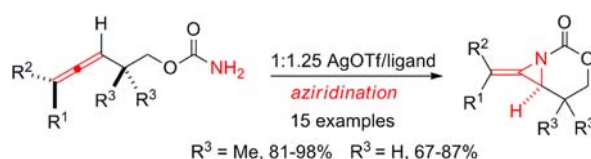# Chemoselective Allene Aziridination via Ag(I) Catalysis

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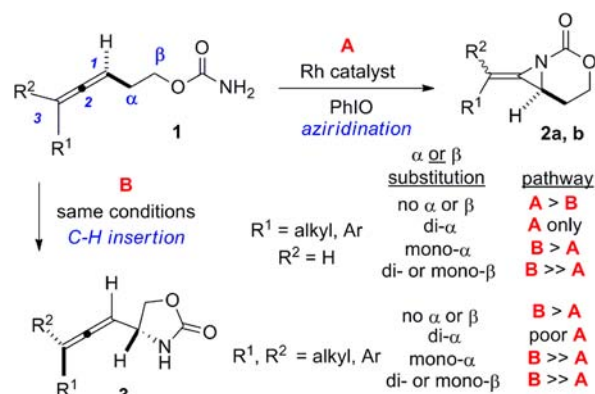schomakerj@chem.wisc.edu

ABSTRACT

Allene aziridination generates useful bicyclic methylene aziridine scaffolds that can be flexibly transformed into a range of stereochemically complex and densely functionalized amine-containing stereotriads. The scope of this chemistry has been limited by the poor chemoselectivity that often results when typical dinuclear Rh(II) catalysts are employed with homoallenic carbamates. Herein, Ag(I) catalysts that significantly improve the scope and yield of bicyclic methylene aziridines that can be prepared via allene aziridination are described.

The chemoselective amination of unsaturated compounds can be a challenging endeavor. In the case of alkene amination, the aziridination of a π-bond is often favored over competing amination of an allylic C−H bond.[1,2] However, our recent studies in allene aziridination have uncovered several examples where the chemoselectivity of the reaction depends more heavily on the structural features of the allene than we had expected.[1] As typical Rh-based catalysts did not permit successful tuning of the selectivity of allene amination, we needed an alternative catalyst system that would favor aziridination over C−H insertion (Scheme 1).

Bicyclic methylene aziridines **2a** and **2b** and allenic amines **3** (Scheme 1, Figure 1) are valuable intermediates for the preparation of complex amine-containing
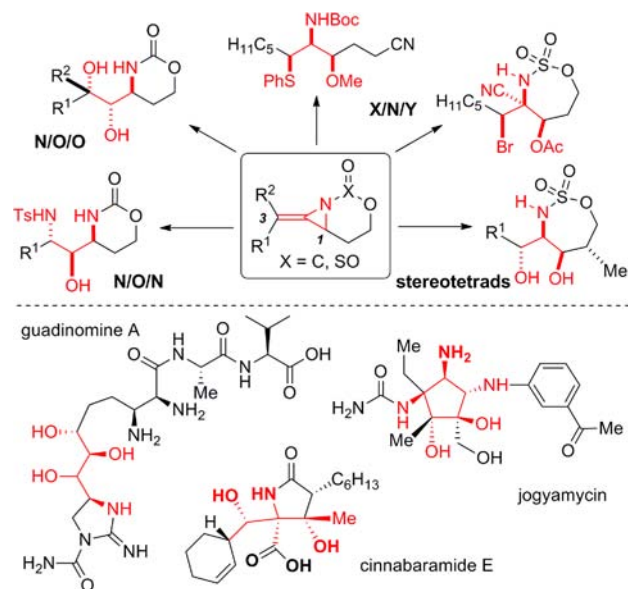
Scheme 1. Rh-Catalyzed Amination of Homoallenic Carbamates

stereotriads, tetrads, and heterocycles.[1] In our previous studies, we have described the treatment of homoallenic carbamates **1** with tetra-bridged dirhodium(II) carboxylate complexes to promote the formation of **2a** and **2b** as the major products.[1a−d] However, good chemoselectivity was reliant on the specific substitution of the allene and the presence or absence of branching in the tether.[1e] Competing C−H insertion to yield **3** was exacerbated when the allene was trisubstituted or branching in the tether between

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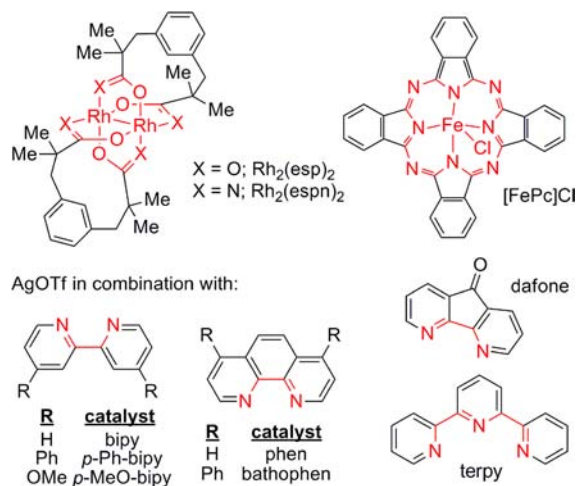
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Figure 1. Synthetic utility of bicyclic methylene aziridines and potential natural product targets.

the allene and the nitrogen source was present.[1e] Efforts to improve chemoselectivity by tuning Rh-based catalysts via the ligand were disappointing. Thus, we needed to identify another catalyst system capable of delivering predictable and superior selectivity for allene aziridination, independent of substrate structure.

Figure 2. Catalysts for chemoselective allene amination.

Several transition metals, including Rh, Cu, Ru, Fe, Co, Au, and Ag, are known to promote C−N bond formation via presumed nitrene intermediates (Figure 2).[2−8] Recent studies have shown that changing the identity of the metal in the catalyst can control whether predominantly aziridination or C−H amination is observed when both C−H and π-bonds are present.[9,10] We focused on two substrates **4a** and **4b** that gave poor chemoselectivity in Rh-catalyzed aziridination. Treatment of **4a** with $Rh_2(esp)_2$ (esp = α,α, α′,α′-tetramethyl-1,3-benzene-dipropionic acid, Table 1, entry 1) gave only a 35% yield of **5a** and significant C−H insertion to **6a**. $Rh_2(espn)_2Cl$ (entry 2) performed better, yet further attempts to improve the chemoselectivity by changing the nature of the carboxylate ligands on the Rh were unsuccessful.[11] A series of Cu catalysts gave poor reactivity, and attempts to isolate the iodinane prior to amination were unsuccessful (see Supporting Information for details). However, $Cu(MeCN)_4PF_6$ (entry 5) could be induced to give low yields of amination products by premixing **4a** with PhIO before the addition of catalyst.[12] However, this did not improve the results using Ru- and Fe-based catalysts, even when 20 mol % of the metal was employed (entries 6−7).[3c,4a,5e] While treatment of **4a** with AgOTf in the presence of PhIO gave very little **5a** (entry 8), the addition of dafone (4,5-diazafluoren-9-one, entry 9) improved the conversion and, encouragingly, yielded > 20:1 chemoselectivity for aziridination over C−H insertion. A series of bipyridine (bipy) ligands (entries 10−12) also gave excellent chemoselectivity for aziridination with good yields.[8a−d] Phen (entry 13) increased the yield to 79%, but the additional bulk in bathophen (entry 14) was not necessary. To our surprise, switching to a terpyridine ligand (terpy, entry 15) reversed the chemoselectivity in favor of **6a**.[8a] Interestingly, the nature of the Ag

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Table 1. Investigation of Catalysts for Chemoselective Allene Amination Reactions

4a R¹, R² = Me; R³ = H
4b R¹ = C₅H₁₁; R² = H; R³ = Me

entry	catalyst[a]	A:I[b]	% 5a(6a)[c]	entry	catalyst[a]	E:Z	A:I[b]	% 5b(6b)[c]
1	Rh₂(esp)₂	2:1	35 (17)	18	Rh₂(esp)₂	2:1	1:17	5 (80)
2	Rh₂(espn)₂Cl	2.7:1	40 (15)	19	Rh₂(espn)₂Cl	3:1	1:4.7	9 (42)
3	Cu(MeCN)₄PF₆/phen	---	2 (0)	20	Cu(MeCN)₄PF₆	---	---	0
4	Cu(OTf)₂/phen	---	0 (0)[d]	21	[Ru₂(hp)₄Cl]	---	---	0
5	Cu(MeCN)₄PF₆	3.3:1	13 (4)[d]	22	[FePc]Cl	---	---	0
6	Ru₂(hp)₄Cl	---	0 (4)	23	AgOTf	nd	---	2 (0)[d]
7	[FePc]Cl	---	0 (0)	24	AgOTf/dafone	2.3:1	2.7:1	59 (22)
8	AgOTf	>20:1	6 (0)[e]	25	AgOTf/bipy	2.4:1	6.4:1	68 (11)
9	AgOTf/dafone	>20:1	32	26	AgOTf/p-Ph-bipy	2.3:1	3.1:1	62 (20)
10	AgOTf/bipy	>20:1	60	27	AgOTf/p-MeObipy	2.2:1	6.4:1	73 (11)
11	AgOTf/p-Ph-bipy	>20:1	66	28	AgOTf/phen	2.2:1	5.9:1	80 (14)
12	AgOTf/p-MeObipy	>20:1	72	29	AgOTf/bathophen	1.9:1	7:1	84 (12)
13	AgOTf/phen	>20:1	79	30	AgOTf/terpy	2.3:1	1:6.6	9 (61)
14	AgOTf/bathophen	20:1	57					
15	AgOTf/terpy	1:1.3	27 (35)					
16	AgOAc/phen	1:14.6	0 (29)[f]					
17	AgO₂CCF₃/phen	1:20	0 (40)[g]					

[a] Rh: 5 mol % catalyst, 2.0 equiv of PhIO, CH₂Cl₂, rt. Cu, Ru, Fe: 20 mol % catalyst, 2.0 equiv of PhIO, rt. Ag: 20 mol % AgOTf, 25 mol % ligand, 4 Å MS, 2.0 equiv of PhIO, CH₂Cl₂. [b] A = aziridination **5a,5b**; I = insertion **6a,b**. [c] NMR yields using mesitylene as the internal standard. [d] **4a** and PhIO were mixed for 1 h prior to adding the catalyst. [e] Significant decomposition of the carbamate occurred. [f] 45% conversion. [g] 60% conversion.

counteranion also had a significant impact on the reaction. Substitution of AgOTf with AgOAc (entry 16) or AgO₂CCF₃ (entry 17) gave almost exclusively C−H insertion **6a**, although the reactivity of the catalyst was diminished, as these anions can bind tightly to the metal.

The allenic carbamate **4b** was also a challenging substrate for aziridination. When Rh₂(esp)₂ was employed as the catalyst, an 80% yield of **6b** was obtained (entry 18),[1e] highlighting the impact of substrate structure on the chemoselectivity of Rh-catalyzed C−N bond formation. Neither Rh₂(espn)₂ (entry 19) nor Cu-, Fe-, or Ru-based catalysts (entries 20−22) improved the outcome. However, employing a dafone ligand in the presence of AgOTf (entry 24) reversed the chemoselectivity to 2.7:1 in favor of aziridination. Bipyridine ligands (entries 25−27) improved the chemoselectivity further, resulting in good yields of the aziridine **5b** and A:I selectivities ranging from 3.1:1 to 6.4:1. Phen and bathophen (entries 28−29) gave comparable yields, in contrast to the aziridination of the more sterically demanding **4a** (entries 13−14). As in the case of **4a**, a 2,2′:6′,2″-terpyridine ligand (entry 30) resulted in a reversal of the chemoselectivity, providing a **5b:6b** ratio of 1:6.6. To our knowledge, these results represent the first examples of reagent-controlled amination of unsaturated substrates with Ag(I) catalysis.

A series of allenes containing α,α-dimethyl groups (Table 2) were investigated with Ag(I) catalysts as an attractive alternative to Rh catalysts. Gratifyingly, treatment of **7a** with AgOTf/phen gave an excellent yield of **8a** (entry 1), which compared well with our previous results

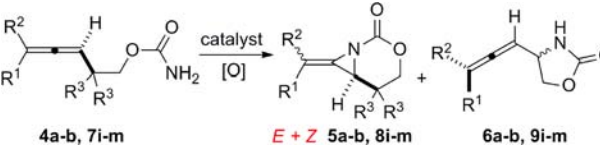**Table 2.** Aziridination of α,α-Disubstituted Allene Carbamates

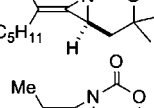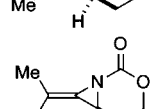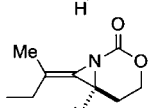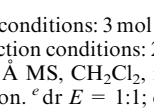| entry	desired product	catalyst[a,b]	E:Z	yield
1	8a	Rh₂TPA₄	4:1	92%
		AgOTf/phen	4:1	88%
2	8b	Rh₂(esp)₂	2.3:1	88%
		AgOTf/phen	2.3:1	81%
3	8c	AgOTf/phen	3:1	87%
4	8d	AgOTf/phen	2.6:1	83%
5	8e	AgOTf/phen	---	98%
6	8f	AgOTf/phen	3:1	90%
7	8g	AgOTf/phen	2.3:1	97%
8	8h	Rh₂(esp)₂	1:2.8	86%
		AgOTf/phen	2.2:1	85%
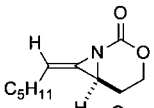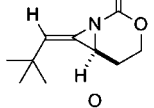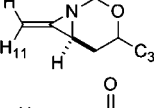
[a] Rh conditions: 3 mol % catalyst, 2 equiv of PhIO, 4 Å MS, CH₂Cl₂, rt. [b] Reaction conditions: 20 mol % AgOTf, 25 mol % ligand, 2 equiv of PhIO, 4 Å MS, CH₂Cl₂, rt.

using Rh₂TPA₄ (TPA = triphenylacetate). Interestingly, the E:Z ratio was not greatly affected by the nature of the catalyst. AgOTf/phen also performed on par with Rh when a 1,3,3-trisubstituted homoallenic carbamate was employed (entry 2), and other 1,3-disubstituted allene carbamates (entries 3−4, 8) gave good to excellent yields of the methylene aziridines **8c**, **8d**, and **8h**. The presence of a polar carboxyethyl group in **7h** (entry 8) resulted in very different behavior depending on whether a Rh- or Ag-based catalyst was employed. While Ag gave the E methylene aziridine as the expected stereoisomer, Rh₂(esp)₂ unexpectedly yielded the Z isomer as the major product. In addition to the 1,3,3-trisubstituted homoallenic carbamate **7b**, other highly substituted allenes bearing

Table 3. Chemoselective Aziridination of Homoallenic Carbamates Using Ag(I) Catalysis

entry	desired product	catalyst[a,b]	E:Z	A:I[c]	yield
1	8i	Rh$_2$TPA$_4$	4:1	4:1	80%
		Rh$_2$(esp)$_2$	3:1	4:1	66%
		AgOTf/bipy	3:1	4:1	72%
2	8j	Rh$_2$(esp)$_2$	>99:1	2:1	49%
		AgOTf/phen	>99:1	1:1	40%[d]
		AgOTf/bipy	>99:1	3.7:1	67%
3	8k	Rh$_2$(esp)$_2$	---	1:1	34%
		AgOTf/phen	4.8:1	9:1	80%[e]
4	5b	Rh$_2$(esp)$_2$	2:1	1:17	5%
		AgOTf/phen	1.9:1	5.9:1	70%
5	5a	Rh$_2$(esp)$_2$	---	2:1	35%
		AgOTf/phen	---	>20:1	79%
6	8l	Rh$_2$(esp)$_2$	2.3:1	1:1.3	34%
		AgOTf/phen	2.6:1	11.5:1	87%
7	8m	Rh$_2$(esp)$_2$	---	1.1:1	32%
		AgOTf/phen	2.3:1	19:1	70%

[a] Rh conditions: 3 mol % catalyst, 2 equiv of PhIO, 4 Å MS, CH$_2$Cl$_2$, rt. [b] Reaction conditions: 20 mol % AgOTf, 25 mol % ligand, 2 equiv of PhIO, 4 Å MS, CH$_2$Cl$_2$, rt. [c] A = aziridination; I = insertion. [d] 73% conversion. [e] dr E = 1:1; dr Z = 3:1.

α,α-dimethyl branching (entries 5−7) gave good yields of methylene aziridines **8e**−**g**.

The next challenge for Ag(I)-based catalysts was to explore the chemoselectivity of amination in substrates where C−H insertion was a competing process (Table 3).

When 1,3-disubstituted allenes **7i** and **7j** were employed (entries 1−2), AgOTf in the presence of bipyridine and phenanthroline ligands gave comparable to slightly improved yields of bicyclic methylene aziridines. The benefit of substituting Ag catalysts for Rh became apparent when substitution was present in the tether between the allene and the carbamate (entries 3−4). AgOTf/phen increased the aziridination/insertion (A:I) ratio from 1:1 to 9:1 in the amination of **7k** to **8k** (entry 3). This effect was even more

dramatic in the case of **4b**, with a change in the A:I ratio of 1:17 to 5.9:1 (entry 4). Surprisingly, the 1,3,3-trisubstituted allene carbamates **5a** and **8l**−**m** (entries 5−7) exhibited much greater chemoselectivity for aziridination using AgOTf/phen catalysts compared to conventional Rh catalysts. This was counterintuitive, as we expected the increased steric congestion around the allene to favor more of the C−H insertion product. The ability to prepare such highly substituted bicyclic methylene aziridines represents a valuable step forward in our ability to prepare densely functionalized and complex nitrogen-containing stereotriads using these reactive scaffolds (Figure 1).

In conclusion, we have demonstrated that the scope and utility of allene aziridination can be greatly increased by employing readily available and tunable Ag(I)-based catalysts. These complexes promote aziridination with superior chemoselectivity over conventional Rh-based catalysts, and the resultant bicyclic methylene aziridines are being studied as scaffolds for the synthesis of complex amines. However, the reasons for the high chemoselectivity exhibited by Ag(I) catalysts compared to Rh$_2$(L)$_n$ are not yet clear.[13] One major difference between the two systems is that Rh$_2$(L)$_n$ complexes adopt only paddlewheel or "lantern-type" geometries, while Ag(I) complexes can adopt a variety of coordination geometries depending on the ligand, solvent, counteranion, and concentration of the reaction.[3a−c,14,15] Studies to address our hypothesis that the coordination geometry of the Ag catalyst impacts chemoselectivity are underway and will be reported in due course.

Supporting Information Available. Experimental procedures and full characterizations are available for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.