (m, 4H), 5.98 (ddd, J = 16.6, 10.6, 7.8 Hz, 1H), 5.19−5.08 (m, 2H), 4.65−4.26 (m, 4H), 3.92 (dt, J = 7.1, 3.4 Hz, 1H), 3.52 (dd, J = 11.2, 3.5 Hz, 1H), 3.23 (dd, J = 11.2, 3.5 Hz, 1H).

*4-Benzyl-3-vinyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**5r**)*[58] *and 4-Benzyl-2-vinyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**5r′**)*.[59] Procedure H. Yield = 83%, 83 mg. R_f = 0.37 (SiO_2, hex/EtOAc = 19:1). **5r**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39−7.20 (m, 5H), 6.98−6.72 (m, 2H), 6.71−6.46 (m, 2H), 6.03−5.80 (m, 1H), 5.57−5.13 (m, 2H), 4.62 (d, J = 16.9 Hz, 1H), 4.29 (d, J = 16.8 Hz, 1H), 4.22 (dd, J = 7.9, 3.4 Hz, 2H), 3.94−3.82 (m, 1H). **5r′**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ

dx.doi.org/10.1021/jo3025253 | J. Org. Chem. 2013, 78, 1559−1575

7.39−7.20 (m, 5H), 6.98−6.72 (m, 2H), 6.71−6.46 (m, 2H), 6.03−5.80 (m, 1H), 5.57−5.13 (m, 2H), 4.67−4.63 (m, 1H), 4.45 (s, 2H), 3.32 (dd, J = 11.8, 2.7 Hz, 1H), 3.20 (dd, J = 11.8, 7.8 Hz, 1H).

1-Benzyl-4-methyl-4-vinylazetidin-2-one (5w).[60] Procedure H. Yield = 97%, 114 mg. R_f = 0.23 (SiO_2, hex/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26−7.25 (m, 5H), 5.27−5.19 (m, 1H), 3.52−3.46 (m, 2H), 3.02−2.92 (m, 2H), 2.50−2.41 (m, 2H), 2.19 −2.13 (m, 2H), 1.50 (s, 3H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ayudin@chem.utoronto.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSERC and the University of Toronto for financial support. Prof. Robert Morris and Mr. Marco Zimmer de Iuliis are thanked for stimulating discussions. I.D. acknowledges an NSERC PGS-D graduate fellowship.

■ REFERENCES

(1) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

(2) Ricci, A. *Modern Amination Methods*; Wiley-VCH: Weinheim, 2000.

(3) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

(4) (a) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508. (b) Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, *129*, 774. (c) Nemoto, T.; Sakamoto, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 8737. (d) Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546. (e) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.—Eur. J.* **2006**, *12*, 3596. (f) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506. (g) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int, Ed.* **2003**, *42*, 2054. (h) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272. (i) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (j) Shu, C. T.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *44*, 4797. (k) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525.

(5) (a) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220. (b) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377. (c) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (d) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 12214.

(6) (a) Åkermark, B.; Åkermark, G.; Hegedus, L. S.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037. (b) Åkermark, B.; Vitagliano, A. *Organometallics* **1985**, *4*, 1275. (c) Amatore, C.; Génin, E.; Jutand, A.; Mensah, L. *Organometallics* **2007**, *26*, 1875.

(7) Åkermark, B.; Hansson, S.; Krakenberger, B.; Vitaglio, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679.

(8) (a) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (b) Hayashi obtained high selectivities for branched products with palladium in the presence of a 2.5-fold excess of benzylamine: Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743. (c) Faller, J. W.; Wilt, J. C. *Org. Lett.* **2005**, *7*, 633.

(9) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297.

(10) Kawatsura, M.; Hirakawa, T.; Tanaka, T.; Ikeda, D.; Hayase, S.; Itoh, T. *Tetrahedron Lett.* **2008**, *49*, 2450.

(11) (a) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516. (b) Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5086.

(12) Johns, A. M.; Liu, Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7259.

(13) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172.

(14) Paisner, S. N.; Burger, P.; Bergman, R. G. *Organometallics* **2000**, *19*, 2073.

(15) Rodima, T.; Kaljurand, I.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. *J. Org. Chem.* **2002**, *67*, 1873.

(16) Benfatti, F.; Cardillo, G.; Gentilucci, L.; Mosconi, E.; Tolomelli, A. *Org. Lett.* **2008**, *10*, 2425.

(17) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 87th ed.; CRC Press: Boca Raton, FL, 2006.

(18) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem.* **2005**, *44*, 6924.

(19) (a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (b) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem.* **2006**, *45*, 3109. (c) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180.

(20) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354.

(21) Buchwald and co-workers pioneered the utility of this ligand in (a) Borylation: Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589. Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359. (b) Silylation: McNeill, E.; Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3785. (c) Amination: Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (d) Suzuki cross-coupling of aryl halides: Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (e) Indole arylation: Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (f) Ketone arylation: Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(22) Dubovyk, I.; Pichugin, D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5924.

(23) Ascic, E.; Le Quement, S. T.; Ishoey, M.; Daugaard, M.; Nielsen, T. E. *ACS Comb. Sci.* **2012**, *14*, 253.

(24) Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 3584.

(25) See the Supporting Information of: Dubovyk, I.; Pichugin, D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5924.

(26) (a) Kollmar, M.; Helmchen, G. *Organometallics* **2002**, *21*, 4771. (b) Braunstein, P.; Naud, F.; Dedieu, A.; Rohmer, M.-M.; DeCian, A.; Rettig, S. J. *Organometallics* **2001**, *20*, 2966.

(27) (a) Åkermark, B.; Åkermark, G.; Hegedus, L. S.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037. (b) Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L. *Chem.—Eur. J.* **1999**, *5*, 466. (c) Bouquillon, S.; Muzart, J. *Eur. J. Org. Chem.* **2001**, 3301.

(28) Zimmer-De Iuliis, M.; Watson, I. D. G.; Yudin, A. K.; Morris, R. H. *Can. J. Chem.* **2008**, *87*, 1.

(29) García-Iglesias, M.; Buñuel, E.; Cárdenas, D. J. *Organometallics* **2006**, *25*, 3611.

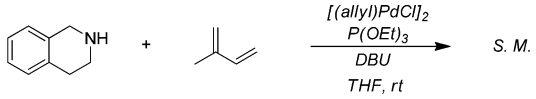
(30) Triphenylphosphine had to be used as a ligand in this study because alkylphosphine ligand signals overlap with the signals produced by the allyl−Pd complex.

(31) Hartwig and co-workers have previously demonstrated how THF acted as a ligand to palladium: Hanley, P. S.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 6302.

(32) Coordinating solvents have been previously shown to affect the rate of π-σ equilibration. For references, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Crociani, B.; Di Biance, F.; Giovenco, A.; Boschi, T. *Inorg. Chem. Acta* **1987**, *127*, 169.

(33) (a) Skinner, H. A.; Connor, J. A. *Pure. Appl. Chem.* **1985**, *57*, 79. (b) Connor, J. A. *Top. Curr. Chem.* **1977**, *71*, 71. (c) Mondal, J. U.;

Blake, D. M. *Coord. Chem. Rev.* **1982**, *47*, 205. (d) Nolan, S. P.; Hoff, C. D. *J. Organomet. Chem.* **1985**, *290*, 365.
(34) Cantat, T.; Génin, E.; Giroud, C.; Meyer, G.; Jutand, A. *J. Organomet. Chem.* **2003**, *687*, 365.
(35) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988.
(36) Both Trost and Guiry observed faster equilibration of allylpalladium intermediates in polar solvents especially in the presence of crown ethers: (a) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(37) Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. Y.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.* **2011**, *76*, 391.
(38) It is interesting to note that acetate isomerization proceeds only in the presence of DBU. We therefore hypothesized that DBU may have initiated elimination, after which the resulting isoprene would undergo palladium-catalyzed hydroamination (see below). To test for the former hypothesis, prenyl acetate was replaced with isoprene and subjected to the reaction conditions in the presence or absence of DBU. No allylic amine product was formed, which is not consistent with hydroamination happening under these conditions. A potential involvement of DBU in an uncatalyzed reaction with allyl acetate has also been ruled out.



(39) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681.
(40) Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc., Chem. Commun.* **1970**, 1392.
(41) Young, W. G.; Webb, I. D. *J. Am. Chem. Soc.* **1951**, *73*, 780.
(42) Ingold, E. H.; Ingold, C. K. *J. Am. Chem. Soc.* **1932**, 756.
(43) Baeckvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615.
(44) Garcia Martinez, A.; Oliver Ruiz, M.; Contelles, J. L. M. *Synthesis* **1986**, *2*, 125.
(45) Babin, D.; Fourneron, J. D.; Julia, M. *Bull. Chim. Soc. Fr.* **1980**, *11*, 588.
(46) Moreno-Manas, M.; Ribas, J.; Virgili, A. *J. Org. Chem.* **1988**, *53*, 5328.
(47) Bienvenue-Goetz, E.; Dubois, J. E. *J. Am. Chem. Soc.* **1981**, *103*, 5388.
(48) Salomon, R. G.; Reuter, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 4372.
(49) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.
(50) Crociani, B.; Antonaroli, S.; Bandoli, G.; Canovese, L.; Visentin, F.; Uguagliati, P. *Organometallics* **1999**, *18*, 1137.
(51) Spaltenstein, A.; Carpino, P. A.; Hopkins, P. B. *Tetrahedron Lett.* **1986**, *27*, 147.
(52) Katritzky, A. R.; Yao, J.; Qi, M. *J. Org. Chem.* **1998**, *63*, 5232.
(53) Yamaguchi, H.; Nakanishi, S.; Okamoto, K.; Takata, T. *Synlett* **1997**, *6*, 722.
(54) Rancourt, J.; Gorys, V.; Jolicoeur, E. *Tetrahedron Lett.* **1998**, *39*, 5339−5342.
(55) Powell, J.; Shaw, B. L. *J. Chem. Soc. A* **1967**, 1839.
(56) Koya, S.; Yamanoi, K.; Yamasaki, R.; Azumaya, I.; Masu, H.; Saito, S. *Org. Lett.* **2009**, *11*, 5438.
(57) Iorio, M. A.; Ciuffa, P.; Damia, G. *Tetrahedron* **1970**, *26*, 5519.
(58) Merisor, E.; Conrad, J.; Klaiber, I.; Mika, S.; Beifuss, U. *Angew. Chem., Int. Ed.* **2007**, *46*, 3353.
(59) Yamazaki, A.; Achiwa, I.; Achiwa, K. *Tetrahedron: Asymmetry* **1996**, *7*, 403.
(60) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.