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Metallocene catalyzed synthesis of fungistatic vicinal aminoalcohols under solvent free conditions

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ABSTRACT

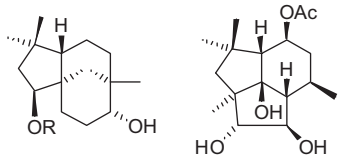
Group 4 and 5 metallocenes, Cp_2TiCl_2, Cp_2ZrCl_2 and Cp_2VCl_2, have been evaluated as catalyst in the solvent free, room temperature, preparation of vicinal aminoalcohols. The regioselectivity of the reaction and the fungistatic activity of the prepared compounds against *Botrytis cinerea* and *Colletotrichum gloeosporioides* are discussed.

Vicinal amino alcohol functionality is a structural component which can be found in an ample group of naturally occurring and synthetic molecules. The substitution pattern and stereochemistry of this moiety play an important role in the biological activity of molecules containing an 1,2-amino alcohol group in their structure.[1] For instance, sphingosine,[2] as well as other related compounds,[3] has been described to present antifungal activity.

The classical route for the preparation of these compounds from epoxides is the direct aminolysis of 1,2-epoxides[4] however, this procedure has limitations such as the requirement of excess of amines and elevated temperature, often works less well with poorly nucleophilic and sterically hindered amines and lacks of appreciable regioselectivity. New methods have been developed to overcome these handicaps,[5] which can broadly be grouped either in those using metal amides or those using Lewis acids.[6]

In order to reduce the environmental impact of the use of organic solvents in the preparation of vicinal aminoalcohols, some alternative procedures have been described in the literature, such as the use of supercritical carbon dioxide,[7] microwave irradiation,[8] or ionic liquids.[9] The use of solvent free conditions is an additional strategy, which can be used on its own,[10] combined with microwave irradiation[11] or with the use of catalysts,[12] some of them involving transition metals.[13]

Group 4 and 5 metallocenes, (Ti, Zr, V) have been used as Lewis acid catalysts in transformations of organic compounds,[14] but to our knowledge, there are not precedents of their application to the opening of epoxides by amines to yield aminoalcohols. On the other hand, other complexes of such metals like $ZrCl_4$,[15] $Ti(OiPr)_4$[16] and VCl_3[17] have been described in the preparation of aminoalcohols by oxirane ring opening.



1 R=alkyl
1a R=$CH_2CH_2NH_2$

2

Our research group is interested in the synthesis of environmentally friendly and selective inhibitors of the fungus *Botrytis cinerea*.[28] 2-Alkoxyclovane-9-ol derivatives **1**,[29] possess a structural similarity to the proposed key intermediate **2**[30] in the biosynthesis[31] of the phytotoxic[32] botryane metabolites produced by the fungus *B. cinerea*, and they have been shown to inhibit the growth of this fungus.[33] Some of the more active alkoxyclovanols **1a**[34] present nitrogen atoms in the side chain at C-2. Further research requires the exploration of structure–activity relationships, and we postulated the use of simpler templates, like styrene oxide, which could yield vicinal aminoalcohols with similar or improved activities and which could be prepared in better yields.

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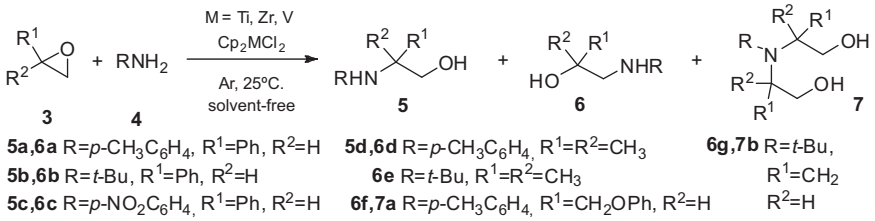

Scheme 1.

In this paper we explore the use of group 4 and 5 metallocenes (Cp_2TiCl_2, Cp_2ZrCl_2 and Cp_2VCl_2) as catalysts, under solvent free conditions, in the cleavage of epoxides by amines to give aminoalcohols with potential antifungal activity.

Non-symmetrically substituted epoxides styrene oxide (**3a**), 2-methylpropene oxide (**3b**) and 2-(phenoxymethyl)oxirane (**3c**) (1 mmol) were treated at 25 °C, under absence of further solvents, with *p*-methylaniline (**4a**) and *tert*-butylamine (**4b**) (1.1 mmol) and a catalytic amount (10 mol%) of metallocene (Cp_2TiCl_2, Cp_2ZrCl_2 and Cp_2VCl_2) (Scheme 1). Reactions times, yields and products obtained are detailed in Table 1. All crude reaction mixtures were purified by column chromatography on silica gel. The structures of known compounds were determined by comparison of spectroscopic and physical data with the literature. A combination of 1D and 2D NMR techniques, together with IR spectroscopy and mass spectrometry data allowed the assignation of the structures for novel compounds.

Yields and regioselectivity were variable, but some trends could be drawn. Best yields and regioselectivity are observed for the combination of styrene oxide (**3a**) and *p*-methylaniline (**4a**), being Cp_2TiCl_2 the catalyst which gives the best results (entry 1). The preference of attack on the benzylic position of the oxirane has been described before for the reaction of anilines with styrene oxide (**3a**).[5,17,35] On the other hand, the opposite regioselectivity is observed for tertiary epoxide **3b**, even when *p*-methylaniline (**4a**) is used. For both epoxides **3b** and **3c**, the most abundant regioisomeric aminoalcohol originates by preferential attack on the least substituted position of the oxirane (compounds **6d–g**). Reaction between *tert*-butyl amine and epoxides **3b** and **3c** also yield the least substituted regioisomer.[36] This is not the case for styrene oxide, where little or none regioselection is observed.

2-(Phenoxymethyl)oxirane (**3c**) yields a minor regioisomer by an attack of the amine on two units of epoxide. The amine attaches at two epoxide units at the substituted (secondary) position of the oxirane ring, leading to 2,2′-(*p*-tolylazanediyl)bis(3-phenoxypropan-1-ol) (**7a**) or 2,2′-(*tert*-butylazanediyl)bis(3-phenoxypropan-1-ol) (**7b**), depending on the amine.

The preliminary antifungal activity of compounds **5a–d**, **6a–f** and **7a–b**, against the phytopathogenic fungi *Botrytis cinerea* and *Colletotriuchum gloeosporioides*, was evaluated at a concentration of 100 mg/L using a reported procedure.[33,34] The inhibition rates of a selection of these compounds are listed in Table 2. Compounds **5a**, **5c** and **6f** are the most active ones for both fungi. Compound **6f** possess an activity against *B. cinerea* comparable to that of the commercial fungicide dichofluanid (rel. inhib. >95%, 100 mg/L).[37] On the other hand, compounds **6d** and **7a** are moderately active, but only against *B. cinerea*. Compounds not presented in Table 2 were not active either against *B. cinerea* or against *C. gloeosporioides*.

In conclusion, Group 4 and 5 metallocenes, Cp_2TiCl_2, Cp_2ZrCl_2 and Cp_2VCl_2, proved to be efficient catalysts in the opening at room temperature of epoxides by aromatic amines. Yields are dependent of the combination of amine and epoxide, and reaction times were kept between 3 and 1.5 h. Aliphatic amines showed to be less reactive under evaluated conditions, giving lower yields. Best and opposite regioselectivities were observed for the combination of *p*-methylaniline (**4a**) and styrene oxide (**3a**) (most substituted regioisomer, compound **5a**) and of 2-methylpropene oxide and *tert*-butyl amine (less substituted regioisomer, compound **6e**).

Finally, biological activity against *B. cinerea* seemed to be correlated with the presence of an aromatic moiety in the molecule, especially if it is bound to the nitrogen atom. On the other hand,

Table 1
Treatment of epoxides (**3a**–**3c**), with amines catalyzed by Cp_2MCl_2 (M = Ti, Zr, V)[a]

Entry	Epoxide (**3**)	Amine (**4**)	Catalyst	Time (h)	Yield (%)[b]	Product/s (ratio)[b]	References[c]
1	Styrene oxide (**3a**)	*p*-Methylaniline (**4a**)	Cp_2TiCl_2	2	>99	**5a** + **6a** (99.5:0.5)	
2	**3a**	**4a**	Cp_2ZrCl_2	2	92	**5a** + **6a** (93:7)	18, 36b
3	**3a**	**4a**	Cp_2VCl_2	2	>99	**5a** + **6a** (95:5)	
4	**3a**	*tert*-Butylamine (**4b**)	Cp_2TiCl_2	70	43	**5b** + **6b** (50:50)	
5	**3a**	**4b**	Cp_2ZrCl_2	23	89	**5b** + **6b** (20:80)	19, 20
6	**3a**	**4b**	Cp_2VCl_2	70	53	**5b** + **6b** (29:71)	
7	**3a**	*p*-Nitroaniline (**4c**)	Cp_2TiCl_2	48	38	**5c** + **6c** (96:4)	
8	**3a**	**4c**	Cp_2ZrCl_2	1.5	68	**5c** + **6c** (98:2)	35
9	**3a**	**4c**	Cp_2VCl_2	48	58	**5c** + **6c** (99:1)	
10	2-Methylpropene oxide (**3b**)	*p*-Methylaniline (**4a**)	Cp_2TiCl_2	1.5	37	**5d** + **6d** (8:92)	
11	**3b**	**4a**	Cp_2ZrCl_2	1.5	49	**5d** + **6d** (17:83)	21, 22
12	**3b**	**4a**	Cp_2VCl_2	1.5	28	**5d** + **6d** (5:95)	
13	**3b**	*tert*-Butylamine (**4b**)	Cp_2TiCl_2	3.5	28	**6e**	23
14	**3b**	**4b**	Cp_2ZrCl_2	3.5	30		
15	**3b**	**4b**	Cp_2VCl_2	3.5	20		
16	2-(Phenoxymethyl) oxirane (**3c**)	*p*-Methylaniline (**4a**)	Cp_2TiCl_2	2	>99	**6f** + **7a** (70:30)	
17	**3c**	**4a**	Cp_2ZrCl_2	3	32	**6f** + **7a** (75:25)	24, 25
18	**3c**	**4a**	Cp_2VCl_2	2	98	**6f** + **7a** (70:30)	
19	**3c**	*tert*-Butylamine (**4b**)	Cp_2TiCl_2	18	55	**6g** + **7b** (70:30)	
20	**3c**	**4b**	Cp_2ZrCl_2	10	40	**6g** + **7b** (67:33)	26, 27
21	**3c**	**4b**	Cp_2VCl_2	18	88	**6g** + **7b** (75:25)	

[a] Reaction conditions: epoxide (**3**): (1 mmol), amine (**4**): (1.1 mmol), Cp_2MCl_2: (10 mol%).
[b] Yields and product ratios obtained after chromatographic purification.
[c] References including spectroscopic data.

Table 2
Antifungal activity (relative inhibition (%), 100 mg/L) of selected aminoalcohols (relative inhibition at 100 mg/L ⩾30%)

Compound	*Botrytis cinerea*	*Colletotrichum gloeosporioides*
5a	63	40
5c	69	55
6d	62	—[a]
6f	87	72
7a	53	—[a]
7b	43	—[a]

[a] Relative inhibition at 100 mg/L <30%.

the presence of an aniline fragment seems to be necessary for activity against *C. gloeosporioides*.

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21. *Compound* **5d**. Yellow oil. IR (KBr) ν_{max} (cm^{-1}): 3390, 2972, 2866, 1620, 1380, 1365, 1318, 1250, 1126, 808; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20 (s, 6H, H-3, H-4), 2,08 (br s, 2H, OH, NH), 2.25 (s, 3H, H–ArCH3), 3.49 (s, 2H, H-1), 6.73 (d, J = 8.3 Hz, 2H, H-2′, H-6′), 7.00 (d, J = 8.0 Hz, 2H, H-3′, H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.5 (c, C-$ArCH_3$), 27.1 (c, 2C, C-3, C-4), 57.7 (s, C-2), 71.1 (t, C-1), 122.4 (d, 2C, C-2′, C-6′), 131.5 (d, 2C, C-3′, C-5′), 132.2 (s, C-4′), 144.8 (s, C-1′); EIMS m/z (rel. int.): 179 $[M]^+$ (35); 106 (100); 91(29); 77 (9); HREIMS: for $C_{11}H_{17}NO$ calcd 179.1310, found 179.1314.
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25. *Compound* **7a**. White solid: mp: 58–61 °C; IR (KBr) ν_{max} (cm^{-1}): 3345, 3063, 2922, 1599, 1245, 1043, 753, 691. ^1H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) 2.15 (s, 3H, H–CH_3), 3.72 (dd, J = 11.2, 5.6 Hz, 2H, H-1a (bis)), 3.81 (dd, J = 11.2, 4.8 Hz, 2H, H-1b (bis)), 4.07 (d, J = 5.6 Hz, 4H, H-3 (bis)), 4.19 (q, J = 4.6 Hz, 2H, H-2 (bis)), 4.32 (br s, 2H, OH), 6.56 (dt, J = 6.4, 2.0 Hz, 2H, H-3″, H-5″), 6.86 (dd, J = 8.0, 0.8 Hz, 2H, H-2″, H-6″), 6.95 (dd, J = 8.0, 0.8 Hz, 6H, H-3′ (bis), H-4′ (bis), H-5′ (bis)), 7.28 (dd, J = 8.8, 7.2 Hz, 4H, H-2′ (bis), H-4′ (bis)); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ (ppm) 20.4 (c, C–CH_3), 47.1 (t, 2C, C-1 (bis)), 69.8 (t, 2C, C-3 (bis)), 70.4 (d, 2C, C-2 (bis)), 115.3 (d, 6C, C-3′ (bis), C-5′ (bis), C-3″, C-5″), 121.6 (d, 2C, C-4′ (bis)), 126.1 (s, C-4″), 130.1 (d, 2C, C-2″, C-6″), 130.2 (d, 4C, C-2′ (bis), C-6′ (bis)), 146.6 (s, C-1″), 159.6 (s, 2C, C-1′ (bis)); EIMS m/z (rel. int.): 407 $[M]^+$ (11); 270 (100); 134 (70); 120 (20); 77 (10); 91 (8); HREIMS: for $C_{25}H_{29}NO_4$ calcd 407.2096, found 407.2079.
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27. *Compound* **7b**. White solid: mp: 61–63 °C; IR (KBr) ν_{max} (cm^{-1}): 3360, 3062, 2970, 1599, 1244, 1041, 752, 690; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) 1.13 (s, 9H, H–$C(CH_3)_3$), 2.60 (dd, J = 14.4, 8.5 Hz, 2H, H-1a (bis)), 3.07 (dd, J = 14.4, 4.1 Hz, 2H, H-1b (bis)), 3.96 (d, J = 5.1 Hz, 4H, H-3 (bis)), 4.05–4.00 (m, 2H, H-2 (bis)), 6.92 (ddd, J = 13.7, 8.0, 4.2 Hz, 6H, H-3′ (bis), H-4′ (bis), H-5′ (bis)), 7.23–7.28 (m, 4H, H-2′ (bis), H-6′ (bis)); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ (ppm) 27.4 (c, 3C, C–$C(CH_3)_3$), 56.4 (s, C–$C(CH_3)_3$), 57.0 (t, 2C, C-1 (bis)), 70.1 (d, 2C, C-2 (bis)), 71.4 (t, 2C, C-3 (bis)), 115.3 (d, 4C, C-2′ (bis), C-6′ (bis)), 121.3 (d, 2C, C-4′ (bis)), 160.0 (d, 4C, C-3′ (bis), C-5′ (bis)); EIMS m/z (rel. int.): 373 $[M]^+$ (1); 358 $[M-CH_3]^+$ (4); 236 (100); 180 (54); HREIMS: for $C_{22}H_{31}NO_4$ calcd 373.2253, found 373.2251 [M].
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