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# Direct Vinylation and Ethynylation of Nitrones. Stereodivergent Synthesis of Allyl and Propargyl Amines.

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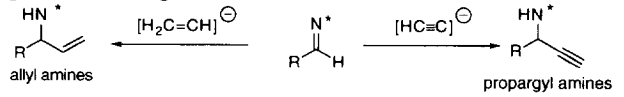
**Abstract:** The addition of vinyl and ethynyl organometallic reagents to the nitrone derived from D-glyceraldehyde affords allyl and propargyl hydroxylamines which are easily converted into the corresponding allyl and propargyl amines. The stereoselectivity of the addition step can be controlled by the presence (or absence) of diethyl aluminium chloride.


Introduction of vinyl and ethynyl substituents into acyclic compounds bearing a carbon-nitrogen double bond appears as an interesting valuable goal in view of the synthetic and biological importance of the resulting allyl and propargyl amines.[1] Propargyl amines are usually prepared by direct amination of propargyl substrates such as esters, halides, oxyphosphonium salts or triflates[1e] and only one report concerning the direct ethynylation of a chiral imine has been published.[2] The classical approaches to chiral allyl amines involve the introduction of an amino function into the allylic position,[3] olefination of α-aminoaldehydes,[4] reduction of propargyl amines,[1a] and deoxygenation of 3-amino-1,2-diols.[5] More recently, a report from Enders and co-workers[6] made use of the addition of vinyl and ethynyl organometallic reagents for preparing both allyl and propargyl amines in an enantioselective way.

Apart from the above-mentioned reports,[2,5] we are aware of only a few examples[7] in which a vinyl (or ethynyl) organometallic reagent has been added to a chiral imine. Moreover, in such cases the allyl and propargyl amines are difficult to obtain with high yields and stereocontrol. Alternative approaches using other chiral, non racemic substrates bearing a carbon-nitrogen double bond[8] different from imines have been scarcely studied.[9]

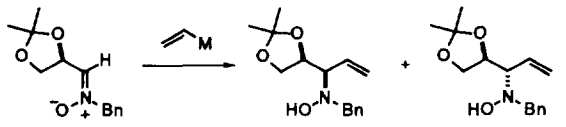



allyl amines propargyl amines

N* = NR, NOR, N-NR$_2$, N$^+$(O$^-$)R

We have extensively demonstrated the utility of nitrones as suitable building blocks for the synthesis of a variety of nitrogen-containing compounds such as α-amino aldehydes, α-amino acids, aminosugars, and α-amino nitriles.[10] In particular we have recently reported the reaction of vinylmagnesium bromide with several non-chiral nitrones to give the corresponding allyl amines in high yields.[11] Now, we wish to report herein the first totally stereocontrolled addition of both vinyl and ethynyl organometallic reagents to nitrone **1**, leading to a stereodivergent synthesis of allyl and propargyl amines. The results of the addition of vinyl organometallic reagents to the nitrone **1** are summarized in Table I (see Scheme 1).

Scheme 1



1 2a 2b

**Table I.** Diastereoselective Addition of Vinyl Reagents to Nitrone **1**.

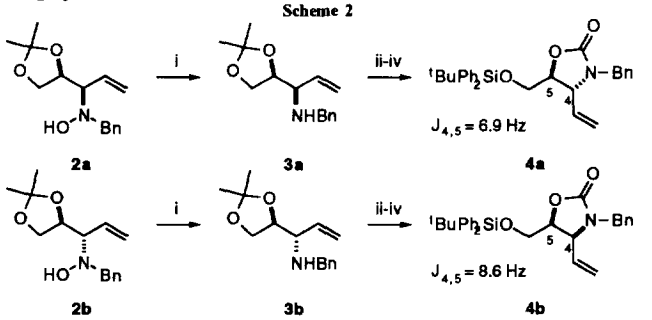
| entry | M (eq) | Lewis acid[a] | solvent (T°) | time | syn/anti[b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | MgBr (1.2) | none | THF (0 °C) | 1 h | 76 : 24 | 86 |
| 2 | MgBr (1.2) | $ZnBr_2$ | $Et_2O$ (0 °C) | 1 h | 53 : 47 | 84 |
| 3 | MgBr (1.2) | $MgBr_2$ | $Et_2O$ (0 °C) | 1 h | 56 : 44 | 80 |
| 4 | MgBr (1.2) | $Et_2AlCl$ | $Et_2O$ (0 °C) | 1 h | 8 : 92 | 86 |
| 5 | $CeCl_3$ (1.2) | none | THF (-40 °C) | 2 h | 58 : 42 | 74 |
| 6 | $CeCl_3$ (1.2) | $Et_2AlCl$ | THF (-40 °C) | 2 h | 30 : 70 | 78 |
| 7 | $CuLi)_{1/2}$ (1.0) | none | THF (-80 °C) | 2 h | 70 : 30 | 80 |
| 8 | $CuLi)_{1/2}$ (1.0) | $Et_2AlCl$ | THF (-80 °C) | 2 h | 22 : 78 | 79 |
| 9 | Li (1.5) | none | THF (-80 °C) | 15 min | 35 : 65 | 90 |
| 10 | Li (1.5) | $Et_2AlCl$ | $Et_2O$ (-80 °C) | 15 min | 4 : 96 | 92 |
| 11 | $AlEt_2$ (1.1) | none | $Et_2O$ (-40 °C) | 2 h | 52 : 48 | 86 |
| 12 | $AlEt_2$ (3.0) | none | $Et_2O$ (-40 °C) | 2 h | 32 : 68 | 87 |

[a] Nitrone was precomplexed with 1.0 eq of the Lewis acid prior to the addition. [b] Measured from the intensities of $^1H$ NMR signals. [c] Determined on isolated mixtures of syn and anti adducts.

The best result for preparing the syn-hydroxylamine **2a** was obtained using 1.2 eq of vinyl magnesium bromide at 0 °C in THF as a solvent (Table I, entry 1). The stereoselective course of the reaction changes dramatically when several Lewis acids were used for precomplexing nitrone **1** (Table I, entries 2-4). With $Et_2AlCl$ a complete reversal of the selectivity was achieved (Table I, entry 4). This behaviour had been observed in our laboratories with other nucleophiles[12] and models for explaining the course of the reaction were proposed by us.[13] Similar results were obtained with vinylcerium (Table I, entries 5 and 6) and vinylcuprate (Table I, entries 7 and 8) derivatives. On the other hand, vinyllithium was not selective in the absence of Lewis acids (Table I, entry 9), although in the presence of $Et_2AlCl$ a high anti-selectivity was observed (Table I, entry 10). The stereoselectivity of the addition of diethylvinylaluminium could be controlled by the stoichiometry of the organometallic reagent (Table I, entries 11 and 12).

The obtained hydroxylamines[14] **2** were transformed into the corresponding allyl amines[14] **3** by using the $Zn^0/Cu^{II}$ couple as reducing system[15] (Scheme 2).

Scheme 2



2a 3a 4a

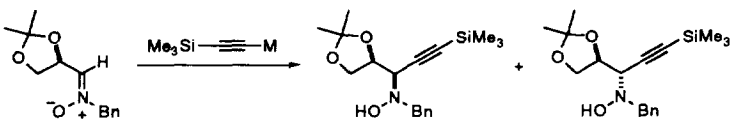
2b 3b 4b

**Reagents and conditions.** i, Zn, $Cu(OAc)_2$, AcOH, 70°C, 1 h. ii, p-TosOH, MeOH, reflux, 1 h. iii, $^t$BuMeSiCl, $CH_2Cl_2$, DMAP, 16 h, r.t. iv, $In_2CO$, THF, 24 h, r.t.

The relative stereochemical assignment for **2** was derived from that of the oxazolidinones[14] **4**, which were prepared as depicted in Scheme 2. The relative stereochemistry of **4** was determined on the basis of the

coupling constant ($J_{H4}$-$J_{H5}$) and nOe data.[16] The addition of lithium trimethylsilylacetylide to **1** took place smoothly at -80 °C in THF as a solvent (Scheme 3). The reaction showed to be quantitative and only the syn diastereomer **5a** could be detected by $^1$H NMR and GC (Table II, entry 1). Consistent with the previously described results, when nitrone **1** was precomplexed with 1.0 eq of $Et_2AlCl$, the anti hydroxylamine **5b** was obtained as major product (Table II, entry 2).

**Scheme 3**




**1** **5a** **5b**

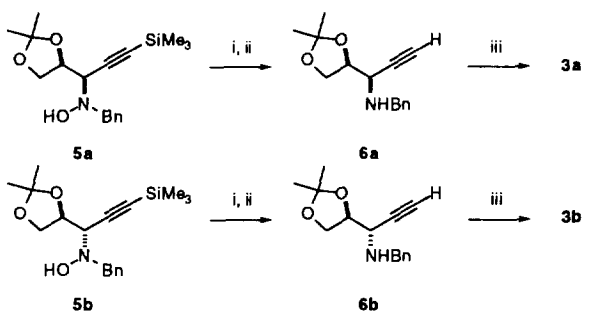
**Table II.** Diastereoselective Addition of Ethynyl Reagents to Nitrone **1**.

| entry | M (eq) | Lewis acid[a] | solvent (T°) | time | syn/anti[b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | Li (1.5) | none | THF (-80 °C) | 1 h | ≥ 95 : 5 | 100 |
| 2 | Li (1.5) | $Et_2AlCl$ | THF (-80 °C) | 1 h | 29 : 71 | 96 |

[a] Nitrone was precomplexed with 1.0 eq of the Lewis acid prior to the addition. [b] Measured from the intensities of $^1$H NMR signals. [c] Determined on isolated mixtures of syn and anti adducts.

Hydroxylamines[17] **5** were desilylated and deoxygenated to yield the enantiomerically pure propargyl amines[17] **6** (Scheme 4). The stereochemical assignment for **5** was made by their transformation into the allyl amines **3** whose stereochemistry had been previously determined as described above.

**Scheme 4**




**Reagents and conditions.** i, THF, $Bu_4NF$, r.t., 1 h. ii, Zn, $Cu(OAc)_2$, AcOH, 70°C, 1 h. iii, $H_2$, Lindlar, 1 atm, 1 h, r.t.

Finally, we have also checked the action of several Lewis acids over other D-glyceraldehyde derived substrates such as oximes and imines and no stereocontrol was observed in any case. Only nitrone **1** offers the possibility of preparing both syn and anti adducts.

In conclusion, an efficient stereoselective synthesis of both allyl and propargyl amines has been developed. These results present, to the best of our knowledge, the first example of a totally stereocontrolled diastereoselective addition of a vinyl (and ethynyl) organometallic reagent to a carbon-nitrogen double bond. The extension and application of this new approach to the total synthesis of natural products is currently investigated in our laboratories and it will be reported in due course.

**Acknowledgement.** Financial support by DGICYT (Project PB94-0598, Madrid) is gratefully acknowledged.

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8. $N^*$ refers to a nitrogen functionality such as NR (imine), NOR (oxime), N-$NR_2$ (hydrazone), $N^+(O^-)R$ (nitrone)
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14. Data for **2a**: $[\alpha]_D$ = +28.2 (c 0.43, $CHCl_3$); **2b**: $[\alpha]_D$ = -44.8 (c 1.10, $CHCl_3$); **3a**: $[\alpha]_D$ = -27.4 (c 1.21, $CHCl_3$); **3b**: $[\alpha]_D$ = +10.0 (c 0.47, $CHCl_3$); **4a**: $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 3.75 (dd, 1H, J = 4.6, 11.5 Hz), 3.80 (dd, 1H, J = 3.6, 11.5 Hz), 3.93 (d, 1H, J = 14.9 Hz), 4.10 (dd, 1H, J = 8.6, 9.1 Hz), 4.52 (ddd, 1H, J = 3.6, 4.6, 8.6 Hz), 4.83 (d, 1H, J = 14.9 Hz), 5.20 (d, 1H, J = 17.1 Hz), 5.35 (d, 1H, J = 10.1 Hz), 5.87 (ddd, 1H, J = 9.1, 10.1, 17.1 Hz), 7.30-7.70 (m, 15H); **4b**: $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 9H), 3.62 (dd, 1H, J = 3.4, 11.6 Hz), 3.83 (dd, 1H, J = 3.7, 11.6 Hz), 3.98 (d, 1H, J = 15.0 Hz), 4.03 (dd, 1H, J = 6.9, 8.7 Hz), 4.15 (ddd, 1H, J = 3.4, 3.7, 6.9 Hz), 4.81 (d, 1H, J = 15.0 Hz), 5.14 (d, 1H, J = 17.0 Hz), 5.30 (d, 1H, J = 9.9 Hz), 5.65 (ddd, 1H, J = 8.7, 9.9, 17.0 Hz), 7.28-7.64 (m, 15H).
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16. While a strong nOe was observed between $H_4$ and $H_5$ for **4b**, no nOe was detected between the same protons for **4a**.
17. Data for **5a**: $[\alpha]_D$ = -28.2 (c 0.68, $CHCl_3$); **5b**: $[\alpha]_D$ = +43.5 (c 0.32, $CHCl_3$); **6a**: $[\alpha]_D$ = -50.3 (c 0.45, $CHCl_3$); **6b**: $[\alpha]_D$ = +36.8(c 0.71, $CHCl_3$).

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