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# Synthesis of 1,2-Dihydropyridines Using Vinyloxiranes as Masked Dienolates in Imino-Aldol Reactions

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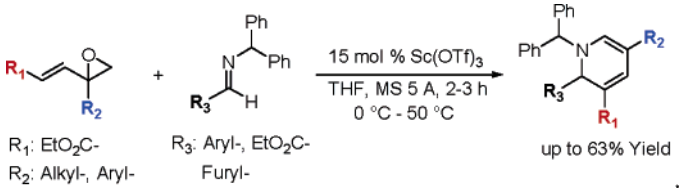
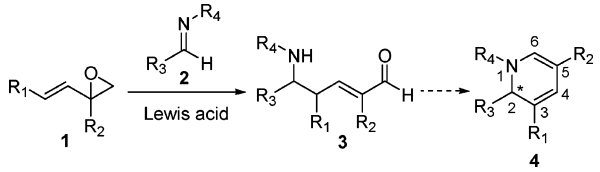
## ABSTRACT




**The application of vinyloxiranes, substituted with an electron-withdrawing group, as masked dienolates in vinylogous imino-aldol reactions was achieved. Under the reaction conditions highly substituted 1,2-dihydropyridines were obtained in moderate to good yields. Mechanistic studies indicate that the reaction proceeds via the formation of an (*E*)-amino-α,*β*-unsaturated aldehyde, followed by isomerization to the (*Z*)-isomer, cyclization, and elimination of a water molecule, leading to the formation of the 1,2-dihydropyridine.**

Vinyloxiranes are valuable building blocks for a variety of synthetic transformations and have found wide applications in organic synthesis.[1] In particular, transition metal and Lewis acid catalyzed ring opening of the epoxides, with subsequent rearrangement, gives access to useful products for the synthesis of biologically active compounds.[2,3] Recently, our group reported the amphoteric character of 2-vinyloxiranes in the presence of a Lewis acid.[4a] The 2-vinyloxiranes are either used as synthetic equivalents for *β*,*γ*-unsaturated aldehydes (electrophiles) or dienols (nucleophiles). Thus, the reaction of 2-vinyloxiranes with aldehydes[4a] and subsequently with aldimines[4b,4c] (Scheme 1) was demonstrated, and the preparation of silyl-dienolates was avoided.[5] We now apply this methodology to a new synthesis of 1,2-dihydropyridines, which are not easily accessible by other methods. Usually,

**Scheme 1.** Vinylogous Imino-Aldol Reactions with Substituted 2-Vinyloxiranes and Their Proposed Transformation to 1,2-Dihydropyridines **4**




1,2-dihydropyridines are synthesized through a nucleophilic addition onto *N*-acyl- or *N*-alkylpyridinium salts.[6] However,

(1) For a review, see: (a) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503−1511. For recent examples, see: (b) Trost, B. M.; Brown, B. S.; McEachern, E. J. *Chem. Eur. J.* **2003**, *9*, 4442−4451. (b) Restorp, P.; Somafai, P. *Chem. Commun.* **2004**, 2086−2087, (c) Pineschi, M.; Bertolini, F.; Haak, R. M.; Crotti, P.; Macchia, F. *Chem. Commun.* **2005**, 1426−1428.

(2) For recent examples with transition metals, see: (a) Marion, F.; Calvet, S.; Marie, J.-C.; Courillon, C.; Malacria, M. *Eur. J. Org. Chem.* **2006**, 453−462. (b) Courillon, C.; Fol, R. F.; Vandendris, E.; Malacria, M. *Tetrahedron Lett.* **1997**, *38*, 5493−5496

(3) For recent examples with Lewis acids, see: (a) Deng, X.-M.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6537−6540. (b) Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605−2608. (c) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825−826.

(4) (a) Lautens, M.; Quellet, S. G.; Raeppel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4079−4082. (b) Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, *6*, 345−347. (c) Lautens, M.; Tayama, E.; Nguyen, D. *Tetrahedron Lett.* **2004**, *45*, 5131−5133.

(5) For a review of vinylogous aldol reactions, see: (a) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682−4698. For a review on vinylogous Mannich reactions, see: (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221−3242.

(6) For reviews of dihydropyridines, see: (a). Lavilla, R. *J. Chem.* Soc., *Perkin Trans. 1* **2002**, 1141−1156. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223−243. For representative procedures for the preparation of 1,2-dihydropyridines, see: (c) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830. (d) Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197−7199.

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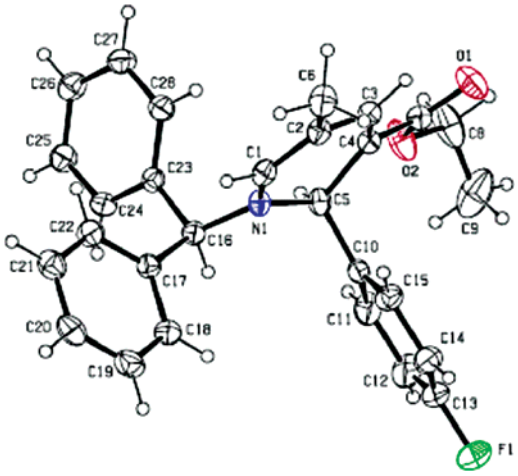
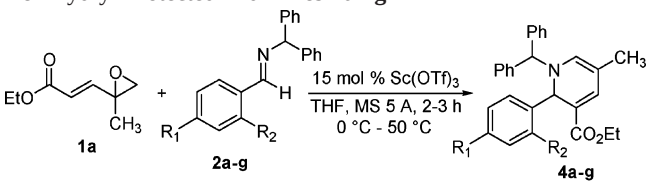



**Figure 1.** Crystal structure of 1,2-dihydropyridine **4a**.

unsymmetrically substituted pyridinium salts often result in inseparable mixtures because the nucleophile attacks at the 2, 4, or 6 position.[6,7] Herein, we report a novel method that overcomes these selectivity problems and allows the synthesis of 2-, 3-, and 5-substituted 1,2-dihydropyridines (Scheme 1).

We focused our studies on the investigation of 2-vinyloxirane **1** bearing an electron-withdrawing group on the vinyl moiety (e.g., $R_1 = EtO_2C-$, Scheme 1), on the basis of the following considerations: the vinyloxiranes are (1) easily accessible[8] and (2) relatively stable during purification and storage, and most importantly (3) cyclization of **3** to the corresponding 1,2-dihydropyridine **4** was possible. We assumed that the presence of an electron-withdrawing group $R_1$ would facilitate the *E*/*Z*-isomerization that is required for the cyclization. We initiated our investigations with the reaction of vinylepoxide **1a** with a benzhydryl-protected aldimine **2a** in the presence of a catalytic amount of Sc(OTf)$_3$.[9] Under the optimized reaction conditions (15 mol % Sc(OTf)$_3$, 1.5 equiv of vinylepoxide **1a**, 1.0 equiv of aldimine **2a**, 0−50 °C in THF),[10] the desired 1,2-dihydropyridine **4a** was obtained in 61% isolated yield as a stable crystalline compound.[11] The structure was confirmed by X-ray analysis (Figure 1).[12] The crystal structure shows that the *p*-fluorophenyl group is almost orthogonal to the dihydropyridine ring.[13] It is important to note that a water-stable Lewis acid must be employed because of the release of 1 equiv of water during the reaction. Other Lewis acids such as $BF_3$·$OEt_2$ were far less effective.[14] In general the conversions of the aldimines were high (>70%)[15] using *para*-halogen-substituted aldimines **2a**−**c**, and so 1,2-dihydropyridines **4a**−**c** were obtained in good yields.

**Table 1.** Scope of the Reaction Using Vinylepoxide **1a** and Benzhydryl-Protected Aldimines **2a**−**g**

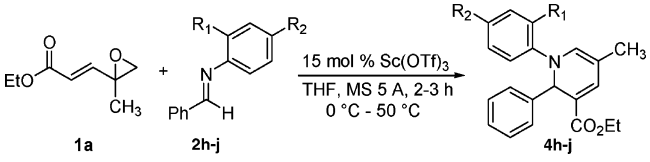



| entry[a] | $R_1$ | $R_2$ | **2**; **4** | conv **2** [%][b] | yield **4** [%][c] |
|---|---|---|---|---|---|
| 1 | F | H | **a** | 70 | 61 |
| 2 | Cl | H | **b** | 70 | 60 |
| 3 | Br | H | **c** | 75 | 62 |
| 4 | H | H | **d** | 65 | 37 |
| 5 | $NO_2$ | H | **e** | 75 | 43 |
| 6 | Cl | Cl | **f** | 70 | 53 |
| 7 | H | Bpin | **g** | 47[d] | 19 |

[a] All reactions were performed by using 0.75 mmol of **1** and 0.5 mmol of **2** in 1.0 mL of dry THF. [b] Determined via $^1$H NMR spectroscopy from the crude product. [c] Isolated yields. [d] 15% of the aldimine is hydrolyzed into the corresponding aldehyde.

Nitro- and boronic ester substituted aldimines **2e** and **2g** were also reactive and stable under the reaction conditions. The decreased conversion of aldimine **2g** is probably due to the bulky *ortho*-substituent. We next turned our attention to the reaction of vinyloxiranes with aryl-protected aldimines (Table 2). The aryl-protected aldimines showed higher reactivity but less stability in the presence of the Lewis acid, resulting in partial hydrolysis of the aldimine to give the corresponding amine and aldehyde moiety. Fortunately, *ortho*-substituted aldimines ($R_1$ = I, Br) are sufficiently stable

**Table 2.** Scope of the Reaction Using Vinylepoxide **1a** and Aryl-Protected Aldimines **2h**−**j**




| entry[a] | $R_1$ | $R_2$ | **2**; **4** | conv **2** (%)[b] | yield **4** (%)[c] |
|---|---|---|---|---|---|
| 1 | I | H | **h** | 100[d] | 51 |
| 2 | Br | H | **i** | 100[d] | 37 |
| 3 | Br | $OCH_3$ | **j** | 88[e] | 41 |

[a] All reactions were performed by using 0.75 mmol of **1** and 0.5 mmol of **2** in 1.0 mL of dry THF. [b] Determined via $^1$H NMR spectroscopy from the crude product. [c] Isolated yields. [d] 20−30% of the aldimine is hydrolyzed into the corresponding aldehyde. [e] 10% of the aldimine is hydrolyzed into the aldehyde

(7) Bennasar, M. L.; Roca, R.; Monerris, M.; Juan, C.; Bosch, J. *Tetrahedron* **2002**, *58*, 8099−8106.

(8) For the preperation of the vinyloxiranes **1a** and **1b**, see Supporting Information.

(9) Other *N*-alkyl aldimines (e.g., *N*-phenyl, *N*-allyl) showed no or poor reactivity, and no or just minor product formation was observed.

(10) For a solvent screening, see Supporting Information.

(11) It is highly recommended to perform the reactions at a scale of at least 0.5 mmol; otherwise reduced yields are obtained as a result of decomposition of the product on silica gel.

(12) Product **4f** gave also crystals suitable for X-ray analysis. See Supporting Information.

(13) For a previously reported crystal structure, see: Krow, G. R.; Raghavachari, R. *J. Org. Chem.* **1986**, *51*, 1916−1918.

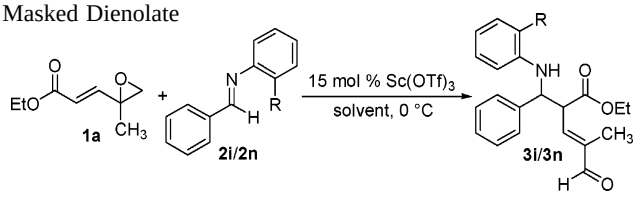
(14) Results with $BF_3$·$OEt_2$ as a Lewis acid in the reaction of **1a** with **2a** to **4a**: 30 mol % $BF_3$, messy reaction; 1.5 equiv of $BF_3$, 18% isolated yield of **4a**.

(15) We assume that the nonquantitative conversions are due to the coordination of the product **4** to Sc(OTf)$_3$, which results in an inhibition of the catalytic cycle and therefore product inhibition.

in the presence of strong Lewis acids to afford dihydropyridines **4h**−**4j** in moderate yields (37−51%).

During our studies on the reactions of vinylepoxide **1a** with benzhydryl- and aryl-protected aldimines, we observed that aryl-protected aldimines are more reactive than the benzhydryl-protected aldimines in the vinylogous imino-aldol reaction (Table 3) as a result of their increased electrophilic

**Table 3.** Synthesis of $\beta$-Aminoesters **3** through a Direct Vinylogous Imino-Aldol Reaction Using Vinyloxirane **1a** as Masked Dienolate

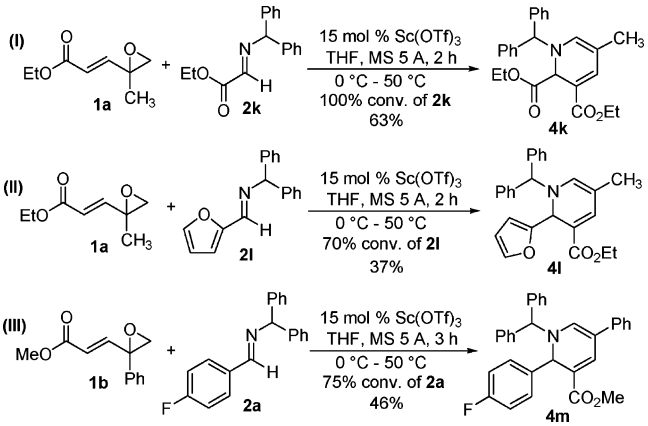



| entry | R | condition[a] | **2**; **3** | yield (%)[b] |
|---|---|---|---|---|
| 1 | Br | A | **i** | 48[c] |
| 2 | Br | B | **i** | 74 |
| 3 | $CF_3$ | B | **n** | 81 |

[a] Condition A: reaction was performed by using 0.75 mmol of **1a** and 0.5 mmol of **2** in 1.0 mL dry THF. Condition B: reactions were performed by using 0.75 mmol of **1a** and 0.5 mmol of **2** in a solvent mixutre of 1.0 mL of THF and 1.0 mL of toluene. [b] Isolated yields. [c] 35% of the aldimine is hydrolyzed into the corresponding aldehyde and amine.

character. However, the cyclization to the 1,2-dihydropyridine occurs faster using the benzhydryl-protected aldimine as a result of the higher nucleophilicity of the nitrogen. Therefore, we decided to explore α-iminoester **2k** (Scheme 2 (I)), which should combine the two advantages. A clean

**Scheme 2.** Variation of the Substituents on the Aldimine Building Block **(**I, II**)** and the Vinyloxirane Building Block **(III)**



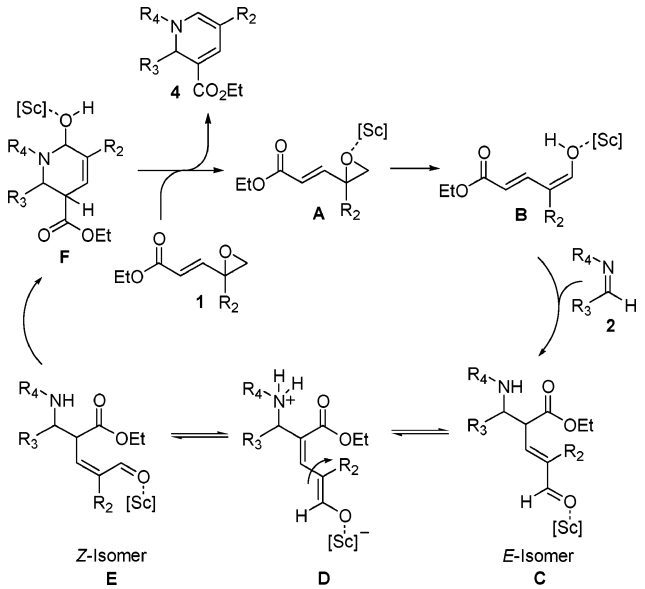

reaction was observed, and the desired 1,2-dihydropyridine **4k** was obtained in 63% yield after column chromatography. The heteroaryl-aldimine **2l** was also stable and reactive under the standard reaction conditions, and the corresponding 1,2-dihydropyridine was isolated in 37% yield. The variation of substituent $R_2$ ($R_2$ = Ph, Scheme 2 (III)) at the vinyloxirane was also perfomed. We found, that the phenyl-substituted vinyloxirane **1b** is still reactive in the vinylogous imino-aldol reaction, giving 1,2-dihydropyridine **4m** in 46% isolated yield.

When we used aldimines **2i/n** substituted with electron-withdrawing groups (**2i** R = Br, **2n** R = $CF_3$) and performed the reaction at 0 °C, the corresponding (*E*)-amino-α,$\beta$-unsaturated aldehydes **3i** and **3n** were obtained in moderate to good isolated yields (Table 3).[16,17] This discovery confirmed our assumption that an (*E*)-amino-α,$\beta$-unsaturated aldehyde is a likely reaction intermediate (Scheme 1).

When a mixed solvent (toluene/THF 1:1) was used, satisfactory yields were achieved with 74% and 81% for the formation of the addition-only products, **3i** and **3n** (Table 3, entries 2 and 3).[18] When $\beta$-aminoester **3i** was subjected to the reaction conditions without $Sc(OTf)_3$, no desired product **4i** was observed. Only after the addition of 15 mol % $Sc(OTf)_3$ to the reaction mixture at 50 °C was the corresponding 1,2-dihydropyridine **4i** formed. The crude $^1H$ NMR spectrum showed a complete conversion of the (*E*)-amino-α,$\beta$-unsaturated aldehyde **3i** to the dihydropyridine **4i**. However, after column chromatography the 1,2-dihydropyridine was isolated in poor yield (28%), which again demonstrates the low stability of this type of 1,2-dihydropyridines.[11]

Based on the experimental data, we propose the mechanism described in Scheme 3 for the formation of the 1,2-

**Scheme 3.** Proposed Catalytic Cycle for the Formation of 1,2-Dihydropyridines




dihydropyridines. Following a coordination of $Sc(OTf)_3$ to

(16) The *E*-configuration of the double bond was confirmed by ROESY NMR spectroscopy.

(17) The diastereomeric ratios of the products are 1.3:1 for **3n** and 1.9:1 for **3i**.

(18) (a) This is not just an effect of the lower concentration of the reaction mixture (0.25 M). When the reaction was performed solely in THF (0.25 M) or toluene (0.25 M), messy reactions were observed in both cases. (b) Application of this solvent system for the synthesis of the 1,2-dihydropyridines in Tables 1 and 2 gave no improvement in the yields.

the vinyloxirane **1** to give complex **A**, intermediate **B** is generated by ring opening of the epoxide followed by a 1,2-hydride shift and a subsequent enolization.[4] Intermediate **B** reacts with aldimine **2** in a vinylogous imino-aldol reaction to give the (*E*)-amino-α,*β*-unsaturated aldehyde **C**. The (*E*)-isomer **C** isomerizes under the influence of $Sc(OTf)_3$ to the (*Z*)-isomer **E**. The *E*/*Z*-isomerization probably occurs via the dienolate intermediate **D**, whose formation is accelerated by the ester group. The (*Z*)-amino-α,*β*-unsaturated aldehyde **E** can cyclize to the hemiaminal **F**, and in the last step the elimination of water occurs to give the corresponding 1,2-dihydropyridine **4**.

In summary, we have developed a new one-pot procedure for the synthesis of substituted 1,2-dihydropyridines by a $Sc(OTf)_3$-catalyzed reaction of 2-vinyloxiranes with aldimines. The process is very flexible with regard to the substituents on the aldimine as well as the vinyloxirane moiety and gives access to 1,2-dihydropyridines that are selectively substituted at the 1, 2, 3, and 5 position.

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**Supporting Information Available:** Experimental procedures and characterization of all new compounds, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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