

Chemo-, Regio-, and Stereoselective Silver-Catalyzed Aziridination of Dienes: Scope, Mechanistic Studies, and Ring-Opening Reactions

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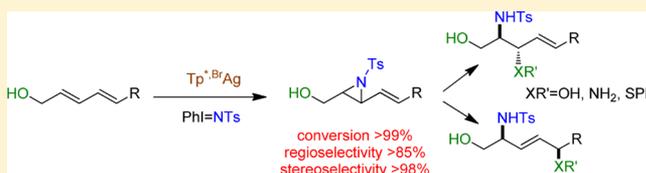
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Supporting Information

ABSTRACT: Silver complexes bearing trispyrazolylborate ligands (Tp^x) catalyze the aziridination of 2,4-diene-1-ols in a chemo-, regio-, and stereoselective manner to give vinylaziridines in high yields by means of the metal-mediated transfer of NTs (Ts = *p*-toluenesulfonyl) units from $\text{PhI}=\text{NTs}$. The preferential aziridination occurs at the double bond neighboring to the hydroxyl end in ca. 9:1 ratios that assessed a very high degree of regioselectivity. The reaction with the silver-based catalysts proceeds in a stereospecific manner, i.e., the initial configuration of the C=C bond is maintained in the aziridine product (*cis* or *trans*). The degree of regioselectivity was explained with the aid of DFT studies, where the directing effect of the OH group of 2,4-diene-1-ols plays a key role. Effective strategies for ring-opening of the new aziridines, deprotection of the Ts group, and subsequent formation of β -amino alcohols have also been developed.

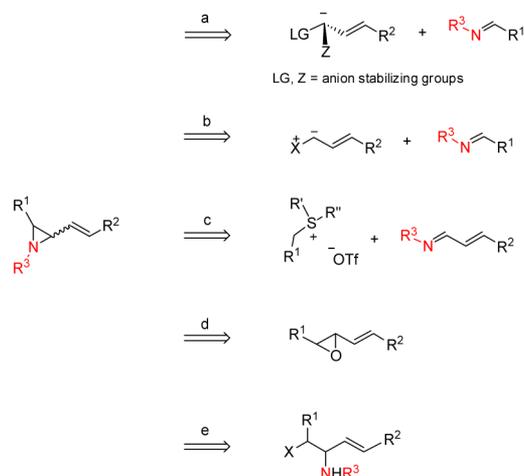


INTRODUCTION

Vinylaziridines are versatile and powerful three-membered heterocyclic intermediates that allow a direct access to biologically relevant structural moieties due to their high reactivity and ability to act as carbon electrophiles.¹ With the appropriate selection of substituents, vinylaziridines can be opened regio- and stereoselectively by different nucleophiles to further afford functionalized allyl- and homoallyl-amines.² They are also known to provide a wide spectrum of heterocycles, such as β -lactams,³ pyrrolidines,⁴ tetrahydropyridines,⁵ azepines,^{6a} cyclic ureas,^{6b} oxazolidinones,^{7a} and pyrrolo- and indolo-piperazinones^{7b,c} through opening/cyclization tandem processes.

Not surprisingly, the above applications of vinylaziridines have triggered the development of a number of synthetic routes for their preparation. Most of them are based on stoichiometric procedures through nucleophilic intramolecular substitutions. Scheme 1 shows some of those protocols, the aza Darzens-type reaction being (Scheme 1a), for instance, a well-known method for the preparation of aziridines with an array of functional groups, including vinyl substituents.⁸ The reaction between an allylic ylide and imines or sulfinimines⁹ (Scheme 1b) has also been described as a route to vinylaziridines. These two methods have usually led to thermodynamically stable *cis*-vinylaziridines.¹⁰ The reaction of benzylium salts with imines (the so-called aza Corey–Chaykovsky reaction) constituted an alternative route for the synthesis of chiral *cis*-vinylaziridines (Scheme 1c).¹¹

Scheme 1. Vinylaziridines Reported Synthetic Methods



Trans-vinylaziridines have been prepared in a stereoselective manner, with the latter route driving the reaction under steric and kinetic control.^{9j} Vinylepoxides have served as precursors to the aziridine product by means of ring-opening/-closing reactions

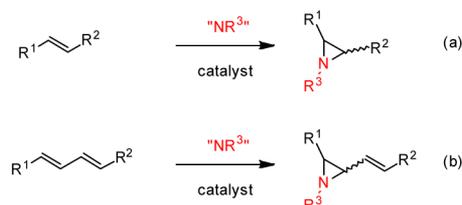
Received: December 10, 2013

Published: March 12, 2014

with azides¹² or ammonia¹³ (Scheme 1d). Ring-closing of 1,2-amino halides (Scheme 1e)¹⁴ or conjugate addition processes complete the array of stoichiometric methods toward vinylaziridines.¹⁵

The metal-catalyzed nitrene transfer reaction to olefin constitutes a well-known strategy for the synthesis of aziridines (Scheme 2a).¹⁶ However, in spite of the large number of

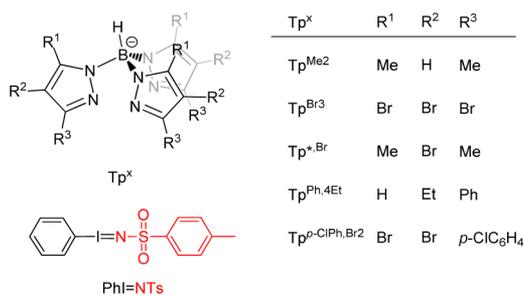
Scheme 2. Aziridination of Olefins or Dienes by Metal-Catalyzed Nitrene Transfer Reactions



catalytic systems described for such purpose, the use of this methodology with dienes as substrates to yield vinylaziridines (Scheme 2b) is yet scarce, and regioselectivity remains a challenge. Also, several copper-, manganese-, and ruthenium-based catalysts¹⁷ were reported for this reaction, where two general features being observed: mixtures of isomers (derived from aziridination of one or the other double bond) were obtained with nonsymmetric dienes ($R^1 \neq R^2$), and the *cis/trans* ratios (in each isomer) were low, as the result of the poor selectivity induced by the metal center.

With the aim of developing a metal-catalyzed route to vinylaziridines via nitrene transfer methodology, we have studied the catalytic activity of copper and silver complexes bearing trispyrazolylborate ligands (Tp^x , Scheme 3) in the

Scheme 3. Trispyrazolylborate Ligands and the Nitrene Precursor Employed in This Work



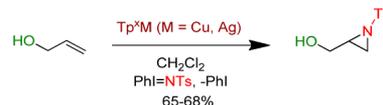
reaction of dienes and $PhI=NTs$ (Scheme 3) as the nitrene precursor, taking advantage of our previous studies related to olefin aziridination.¹⁸ In this contribution, we describe the catalytic properties of a silver-based catalyst for the regio- and stereoselective aziridination of dienes, particularly those bearing terminal OH groups,¹⁹ with a broad scope. Experimental data and DFT studies have provided a mechanistic explanation for this highly selective transformation. In addition, to prove the validity of this methodology from a synthetic point of view, selective aziridine ring-opening with N-, O-, and S-nucleophiles has provided an easy route to allylic and homoallylic amines.

RESULTS AND DISCUSSION

Catalyst Screening. We aimed at developing a catalytic system for the aziridination of dienes bearing OH groups at the

allylic position.^{18b} This target was established on the basis of the importance of β -amino alcohol moieties in biologically active compounds. However, the tolerance of the catalytic system to such hydroxyl functionality was unknown, and therefore we first examined allylic alcohol as a simple substrate to evaluate this variable. With $Tp^{Br_3}Cu(NCMe)$ and $Tp^{*Br}Ag$ as representative catalysts, allylic alcohol was converted into the corresponding aziridine with 68% and 65% isolated yields (Scheme 4), respectively, based on initial $PhI=NTs$ (the

Scheme 4. Aziridination of Allyl Alcohol

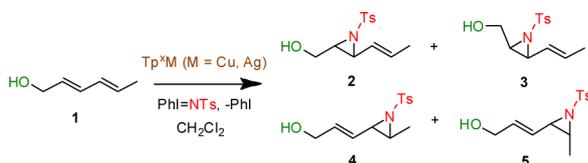


remaining of the initial nitrene precursor can be decomposed into $TsNH_2$). When O-protected derivatives (methyl, benzyl and silyl ether, acetyl, or carbamate) were employed, the yields decreased significantly.

After the above experiments, we have carried out a catalyst screening with several copper- and silver-complexes bearing the ligands shown in Scheme 3, and (2*E*,4*E*)-hexa-2,4-dien-1-ol (**1**) as the substrate. A set of four (2–5) different aziridines can be expected from this dienol, depending on the functionalized double bond and the geometry of the substituents in the aziridine. Regioselectivity is therefore provided by 2+3:4+5 ratio, whereas stereoselectivity corresponds to 2:3 and 4:5 in each case. Under the reaction conditions (1:20:30 ratio of catalyst:PhINTs:1), high to quantitative yields were observed (Table 1), even with the catalyst loadings as low as 0.5% (entries 9 and 11) or using stoichiometric mixtures of PhINTs and the dienol (entry 11). In all cases a ca. 90:10 regioselectivity toward the aziridines derived from the functionalization of the double bond neighboring to the hydroxyl end was found, and no diaziridination products were observed in all cases. The OH group was not affected during the catalytic reaction. The main distinction between the copper- and silver-based catalyst is observed for the stereoselection, where a certain degree of inversion of the initial *E*-configuration of the C=C bond leading to the final *E:Z* aziridine mixtures within the interval 1:1 to 2:1 was obtained for the copper-based systems, while the silver-based catalysts give rise to complete stereoretention (within experimental error). Therefore, the first catalyst screening has shown that (i) both Tp^xCu and Tp^xAg complexes catalyze the aziridination of the probe dienol in an effective manner with no effect on the hydroxyl group; (ii) the reaction takes place preferentially in the double bond neighboring to the OH group; and (iii) full stereoretention is only ensured with the silver catalysts.

General Aziridination Reaction of 2,4-Dien-1-ols. To verify the generality of this procedure, a series of 2,4-diene-1-ol derivatives **6–16** (Scheme 5) were employed as the substrate, with a certain variability of structural features such as configuration 2*E*,4*E* with several different substituents at the ω position (**6–9**) or with substituents at the double bonds (**10–12**) as well as configurations 2*Z*,4*E* (**13**), 2*Z*,4*Z* (**14**), and 2*E*,4*Z* (**15**, **16**). The previous behavior observed with (2*E*,4*E*)-hexa-2,4-dien-1-ol has been extended to this series of dienols. Overall, regioselection toward the aziridines derived from the addition of the nitrene moiety to the double bond vicinal to the OH group ranged from 72:28 to 93:7, even for C2- or

Table 1. Aziridination of (2*E*,4*E*)-hexa-2,4-dien-1-ol (1) with Tp^*M (M = Cu, Ag) Catalysts Using $\text{PhI}=\text{NTs}$ As Nitrene Source^a



entry	catalyst	yield (%) ^b	regioselect. ^b (2+3):(4+5)	ratio 2:3 ^b
1	$\text{Tp}^{\text{Ph,4Et}}\text{Cu}$	60	83:17	60:40
2	$\text{Tp}^{\text{p-ClPh,Br2}}\text{Cu}$	80	81:19	51:49
3	$\text{Tp}^{\text{Me2}}\text{Cu}$	67	82:18	66:34
4	$\text{Tp}^{\text{Br3}}\text{Cu}$	>99	86:14	66:34
5	$\text{Tp}^{\text{Me2}}\text{Ag}$	>95	90:10	>98:<2 ^c
6	$\text{Tp}^{*,\text{Br}}\text{Ag}$	>99	90:10	>98:<2 ^c
7	$\text{Tp}^{*,\text{Br}}\text{Ag}^d$	>99	90:10	>98:<2 ^c
8	$\text{Tp}^{*,\text{Br}}\text{Ag}^d$	>99	88:12	>98:<2 ^c
9	$\text{Tp}^{*,\text{Br}}\text{Ag}^d$	>99	89:11	>98:<2 ^c
10	$\text{Tp}^{*,\text{Br}}\text{Ag}^d$	80	89:11	>98:<2 ^c
11	$\text{Tp}^{*,\text{Br}}\text{Ag}^{d,e}$	>99	88:12	>98:<2 ^c

^a[catalyst]:[PhINTs]:[1] = 1:20:30, referred to 0.0125 mmol of catalyst, 5% mol catalyst loading. Reaction time 8 h, rt. TsNH₂ accounted for 100% initial PhINTs not converted into aziridines. ^bDetermined by ¹H NMR. ^c*cis* isomer was not detected by ¹H NMR. ^dCatalyst loading 7.5%, 1.25%, 0.5%, 0.1%, and 0.5%, respectively, for entries 7–11. ^e[PhINTs]:[1] = 1:1.

C3-substituted substrates (Table 2, entries 9 and 3). The exception was found with trisubstitution at the distal double bond (additional substituent at C4 or C5, substrates 11 and 12), and in spite of the complete consumption of the starting material, an unextractable mixture of compounds was obtained. We have observed that when the dienol is less reactive, $\text{PhI}=\text{NTs}$ decomposition into TsNH₂ takes place, and this amine provides a basic medium in which aziridine decomposition takes place. Actually, the more reactive dienols 6–10 and 13 can be converted into aziridines using a 1:1 mixture with $\text{PhI}=\text{NTs}$, whereas for the less reactive 14–16 a 1:1.5 ratio of $\text{PhI}=\text{NTs}$ and dienol was employed.

The retention of the stereochemistry was also observed along the series of dienes studied that were converted into the corresponding aziridines maintaining the initial geometry of the double bond in the final aziridine (i.e., *cis* or *trans* double bonds were stereospecifically transformed into *cis* or *trans* aziridines, respectively).

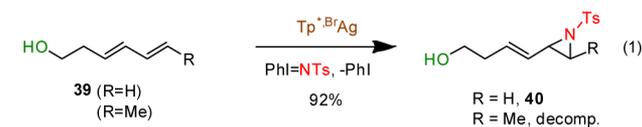
The Role of the Hydroxyl Group and Diene Conjugation. In order to check the effect of the structure of the starting dienol, in which the hydroxyl group occupies the

Table 2. Aziridination of Dienols 6–16 using $\text{Tp}^{*,\text{Br}}\text{Ag}$ as the Catalyst^a

entry	dienols	yield (%) ^b	PhINTs:dienol	regioselect. ^b	<i>trans</i> : <i>cis</i> ratio ^{b,c}
1	$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$ (6)	>99	1:1	17/24, 88:12	>98:<2
2	$\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$, $\text{R}^3 = \text{Et}$ (7)	>99	1:1	18/25, 85:15	>98:<2
3	$\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$, $\text{R}^3 = \text{Ph}$ (8)	>99	1:1	19/26, 93:7	>98:<2
4	$\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$, $\text{R}^3 = \text{C}_{13}\text{H}_{27}$ (9)	>99	1:1	20/27, 86:14	>98:<2
5	$\text{R}^1 = \text{R}^3 = \text{Me}$, $\text{R}^2 = \text{R}^4 = \text{H}$ (10)	>99	1:1	21/28, 86:14	>98:<2
6	$\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$, $\text{R}^3 = \text{C}_{13}\text{H}_{27}$ (13)	>99	1:1	31/33, 90:10	<2:>98
7	$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$, $\text{R}^4 = \text{Me}$ (14)	>99	1:1.5	32/34, 87:13	<2:>98
8	$\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{R}^4 = \text{Me}$ (15)	>99	1:1.5	35/37, 86:14	>98:<2
9	$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$, $\text{R}^4 = \text{Me}$ (16)	>99	1:1.5	36/38, 72:28	>98:<2

^a0.0125 mmol of catalyst, 5% with respect to PhINTs in all cases, 8 h, rt. ^bDetermined by ¹H NMR, as initial PhINTs converted into aziridines. ^cThe minor isomer was not detected by ¹H NMR.

allylic position with respect to one of the C=C bonds, we have performed further experiments to assess the role of each particular element. First, the homoallyldiene 39 (R = H) was investigated as the substrate (eq 1) in the reaction with PhINTs



using $\text{Tp}^{*,\text{Br}}\text{Ag}$ as the catalyst. Compound 40 was obtained with a high yield (92%) and high regioselectivity (>98:<2), as the result of the preferential aziridination at the distal double bond. It is clear that the loss of the allylic relative position of the OH with respect to the C=C double bond dramatically affects the reaction outcome. The methyl homologue did not provide similar results, since major decomposition was observed, probably due to the aforementioned effect of a lower reactivity of this substrate and formation of TsNH₂ that triggers aziridine decomposition.

To evaluate such role of the OH group, we carried out the aziridination of O-protected (2*E*,4*E*)-hexa-2,4-dien-1-ol with both copper and silver catalysts (Table 3). As shown in Table 3, yields and regioselectivities decreased with both metals compared with the parent dienol. The observed loss of regioselectivity

Scheme 5. Dienols 6–16 Tested in Nitrene Transfer Reactions with $\text{Tp}^{*,\text{Br}}\text{Ag}$ as the Catalyst

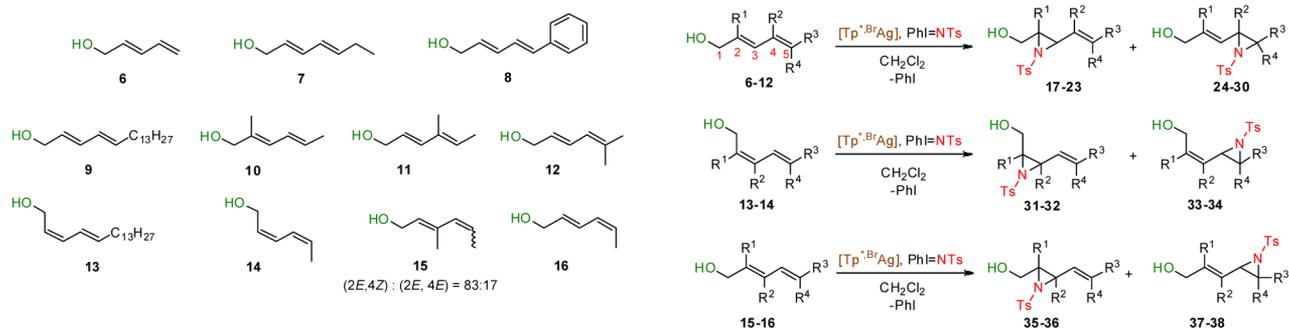


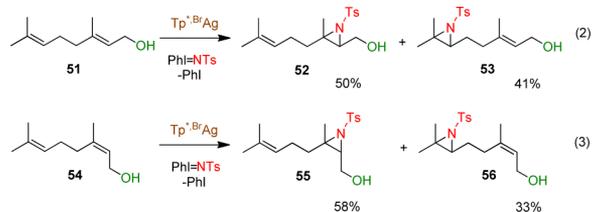
Table 3. Conversions and Selectivities of the Reaction of 1-O-Protected-(2*E*,4*E*)-hexa-2,4-dien-1-ols 41 and 42 with Tp^*M Catalysts using $\text{PhI}=\text{NTs}$ as Nitrene Source^a

entry	catalyst	diene	yield (%) ^b	regioselect. ^b	trans:cis ratio ^b
1	$\text{Tp}^{\text{Br}^3}\text{Cu}$	41	77	78:22 ^c	62:38 ^f
2	$\text{Tp}^{\text{Br}^3}\text{Ag}$	41	80	53:47 ^c	>98:<2 ^{f,g}
3	$\text{Tp}^{\text{Br}^3}\text{Cu}$	42a	80	65:35 ^d	58:42 ^g
4	$\text{Tp}^{\text{Br}^3}\text{Ag}$	42a	66	60:40 ^d	>98:<2 ^{h,g}
5	$\text{Tp}^{\text{Br}^3}\text{Cu}$	42b	67	58:42 ^e	58:42
6	$\text{Tp}^{\text{Br}^3}\text{Ag}$	42b	68	54:46 ^e	>98:<2 ^{i,g}

^a[cat]:[PhINTs]:[diene] = 1:20:30, referred to 0.0125 mmol of catalyst, 5% mol catalyst loading. Reaction time is 8 h in all cases, rt. TsNH₂ accounted for 100% initial PhINTs not converted into aziridines. ^bDetermined by ¹H NMR of the major regioisomer. ^cAs (43+45):(47+49). ^dAs (44a+46a):(48a+50a). ^eAs (44b+46b):(48b+50b). ^fAs 43:45. ^gcis isomer was not detected by ¹H NMR. ^hAs 48a:50a. ⁱAs 48b:50b.

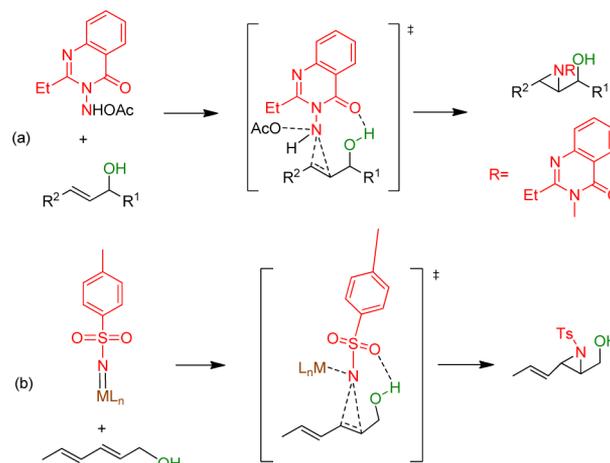
seems to be independent of the nature of the protecting group since Ac, Bn, or even the less sterically demanding Me substituents provided the same negative effect in the reaction outcome. However, the silver catalyst induced the same excellent stereoselectivity with only *trans* aziridines being observed. Therefore, the presence of the hydroxyl functionality at the allylic position seems to be crucial in the aziridination reaction. Atkinson and co-workers have proposed²⁰ that the stoichiometric aziridination of allyl alcohols with (3-(acetoxymino)-2-ethylquinazolin-4-(3H)-one takes place in a preferential manner due to the formation of a hydrogen bond between the OH group and -C=O unit that directs the C=C bond in the vicinity of the nitrogen atom (Scheme 6a). On the basis of this, it could be possible that in the case of our copper- or silver-catalyzed aziridination, the OH bond may support for the nitrene transfer toward the C=C double bond proximal to the hydroxyl group (Scheme 6b). This proposal will be discussed in the computational part of this work.

The effect of conjugation of both double bonds was evaluated with geraniol (51) and nerol (54) as the starting dienes (eqs 2 and 3) that only differ in the stereochemistry of



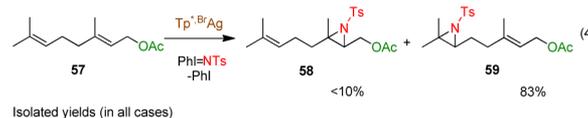
the C=C bond (*E* or *Z*, respectively) close to the hydroxyl functionality. Regioselectivity decreased in both cases when compared with the values obtained with the conjugated dienes. Since steric and/or electronic factors are similar to the dienes

Scheme 6. Directing Effect of the OH Group in the Aziridination Reaction^a



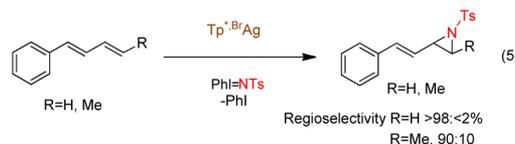
^a(a) The stoichiometric reaction by Atkinson and co-workers. (b) A plausible related explanation for the metal-catalyzed aziridination.

shown in Scheme 5, such behavior must be related to the loss of conjugation. Moreover, the use of the O-protected geranyl-derivative 57 (eq 4) led to the formation of aziridine 59 as the



major product, which is in good agreement with the above results that evidence the allylic OH groups significantly enhance the aziridination of the proximal C=C bond.

An additional experiment has been carried out in which conjugated dienes lacking of hydroxyl groups were employed. As shown in eq 5, when R = H only aziridination at terminal



double bond was observed, in line with the reactivity observed for the related dienol 8. In the former, the aziridination takes place in the double bond remote to the aryl ring. When R = Me, the aziridination of double bond farthest of phenyl group takes also place. The phenyl substituent of the dienic system provides additional stabilization of the radical intermediate generated during the reaction.

Overall, the collected data in this section indicated that the highly selective aziridination of dienols in Table 2 seems to be favored by the presence of the -OH group in the allylic position, in a clear example of substrate-directed aziridination.²¹ In the case of the silver-based catalyst, the aziridination takes place with very high regioselectivity and complete stereoselection. In order to collect additional information to explain such behavior, we have *in silico* studied these aziridination reactions, with the results described below.

Computational Study on the Origin of Regioselectivity. We have carried out DFT calculations on the reaction between the parent molecule (2*E*,4*E*)-hexa-2,4-dien-1-ol (1) and the $\text{Tp}^{\text{Br}^3}\text{Ag}$ complex. Experimental data reported above

showed a regioselectivity of 90:10 for this system in favor of aziridination on the double bond closer to the hydroxyl substituent, and it is a representative example of the systems experimentally studied. First, we have analyzed the overall energy profile for reaction between the silver-nitrene complex and the diene. The results, summarized in Figure 1, show a

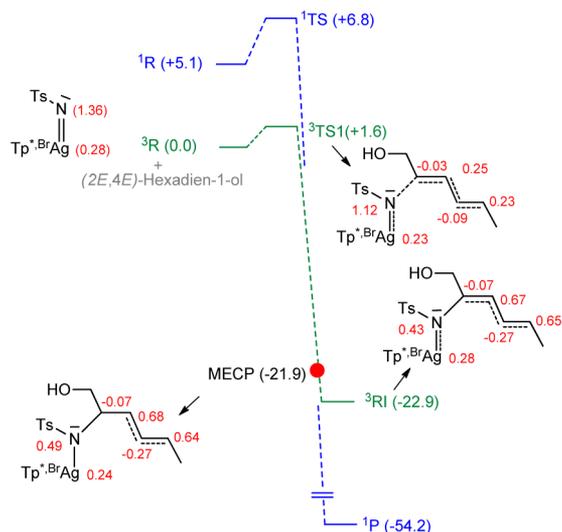


Figure 1. Calculated free energy profiles (kcal mol^{-1}) for aziridination of (2E,4E)-hexa-2,4-dien-1-ol catalyzed by $\text{Tp}^{*\text{Br}}\text{Ag}$. Spin population (atomic units) is indicated for key atoms.

similar picture to that previously reported by us on the reaction of silver-nitrene complexes with more simple olefins,²² although the more complex nature of the dienols employed in this work have added certain clues that need to be explained. It is first important to recognize the electronic complexity of the systems that was discussed at length in the previous publication.²² The reaction is formally simple as the catalyst reacts with the PhINT's nitrene source, resulting in a nitrene complex that can transfer the nitrene function to an olefin, resulting in an aziridine. The detailed picture is however more subtle, because the resting state of the nitrene complex is a triplet (see Figure 1 for spin localization), which reacts with the singlet diene to produce two singlet molecules (the product and the metal catalyst). Therefore, a spin-crossing through a minimum energy crossing point (MECP) must take place in the course of the reaction. The behavior of the silver and copper catalysts differs on the placement of this MECP in the free energy profile. In the case of silver, it is before the open ring intermediate, which results in a stereoselective process (see Figure 1). For copper, stereoselectivity is lower because the spin crossing takes place later in the free energy profile, which allows for scrambling. We will report here our results for the silver species and comment briefly on how these results could be modified in the case of copper.

For the silver catalyzed process, starting from the stable triplet metal-nitrene intermediate (^3R), the first N–C bond formation has a barrier of only 1.6 kcal mol^{-1} ($^3\text{TS1}$), while the corresponding singlet transition state is further, 5.2 kcal mol^{-1} higher in energy. Beyond ^3TS , there is a MECP between the triplet and closed-shell singlet profiles. Therefore, the singlet product ^1P (same as compound 2, Table 1) can be formed with a complete retention of the stereochemistry of the olefin, and $^3\text{TS1}$ becomes the selectivity determining transition state. This means that we can concentrate on the study of regioselectivity on this triplet transition state.

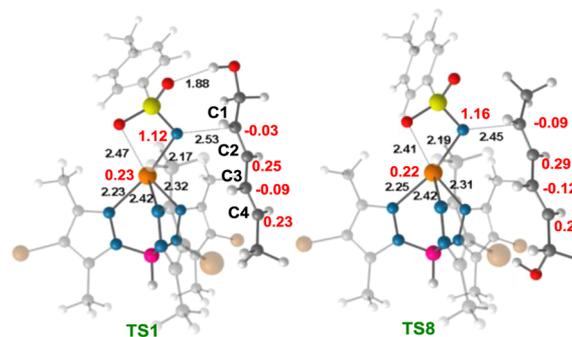


Figure 2. The two lowest energy transition states leading to aziridine products of (2E,4E)-hexa-2,4-dien-1-ol catalyzed by $\text{Tp}^{*\text{Br}}\text{Ag}$. Selected distances (Å) in black. Selected atomic spin populations in red.

The structures for the two most stable conformers of this triplet transition state are presented in Figure 2, where selected interatomic distances and atomic spin densities are included. It is clear from the overall view of the structure that the diene ligand places itself in a parallel orientation along the side of the $\text{Tp}^{*\text{Br}}\text{Ag}$ ligand. The two transition states in Figure 2 differ in the position of the terminal groups of the diene. The upper position is occupied by the hydroxyl in TS1 or by the methyl in TS8 . It is worth noting that in this triplet transition state only one N–C bond is being formed, and the second N–C bond will be formed further down in the energy profile, as the system moves to the singlet electronic state.

The translation of transition state relative energies to product populations can be made through a similar scheme to that used in enantioselectivity studies.^{23,24} First, we need to analyze different conformations of this transition state. If we assume that the probability of crossing a given transition state follows a Boltzmann distribution, their relative energies will give the ratio of the different products. In order to make a systematic conformational search, we followed two criteria: (i) identify the carbon making the first bond to nitrogen and (ii) orientation of the diene molecule with respect to the $\text{Tp}–\text{Ag}–\text{N}$ axis. There are four carbons available for the first bond to nitrogen (two per double bond), and there are two possible orientations for the diene (hydroxyl-up or methyl-up). This results in the eight isomers shown in Scheme 7 and Figure S1. We carried out transition state searches starting from each of these eight

Scheme 7. Schematic View of the Possible Isomers Considered As Starting Geometry for the Transition State of the Aziridination of (2E,4E)-Hexa-2,4-dien-1-ol catalyzed by $\text{Tp}^{*\text{Br}}\text{Ag}$

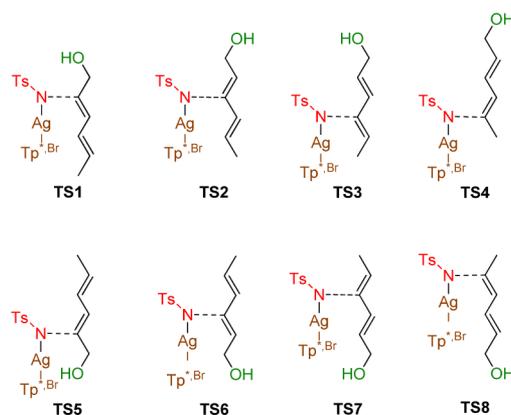


Table 4. Relative Energies of the Different Isomers for the Transition States and Their Reaction Path Ratios for Aziridination of (2*E*,4*E*)-Hexa-2,4-dien-1-ol Catalyzed by $\text{Tp}^{*\text{Br}}\text{Ag}$

label	attacked C atom	diene orient.	energy (kcal mol ⁻¹)	reaction path (%)
³ TS1	2	OH-up	1.6	80.1
³ TS2	3	OH-up	9.6	0.0
³ TS3	4	OH-up	12.8	0.0
³ TS4	5	OH-up	5.7	0.1
³ TS5	2	Me-up	4.4	0.7
³ TS6	3	Me-up	6.9	0.0
³ TS7	4	Me-up	5.0	0.3
³ TS8	5	Me-up	2.5	18.9

conformations. The results are summarized in Table 4 (see Table S1 for further details).

Transition states **TS1**, **TS2**, **TS5**, and **TS6** lead to the major product **2**, with the aziridination of the double bond closer to the OH group. The other four transition states lead to the minor product **4**, where aziridination occurs at the other double bond. The main result in Table 4 is in good agreement of the computed regioselectivity of 81:19 for product **2**, with the experimental value of 90:10 for the same product. The comparison of the energies of the eight transition states also allows the understanding of the origin of selectivity. There are three trends that can be easily identified. First, the transition states with the nitrene attacking one “terminal” carbon of the diene (carbons 2 or 5) are in general lower in energy. This happens in **TS1**, **TS4**, **TS5**, and **TS8**. This can be understood by checking the atomic spin populations in Figure 2 (and also in Figure S1). This has an electronic origin. When the nitrene attacks a terminal carbon, the spin is delocalized on the whole chain, and the barrier is lowered. When the nitrene attacks a “central” carbon (carbons 3 or 4), there is no spin delocalization into the other double bond, but only into the next carbon of the same double bond, and this results a higher barrier. The second trend is that the most stable structures, **TS1** and **TS8**, place the diene chain parallel alongside the $\text{Tp}^{*\text{Br}}$ ligand. There seems to be a favorable dispersion interaction between the diene chain and the ligand. The third and decisive factor for regioselectivity is the presence of a hydrogen bond between the terminal OH group and one of the oxygen atoms of the OTs ligand. Therefore, the hydrogen bond plays a critical role in deciding between the two most stable transition states, **TS1** and **TS8**, leading each to one regioisomer, but this becomes critical only when the electronic and dispersion effects are also playing their role.

We further confirmed the importance of the hydrogen bond by carrying an additional set of calculations on a system where this was precluded by replacing OH by OAc. The detailed results on the study of the aziridination of (2*E*,4*E*)-hexa-2,4-dien-1-yl acetate are provided in Table S2, but the key result was that the most stable transition states were still **TS1** and **TS8**. However, the energy difference between them was so small that the predicted regioselectivity ratio decreased to 53:47, in agreement with experimental results.

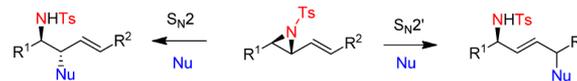
The rationale emerging from our calculations on (2*E*,4*E*)-hexa-2,4-dien-1-ol (**1**) and the $\text{Tp}^{*\text{Br}}\text{Ag}$ complex can be also applied to other experimental systems reported above. The regioselectivity of the systems with a phenyl group (see eq 5; 98% of the terminal aziridine) is associated to the same

delocalization effect that directs the nitrene attack toward the “terminal” carbons of the dien-1-ol **39**. The attack on the carbon further away from the phenyl substituent places the unpaired electron in the adjacent carbon, with a favorable delocalization toward the other double bond and the phenyl ring. If the nitrene attack takes place on the carbon closest to the phenyl ring, delocalization can only take place toward the other double bond. The key factor for the systems shown in eq 5 is thus purely electronic and is simpler than that computed above, where there is a combination of electronic and hydrogen-bond effects.

A second experimental result worth commenting is the lower selectivity observed when silver is replaced by copper in the catalyst (Table 1). We think that the origin of the difference is in the electronic differences between the copper and silver-catalyzed processes discussed in our previous computational study work with more simple olefins.²² For the copper system, the free energy profile described in Figure 1 is no longer valid, as the crossing between the triplet and singlet surfaces takes place after the triplet intermediate ³**RI**. Therefore, regioselectivity is not exclusively decided in transition state ¹**TS**, as scrambling in the triplet intermediate is still possible. This will surely reduce selectivity and make the directing effect of the OH groups less efficient in the copper case.

Ring-Opening Reactions. As mentioned in the Introduction, ring-opening reactions of vinylaziridines^{1a,2} through $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}2'$ processes constitute a tool for the synthesis of a variety of functionalized amine derivatives such as sphingosines,^{13,25} allyl amines,²⁶ (*E*)-alkene dipeptide isosteres,²⁷ or boron derivatives (Scheme 8).²⁸ Different strategies have been studied

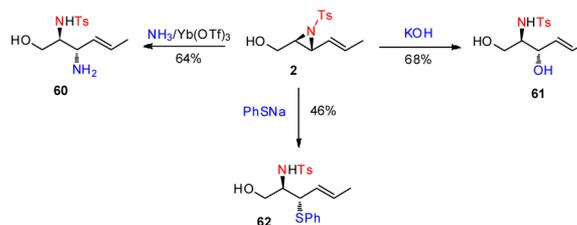
Scheme 8. Ring-Opening Reactions to Vinylaziridines



since aziridines are valuable building blocks in organic chemistry.²⁹ Both $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}2'$ processes afford a set of products that can be transformed in highly functionalized synthons by functionalization of the double bond.

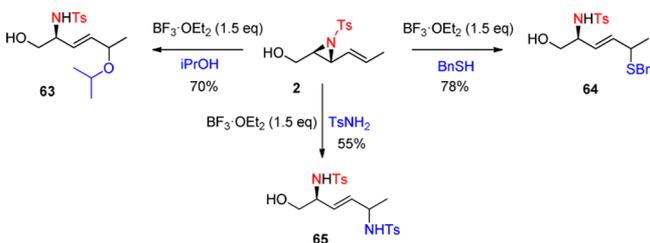
The vinylaziridine **2** was employed as a model substrate for ring-opening reactions using different S, N, and O nucleophiles. Under basic conditions (Scheme 9) such as KOH, the amino

Scheme 9. Ring-Opening of Vinylaziridine 2 by $\text{S}_{\text{N}}2$ Reactions



diol **61** was obtained in a 68% yield over two consecutive steps, namely aziridination and ring-opening. The use of NH_3 or PhSNa as nucleophiles provided the 1-hydroxy-2,3-diamino derivative **60** or the 1-hydroxy-2-amino-3-thio derivative **62** in 64% and 46% yield, respectively. Ring-opening has also been achieved under acid conditions (Scheme 10). Vinylaziridine **2** reacted with ⁱPrOH, BnSH , and TsNH_2 in the presence of

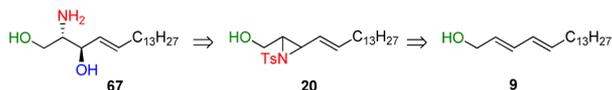
Scheme 10. Ring-Opening of Vinylaziridine **2** by S_N2' Reactions



$\text{BF}_3 \cdot \text{OEt}_2$ through a S_N2' process affording compounds **63–65** in 70%, 78%, and 55% yields, respectively, over two steps but in a one-pot procedure. We have not been able to isolate nor detect the products derived from the less abundant vinylaziridines obtained in <10% yield.

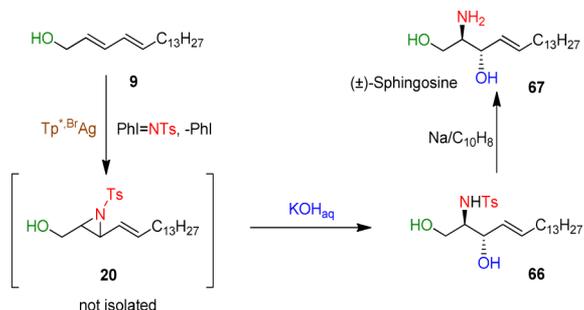
A Practical Case: Synthesis of (\pm)-Sphingosine. As a proof of the concept for the overall strategy developed in this contribution, we have applied the methodology of aziridination of 2,4-hexadien-1-ols and further ring-opening to the preparation of racemic sphingosine, the most representative member of the sphingolipid family.^{30,31} As described in our preliminary work, this aminodiol could be prepared by the selective opening of aziridine **20**, that would be obtained via aziridination of the dienol **9** (Scheme 11). The latter reaction

Scheme 11. Retrosynthetic Analysis of Sphingosine



has already been discussed (see Table 2, entry 4), providing aziridine **20** as a 86:14 mixture with aziridine **27** and complete retention of stereochemistry. Ring-opening of **20** can be carried out in a one-pot manner by treating the resulting mixture with KOH in DMSO to give the N-protected sphingosine **66** in 72% yield for the two steps. Deprotection was performed with sodium/naphthalene to give racemic sphingosine in 65% overall yield (Scheme 12). This result demonstrates that the above

Scheme 12. Synthesis of (\pm)-Sphingosine from Dienol **9**



route opens a new area in which the design of chiral catalysts for the aziridination reaction would provide the final product enantiomerically enriched.

CONCLUSIONS

The selective (mono)aziridination of 2,4-dien-1-ols have been achieved in a chemo-, regio-, and stereoselective manner by means of silver-catalyzed nitrene transfer from $\text{PhI}=\text{NTs}$.

Nearly quantitative yields (based on the nitrene source) with very high regioselection (ca. 9:1) toward the double bond vicinal to the hydroxyl group have been obtained, the latter remaining unreacted as an additional feature of this system. In addition, this process is stereospecific regarding the initial geometry of the double bond, that is maintained in the aziridine product (*Z* or *E* olefins gave *cis* or *trans* aziridines, respectively). The synthesized vinylaziridines can be selectively opened with oxygen, nitrogen, or sulfur nucleophiles through selective S_N2 or S_N2' processes to afford a variety of unsaturated amino-alcohols. Mechanistic studies, based on experimental data and DFT calculations, have shown the directing effect of the OH bond that through hydrogen bond with an oxygen atom of the tosyl group favors a given geometry that drives the reaction toward the observed outcome. The development of the chiral version of this catalytic system is currently underway in our laboratories.

EXPERIMENTAL SECTION

General. All chemicals used in this work were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-4). ^1H and ^{13}C NMR spectra were recorded on a Mercury VX 400 or Varian 400-MR spectrometer in CDCl_3 as solvent, with chemical shifts referenced to internal standards. ESI MS were run on an Agilent 1100 Series LC/MSD instrument. Melting points were determined with Reichert apparatus. Reactions were monitored by TLC carried out on 0.25 mm E. Merck silica gel 60 F_{254} glass or aluminum plates. Developed TLC plates were checked with a short-wave UV lamp (250 nm) after heating plates previously treated with ethanol/ H_2SO_4 (15:1), a basic solution of potassium permanganate and cerium molybdate. Flash column chromatography was carried out using forced flow of the indicated solvent on silica gel 60 (230–400 mesh) using a solvent polarity correlated with TLC mobility. Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. All the dienes employed as reactants were prepared according with literature methods. See Supporting Information for the complete description of their preparation, literature reference, and spectroscopic characterization.

General Procedure for Aziridination of 2,4-dien-1-ols. A Schlenk tube containing a magnetic stirring bar was charged with catalyst and the dienol. The flask was cooled in an acetone dry ice bath and flushed three times with nitrogen, and then anhydrous dichloromethane (5 mL) was added. Freshly prepared PhINTs was added in 3–4 portions over 2 h, and the mixture was stirred for an additional hour after the last addition. For the exact amounts of reactants see Supporting Information. Finally, the solvent was removed under vacuum, and the resulting crude was characterized by NMR without purification given the low stability of the vinylaziridines toward silica gel or neutral alumina. See the Supporting Information for full spectroscopic description of the vinylaziridines synthesized in this work.

General Aziridination of Dienols **51, **54**, and **57**.** Tp^*BrAg (3.2 mg, 0.05 mmol) was dissolved in dichloromethane (10 mL), along with the corresponding terpene (1 mmol). PhINTs (407 mg, 1.1 mmol) was added in four portions over 4 h. The reaction mixture was stirred for additional 3 h at room temperature before volatiles were removed under vacuum. The residue was purified by flash chromatography using hexanes:ethyl acetate (7:3 to 1:1) to afford the desired products. See Supporting Information for details and characterization.

General Procedure for Ring-Opening Aziridines with KOH, Ammonia, or Sodium Thiophenolate. *KOH.* Vinylaziridine **2** (0.25 mmol) was dissolved in DMSO (0.75 mL), and an aqueous solution of KOH (10%, 0.75 mL) was added. The solution was stirred for 1 h at 40 °C. The crude was neutralized with a saturated NH_4Cl aqueous solution. The aqueous solution was extracted with diethyl

ether (3 × 25 mL), and the combined organic layers were washed with brine and dried over anhydrous MgSO₄. The solvent was removed under vacuum and purified by radial chromatography using 4:6 hexanes:ethyl acetate to afford 56 mg of **61** as a white solid (68%). See Supporting Information for spectroscopic and analytical characterization.

NH₃. Vinylaziridine **2** (5 mmol) and ytterbium triflate were dissolved into an ammonia solution (8 mL, 30%), and the mixture was stirred at 95 °C for 8 h. The crude was extracted with three portions of ethyl acetate. The combined organic layers were washed with a HCl aqueous solution (5%) and brine and dried over magnesium sulfate. The crude was purified by radial chromatography using 4:6 hexanes:ethyl acetate to afford 188 mg of **60** as a colorless oil (64%). See Supporting Information for spectroscopic and analytical characterization.

Sodium phenolate. Aziridine **2** (0.25 mmol) was dissolved in dry THF (4 mL), and sodium thiophenolate (0.28 mmol, 36 mg) was added. The mixture was stirred for 12 h at room temperature. Water was then added to the mixture, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a NaHCO₃ aqueous solution and later with water and brine. The organic layers were dried over anhydrous MgSO₄, and the solvent was removed under vacuum. The crude was purified by radial chromatography using 7:3 to 6:4 hexanes:ethyl acetate to afford 74 mg of compound **62** as a yellow solid (46%). See Supporting Information for spectroscopic and analytical characterization.

General Procedure for Ring-Opening of Aziridines with BF₃·OEt₂. The nucleophile (10 equiv, 2.5 mmol) was added to a solution of the vinylaziridine (0.25 mmol) in dichloromethane (4–6 mL). The stirred mixture was cooled at 0 °C, and the acid (10 mol %, 0.025 mmol) was added over 30 min. Smooth warming to room temperature and additional stirring for 3h led to a solution that was diluted with dichloromethane and washed with water. The organic layer was dried over MgSO₄ before the solvent was removed under vacuum. The residue was purified by flash or radial chromatography to give the corresponding products. See Supporting Information for details and characterization.

Computational Details. Gas-phase structure optimizations were performed using DFT with the M06 functional³² as implemented in Gaussian09 program.³³ Silver was treated with the SDD basis set,³⁴ and the 6-31G(d) basis sets were used for the remaining atoms.³⁵ Final potential energies were obtained by performing single-point calculations on the optimized structures, where silver was still described with SDD, and the remaining atoms were treated with the 6-311++G(d,p) basis sets. Free energy corrections at 298.15 K and 10⁵ Pa pressure were applied, including zero point energy corrections. Vibrational frequency calculations were performed to understand the nature of the stationary points (i.e., minima or transition states). Connectivity of the transition states was confirmed by relaxing the transition-state structure to both reactant and the product. MECP was calculated by using the MECP program of Harvey and co-workers.³⁶ Energy differences between transition states were translated to product populations by assuming a Boltzmann distribution of transition states at 298.15 K.

■ ASSOCIATED CONTENT

● Supporting Information

Detailed experimental catalytic and mechanistic procedures, including substrates preparation and characterization of products. Computational data including transition states geometries and Cartesian coordinates and energies of all stationary points reported in the text. This information is available free of charge via the Internet at <http://pubs.acs.org>

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Notes

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■ ACKNOWLEDGMENTS

We thank MINECO (Grants CTQ2011-28942-CO2-01, CTQ2011-27033, CTQ2011-22872-BQU and Consolider Ingenio 2010 CSD2006-0003), Fondos FEDER, Junta de Andalucía (Proyecto P10-FQM-06292), and the ICIQ Foundation. J.L. thanks MICINN and AB Universidad de Huelva for fellowships. We also thank Miriam Díaz de los Bernardos and Sebastian Soriano for additional experimental work. This paper is dedicated to the memory of Prof. Gregory L. Hillhouse (1955-2014).

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