Conference paper

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Chemoselective silver-catalyzed nitrene insertion reactions[1]

Abstract: A review of recent developments in silver(I)-catalyzed nitrene insertions into olefin and C–H bonds is presented, with a particular emphasis on reactions where the chemoselectivity can be tuned to promote either aziridination or C–H amination. The scope and synthetic utility of various silver catalysts are described, as well as preliminary investigations into the mechanisms of silver-catalyzed aminations.

Keywords: aziridines; catalysis; C–H bond reactivity; coordination chemistry; homogeneous catalysis; OMCOS-17; silver.

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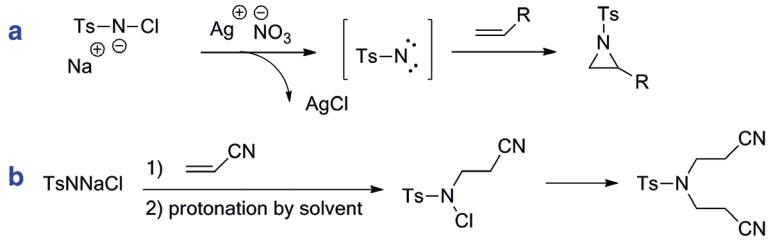
Introduction

Transition metal-catalyzed nitrene transfer reactions represent a powerful approach towards the installation of new carbon-nitrogen bonds [1]. However, issues of chemoselectivity often arise when more than one potential reactive site is present in a substrate [2]. While Rh, Cu, Ru and Fe-catalyzed nitrene transfer reactions have been described that are capable of favoring *either* aziridination *or* C–H insertion, to date, no transition metal-catalyzed nitrene transfer reactions have been described that permit tunability in terms of choosing between a reactive C=C or C–H bond without altering the metal selection. We have recently discovered that silver offers promise for promoting chemoselective nitrene transfer reactions due to the unique ability of Ag to readily adopt a variety of coordination geometries by simple changes in the nature of the supporting ligand, the counteranion of the silver salt and the metal:ligand ratio. This observation has led to the development of protocols capable of the tunable, chemoselective amination of homoallenic and homoallylic carbamates using a single silver salt and a single commercially available ligand. These studies have the potential to yield new silver catalysts capable of promoting chemoselective intra- and intermolecular aminations based solely on catalyst control, rather than the substrate control that has characterized nitrene transfer chemistry to date.

Stoichiometric aziridinations of olefins with silver nitrate

One of the earliest examples of a Ag(I)-promoted aziridination process was reported in 2001 by Rai and coworkers [3]. Chloramine-T was employed as the nitrene source for the aziridination of terminal olefins such as styrene and acrylonitrile (Scheme 1a). The proposed mechanism involves dechlorination of the chloramine-T by a stoichiometric amount of $AgNO_3$ to yield the nitrene intermediate and AgCl. The nitrene subsequently adds to the terminal olefin substrate to produce the aziridine product, but investigations into whether the reaction proceeds in a concerted or step-wise fashion were not carried out. Although this initial report was not catalytic with respect to silver, it nonetheless established the potential of silver(I) to promote nitrene addition to alkenes. Reaction of chloramine-T with acrylonitrile in the absence of the silver salt (Scheme 1b)



Scheme 1 Reactions of olefins with chloramine-T [3]. a. Silver-catalyzed aziridination. b. Addition of chloramine-T to acrylonitrile in the absence of a silver salt.

affords a product resulting from the addition of two equivalents of the alkene to the nitrogen source in lieu of aziridination, indicating that silver plays a role in the formation of a nitrene intermediate.

Catalytic aziridination using silver(I) complexes

Although the discovery of the stoichiometric silver-mediated aziridination reaction established the capability of silver to promote nitrene transfer reactions, further research was required to establish silver as a legitimate alternative to other transition metals typically employed for this type of chemistry. A variety of transition metal complexes are known to promote nitrene insertion into C=C and C–H bonds under catalytic conditions, including Rh, Cu, Ru, Co, Fe, and Mn [4–8]. The He group in particular has made important contributions in their investigations directed towards the catalytic use of silver for nitrene transfer reactions [9]. Initial studies employed ligands based on a pyridine scaffold, which are well-known to stabilize high-valent silver ions in the presence of strong oxidants [10, 11]. Continued screening of other classes of nitrogen-containing ligands revealed that the tridentate 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (^{t}Bu$_3$tpy) ligand, combined with an equimolar amount of a silver(I) salt (Fig. 1), was capable of promoting catalytic aziridination when sulfonyliminoiodinane (PhI=NTs) was employed as the nitrogen source in the presence of simple terminal and cyclic alkenes (selected results illustrated in Table 1). Unfortunately, less expensive and more convenient ligands were inferior to ^{t}Bu$_3$tpy in the aziridination reaction, as pyridine and 4-*tert*-butyl-pyridine provided only trace amounts of products. Bidentate ligands, including 2,2′-bipyridine and 1,10-phenanthroline, gave 30–50 % GC yields of the desired aziridines, but also resulted in significant by-product formation. Silver sources containing non-coordination counteranions, including $AgNO_3$, AgOTf, $AgClO_4$, and $AgBF_4$, all gave similar results in the aziridination reaction.

To gain insight into the role of ^{t}Bu$_3$tpy, a crystal structure of the silver complex $[Ag_2(^tBu_3tpy)_2(NO_3)](NO_3)$ (Fig. 1) was obtained using $AgNO_3$ as the metal source [9]. Interestingly, the complex contained a dinuclear Ag core, with a Ag-Ag 'bond' length of 2.842(2) Å. It should be noted that the dinuclear nature of this silver complex mimics that of conventional Rh-based catalysts used in nitrene transfer reactions, including

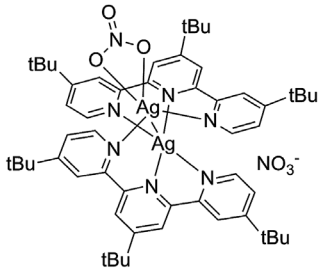
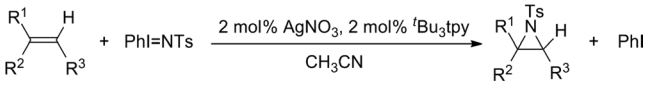


Fig. 1 $[Ag_2(^tBu_3tpy)_2(NO_3)](NO_3)$.

Table 1 Aziridination of simple alkenes with a Ag(I) catalyst [9]. Reactions were run at temperatures ranging from 0 °C to room temperature.



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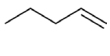
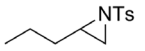
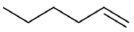
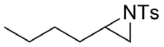
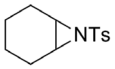
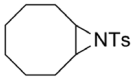
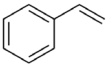
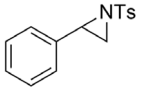
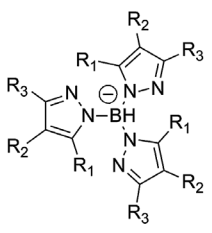
1			66 %
2			71 %
3			81 %
4			88 %
5			91 %

$Rh_2(OAc)_4$ and $Rh_2(O_2CCPh_3)_4$. He and co-workers hypothesized that this silver-silver interaction, in conjunction with ligand effects, aids in the stabilization of a proposed high-valent Ag intermediate that arises during the catalytic amination process. However, no attempts were made to ensure that the solid-state geometry of $[Ag_2(^tBu_3tpy)_2(NO_3)](NO_3)$ correlates with its solution-state behavior and no mechanistic or kinetic studies were conducted to support this mechanistic hypothesis.

The Perez group further demonstrated the synthetic utility of silver(I) catalysis in the chemoselective aziridination of conjugated dienes bearing a terminal alcohol group [12]. Silver(I) complexes supported by trispyrazolylborate scorpionate ligands (Tp^x; Fig. 2) resulted in a good regioselectivity for transformation of the double bond proximal to the hydroxyl group (Table 2). The reaction also demonstrated a high degree of stereoselectivity, as *cis* olefins yielded only *cis* aziridines and *trans* alkenes yielded only the corresponding *trans* aziridines. These results were superior to those observed using the analogous $Cu(Tp^x)$ complexes, which gave inferior regioselectivity, poorer conversion and alkene isomerization. Notably, the Ag-catalyzed reaction proceeded with high regioselectivity only when allylic alcohols were employed as the substrate, indicating the importance of the directing group for regioselective aziridination. The utility of the method was illustrated in the synthesis of (±)-sphingosine, which proceeded in an overall yield of 65 % over three steps starting from a simple conjugated allylic hydroxydiene (Fig. 3).

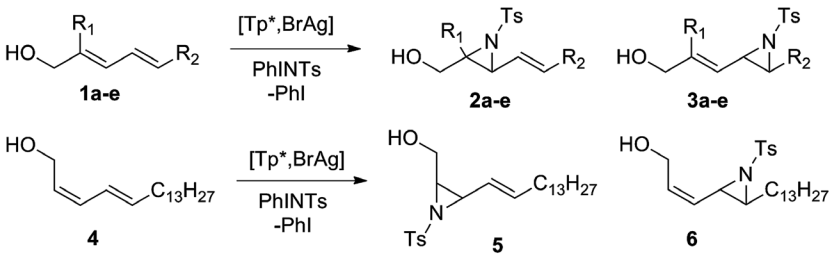
The mechanism of Ag(I)-catalyzed olefin aziridination was investigated by Perez to determine whether nitrene insertion proceeds *via* a concerted triplet radical pathway or a stepwise singlet pathway [13]. Initial studies were performed on a variety of *Z*- and *E*-olefins to determine the extent to which the stereochemistry of the olefin was eroded during the course of the reaction. In all cases where $Ag(Tp^x)$ complexes were



Tpx	R_1	R_2	R_3
Tp*	Me	H	Me
$TpBr_3$	Br	Br	Br
Tp*,Br	Me	Br	Me
TpH,4Et	H	Et	Ph
$TppClPh,Br_2$	Br	Br	p-ClC_6H_4

Fig. 2 Tripyrazolylborate ligands employed in Ag(I)-catalyzed nitrene insertions [12].

Table 2 Aziridination of conjugated dienes with a high preference for aziridination proximal to the hydroxyl group [12].



Entry	Diene		% conversion	Ratio of 2:3		*trans:cis*
1	R_1=R_2=H	**1a**	>99	88:12	**2a:3a**	>98:<2
2	R_1=H, R_2=Et	**1b**	>99	85:15	**2b:3b**	>98:<2
3	R_1=R_2=Me	**1c**	>99	86:14	**2c:3c**	>98:<2
4	R_1=H, R_2=Ph	**1d**	>99	93:7	**2d:3d**	>98:<2
5	R_1=H, R_2=$C_{13}H_{27}$	**1e**	>99	86:14	**2e:3e**	>98:<2
6	**4**		>99	**5:6**, 90:10		<2:>98

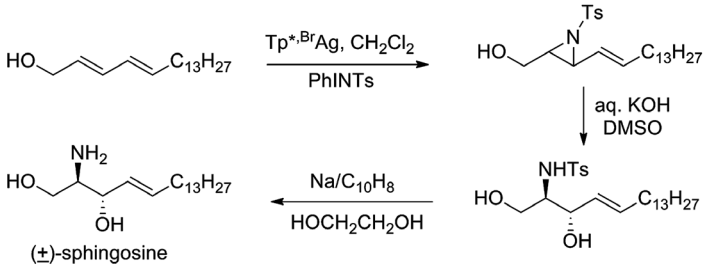


Fig. 3 Synthesis of (±)-sphingosine using Ag(I)-catalyzed aziridination [12].

employed, the aziridination proceeded with complete retention of the stereochemistry, irrespective of any other functionality in the substrate. Hammett studies were conducted using substituted styrenes to probe the electronic nature of the transition state. The Hammett values for a series of *para*-substituted styrenes closely fit a dual parameter equation indicating both radical and polar cationic contributions to the transition state of the reaction. Small negative values of ρ^+ (−0.25 to −0.49) for the styrenes suggested that electrophilic attack of the double bond occurs early in the reaction mechanism. The small positive values for the radical contribution ($\rho^\bullet$) further supported that this interaction occurs early along the reaction coordinate. The positive values indicated that aryl substituents participate in spin delocalization. When the aziridination of styrene was carried out in the presence of the known radical inhibitor 2,6-di-*tert*-butylhydroxytoluene (BHT), no significant decrease in product yield was observed. This argued against the presence of a radical intermediate in the reaction, a conclusion that was further supported by employing 1,1-dicyclopropylethylene as a radical clock in the aziridination, which produced only an imine in the presence of Ag(Tp^x)-based catalysts. The authors noted that the results of the aforementioned experiments did not apply to Cu(Tp^x) catalysts, which demonstrated reduced efficacy in the presence of BHT.

Although the results of these initial studies implied a concerted mechanism for Ag-catalyzed aziridination, the radical contribution indicated by the Hammett study suggested there was some radical character to the reaction pathway [13]. To clarify this issue, DFT calculations were carried out and the calculated free energy profiles for different points on the reaction coordinate in the aziridination of *E*-2-hexene showed that the most favorable transition state contained a triplet diradical, implying a stepwise pathway. However, instead of forming an intermediate leading to stereoinversion, the system undergoes a spin-crossing event with the closed shell singlet diradical, leading to the same product observed in a singlet pathway. Based on

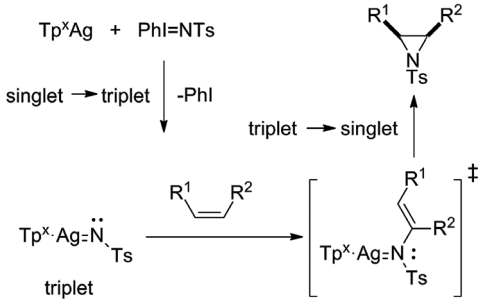


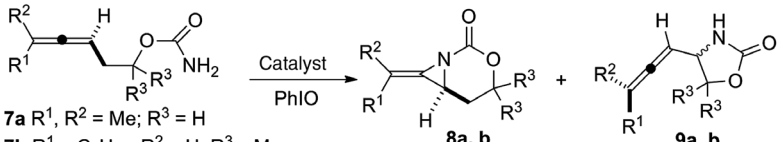
Fig. 4 Proposed mechanism for Ag(I)-catalyzed amination of alkenes invoking nitrene intermediates [13].

these computational results, Perez and co-workers proposed an unexpected stepwise mechanism for Ag(I)-catalyzed olefin aziridination (Fig. 4). In the first step, the triplet silver-nitrene intermediate attacks the olefin double bond to form the initial C–N bond. Subsequently, spin-crossing to the singlet radical forms the second C–N bond without the intermediacy of a carbon radical intermediate capable of bond rotation prior to formation of the final C–N bond. Thus, stereochemistry is conserved despite the stepwise nature of the reaction. Further computational analysis revealed a silver nitrene intermediate with the two unpaired electrons localized on the nitrogen atom and an intact double bond, supporting a structure incapable of rotation. In contrast, the analogous copper nitrene intermediate showed a more delocalized diradical, wherein the double bond was broken, enabling rotation. These results rationalized the observed differences in isomerization for the Ag *vs.* the Cu catalyst systems.

Simultaneously with the mechanistic studies described by Perez, the Schomaker group applied silver(I) catalysis to the intramolecular aziridination of homoallenic and homoallylic carbamates [14–16]. Schomaker found that typical dinuclear Rh(II) catalysts for nitrene insertion gave poor chemoselectivity and limited substrate scope in the amination of homoallenic carbamates **7a** and **7b** (Table 3, entries 1–2 and 6–7). In contrast, catalysts based on silver proved far more chemoselective for the aziridination products **8a** and **8b** when bidentate ligand 2,2′-bipyridine (bipy) and 1,10-phenanthroline (phen) were employed (entries 3–4 and 8–9). This distinction was particularly striking when a bulky allene **7b** was employed, as Rh catalysis promoted almost exclusive C–H insertion to form the oxazolidinone **9a** (entry 6).

The scope of silver-catalyzed aziridination of allenes was explored by blocking sites of potential C–H insertion with methyl groups (Table 4). Aziridine yields using the less expensive AgOTf/phen catalyst system were high for all substrates studied [14]. After establishing the aziridination activity of these catalysts,

Table 3 Comparison of Rh and Ag catalysts for amination of allenes [14, 15].

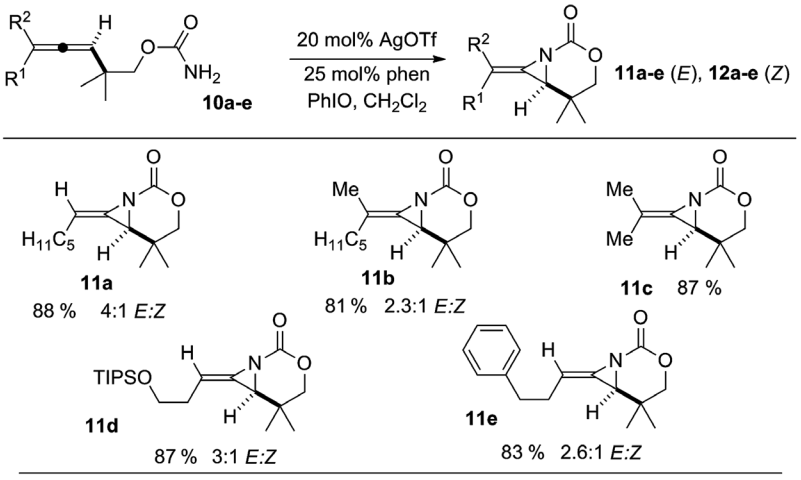


7a R^1, R^2 = Me; R^3 = H
7b R^1 = C_5H_{11}; R^2 = H; R^3 = Me

Entry	Catalyst	8a(8b) (%)	A:I	Entry	Catalyst	*E:Z*	%9a(9b) (%)	A:I
1	$Rh_2(esp)_2$	35 (17)	2:1	6	$Rh_2(esp)_2$	2:1	5 (80)	1:17
2	$Rh_2(espn)_2Cl$	40 (15)	2.7:1	7	$Rh_2(espn)_2Cl$	3:1	9 (42)	1:4.7
3	AgOTf/phen	79	>20:1	8	AgOTf/phen	2.2:1	80 (14)	5.9:1
4	AgOTf/bipy	60	>20:1	9	AgOTf/bipy	2.4:1	68 (11)	6.4:1
5	AgOTf/terpy	27 (35)	1:1.3	10	AgOTf/terpy	2.3:1	9 (61)	1:6.6

Rh conditions: 5 mol% cat, 2.0 equiv. PhIO, CH_2Cl_2, rt. Ag conditions: 20 mol% AgOTf, 25 mol% ligand, 4 Å MS, 2.0 equiv. PhIO, CH_2Cl_2, rt. A:I = aziridination:insertion.

Table 4 Aziridination of homoallenic carbamates [14].



chemoselectivity was explored with homoallenic carbamates containing C–H insertion sites that would compete for nitrene insertion with the allene double bond. The AgOTf/phen system proved to be equal to or better than Rh catalysts in all cases, with most substrates showing a vast increase in aziridination in the presence of silver complexes with bidentate ligands. Intriguingly, a AgOTf/terpyridine catalyst similar to that previously employed toward alkene aziridination by the He group gave poor results, indicating that aziridination of allenes may proceed by a pathway distinct from that of more conventional unsaturated C–C bonds [9].

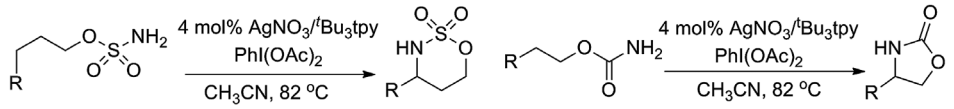
Catalytic C–H amination reactions with silver(I) complexes

Silver-catalyzed nitrene insertion into C–H bonds was first explored in detail by the He group [17]. The dinuclear complex $[Ag_2(tBu_3tpy)_2(NO_3)](NO_3)$ enabled the intramolecular cyclization of sulfamates and carbamates to amines using $PhI(OAc)_2$ as the oxidant (Table 5). In contrast to the Ag-catalyzed aziridination, C–H insertion required elevated temperatures. In certain cases, the addition of a small amount of 4-*tert*-butyl-pyridine provided better yields and cleaner reactions, but an excess of the additive led to catalyst poisoning. The He group proposed that the role of the additive was to increase coordination at one of the silver atoms in the dinuclear catalyst to influence the reactivity at the other Ag. When the C–H insertion reaction was conducted on an enantioenriched substrate (Table 5, entry 4), complete retention of stereochemistry was observed, strongly suggesting that the insertion event is a concerted process.

Despite these encouraging results, a major problem with current approaches to metal-catalyzed aminations that proceed via nitrene intermediates is the lack of chemoselectivity if more than one reactive site is available. The Schomaker group has recently described an interesting solution to this problem by harnessing the unique ability of silver complexes to adopt different coordination geometries in response to minor changes in the reaction conditions (Table 6) [18]. A simple change in the metal:ligand ratio diverts the reaction pathway to favor either aziridination or C–H insertion [14, 15]. These complementary Ag(I) catalyst systems employ AgOTf as the silver source and 1,10-phenanthroline (phen) as the ligand. While the group's earlier results employing a 1:1.25 ratio of AgOTf:phen promoted mainly aziridination, a 1:3 Ag:phen ratio yielded excellent selectivity for C–H insertion in a series of homoallenic and homoallylic carbamates (results not shown). The silver catalyst systems were superior to $Rh_2(esp)_2$ in most cases, and more importantly, allowed for ready tuning of the chemoselectivity of the reaction.

Homoallylic carbamates were also successful substrates for silver-catalyzed chemoselective amination (Table 7). A *trans* disubstituted alkene **15a** gave moderate selectivity for aziridination using $Rh_2(OAc)_4$ as the

Table 5 Intramolecular amination of sulfamates and carbamates [17].



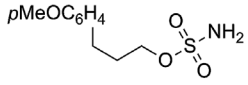
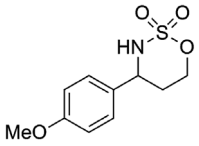
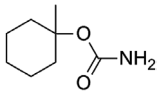
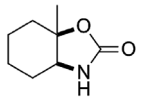
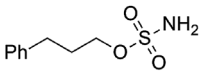
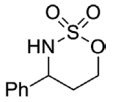
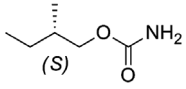
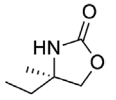
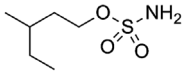
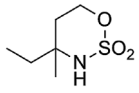
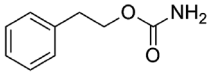
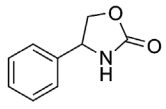
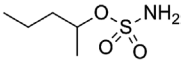
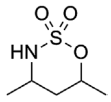
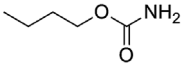
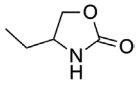
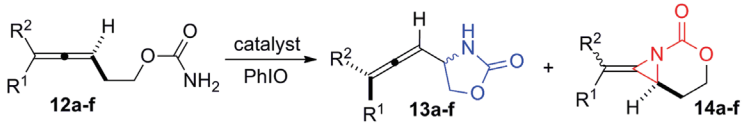
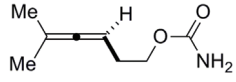
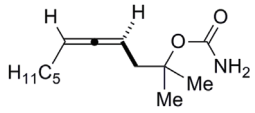
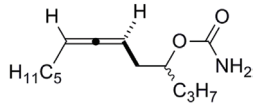
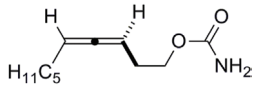
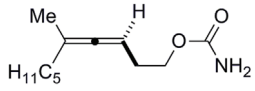
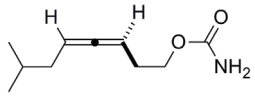
Entry	Substrate	Product	% Yield	Entry	Substrate	Product	% Yield
1			78	5			85
2			87	6			73
3			90	7			81
4			53	8			58

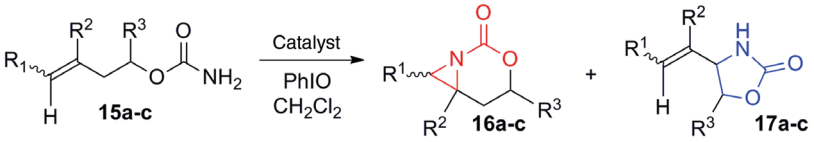
Table 6 Chemoselective intramolecular Ag-catalyzed amination [15].

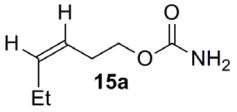
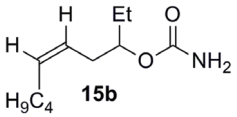
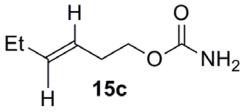


Entry	Allene		AgOTf:phen[a,b]	I:A[c]	% Yield 13 (14 or 12)
1		**12a**	1:1.25	**1:20**	<4 (79)
			1:3	**100:0**	81
			$Rh_2(esp)_2$	**1:2**	17 (35)
2		**12b**	1:1.25	**1:5.9**	13 (79)
			1:3	**76:1**	76 (1)
3		**12c**	1:1.25	**1:9**	9 (80)
			1:3	**100:0**	76
			$Rh_2(esp)_2$	**1:1**	34 (34)
4		**12d**	1:1.25	**1:4**	18 (72)
			1:3	**13:1**	65(11; **12d**)
			1:3[d]	**100:1**	71
5		**12e**	1:1.25	**1:11.5**	7 (87)
			1:3	**100.0**	88
			$Rh_2(esp)_2$	**1.3:1**	44 (34)
6		**12f**	1:1.25	**1:4.8**	12 (57)
			1:3	**19:1**	74 (10; **12f**)
			1:3[d]	**100.1**	68

[a]Aziridination: 20 mol% AgOTf, 25 mol% phen, 2 equiv PhIO, 4 Å MS, CH_2Cl_2. [b]C–H insertion: 10 mol% AgOTf, 30 mol% phen, 3.5 equiv PhIO, 4 Å MS, CH_2Cl_2. [c]I = insertion, A = aziridination. [d]10 mol% BHT added.

Table 7 Chemoselective intramolecular silver-catalyzed amination of homoallylic carbamates [15].



Entry	Substrate	Catalyst[a,b,c]	A:I	16a-c	17a-c	*dr* (*cis:trans*)
1	 **15a**	$Rh_2(OAc)_4$	3.2:1	58 %	18 %	(100:0
		1:1.25 AgOTf:phen	15.7:1	67 %	4 %	–
		1:3 AgOTf:phen	0:100	0 %	93 %	–
2	 **15b**	$Rh_2(esp)_2$	1.8:1	45 %	25 %[d]	nd
		1:1.25 AgOTf:phen	9:1	89 %	9 %	3.2:1
		1:3 AgOTf:phen	1:20	4 %	87 %	3:1
3	 **15c**	$Rh_2(OAc)_4$	4.9:1	68 %	14 %	(0:100)
		1:1.25 AgOTf:phen	24:1	88 %	3 %	–
		1:3 AgOTf:phen	1:6.6	11 %	73 %	–

[a]Rh cat: 3 mol%, 2 equiv PhIO, 4 Å MS, CH_2Cl_2. [b]Aziridination: 20 mol% AgOTf, 25 mol% phen, 2 equiv PhIO, 4 Å MS, CH_2Cl_2. [c]C–H insertion: 10 mol% AgOTf, 30 mol% phen, 3.5 equiv PhIO, 4 Å MS, CH_2Cl_2. [d]NMR yields using mesitylene as an internal standard.

catalyst (entry 1), but employing a 1:1.25 ratio of AgOTf:phen greatly improved the preference for the aziridine **16a**. In contrast, switching the catalyst to a 1:3 ratio of AgOTf:phen gave exclusively the allylic amine **17a** in 93 % yield. No isomerization of the alkene geometry was noted for any of the substrates **15a-c**.

In contrast to the observations made by He, where a silver catalyst supported by the tridentate $^tBu_3$tpy ligand resulted in a dinuclear complex (Fig. 1), studies by the Schomaker group suggest that the active species in their chemoselective aminations are mononuclear in nature (Fig. 5). Employing excess ligand favors $Ag(phen)_2OTf$ in solution and leads to exclusive preference for C–H insertion over aziridination [15]. NMR titration experiments using 4,4′-di-*tert*-butylbipyridine ($^tBu_2$bipy) and AgOTf showed a continuous shift in the ligand proton as the metal:ligand was varied, suggesting that a dynamic equilibrium exists in solution between Ag(I), Ag:ligand complex and ligand.

The Schomaker group conducted kinetic experiments to investigate whether C–H insertion proceeds *via* a stepwise or concerted pathway. Kinetic isotope studies on a monodeuterated homoallylic carbamate yielded

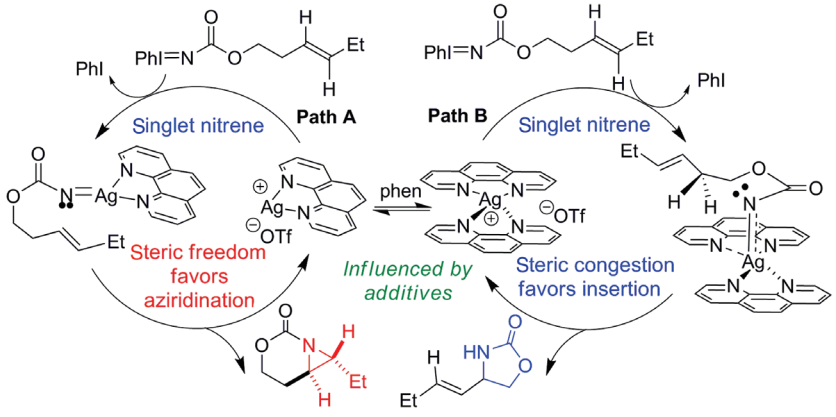


Fig. 5 Proposed mechanism for Ag-nitrene aziridination and amination controlled by the metal-ligand ratio [15].

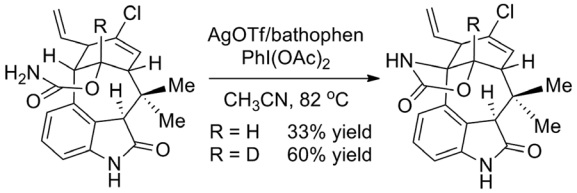


Fig. 6 Ag-catalyzed C–H insertion in the synthesis of (-)-N-methylwelwitindolinone C isonitrile [20].

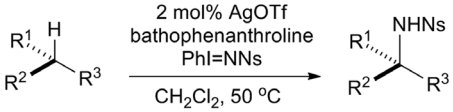
a KIE of 3.4±0.1, similar to values reported for Rh-catalyzed reactions believed to occur through concerted pathways (typically 1–3), as opposed to stepwise pathways that exhibit KIEs on the order of 6–12 [19]. Additionally, a cyclopropyl-containing substrate did not open during amination, arguing against the intermediacy of radical species. It was also noted that alkenes do not isomerize during amination and that stereochemistry is retained when insertion occurs at a chiral center. These results are all consistent with a concerted amination pathway, suggesting a singlet metal nitrene is the active species (Fig. 5). In this proposed mechanism, the reaction pathway is determined by the steric influence of the ligand. Monoligated complexes yield the kinetic aziridine products, while the bulky diligated complex cannot accommodate proper alignment of the site of unsaturation with the nitrene, thus C–H insertion is the more favorable reaction pathway.

In an example of the synthetic utility of silver-catalyzed amination using a variation of the silver(I) bathophenanthroline system, Garg and co-workers utilized a late-stage amination in their synthesis of (-)-N-methylwelwitindolinone C isonitrile and several of its analogues (Fig. 6) [20]. Subsequent cleavage of the carbamate motif allowed for the later facile installation of isocyanate and isothiocyanate moieties characteristic of the final synthetic products.

Catalytic intermolecular aminations with silver(I) complexes

Another significant advance in silver-catalyzed amination was the development of an intermolecular C–H insertion by the He group [21]. Despite the previous success of dinuclear silver(I) complexes supported by $^{t}Bu_3$tpy for intramolecular aziridinations and C–H insertions at elevated temperatures, this catalyst did not perform well in intermolecular reactions. He hypothesized that less electron-donating ligands would increase the electrophilicity of the putative nitrene intermediate and provides increased reactivity. Indeed, a catalyst consisting of 4,7-diphenyl-1,10-phenanthroline (bathophen) and AgOTf facilitated the intermolecular insertion of PhI=NNs into sp^3 C–H bonds, including benzylic and secondary C–H bonds, with activity comparable to known Ru and Rh nitrene transfer catalysts (Table 8) [4–6]. The basis of this reactivity was probed by determining the solid state crystal structure of the silver catalyst. A dinuclear interaction similar to that of a previously reported silver catalyst (Fig. 1) was observed and proposed to be crucial for good reactivity. However, recent studies by Schomaker and co-workers suggest that the coordination state geometries in solution may be different from those observed in the solid state and X-ray crystallography cannot be taken as definitive proof of the actual catalyst structure in solution [15]. The silver-pyrazolylborate catalyst systems developed by Perez and coworkers (*vide supra*) were also applied to intermolecular insertions of PhI=NTs into simple alkanes [22]. Ligands containing methyl, bromo, and mesityl substituents on the pyrazolylborate ring were investigated and a silver complex containing the $Tp^{*,Br}$ ligand (Fig. 2) proved to be the most effective for nitrene insertion into simple hydrocarbons (Table 9). Tertiary C–H bonds were preferentially transformed over secondary C–H bonds (entries 1 and 3), while primary C–H bonds showed minimal reactivity. The addition of two equivalents of BHT to the reaction resulted in a significant decrease in the yield, supporting the existence of a radical pathway. A radical trapping experiment using carbon tetrachloride and cyclohexane as the substrate led to the formation of chlorocyclohexane as a minor side product, indicating that a carbon radical with a lifetime sufficient to abstract a chlorine atom from the solvent was formed. A stepwise nitrene insertion mechanism was proposed for these silver-catalyzed C–H insertions (Fig. 7). Reaction of the Ag(I)

Table 8 Intermolecular aminations of secondary and tertiary alkyl C–H bonds [21].



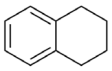
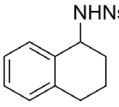
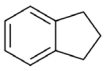
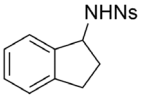
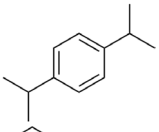
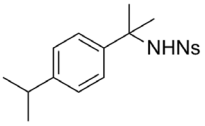
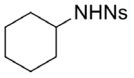
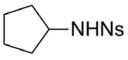
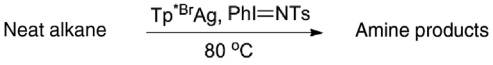
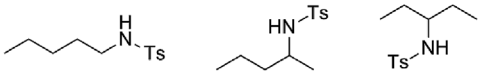
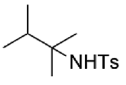
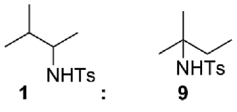
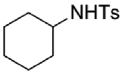
Entry	Substrate	Product	% Yield
1			70
2			68
3			57
4			40
5			35

Table 9 Intermolecular aminations employing $Tp^{*,Br}Ag$ as a catalyst. Reactions were conducted in neat alkane with PhI=NTs as the limiting reagent [22].



Entry	Substrate	Major products	% Total yield
1		 **1 : 6 : 3**	85
2			75
3		 **1 : 9**	80
4			90

catalyst with the nitrene precursor PhI=NTs leads to an intermediate metal-supported nitrene. This complex abstracts a hydrogen atom from the alkyl C–H bond of the substrate. Attack of the carbon radical on the protonated Ag-nitrene complex yields the organic amine and regenerates the silver(I) catalyst.

Thus far, intermolecular silver-catalyzed aminations have relied on the use of pre-formed iodinanes, such as PhI=NNs or PhI=NTs. Unfortunately, these compounds are not stable and are inconvenient to handle, as they must be prepared fresh immediately prior to use. The Schomaker group has explored a variety of more convenient nitrene precursors for silver-catalyzed intermolecular amination and found that 4-nitrobenzenesulfonamide, 2,2,2-trichloroethoxysulfonamide and 2,2,2-trichloroethoxycarbamate can all be employed

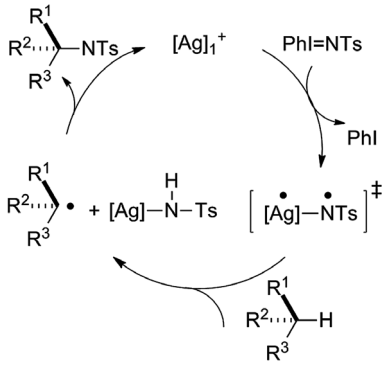
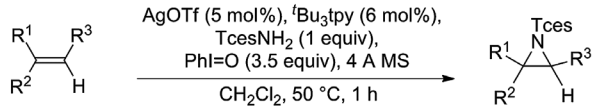
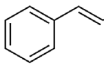
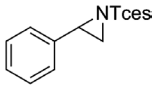
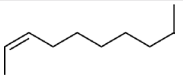
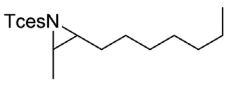
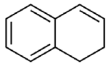
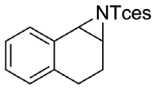
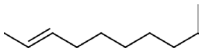
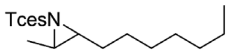
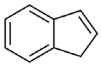
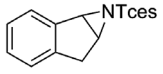
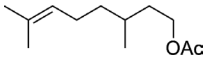
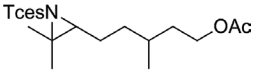


Fig. 7 Proposed mechanism for inter-molecular Ag-catalyzed amination [22].

Table 10 Intermolecular silver-catalyzed aziridination.



Entry	Substrate	Product	% Yield	Entry	Substrate	Product	% Yield
1			92	4			60
2			96	5			46
3			55	6			63

as nitrene precursors using PhIO as the oxidant [23]. For example, using 2,2,2-trichloroethoxysulfonamide (Tces) as a nitrene precursor in the presence of PhIO gave good yields in the intermolecular aziridination of 1,2-disubstituted and trisubstituted alkenes (Table 10). Styrenyl alkenes were particularly reactive (entries 1–3), although particularly strained products (entry 3) were somewhat unstable under the reaction conditions. Both *cis* and *trans* disubstituted alkenes also underwent aziridination with no observable isomerization (entries 4–6).

Conclusion

Silver-catalyzed nitrene transfer reactions represent a powerful approach towards the formation of new carbon-nitrogen bonds. The addition of silver-supported nitrenes to C=C and C–H bonds is a relatively recent development among transition metal-catalyzed aminations, but offers several advantages over more traditional catalysts, such as Cu, Fe and Rh. In contrast to Cu and Fe, silver-catalyzed aminations often occur through pathways that do not result in significant erosion of stereochemistry. Ag is also significantly less expensive and more readily available than Rh, therefore offering a more economical alternative to costly large-scale chemical processes. However, the most unique feature of Ag catalysis compared to other known transition metals for amination is the tunability for either aziridination or C–H insertion that can be invoked

by simple changes in the Ag:ligand ratio. Future research is directed towards the development of more electrophilic silver catalysts that will increase the scope of intermolecular amination, leading to reactions that are both highly chemoselective and tunable. These studies will help to better define the potential of these transformations in the synthesis of complex natural products and useful analogues containing nitrogen moieties, and may one day pave the way for the extension of Ag-catalyzed transformations to achieve selective intermolecular C–O, C–C and C–X functionalizations.

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