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Tunable, Chemoselective Amination *via* Silver Catalysis

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Abstract

Organic N-containing compounds, including amines, are essential components of many biologically and pharmaceutically important molecules. One strategy for introducing nitrogen into substrates with multiple reactive bonds is to insert a monovalent N fragment (nitrene or nitrenoid) into a C–H bond or add it directly to a C=C bond. However, it has been challenging to develop well-defined catalysts capable of promoting predictable and chemoselective aminations solely through reagent control. Herein, we report remarkable chemoselective aminations that employ a single metal (Ag) and a single ligand (phenanthroline) to promote either aziridination or C–H insertion by manipulating the coordination geometry of the active catalysts.

Amines are present in a multitude of pharmaceuticals and natural products with useful biological activities. As a result, the development of synthetic methodologies for the chemo-, regio-, and stereoselective introduction of C–N bonds has been vigorously pursued.^{1a–e} One attractive approach is the direct insertion of a nitrene or nitrenoid species into a C–H or C=C bond of an unsaturated substrate, and many catalysts based on Rh, Ru, Fe, Co, Cu, Mn, Au, and Ag have been exploited in this context.^{2a–m} However, chemoselective C–N bond formation in substrates bearing both reactive C–H and C=C bonds is a particularly challenging task, as these compounds (Figure 1) often give rise to multiple products or exhibit substrate-controlled selectivity.^{3a–g}

One strategy employed to overcome the problem of substrate control in metal-catalyzed amination is to change the identity of the transition metal. For example, Ru- and Fe-based catalysts favor C–H amination over the aziridination pathway that is preferred using Rh(II) carboxylates.^{4a,b} A second tactic is to utilize different supporting ligands with a single metal, but this has been only marginally successful for chemoselective amination.^{3a–d} Finally, the nature of the nitrene precursor can influence the reaction outcome.^{5a–c} We refer to strategies employing a single, well-defined complex to control a specific amination event as ‘static’ approaches to catalysis (Figure 1, top).

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Notes

The authors declare no competing financial interest.

Supporting Information

Experimental procedures and characterization for new compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Our previous studies on the chemoselective aziridination of homoallylic carbamates to bicyclic methylene aziridines (Table 1) showed that Ag complexes supported by bidentate N ligands provided superior chemoselectivity for aziridination compared to $\text{Rh}_2(\text{esp})_2$, irrespective of the substrate identity (compare entry 1 vs 2–7 and 9 vs 10–15).^{6,7a–f} However, a tridentate ligand reversed this selectivity (entries 8 and 16). This result stimulated our curiosity, and a further perusal of the literature showed that Ag has the unique ability to change coordination geometry in response to changes in the Ag counteranion, the ligand identity, or the metal/ligand ratio.⁸ If these changes in the coordination geometries of the Ag catalysts were indeed responsible for inducing divergent chemoselectivity, a ‘dynamic approach’ to catalytic amination could be envisioned (Figure 1, bottom). In this scenario, treatment of a single Ag salt with a single ligand would yield a mixture of several potential catalytic species. Simple perturbation of the equilibrium of this mixture could give different catalytic species capable of promoting *divergent* amination using reagent control.

In order to test the potential for developing a dynamic catalyst system, the metal:ligand stoichiometry of a AgOTf:phen catalyst system was varied to determine the effect on chemoselectivity.^{8a–g} Phenanthroline was chosen for its high yield in the amination and its relatively low cost. To our delight, a clear impact on the amination of **3b** was observed (Table 2). AgOTf:phen ratios close to 1:1 (entries 1–4) promoted aziridination to **4b** as the major reaction pathway, while increasing the amount of phen gave C–H insertion to **5b** as the dominant mode of reactivity (entries 5, 6). The dramatic reversal in the reaction outcome suggests that an equilibrium between Ag(phen)OTf and Ag(phen)₂OTf exists and that each complex favors a different mode of reactivity.

The scope of the ‘dynamic’ amination was explored using homoallylic carbamates (Table 3). In all cases, a 1:1.25 ratio of AgOTf:phen favored aziridination,⁶ while a 1:3 ratio of AgOTf:phen yielded mainly C–H insertion. Trisubstituted allenes (entries 1, 6–7) exhibited good selectivity under both conditions, while less substituted allenes (entries 2–5, 8) usually gave better selectivity in C–H insertion. Interestingly, the addition of 10 mol % of 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) appeared to improve the conversion of the C–H insertion (entries 4, 8–10).^{7f}

Simple changes in the AgOTf:phen stoichiometry also provided good chemoselectivity in the amination of homoallylic carbamates (Table 4). The *cis*-disubstituted **6a** showed increased selectivity for aziridination in switching from $\text{Rh}_2(\text{OAc})_4$ to 1:1.25 AgOTf:phen (entry 1), while changing the AgOTf:phen ratio to 1:3 promoted exclusive insertion. This trend held for both the *cis*-disubstituted **6b** (entry 2) containing substitution in the tether and the *trans*-disubstituted **6c** (entry 3). The stereochemistry of the olefin was transferred to the resulting aziridines and allylic amines with no detectable isomerization. The 1,1'-disubstituted **6d** gave better selectivity and yield for aziridination compared to $\text{Rh}_2(\text{OAc})_4$, although the C–H insertion was moderate. Substrate **6e** gave poor results using Ag(phen)OTf, but good selectivity for insertion.

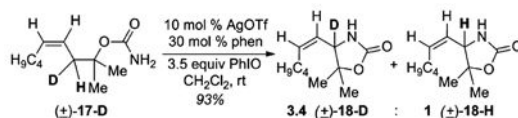
Attempts to isolate the proposed 1:1 and 1:2 AgOTf:phen complexes in the solid state (Table 2) resulted in the recovery of only Ag(phen)₂OTf.⁹ Nonetheless, Ag(phen)₂OTf was

capable of dissociating and reassembling into two distinct catalytic species capable of divergent amination (Scheme 1). Reaction of **3a** with the preformed $\text{Ag}(\text{phen})_2\text{OTf}$ gave a 90:8 mixture of products in favor of the C–H insertion, consistent with the results described in Table 2. Addition of 10 mol % AgOTf to the initial $\text{Ag}(\text{phen})_2\text{OTf}$ complex *completely reversed* the chemoselectivity to provide **4a** in 92% yield, while an extra 10 mol % of phen shut down the competing aziridination pathway, giving **5a** in 90% yield.

Attempts to corroborate the proposed solution state geometries for the two Ag catalysts illustrated in Table 2 were carried out using NMR titration experiments with 4,4'-di-*tert*-butyl-2,2'-bipyridine (*t*Bu-bipy, substituted for phen to improve solubility) and AgOTf . Unfortunately, rapid dynamic exchange, even at temperatures as low as $-85\text{ }^\circ\text{C}$, prevented direct observation of the individual species present in solution (see Supporting Information (SI) for details). However, the averaged ^1H , ^{13}C chemical shifts indicated that the major species in the mixture changed as the ratio of ligand: AgOTf was increased. A combination of pulse gradient spin echo (PGSE) and MALDI MS experiments showed that a monomeric $\text{Ag}(\text{L})\text{OTf}$ complex was the major species in solution when a 1:1 AgOTf :ligand ratio was used, while a monomeric $\text{Ag}(\text{L})_2\text{OTf}$ complex predominated when a 1:2 AgOTf :ligand ratio was used (details in SI). The additional equivalent of ligand serves to perturb the equilibrium of the $\text{Ag}(\text{L})\text{OTf}$: $\text{Ag}(\text{L})_2\text{OTf}$ mixture to favor the latter.

With information about the nature of the two catalytic species in hand, we wanted to understand the factors responsible for our unexpected and tunable chemoselectivity. The exact mechanisms of metal-catalyzed aminations have been notoriously difficult to unravel and often involve multiple reaction pathways.^{2,7f} Yet, we felt even preliminary insights into the mechanism could help extend our dynamic catalysis beyond the scope here.

Experiments to determine whether Ag-catalyzed amination proceeds through a stepwise or concerted mechanism were carried out using the stereochemical probes (\pm)-**9** and (\pm)-**12** (Scheme 2). Only (\pm)-**10** and (\pm)-**14** were observed and no isomerization was detected, suggesting a concerted event. A substrate **15** containing a radical trap yielded only **16** and no ring-opened product, arguing against long-lived radical intermediates. A kinetic isotope effect (KIE) experiment yielded a 3.4 ± 0.1 mixture of isotopomers (\pm)-**18-D** and (\pm)-**18-H** (eq 1). KIEs in



(1)

the range of 1–3 are believed to correspond to a concerted pathway, while KIEs in the range of 6–12 usually signal a stepwise process involving potential radical intermediates.^{3c,11a–c} This suggests that C–H insertion favors a singlet nitrene pathway over hydrogen atom abstraction.

To shed light on the differences between Ag-catalyzed pathways promoting aziridination vs insertion, initial rates were measured for four homoallylic carbamates **3a**, **3d**, **19**, and **21** (Table 5). As expected, the initial rate of aziridination was faster than C–H insertion for both tri- and disubstituted allenes (compare entries 4 and 6, as well as 11 and 13). When sites for potential C–H insertion were blocked in substrates **19** and **21**, the Ag(phen)OTf catalyst still gave aziridination (entries 1 and 8), but the Ag(phen)₂OTf complex gave either no reaction (entry 2) or significantly decreased reactivity (entry 9). This suggests that the steric congestion around the Ag center plays an important role in dictating the chemoselectivity, with a more hindered Ag center promoting insertion over the aziridination which is favored by a less sterically congested Ag center. This is likely due to the difficulty of overcoming steric clashing with the ligands when the substrate attempts to adopt the appropriate orientation of the olefin for reaction with the nitrene (see **26** in Figure 2, *vide infra*). When two ligands are coordinated to the Ag center, insertion into the C–H bond of **26** presents a more favorable pathway, in contrast to the aziridination that occurs through the proposed 1:1 Ag:L complex **24**.

BHT was initially employed to ascertain the impact of a radical inhibitor on the amination (Table 3), where the presence of this additive appeared to improve the conversion of disubstituted homoallylic carbamates to allenic amines. Closer examination of the role of BHT (Table 5) showed that the initial rates in the aziridination of **19** and **21** were decreased in the presence of the radical inhibitor (compare entries 1 and 3, and entries 8 and 10). However, the effect of BHT on the rate of C–H insertion was variable (compare entries 6–7 and 13–14) and did result in an increase in the rate of insertion when a disubstituted allene was employed (entries 13 vs 14). Interestingly, the addition of BHT to **3d** in the presence of 1:1.25 AgOTf:phen (entry 12) gave a 1:1 ratio of aziridine **4d** to allenic amine **5d**. This suggests BHT may also play a role in altering the Ag(L)OTf:Ag(L)₂OTf equilibrium by shifting it toward Ag(L)₂OTf, but further study will be needed to completely understand its impact on the reaction.

The retention of stereochemistry at a chiral center, the low KIE value, the lack of isomerization in the reactions of homoallylic carbamates (Table 4), and the absence of ring opening in the cyclopropane **15** all support a concerted pathway involving a singlet nitrene for the C–H insertion (Figure 2, Path B).^{3b,c,7e,f} However, the aziridination Path A could involve either singlet or triplet nitrene intermediates, or perhaps both. The differences in energies between these two states can be very small; Pérez and co-workers have recently reported that Ag-catalyzed olefin aziridination may involve both paths.^{7f,12a–c} The decrease in the rates of aziridination in the presence of BHT implies there may a triplet nitrene involved, but the lack of isomerization in the aziridination of homoallylic carbamates (Table 4) argues against this and further mechanistic studies will need to be carried out to clarify this issue. Irrespective of the exact reaction pathways, the best explanation for Ag-catalyzed chemoselectivity resides in the dramatic steric differences in the coordination geometries adopted by Ag(phen)OTf and Ag(phen)₂OTf, respectively.

In conclusion, we have developed a simple Ag-based catalyst system that represents the only method to date capable of employing the same metal and the same ligand to accomplish *either* aziridination *or* C–H insertion in good yields. The ability for Ag to readily adopt

multiple coordination geometries provides a new approach to identify catalysts that can promote other types of chemoselective aminations, including choosing between two different C–H bonds. In addition, the ease with which this methodology can be implemented and hopefully extended to other chemoselective C–heteroatom and C–C bond formations opens a potential gateway in reaction discovery. Computational and further mechanistic studies are currently underway to unveil the electronic and steric nature of the reactive species in these Ag-catalyzed chemoselective aminations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

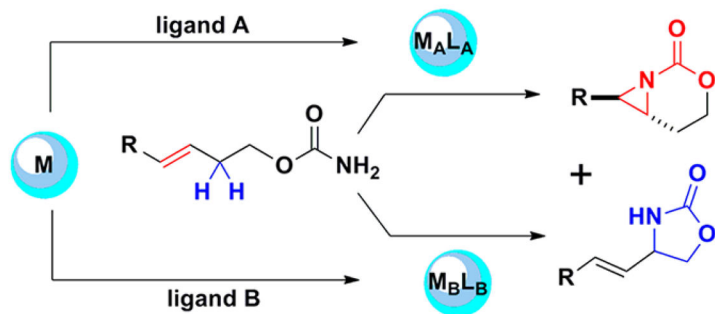
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"static" approach generally produces mixtures of products



This work: "dynamic" approach

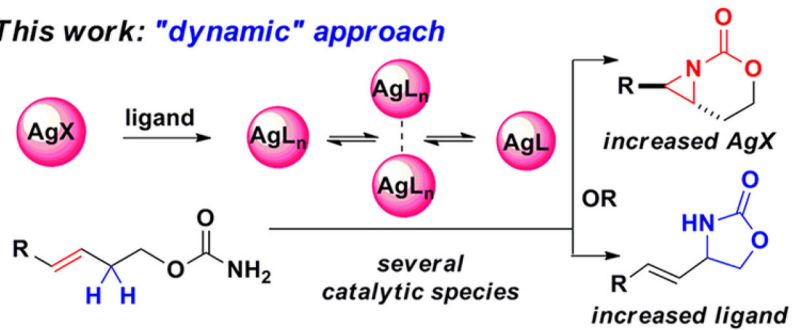


Figure 1.
"Static" vs "dynamic" chemoselective amination.

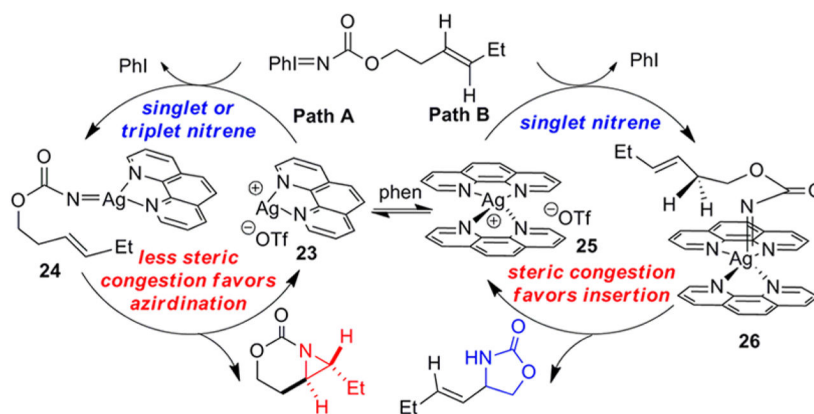
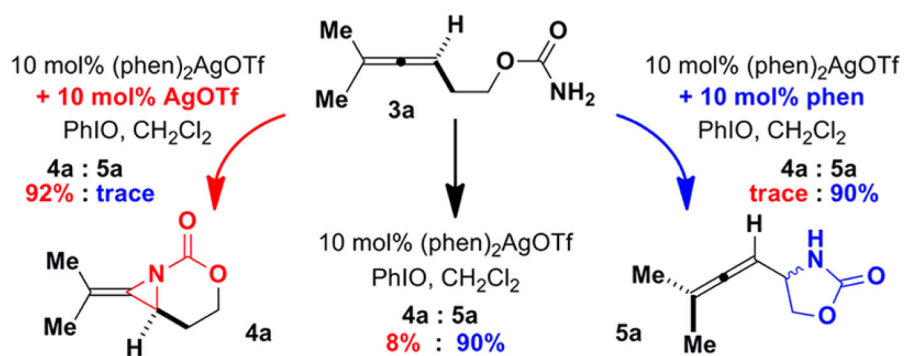
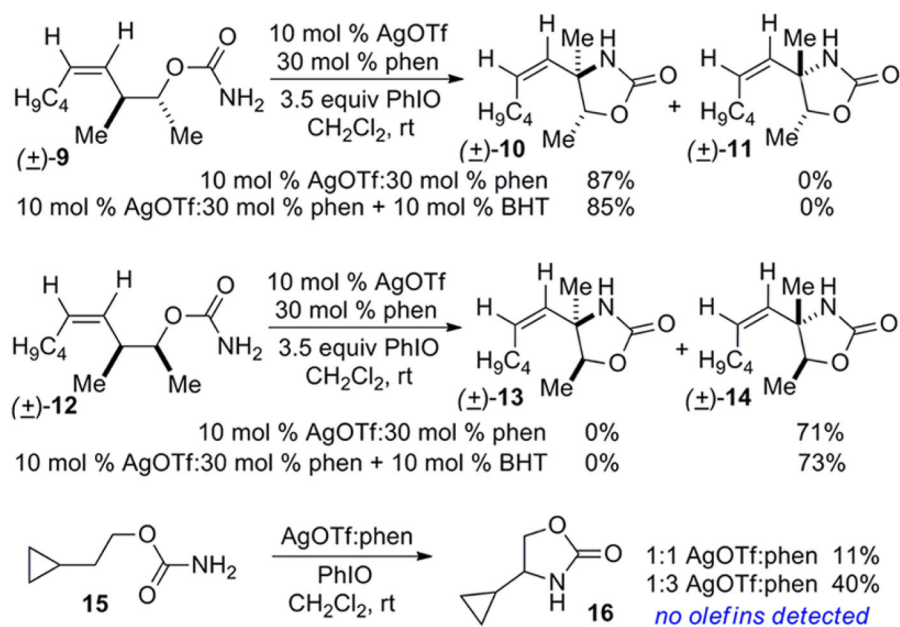


Figure 2.
Possible mechanisms for Ag-catalyzed divergent, chemoselective amination.

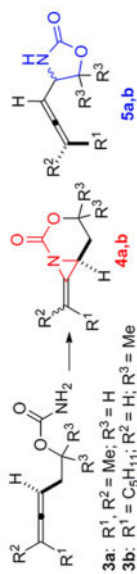


Scheme 1.
Solution-State Behavior of a Preformed $\text{Ag}(\text{phen})_2\text{OTf}$ Catalyst for Chemoselective Amination



Scheme 2.
Stereochemical Probes for Radical Intermediates

Table 1
Chemoselective Aziridination and C–H Amination of Homoallylic Carbamates Catalyzed by Silver Catalysts



entry ^a	catalyst ^{b,c}	A:I ^d	4a	5a	entry ^e	A:I	4b	5b
1	Rh ₂ (esp) ₂	2:1	35%	17%	9	1:16	5%	80%
2	AgOTf/phen	>20:1	79%	---	10	5.7:1	80%	14%
3	AgOTf/bipy	>20:1	60%	---	11	6.2:1	68%	11%
4	AgOTf/bathophen	20:1	57%	---	12	7:1	84%	12%
5	AgOTf/ <i>p</i> -MeObipy	>20:1	72%	---	13	6.6:1	73%	11%
6	AgOTf/dafone	>20:1	32%	---	14	2.7:1	59%	22%
7	AgOTf/ <i>p</i> -Ph-bipy	>20:1	66%	---	15	3.1:1	62%	20%
8	AgOTf/terpy	1:1.3	27%	35%	16	1:6.8	9%	61%

^a Substrate **3a**.

^b 5 mol % Rh₂(esp)₂, 2 equiv PhIO.

^c Ag: 20 mol % AgOTf, 25 mol % ligand, 2 equiv PhIO, 4 Å MS, CH₂Cl₂.

^d A: aziridination. I: insertion.

Substrate **3b**,

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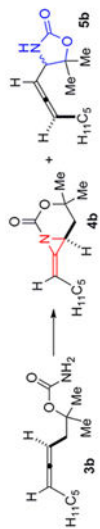
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Table 2

Effect of AgOTf:phen Stoichiometry on the Aziridination/Insertion Ratio



entry ^a	equiv AgOTf:phen	4b:5b (A:I)	4b (5b) ^b
1	0.2/0.1	5:1	60% (12%)
2	0.2/0.2	5.8:1	75% (13%)
3	0.2/0.25	6.2:1	80% (13%)
4	0.2/0.3	5.8:1	70% (12%)
5	0.2/0.4	1:4	18% (72%)
6	0.2/0.6	1:38	2% (76%)

proposed catalytic species

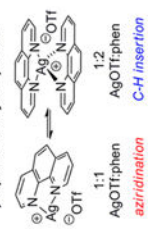
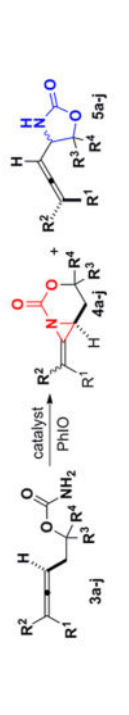
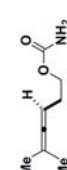
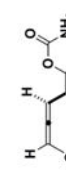
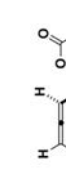


^aReactions were carried out at 0.125 M **3b** in CH₂Cl₂, 2 equiv PhIO, AgOTf:phen, rt.^bNMR yields with mesitylene as the internal standard.

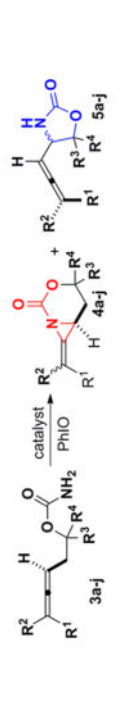
Table 3


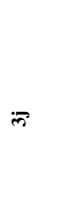
Tunable Amination of Homoallenic Carbamates



entry	allene	AgOTf:phen ^{a,b}	A:I ^d	yield 4	5
1		1:1.25	20:1	79%	<4%
2		Rh ₂ (esp) ₂	2:1	35%	17%
3		1:1.25	6.1:1	79%	13%
4		1:3	1:76	1%	76%
		1:1.25	8.9:1	80%	9%
		1:3	0:100	0%	76%
		Rh ₂ (esp) ₂	1:1	34%	34%
		1:1.25	4:1	72%	18%
		1:3	1:13	5%	65%
		1:3 ^e	1:100	<1%	71%

entry	allene	AgOTf:phen ^{a,b}	A:I ^d	yield 4	5
5		1:1.25 ^c	3.7:1	67%	18%
	3e	1:3	0:100	0%	83%
6		1:1.25	12.4:1	87%	7%
	3f	1:3	0:100	0%	88%
7		Rh ₂ (esp) ₂	1:1.3	34%	44%
	3g	1:1.25	18:1	70%	4%
		1:3	0:100	0%	78%
8		1:1.25	4.8:1	57%	12%
	3h	1:3	1:19	4%	74%
		1:3 ^e	1:100	<1%	68%
9		1:1.25	100:0	61%	0%
	3i	1:3	1:25	3%	74%
		1:3 ^e	1:100	<1%	71%



entry	allene	AgOTf:phen ^{a,b}	A:I ^d	yield 4	5
		1:1.25	100:0	58%	0%
10		1:3	0:100	0%	36%
		1:3 ^e	1:31	2%	62%

^a Aziridination: 20 mol % AgOTf, 25 mol % phen, 2 equiv PhIO, 4 Å MS, CH₂Cl₂.

^b C-H insertion: 10 mol % AgOTf, 30 mol % phen, 3.5 equiv PhIO, 4 Å MS, CH₂Cl₂.

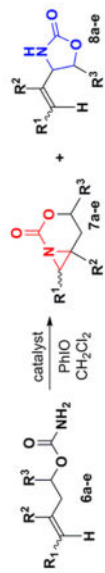
^c 2,2'-bipyridine ligand.

^d I = insertion. A = aziridination.

^e 10 mol % BHT added

Table 4

Selective Amination of Homoallylic Carbamates



entry	substrate	catalyst ^{a,b,c}	A:I	7	8	dr (cis:trans)
1		Rh ₂ (OAc) ₄	3.2:1	58% 7a	18% 8a	(100:0)
		1:1.25 AgOTf:phen	16.8:1	67% 7a	4% 8a	---
	6a	1:3 AgOTf:phen	0:100	0% 7a	93% 8a	---
2		Rh ₂ (esp) ₂	1.8:1	45% 7b	25% 8b^d	nd
		1:1.25 AgOTf:phen	9.9:1	89% 7b	9% 8b	3.2:1
	6b	1:3 AgOTf:phen	1:22	4% 7a	87% 8b	3:1
3		Rh ₂ (OAc) ₄	4.9:1	68% 7c	14% 8c	(0:100)
		1:1.25 AgOTf:phen	29:1	88% 7c	3% 8c	---
	6c	1:3 AgOTf:phen	1:6.6	11% 7c	73% 8c	---
4		Rh ₂ (OAc) ₄	7:1	35% 7d	5% 8d	---
		1:1.25 AgOTf:phen	99:1	85% 7d	<1% 8d	---
	6d	1:3 AgOTf:phen	1:2.9	23% 7d	66% 8d	---

entry	substrate	catalyst ^{a,b,c}	A:I	7	8	dr (cis:trans)
		Rh ₂ (esp) ₂	1.2:1	25% 7e	21% 8e^d	nd
5		1:1.25 AgOTf:phen	1.4:1	54% 7e	39% 8e^d	nd
	6c	1:3 AgOTf:phen	0:100	0% 7e	68% 8e	2.4:1

^a Rh cat.: 3 mol %, 2 equiv PhIO, 4 Å MS, CH₂Cl₂.

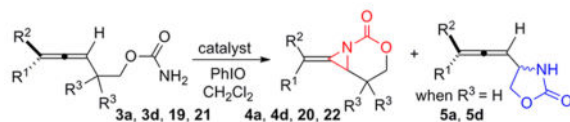
^b Aziridination: 20 mol % AgOTf, 25 mol % phen, 2 equiv PhIO, 4 Å MS, CH₂Cl₂.

^c C–H insertion: 10 mol % AgOTf, 30 mol % phen, 3.5 equiv PhIO, 4 Å MS, CH₂Cl₂.

^d ¹H NMR yields with mesitylene as the internal standard.

Table 5

Relative Rates of Aziridination and C–H Insertion



entry	R ¹ -R ³	catalyst (AgOTf, phen)	product(s)	init rate (mmol/min*mL) ^a
1	Me, Me, Me 19	20 mol%, 25 mol%	20	1.8×10 ⁻³ (98% yield)
2		10 mol%, 30 mol%	20	no reaction
3		20 mol%, 25 mol%, 20 mol% BHT	20	1.4×10 ⁻³ (48% yield)
4	Me, Me, H 3a	20 mol%, 25 mol%	4a	1.3×10 ⁻³
5		20 mol%, 25 mol%, 20 mol% BHT	5a	9.6×10 ⁻⁴
6		20 mol%, 60 mol%	5a	2.8×10 ⁻⁴
7		20 mol%, 60 mol%, 20 mol% BHT	5a	2.1×10 ⁻⁴
8	C ₅ H ₁₁ , H, Me 21	20 mol%, 25 mol%	22	9.85×10 ⁻⁴ (88% yield)
9		20 mol%, 60 mol%	22	36% yield ^b
10		20 mol%, 25 mol%, 20 mol% BHT	22	6.15×10 ⁻⁴
11	C ₅ H ₁₁ , H, H 3d	20 mol%, 25 mol%	4d	5.73×10 ⁻⁴
12		20 mol%, 25 mol%, 20 mol% BHT ^c	4d (26%) 5d (34%)	3.31×10 ⁻⁴ 2.31×10 ⁻⁴
13		20 mol%, 60 mol%	5d	1.58×10 ⁻⁴
14		20 mol%, 60 mol%, 20 mol% BHT	5d	2.94×10 ⁻⁴

^aThe rate of product formation was monitored by ¹H NMR using mesitylene as the internal standards. The indicated initial rates are the average of the three runs, and the standard deviations are included in the SI.

^bYield after 21 h, 73% conversion.

^cThe ratio of **4d**:**5d** was 1:1.