Synthetic Methods

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Efficient Silver-Catalyzed Regio- and Stereospecific Aziridination of Dienes**

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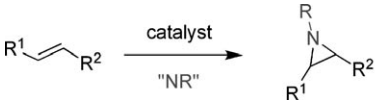
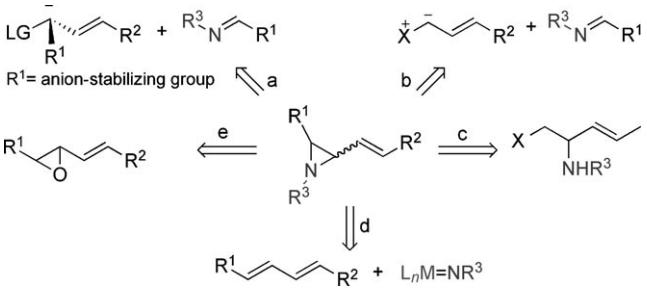
The synthesis of aziridine derivatives through metal-mediated nitrene addition reactions to olefins [Eq. (1)] has been



(1)

extensively developed in the last decades; quantitative conversions as well as complete enantioselection have been already described.[1,2] However, in spite of the large number of reports related to the alkene aziridination reaction by this method and the synthetic interest of vinylaziridines,[3] only few have dealt with conjugated dienes as the substrate. Copper-,[4] manganese-, and ruthenium-based[5] catalysts have provided good yields of vinylaziridines formed by the exclusive aziridination of one C=C bond of the diene, although with the following limitations: 1) only symmetric dienes were employed and 2) selectivity, intended as *cis*/*trans* (or *trans*/*cis*) ratio, was low. These two drawbacks strongly prevent the synthetic application of this method.

In fact, vinylaziridines are commonly synthesized by stoichiometric procedures based on nucleophilic intramolecular substitution. Thus, the Darzens-type reaction (Scheme 1, path a) is one of the oldest and most flexible methods for preparation of functional aziridine derivatives including vinylaziridines.[6] The reaction between an allylic ylide and



Scheme 1. Strategies for the synthesis of vinylaziridines. LG = leaving group.

imines also provides[7] a facile process as it involves the regioselective construction of vinylaziridine (path b). These two methods have usually led to the thermodynamically stable *cis* aziridines.[8] *trans* Aziridines were obtained with high stereoselectivity by the ylide route driving the reaction under kinetic control conditions.[9] Vinylaziridines were also prepared from vinyl epoxides by ring opening with azides (path e), from 1,2-amino halides (path c),[10] and by conjugate addition.[11] The aforementioned nitrene addition to dienes (path d)[4,5] have been described, but they can be yet considered far from successful in terms of regio- and stereoselectivity.

On the basis of the above, we planned to develop a catalytic system capable of inducing the formation of vinylaziridines to achieve the following goals: 1) use of nonsymmetric dienes, 2) tolerance to other functional groups, 3) control of the regioselectivity (given an unsymmetric diene), and 4) control of the stereoselectivity (to obtain either *cis* or *trans* vinylaziridines). We have previously reported that complexes of general formula [Tp^{x}Cu(NCMe)] (Tp^x = homoscorpionate ligand,[12] see Scheme 2 for the structure) effectively catalyze the aziridination of simple alkenes through the nitrene-transfer reaction,[13] using PhINTs as the nitrene source. To drive our work to the above goals, and because the β-amino alcohol moiety is found in a wide variety of biologically active compounds,[14] we chose *trans*,*trans*-2,4-hexadien-1-ol (**1**) as the substrate, which is a nonsymmetric diene containing a hydroxy group.

The reaction of such diene with PhINTs in the presence of the appropriate catalyst might afford two different aziridines, from a regioselective point of view, each of them with a *cis* or *trans* geometry (compounds **2**–**5**, Scheme 2). Aziridines **2** and **3** could be formed by nitrene addition to the double bond vicinal to the hydroxy end of the substrate, whereas aziridines **4** and **5** would correspond to the addition to the double bond vicinal to the methyl end.

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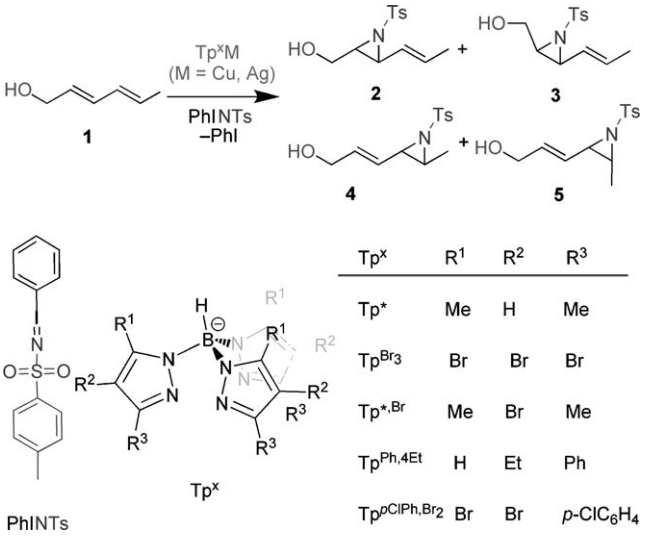


Tp^x	R^1	R^2	R^3
Tp^*	Me	H	Me
Tp^{Br3}	Br	Br	Br
$Tp^{*,Br}$	Me	Br	Me
$Tp^{Ph,4Et}$	H	Et	Ph
$Tp^{pClPh,Br2}$	Br	Br	*p*-ClC_6H_4

Scheme 2. Aziridination of *trans,trans*-2,4-hexadien-1-ol with Tp^xM catalysts (M = Cu, Ag) using PhINTs as the nitrene source. Ts = 4-toluenesulfonyl.

Table 1: Reaction of *trans,trans*-2,4-hexadien-1-ol with Tp^xM catalysts (M = Cu, Ag) using PhINTs as the nitrene source.[a]

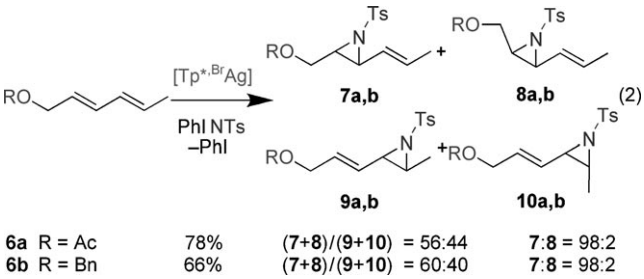
Entry	Catalyst	Conv. [%][b]	Regio.[b,c]	*trans*/*cis*[b,d]
1	[$Tp^{Ph,4Et}$Cu]	60	83:17	60:40
2	[$Tp^{ClPh,Br2}$Cu]	80	81:19	51:49
3	[Tp*Cu]	67	82:18	66:34
4	[Tp^{Br3}Cu]	> 99	86:14	66:34
5	[Tp*Ag]	> 95	90:10	> 98: < 2[e]
6	[$Tp^{*,Br}$Ag]	> 99	90:10	> 98: < 2[e]
7	[$Tp^{*,Br}$Ag][f]	> 99	89:11	> 98: < 2[e]
8	[$Tp^{*,Br}$Ag][g]	80	89:11	> 98: < 2[e]
9	[$Tp^{*,Br}$Ag][h]	> 99	88:12	> 98: < 2[e]
10	[Tp^{Br3}Ag]	< 5	–	–

[a] Reaction conditions: [cat.]/[PhINTs]/[**1**] = 1:20:30, with respect to 0.0125 mmol of catalyst, 5% catalyst loading. Reaction time was 8 hours in all cases. $TsNH_2$ accounted for 100% of the initial PhINTs that was not converted into aziridines. [b] Determined by ^{1}H NMR spectroscopy. [c] As a (**2** + **3**)/(**4**+**5**) ratio. [d] **2**/**3** ratio. [e] *cis* isomer not detected. [f] [cat.]/[PhINTs]/[**1**] = 1:200:300, with respect to 0.0046 mmol of catalyst, 0.5% catalyst loading. [g] [cat.]/[PhINTs]/[**1**] = 1:1000:1500, with respect to 0.003 mmol of catalyst, 0.1% catalyst loading. [h] [cat.]/[PhINTs]/[**1**] = 1:200:200, with respect to 0.00125 mmol of catalyst, 0.5% catalyst loading, ratio of diene/PhINTs = 1:1. See Scheme 2 for Tp* structures.

In a first series of experiments, several Tp^xCu complexes were employed as the catalyst in the reaction of the diene with PhINTs. The results are shown in Table 1. Four copper complexes were tested; variable conversions into aziridines in the range 60–99% (based in initial PhINTs) were obtained (no diaziridination products were observed). In all cases, regioselection toward the aziridine vicinal to the hydroxy end of the substrate was high (81–90%). Unfortunately, the copper catalysts did also induce a certain degree of inversion of the initial *trans* configuration of the olefin, thus leading to final *trans/cis* mixtures in the range of 1:1 to 2:1. This outcome is in agreement with previous proposals in which the aziridination reaction may occur through stepwise or concerted mechanisms.[15] However, it is worth mentioning that in spite of the low selectivities—the nitrene moiety was exclusively added to the double bonds—the hydroxy group remained undisturbed throughout the process.

A second group of Tp^xAg catalysts was then employed under the same reaction conditions.[16] These catalysts provided aziridines with excellent regio- and stereoselectivity. In fact, only *trans* aziridines were observed with all silver catalyst (Table 1, entries 5–9). Initial experiments with the complex bearing the Tp^{Br3} ligand provided very low yields of aziridines; however, those containing either $Tp^{*,Br}$ or Tp* gave nearly quantitative conversions (Table 1, entry 10 versus entries 5 and 6) in experiments carried out with a 5% catalyst loading ([cat.]/[PhINTs]/[**1**] = 1:20:30, with respect to 0.0125 mmol of catalyst). The excellent performance of the silver catalyst based on $Tp^{*,Br}$ allowed us to decrease the relative amount of catalyst to 0.5% without loss of activity (Table 1, entry 7). Only when a [cat.]/[PhINTs]/[**1**] ratio of 1:1000:1500 (with respect to 0.003 mmol of catalyst) was employed, did the conversion drop to 80% (Table 1, entry 8). All these results were obtained with initial PhINTs/diene mixtures of 1:1.5. Remarkably, the use of a 1:200:200 ratio of [cat.]/[PhINTs]/[diene] (Table 1, entry 9) provided quantitative formation of aziridines, with an approximate 9:1 mixture of regioisomers (**2**/**4**) and complete retention of configuration. This result is of importance because usually an excess of the olefin with respect to the nitrene precursor is employed with this method—a drawback when the procedure is applied to more elaborated unsaturated substrates.

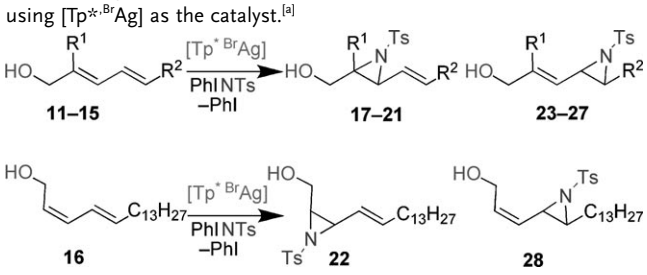
To test if the high regioselectivity observed in diene **1** can be attributed to a directing effect of the hydroxy group,[17,18] we employed O-protected dienes **6a**,**b** bearing acetyl or benzyl groups [Eq. (2); Bn = benzyl]. Under the same catalytic conditions, the results indicate that these substrates are converted into aziridines at lower conversions and, more interestingly, with a substantial decrease in the regioselectivity (ratio (**7** + **8**)/(**9**+**10**)), which confirms the directing role of the hydroxy group.[19]



6a R = Ac 78% (**7**+**8**)/(**9**+**10**) = 56:44 **7**:**8** = 98:2
6b R = Bn 66% (**7**+**8**)/(**9**+**10**) = 60:40 **7**:**8** = 98:2

Given this unprecedented outcome for a metal-catalyzed diene aziridination reaction, we decided to investigate the scope of this system using the series of six different dienes **11**–**16** shown in Table 2. The reactions were carried out in the presence of silver-based catalysts, with a 5% catalyst loading and with equimolar mixtures of the dienes and PhINTs. The

Table 2: Scope of the diene aziridination reaction with various dienes using [Tp*,BrAg] as the catalyst.[a]

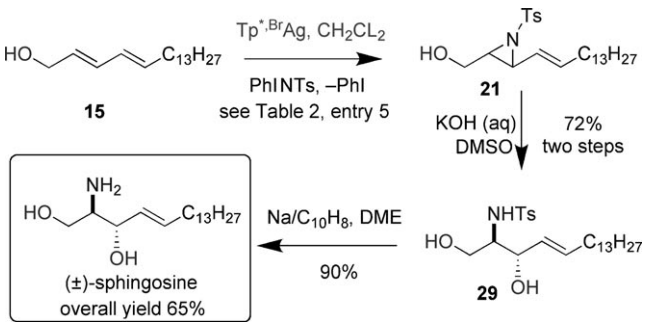


Entry	Diene	Conv. [%][b]	Regio.[b]	*trans*/*cis* [%][b,c]
1	$R^1=R^2=H$ (**11**)	>99	**17**/**23**, 88:12	>98:<2[d]
2	$R^1=H$, $R^2=Et$ (**12**)	>99	**18**/**24**, 85:15	>98:<2[d]
3	$R^1=R^2=Me$ (**13**)	>99	**19**/**25**, 86:14	>98:<2[d]
4	$R^1=H$, $R^2=Ph$ (**14**)	>99	**20**/**26**, 93:7	>98:<2[d]
5	$R^1=H$, $R^2=C_{13}H_{27}$ (**15**)	>99	**21**/**27**, 86:14	>98:<2[d]
6	**16**	>99	**22**/**28**, 90:10	<2:>98[e]

[a] Reaction conditions: [cat.]/[PhINTs]/[diene] = 1:20:20, with respect to 0.0125 mmol of catalyst, reaction time was 4 hours. $TsNH_2$ accounted for 100% of the initial PhINTs that was not converted into aziridines. [b] Determined by ^1H NMR spectroscopy. [c] *trans*/*cis* ratio for the major aziridine. [d] *cis* isomer not detected. [e] *trans* isomer not detected.

results are in agreement with those obtained with **1**, and can be summarized as follows: 1) quantitative conversions into aziridines were obtained in all cases, even with the sterically hindered diene **13**; 2) the product derived from the aziridination of the double bond vicinal to the hydroxy group was preferred in all cases, with regioselectivity being within the interval of 85:15 to 93:7; 3) complete retention of configuration appeared as a constant in all the experiments. It is worth mentioning that when the *cis,trans* diene **16** was employed, aziridination of the internal *cis* double bond was preferred (owing to its vicinity to the hydroxy group), and such geometry was maintained in the resulting aziridine, a fact that indicates that the reaction is stereospecific.

Driven by our interest in developing new methods for the synthesis of amino alcohols with biological interest,[20] we have applied this method to the synthesis of (±)-sphingosine.[21,22] As shown in Scheme 3, diene **15** was employed as the starting material. Aziridination with PhINTs gave a mixture of aziridines in 86:14 ratio (Table 2, entry 5), the major isomer corresponding to the aziridine ring vicinal to the hydroxy group. The final reaction mixture of aziridines was treated with KOH to induce ring opening and the concomitant formation of the N-protected amino alcohol **29**. Further treatment of **29** with Na/naphthalene provided the targeted (±)-sphingosine in 65% yield of isolated product (based on the starting diene **15**).



Scheme 3. Application of the diene aziridination method to the synthesis of (±)-sphingosine. DME = 1,2-dimethoxyethane, DMSO = dimethyl sulfoxide.

In conclusion, we have found that several complexes containing the Tp^xM fragment (M = Cu, Ag) catalyze the aziridination of dienes bearing a terminal hydroxy group, thus affording vinyl aziridines with a low catalyst loading and using stoichiometric mixtures of diene and PhINTs (the nitrene source). The [Tp*,BrAg] catalyst was found to be highly regioselective toward the aziridination of the double bond vicinal to the hydroxy end of the substrate and highly stereospecific with an array of dienes, including a precursor of (±)-sphingosine. The results presented here make the silver-catalyzed aziridination of dienes a promising synthetic tool in organic synthesis. Work aimed to understand the mechanism that governs this transformation as well as to develop the asymmetric version of this catalytic system is currently underway in our laboratories.

Experimental Section

General procedure for aziridination of 2,4-dien-1-ol: A 100 mL Schlenk flask containing a magnetic stirring bar was charged, under an argon atmosphere, with the catalyst (0.0025 mmol, 1%), the alcohol (0.25 mmol), and anhydrous dichloromethane (5 mL). Freshly prepared PhINTs (0.27 mmol) was added in 3–4 portions over 2 h, and the mixture was stirred for an additional hour after the last addition. The solvent was removed under vacuum and the resulting crude residue was characterized without purification because vinyl aziridines are unstable on silica gel and neutral alumina. Spectroscopic data were extracted from the spectra of the isolated crude reaction residues. All procedures for the preparation of the starting dien-1-ols and for the aziridination of such substrates, as well as spectroscopic data (including NMR spectra) are given in the Supporting Information.

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