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Rhodium-catalyzed regio- and stereoselective oxyamination of dienes *via* tandem aziridination/ring-opening of dienyl carbamates†

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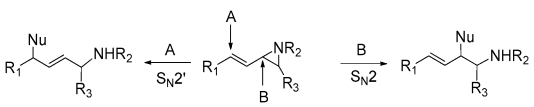
The reaction of dienyl carbamates with $PhI(OR)_2$ in the presence of rhodium catalysts affords vinyl aziridines which are *in situ* regio- and stereoselectively opened to afford oxyamination products resulting from a selective S_N2 ($Rh_2(OAc)_4/PhI(OPiv)_2$) or S_N2' ($Rh_2(OPiv)_4/PhI(OAc)_2$) opening. The scope and limitations of this tandem process are described.

Vinyl aziridines are key starting intermediates for the synthesis of a diversity of functionalized nitrogen-containing products through nucleophilic ring opening processes.[1] Thus, the nucleophilic ring opening of vinylaziridines could proceed through either S_N2 (B) or S_N2' (A) processes (Scheme 1).[2] They also undergo isomerization and cycloaddition reactions affording a wide range of heterocycles through tandem opening/cyclization processes usually catalyzed by transition metal complexes.[1]

In vinylaziridine ring opening, the selective weakening of the allylic C–N bond by the πC=C–σ*C–N overlap[3] intrinsically directs the nucleophilic addition through A and B pathways. An S_N2' pathway is observed with organocopper reagents,[4] whereas oxygen-centered nucleophiles,[5] halogens[6] and sulfur-stabilized carbanions[3,7] preferentially lead to S_N2 products. The latter examples suggest that the regioselectivity of the ring opening reactions of vinylaziridines is governed mainly by the type of nucleophile. However, vinylaziridine substitution, catalysts[8] and solvents also play a role in controlling the regioselective opening. In this sense, controlling the regioselective opening of vinylaziridines remains an unachieved challenge.



Scheme 1 Pathways for the ring-opening of vinylaziridines.

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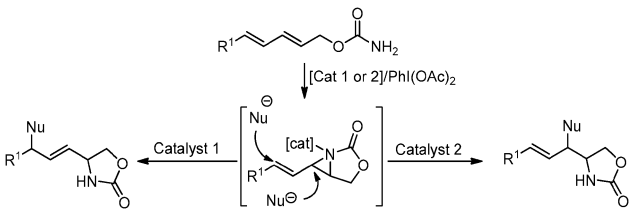
† Electronic supplementary information (ESI) available: Characterization data of main products prepared and ^1H and ^{13}C NMR data, as well as the procedure for determining the relative configuration of S_N2' products. See DOI: 10.1039/c4cc01312c

Ring-opening reactions of vinylaziridines with oxygen nucleophiles constitute a useful pathway for the stereoselective synthesis of unsaturated aminoalcohols.[5,5d,9] We recently developed an efficient silver-catalyzed regio- and stereospecific aziridination of dienols that allowed an easy access to sphingosine.[10] The regioselectivity obtained in the aziridination reaction (9:1) was remarkable. However, we considered that it could be improved by performing an intramolecular version of the reaction. Intramolecular aziridination using sulfamates,[11] sulfonamides,[12] sulfonimidamides,[13] carbamates[14] and tosylcarbamates[15] as nitrene precursors catalyzed by copper or rhodium complexes has been reported. However, there are no examples of their application in the synthesis of vinylaziridines.

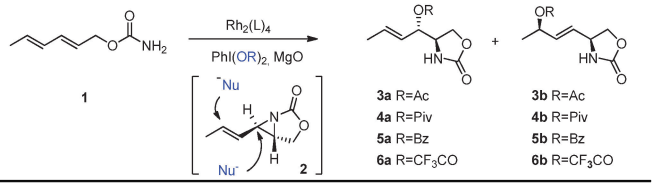
In this communication we report the first tandem transition metal-catalyzed intramolecular aziridination of dienes followed by a regiocontrolled ring-opening with oxygen nucleophiles. The metal catalyst plays a double role, as a nitrene stabilizing agent in the aziridination reaction and eventually as a Lewis acid in the nucleophilic ring opening process (Scheme 2).

At the outset of this study we focused on the intramolecular aziridination of carbamate **1** (Table 1). Initially, Cu, Ag and Rh were tested as catalysts in the presence of iodobenzene diacetate ($PhI(OAc)_2$) and MgO at 20 °C.[16] In all cases the formation of acetates **3a** and **3b** was observed. These compounds arise from the transient vinylaziridine **2** and subsequent S_N2 and S_N2' ring opening, respectively, by the acetate group resulted in the formation of the nitrene transfer reagent.[14a,b] Both reactions were stereoselective, affording a single diastereomer (see Scheme 3 and the ESI† for the determination of relative configuration of compound **3b**). The best results were



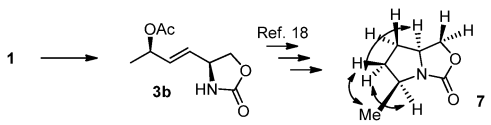
Scheme 2 Tandem intramolecular aziridination-ring opening.

Table 1 Tandem intramolecular aziridination/ring opening of **1** with different nitrene sources using Rh(II)carboxylate as catalysts. Optimization of the reaction conditions[a]



Entry	R	L	Products	Conv.[b] (Yield)[c] (%)	Regiosel. **a,b** ratio[b] (%)
1	Ac	OAc	**3a,b**	95 (87)	75 : 25
2	Piv	OAc	**4a,b**	>99 (89)[d]	91 : 9
3	Bz	OAc	**5a,b**	>99 (91)	66 : 34
4	CF_3CO	OAc	**6a,b**	>99 (0)	—
5	Ac	OPiv	**3a,b**	>99 (82)	10 : 90
6	Piv	OPiv	**4a,b**	>99 (61)	15 : 85
7	Bz	OPiv	**5a,b**	>99 (82)	14 : 86
8	CF_3CO	OPiv	**6a,b**	>99 (0)	—
9[e]	Ac	OPiv	**3a,b**	>99	18 : 82
10[f]	Ac	OPiv	**3a,b**	>99 (74)	<5 : >95

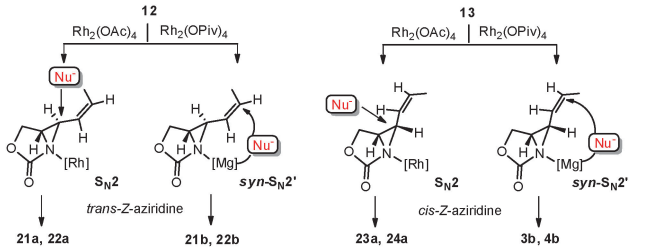
[a] All reactions were performed using a catalyst/**1**/PhI(OR)$_2$/MgO molar ratio of 0.1 : 1 : 2 : 3.3 in a 0.05 M substrate solution in CH_2Cl_2, T = 20 °C, t = 48 h for $Rh_2(OAc)_4$ and 24 h for $Rh_2(OPiv)_4$. [b] Determined by ^{1}H NMR. [c] Isolated yields (combination of regioisomers). [d] Compounds **3a,b** were also obtained in 8% yield. [e] Temperature 45 °C. [f] Temperature 5 °C.



Scheme 3 Determination of relative configuration of **3b**.

obtained using catalytic amounts of dirhodium tetraacetate which afforded acetates **3a** and **3b** in good yield with a regioisomeric ratio of 75 : 25 (Table 1, entry 1).

Replacing PhI(OAc)$_2$ by PhI(OPiv)$_2$ (Table 1, entry 2), products **4a** and **4b** were obtained with a significant increase in the regioisomeric ratio up to 91 : 9. In this case, minor amounts of the acetate derivatives **3** were also obtained. The acetate groups in products **3** come from the rhodium acetate complex. In order to avoid their formation we decided to test the corresponding rhodium pivalate complex. To our delight, using $Rh_2(OPiv)_4$ as the catalyst, a reversion of the regioselectivity was obtained with a **4a**/**4b** (S_N2/S_N2') ratio of 15 : 85 (Table 1, entry 6). The effect of the nucleophile and the catalyst on the regioselectivity was then evaluated by modifying the iodine(III) oxidant and the carboxylate group in the catalyst (Table 1). When the reaction was carried out using different iodine(III) reagents catalyzed by $Rh_2(OAc)_4$ (Table 1, entries 1–4), the regioselectivity appeared to arise mainly from the properties of the nucleophile. Thus, the preferences towards the S_N2 attack of three carboxylates can be related to their respective nucleophilicity. On the other hand, when the reaction was catalyzed by the more sterically demanding $Rh_2(OPiv)_4$ (Table 1, entries 5–10) the S_N2' attack was preferentially produced, and the character of the *O*-nucleophile did not have any influence on the regioselectivity. Comparing entries 2 and 6 it is evident that the catalyst is responsible for the control of the



Scheme 4 Proposed mechanism for the S_N2 and *syn* S_N2' processes.

regioselectivity, which could be initially explained considering that the metal complex remains linked to nitrogen after the aziridination[17] activating the opening process. The effect of the temperature was then evaluated, and when the reaction was carried out at 5 °C, a remarkable S_N2/S_N2' = <5 : >95 of compounds **3a,b** was obtained (Table 1, entries 9 and 10).

When trifluoroacetate iodobenzene was used, no reaction was observed regardless of the catalyst (Table 1, entries 4 and 8).

For determining the relative configuration of stereocentres in the S_N2' products, compound **3b** was transformed into the bicyclic compound **7** following a modified reported procedure[18] (see Scheme 3 and ESI†). From NOE experiments on **7** it can be inferred that the proton on the bridge and the methyl group were *anti*, involving a *syn* orientation of amino and acetate groups in compound **3b**. This fact is not consistent with the classical *anti* stereochemical outcome of an intermolecular S_N2' process. An explanation is proposed in Scheme 4.

To explore the scope and the limitations of this methodology, we applied it to a variety of differently configured and functionalized dienyl carbamates (Fig. 1, Table 2). Carbamates were easily synthesized from the corresponding dienols through the carbamoylation process described by Kocovsky.[19] Tandem aziridination/opening of substrates **8** and **9** with a *trans*/*trans* configuration of the double bonds (Table 2, entries 1–4) provided an excellent regiocontrol with both catalytic systems affording products resulting from an S_N2 attack under conditions A (**14a**, **16a**), and from an S_N2' attack under conditions B (**15b**, **17b**). When the diene was substituted by a phenyl group (**10**) (Table 2, entries 5 and 6), selectivity with both catalytic systems decreased probably due to the high reactivity of the transient phenyl-substituted vinylaziridine. The unexpected effect of the methyl substituent at C-4 in the regioselective outcome is worth mentioning. Thus, unexpectedly, when the reaction was conducted with carbamate **11**, employing $Rh_2(OAc)_4$, and especially $Rh_2(OPiv)_4$, the S_N2' attack was preferred over the S_N2 attack (Table 2, entries 7 and 8). Next, we explored the reaction of *trans–cis* and *cis–cis* dienyl carbamates **12** and **13**, related to carbamate **1** but with different configurations in the double bonds (Table 2, entries 9–12). The regioisomers resulting from an S_N2 attack were obtained in

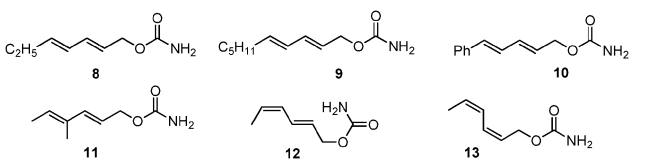
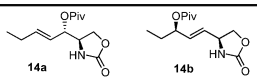
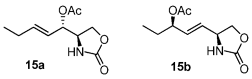
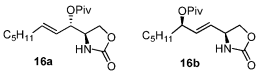
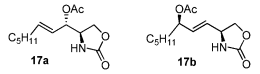
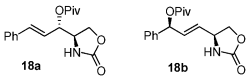
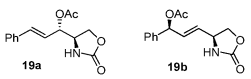
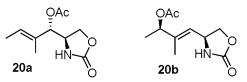
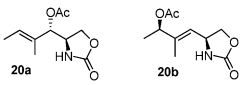
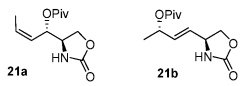
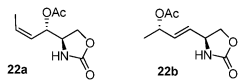
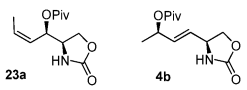
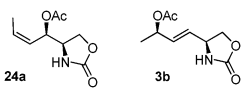


Fig. 1 Substrate scope.

Table 2 Tandem intramolecular aziridination/ring opening. Scope[a]

Entry	SM	Cond.[a]	Products	Yield[b] (%)	a,b ratio[c] (%)
1	**8**	A	 **14a** **14b**	72	86 : 14
2	**8**	B	 **15a** **15b**	65	10 : 90
3	**9**	A	 **16a** **16b**	71	91 : 9
4	**9**	B	 **17a** **17b**	76	13 : 87
5	**10**	A	 **18a** **18b**	54	70/30
6	**10**	B	 **19a** **19b**	60	28/72
7[d]	**11**	A	 **20a** **20b**	71	25 : 75
8	**11**	B[d]	 **20a** **20b**	68	10 : 90
9	**12**	A	 **21a** **21b**	56	90/10
10	**12**	B	 **22a** **22b**	64	39/61
11	**13**	A	 **23a** **4b**	74	90 : 10
12	**13**	B	 **24a** **3b**	71	36 : 64

[a] Conditions A: $Rh_2(OAc)_4$/substrate/$PhI(OPiv)_2$/MgO (0.1 : 1 : 2 : 3.3) in a 0.05 M solution in CH_2Cl_2, T = 20 °C, t = 48 h. Conditions B: $Rh_2(OPiv)_4$/substrate/$PhI(OAc)_2$/MgO (0.1 : 1 : 2 : 3.3) in a 0.05 M solution in CH_2Cl_2, T = 5 °C, t = 24 h. [b] Isolated yields (combination of regioisomers). [c] Determined by ^{1}H NMR. [d] $PhI(OAc)_2$ was used instead of $PhI(OPiv)_2$ since yields were better and selectivity similar.

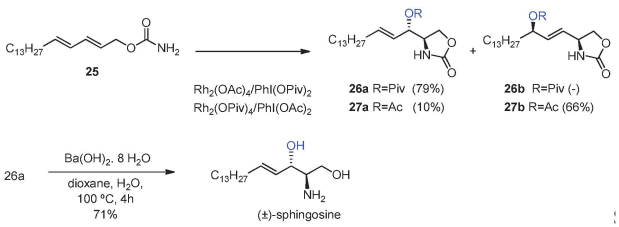
selectivities similar to those obtained with the *trans–trans* dienes, while those resulting from the S_N2' attack suffered a moderate drop. Compounds obtained from carbamate **13** by aziridination and S_N2' opening proved to be identical to **3b** (entry 12) and **4b** (entry 11), which indicates that the reaction follows a similar stereochemical pathway regardless of the double bond configuration. Products **21b** and **22b**, obtained from **12**, showed very similar ^{1}H and ^{13}C NMR spectra compared to **4b** and **3b**, respectively. To elucidate whether related products were configurationally identical, compounds **22b** and **3b** were hydrolyzed and the resulting products were treated with Mosher acid chloride to selectively give the esters. The NMR spectra of the obtained products showed significant differences, proving that both compounds were different. Since a *syn*-relative configuration was confirmed for product **3b** by NOE experiments (Scheme 3), an *anti*-relative configuration was attributed to compound **22b**.[2,4]

Compounds **3b**, **4b** and **14b–22b** resulted from a *syn*-S_N2' process. Scheme 4 shows a plausible mechanism to explain both the regioselectivity and the *syn*-nature of this process. The *syn* process can be justified by a directed transfer of carboxylate from the metal coordinated to the carbamate function. In fact, the coordination of rhodium to the aziridinic nitrogen,[11c] or the directing effect of cations in the opening of aziridines has already been reported.[20] Looking for information about this process we carried out the reaction of **1** using $Rh_2(OPiv)_4$ as a catalyst, under the optimized reaction conditions using sodium, potassium and cesium carbonate as bases, and observed **3a**/**3b** ratios (S_N2/S_N2') of 9 : 91, 37 : 63 and 86 : 14, respectively. These results clearly show the role of cations in the control of regio- and stereoselectivity, which suggest that magnesium plays a determining role in the S_N2' process.

In this context, the strong preference for the S_N2 attack in the $Rh_2(OAc)_4$-catalysed process can be rationalized considering that rhodium remains coordinated to nitrogen, and $Mg(OCOR)_2$ opens the activated aziridine through an S_N2 process. On the other hand, the sterically more demanding $Rh_2(OPiv)_4$ can be easily released from the coordination to nitrogen, which enables $Mg(OCOR)_2$ to coordinate the carbamate function and direct the attack of the carboxylate through a *syn*-S_N2' manner.

The procedure developed can provide a straightforward access to sphingosine and derivatives. For this purpose, diene **25** was treated with $Rh_2(OAc)_4/PhI(OPiv)_2$ under the optimized reaction conditions to afford **26a** in a 79% yield. When the catalytic system $Rh_2(OPiv)_4/PhI(OAc)_2$ was used, compound **27b** was obtained in 66% yield, together with minor amounts of **27a** (10%) (Scheme 5). Treatment of compound **26a** in a basic medium afforded sphingosine.[21] Thus, sphingosine was synthesized in two steps from the dienyl carbamate **25** in a 56% overall yield.

In conclusion, tandem intramolecular aziridination/ring opening of dienol carbamates was regioselectively performed by selecting the rhodium catalyst and the iodine(III) oxidizing reagent. The carboxylate present in the iodine(III) reagent released during the reaction behaves as a nucleophile opening the aziridine intermediate. The use of $Rh_2(OAc)_4$ affords products resulting from an S_N2 attack and the rhodium catalyst plays a double role, first in promoting the metalonitrene formation and second as a Lewis acid in the S_N2 opening process. On the contrary, when $Rh_2(OPiv)_4$ was used as the catalyst, products resulting from an S_N2' attack were selectively obtained. The bulkiness of $Rh_2(OPiv)_4$ might favor the de-coordination from the aziridinic nitrogen, leaving place for coordination of magnesium, which would direct the



Scheme 5 Preparation of (±)-sphingosine.

carboxylate attack in a *syn* S_N2' fashion. The efficiency of the reaction is strongly affected by the presence of substituents in the intermediate framework of the diene system, and the product resulting from the S_N2' attack is obtained with both catalytic systems if a methyl group is present at C-4. The synthetic procedure developed in this work has allowed the synthesis of sphingosine in only two steps from the starting dienyl carbamate.

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