C-Quaternary Vinylglycinols by Metal-Catalyzed Cyclization of Allylic Bistrichloroacetimidates

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Abstract: Bistrichloroacetimidates derived from 2-substituted but-2-ene-1,4-diols are transformed into 4-substituted 4-vinyloxazolines in high yields and excellent regioselectivities when Lewis acids $AlCl_3$, $FeCl_3$, TMSOTf, $BF_3{\cdot}OEt_2$, and $AgBF_4$ are used as catalysts as well as with the $Pd(PPh_3)_2Cl_2/AgBF_4$ catalytic system. Lower regioselectivity is achieved with a neutral $PdCl_2(MeCN)_2$ catalyst and this could be a consequence of a switch to a competitive but less selective reaction mechanism. It is demonstrated that 4-substituted 4-vinyloxazolines can be efficiently transformed to *N*-Boc-protected *C*-quaternary vinylglycinols in a one-pot procedure.

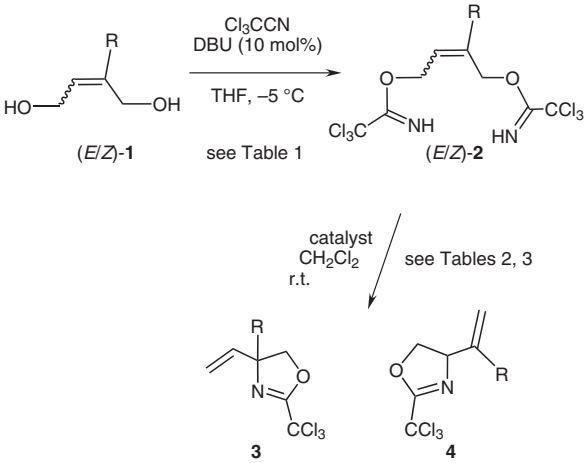
Key words: amino alcohols, Lewis acids, palladium, cyclization, regioselectivity

C-Quaternary vinylglycinols and α-substituted vinylglycines are useful intermediates for the synthesis of natural products and pharmaceutically relevant compounds.[1,2] Numerous methods have been developed for the synthesis of a-substituted vinylglycines.[1a,3–7] In turn, *C*-quaternary glycinols can be obtained by reduction of vinylglycines[1a,8,9] or accessed by specific methods, the most important being rearrangement of allylic *N*-PMP trifluoroacetimidates[10] or cyanates,[11] olefination of serinal derivatives,[12] allylic substitution of isoprenemonoepoxide,[13] addition of vinylmetals to α-hydroxy nitrones,[14] reaction of aldehydes with aminoallylboranes,[1d] Petasis reaction,[15] imidation/rearrangement of vinylsulfides,[16] and aminolysis of vinylepoxides.[17] Although asymmetric versions are known for many of the above-mentioned reactions, synthesis of vinylglycinols from commercially available starting materials is typically a complex multistep process often limited in scope. Short and general alternative routes to racemates are still desirable for the synthesis and biological evaluation of compound libraries.

Our research has focused on the synthesis of vinyloxazolines as highly versatile precursors of vinylglycinols and glycines. We have developed two methods for the synthesis of vinyloxazolines based on Pd(II)-catalyzed cyclization of allylic imidates containing a δ-leaving group[18,19] and a Lewis acid catalyzed cyclization of allylic bisimidates.[20] Using both strategies, the cyclization of bisimidates **2** derived from 2-substituted but-2-ene-1,4-diols **1** can give isomeric vinyloxazolines **3** and **4**. We envisaged that selective formation of products **3** or **4** could be achieved by the appropriate selection of the catalyst and reaction conditions. In this letter we present our regioselective and high-yielding methodology for the cyclization of imidate **2** to 4,4-disubstituted oxazolines **3**.

2-Substituted but-2-ene-1,4-diols (*E*)-**1a–d** and (*Z*)-**1a**,**b** were prepared as described in the literature (see Supporting Information). Treatment of (*E*)-**1a–d** and (*Z*)-**1a**,**b** with trichloroacetonitrile in the presence of a substoichiometric amount of DBU afforded bistrichloroacetimidates (*E*/*Z*)-**2a–e** and (*Z*)-**2a**,**b** (Scheme 1, Table 1).

In initial studies, imidates (*E*)-**2a-d** and (*Z*)-**2a**,**b** were exposed to catalytic amounts of neutral Pd(II) complex $PdCl_2(MeCN)_2$ (10 mol%) and the cationic Pd(II) complex derived from $Pd(PPh_3)_2Cl_2$ (1 mol%) and $AgBF_4$ (3 mol%).



Scheme 1 Synthesis of bisimidates **2** and their metal-catalyzed cyclization to oxazolines **3** and **4**

Table 1 Yields in the Synthesis of Bisimidates **2**

Entry	Diol **1**	R	Yield of imidate **2** (%)[a]
1	(*E*)-**1a**	Me	(*E*)-**2a** 79
2	(*Z*)-**1a**		(*Z*)-**2a** 89
3	(*E*)-**1b**	Ph	(*E*)-**2b** 80
4	(*Z*)-**1b**		(*Z*)-**2b** 88
5	(*E*)-**1c**	4-$MeOC_6H_4$	(*E*)-**2c** 85
6	(*E*)-**1d**	All	(*E*)-**2d** 80
7	(*E*)-**1e**	Bn	(*E*)-**2e** 69

[a] Isolated yield.

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In the case of $PdCl_2(MeCN)_2$ catalyst, formation of both isomeric oxazolines **3** and **4** were observed in a ratio that was mostly dependent on the substituent R (Table 2, entries 2, 4, 6, 8, 10, and 12). As observed for the cyclization of imidates (*E*)- and (*Z*)-**2a** the configuration of the double bond also had influence on the isomeric ratio. The catalytic system $PdCl_2(PPh_3)_2/AgBF_4$ induced the selective formation of 4,4-disubstituted oxazolines **3a–d** from all bistrichloroacetimidates **2a–d** used in this study (Table 2, entries 1, 3, 5, 7, 9, and 11).

Table 2 Pd(II)-Catalyzed Cyclization of Bisimidates **2** to Vinyloxazoline Isomers **3** and **4**

Entry	Imidate **2**	Catalytic system[a]	Time	Ratio **3/4**[b]	Yield (%)[c]
1	(*E*)-**2a** R = Me	A	3 d	8:1	70
2		B	1 h	>99:1	82
3	(*Z*)-**2a** R = Me	A	4 d	7:2	57
4		B	2 h	>99:1	79
5	(*E*)-**2b** R = Ph	A	6 d	3:1	94
6		B	1.5 h	>99:1	92
7	(*Z*)-**2b** R = Ph	A	7.5 h	3:1	74
8		B	1 h	>99:1	97
9	(*E*)-**2c** R = 4-$MeOC_6H_4$	A	2.5 h	28:1	93
10		B	1 h	>99:1	93
11	(*E*)-**2d** R = All	A	3 d	1:1	81
12		B	4 d	>99:1	75

[a] A: $PdCl_2(MeCN)_2$, 10 mol% in CH_2Cl_2; B: $PdCl_2(Ph_3P)_2$, 1 mol% and $AgBF_4$, 3 mol% in CH_2Cl_2.
[b] Determined by GC/MS analysis of a crude product.
[c] Isolated yield.

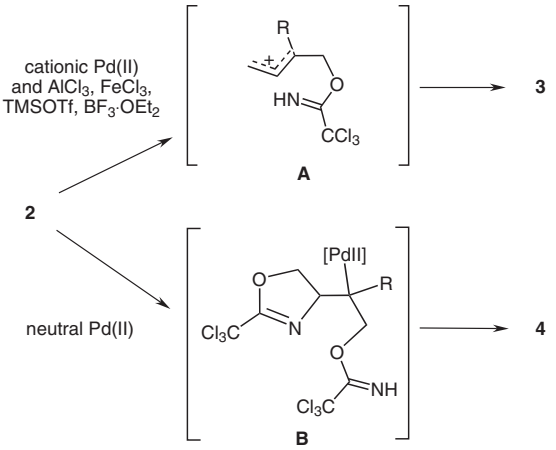
Next, imidates **2a–e** were exposed to a range of Lewis acids in catalytic amounts (Scheme 1, Table 3). From catalysts investigated, $AlCl_3$, $FeCl_3$, TMSOTf, $BF_3{\cdot}OEt_2$ promoted the cyclization of both (*E*)- and (*Z*)-imidates **2** in a short reaction time to give the product **3** in good to excellent yield. According to analysis of the crude reaction mixtures by GC-MS all Lewis acid catalysts examined promoted the formation of 4,4-disubstituted **3a–e** exclusively, with no detectable formation of isomeric oxazolines **4**. With $AgBF_4$ as the catalyst the reaction was very slow (Table 3, entries 5, 10, and 23).

The cationic Pd(II) complex and Lewis acids $AlCl_3$, $FeCl_3$ TMSOTf, $BF_3{\cdot}OEt_2$ catalyzed the formation of oxazoline **3** that can be explained by the abstraction of the imidate leaving group that leads to the most stable tertiary allylic carbenium ion **A**, which is trapped, in an intramolecular fashion, by the second imidate as an *N*-nucleophile.[20,21] On the other hand, neutral-Pd(II)-complex-catalyzed cyclization probably proceeds via a mechanism that involves aminopalladation, yielding intermediate **B** which then undergoes deoxypalladation to give product **4**.[18,19,21] Whether neutral-palladium-complex-catalyzed formation of both oxazolines **3** and **4** is due to an unselective amino-

Table 3 Lewis Acid Catalyzed Cyclization of Bisimidates **2** to Vinyloxazoline **3**

Entry	Imidate **2**	Catalyst[a]	Time	Yield of **3** (%)[c]
1	(*E*)-**2a** R = Me	$AlCl_3$	27 min	92
2		$FeCl_3$	30 min	89
3		TMSOTf	2 min	84
4		$BF_3{\cdot}OEt_2$	1 min	76
5		$AgBF_4$[b]	14 d	ca. 30[d]
6	(*Z*)-**2a** R = Me	$AlCl_3$	12 min	94
7		$FeCl_3$	10 min	64
8		TMSOTf	1 min	68
9		$BF_3{\cdot}OEt_2$	1 min	79
10		$AgBF_4$[b]	4 d	>99[d]
11	(*E*)-**2b** R = Ph	$AlCl_3$	10 min	94
12		$FeCl_3$	10 min	98
13		TMSOTf	1 min	90[e]
14		$BF_3{\cdot}OEt_2$	1 min	89[e]
15	(*Z*)-**2b** R = Ph	$AlCl_3$	5 min	96
16		$FeCl_3$	5 min	81
17		TMSOTf	1 min	86
18		$BF_3{\cdot}OEt_2$	1 min	96
19	(*E*)-**2c** R = 4-$MeOC_6H_4$	$AlCl_3$	20 min	90
20		$FeCl_3$	10 min	89
21		TMSOTf	1 min	80[e]
22		$BF_3{\cdot}OEt_2$	1 min	83[e]
23		$AgBF_4$[b]	1 d	93[d]
24	(*E*)-**2d** R = All	$FeCl_3$	30 min	40[e,f]
25		$BF_3{\cdot}OEt_2$	1 min	70[e,f]
26	(*E*)-**2e** R = Bn	$AlCl_3$[b]	1 h	92
27		$FeCl_3$[b]	2 h	70[e]
28		TMSOTf	5 min	79
29		$BF_3{\cdot}OEt_2$	1 min	85

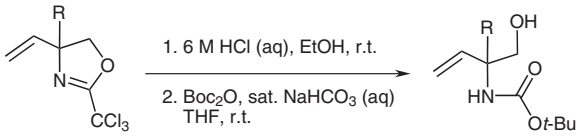
[a] Conditions: 10 mol% in CH_2Cl_2 if not otherwise indicated.
[b] Conditions: 20 mol% in CH_2Cl_2.
[c] Isolated yield if not otherwise indicated.
[d] Conversion.
[e] ^1H NMR yield, using 1,4-(bis-trichloromethyl)benzene as an internal standard.
[f] Formation of unidentified byproducts.



Scheme 2 Potential mechanistic pathways for the formation of isomeric vinyloxazolines **3** and **4**

palladation step or a concurrent pathway via intermediate **A** remains to be determined (Scheme 2).

In order to demonstrate the utility of the cyclization reactions, several 4-substituted 4-vinyloxazolines **3a–c** were transformed to *N*-Boc vinylglycinol derivatives **5a–c** by a one–pot, two-step procedure that involved hydrolysis and subsequent protection (Scheme 3).



3a, R = Me
3b, R = Ph
3c, R = 4-MeOC$_6$H$_4$

5a, 70%
5b, 79%
5c, 66%

Scheme 3 Transformation of vinyloxazolines **3a–c** to the corresponding *N*-Boc vinylglycinols **5a–c**

In summary, we have developed a short and high-yielding procedure for the synthesis of *C*-quaternary vinylglycinols starting from 2-substituted 1,4-butenediols. Our current attempts are devoted to develop an asymmetric version of bisimidate cyclization.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. It contains descriptions of the synthesis and characterization of diols **1** and bisimidates **2**, general procedures for the cyclization of bisimidates **2**, characterization of the cyclization products **3** and **4**, descriptions for the transformation of oxazolines **3** to *N*-Boc-protected vinylglycinols **5**, and copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2–5**.

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References

(1) Selected examples: (a) Jones, M. C.; Marsden, S. P.; Munoz Subtil, D. M. *Org. Lett.* **2006**, *8*, 5509. (b) Jones, M. C.; Marsden, S. P. *Org. Lett.* **2008**, *10*, 4125. (c) Fukuda, T.; Sugiyama, K.; Arima, S.; Harigaya, Y.; Nagamitsu, T.; Omura, S. *Org. Lett.* **2008**, *10*, 4239. (d) Ariza, X.; Cornell, J.; Font-Bardia, M.; Garcia, J.; Ortiz, J.; Sanchez, C.; Solans, X. *Angew. Chem. Int. Ed.* **2007**, *46*, 7704. (e) Oe, K.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2008**, *49*, 7426.

(2) Berkowitz, D. B.; Karukurichi, K. R.; Salud-Bea, R.; Maiti, G.; McFadden, J. M.; Morris, M. L. In *Asymmetric Synthesis and Application of α-Amino Acids, ACS Symposium Series*, Vol. 1009; Chap. 18; Soloshonok, V. A.; Izawa, K., Eds.; American Chemical Society: Washington DC, **2009**, 288.

(3) α-Alkylation of vinyl amino acid derivatives or their precursors: (a) Seebach, D.; Burger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669. (b) Di Giacomo, M.; Vinci, V.; Serra, M.; Colombo, L. *Tetrahedron: Asymmetry* **2008**, *19*, 247. (c) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365.

(4) Formal α-vinylation of amino acids: (a) Ma, D.; Zhu, W. *J. Org. Chem.* **2000**, *66*, 348. (b) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966.

(5) Addition of vinylmetals to α-imino esters: Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449.

(6) Olefination of α-formyl amino acids: (a) Berkowitz, D. B.; Chisowa, E.; McFadden, J. M. *Tetrahedron* **2001**, *57*, 6329. (b) Colson, P. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918.

(7) [2,3]-Sigmatropic rearrangement of selenimides: Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2011**, *13*, 1040.

(8) Murga, J.; Portolés, R.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1807.

(9) Berkowitz, D. B.; Pumphrey, J. A.; Shen, Q. *Tetrahedron Lett.* **1994**, *35*, 8743.

(10) (a) Berkowitz, D. B.; Wu, B.; Li, H. *Org. Lett.* **2006**, *8*, 971. (b) Fischer, D. F.; Xin, Z.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 7704. (c) Fischer, D. F.; Barakat, A.; Xin, Z.; Weiss, M. E.; Peters, R. *Chem. Eur. J.* **2009**, *15*, 8722.

(11) Matsukawa, Y.; Isobe, M.; Kotsuki, H.; Ichikawa, Y. *J. Org. Chem.* **2005**, *70*, 5339.

(12) (a) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220. (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653. (c) Nakamura, T.; Tsuji, T.; Iio, Y.; Miyazaki, S.; Takemoto, T.; Nishi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 2781. (d) Wybrow, R. A. J.; Edwards, A. S.; Stevenson, N. G.; Adams, H.; Johnstone, C.; Harrity, J. P. A. *Tetrahedron* **2004**, *60*, 8869. (e) Flock, S.; Frauenrath, H. *Synlett* **2001**, 839.

(13) (a) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (b) Trost, B. M.; Jiang, C.; Hammer, K. *Synthesis* **2005**, 3335. (c) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836. (d) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713. (e) Keith, F.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.

(14) Portolés, R.; Murga, J.; Falomir, E.; Carda, M.; Uriel, S.; Marco, J. A. *Synlett* **2002**, 711.

(15) Sugiyama, S.; Arai, S.; Kiriyama, M.; Ishii, K. *Chem. Pharm. Bull.* **2005**, *53*, 100.

(16) Bach, T.; Koerber, C. *J. Org. Chem.* **2000**, *65*, 2358.

(17) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irle, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887.

(18) (a) Maleckis, A.; Jaunzeme, I.; Jirgensons, A. *Eur. J. Org. Chem.* **2009**, 6407. The first precedent for Pd (II)-catalyzed formation of 4-vinyloxazoline from allylic bistrichloroacetimidate: (b) Sabat, M.; Johnson, C. R. *Org. Lett.* **2000**, *2*, 1089.

(19) Jaunzeme, I.; Jirgensons, A. *Tetrahedron* **2008**, *64*, 5794.

(20) Grigorjeva, L.; Jirgensons, A. *Eur. J. Org. Chem.* **2011**, 2421.

(21) For discussion on different reaction pathways of cationic and neutral Pd(II) complexes with allylic imidates, see: Overman, L. E.; Hollis, T. K. *J. Organomet. Chem.* **1999**, *576*, 290.