Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 11, pp. 1725–1729, 1997

Printed in Great Britain
PII: S0957-4166(97)00175-4
0957-4166/97 $17.00 + 0.00

Stereocontrolled addition of Grignard reagents to α-alkoxy nitrones. Synthesis of *syn* and *anti* 3-amino-1,2-diols

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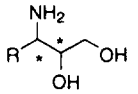
Abstract: The stereoselective addition of Grignard reagents to α-alkoxy nitrones has been achieved with excellent stereocontrol using $ZnBr_2$ and Et_2AlCl as precomplexing agents to obtain the corresponding *syn*- and *anti*- adducts, respectively. The obtained hydroxylamines have been transformed into valuable 3-amino-1,2-diols. © 1997 Elsevier Science Ltd

Internal 1,2-asymmetric induction in nucleophilic additions to C=N bonds is a subject of current interest.[1] These reactions often allow the preparation, in an enantiomerically pure form, of small molecules possessing various functional groups (such as hydroxy or amino) which make them of utility within the field of asymmetric synthesis. Additions to imines bearing a chiral center in α-position have been intensively investigated.[2] Also, several examples of nucleophilic additions to oximes[3] and hydrazones[4] can be found in the recent literature. On the other hand, there are only a few examples regarding nucleophilic additions to chiral nitrones,[5] some of them reported from this laboratory.[6] Good selectivities have been achieved in many cases, both in acyclic systems[2f,h] and when the chiral center in α-position forms a part of a rigid system.[2g] Also, tunable selectivities are achieved by changing the protecting groups arrangement in the starting compound.[2k] Models to rationalize these behaviours have been described.[2h] However, to the best of our knowledge there is only one case in which the nucleophilic addition to the C=N system could be stereocontrolled without changing neither the substrate nor the nucleophile; in other words, by only changing the reaction conditions.[2e]



3-amino-1,2-diols

We have previously reported several nucleophilic additions to α-alkoxy nitrones in which a total stereocontrol could be raised by precomplexing the nitrone with the appropriate Lewis acid.[6e,f] Among the employed nucleophiles are 2-lithiothiazole,[6e] 2-lithiofuran,[6f] 2-lithioimidazole[6g] and vinyl and ethynyl organometallic derivatives.[6c] In this communication we wish to report that an efficient stereocontrol can be exerted over the nucleophilic addition of Grignard reagents to the N-benzyl nitrone derived from 1,2-O-isopropylidene D-glyceraldehyde. The obtained hydroxylamines are direct precursors of both *syn* and *anti* 3-amino-1,2-diols. The synthetic utility of the 3-amino-1,2-diol unit has been well-demonstrated since it is prevalent in a multitude of synthetic processes leading to the preparation of biologically active molecules such as several classes of amino acids as well as dipeptide isosteres.[7]

The readily available[8] nitrone **1** was subjected to Grignard reactions; the results are summarized in Table 1. In the absence of Lewis acid the *syn* adduct was the major product of the reaction, the best results being obtained with THF as a solvent (entries 1, 7 and 12). When the reaction was run after treatment of the nitrone **1** with 1.1 equivalents of $ZnBr_2$ (entries 4, 9 and 13) the *syn* selectivity was

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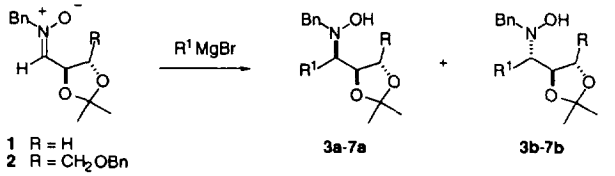
Table 1. Stereoselective additions of grignard reagents to α-alkoxy nitrones **1** and **2**[a]

entry	nitrone	RMgBr[b]	solvent	Lewis acid[c]	hydroxylamine	syn : anti[d]	yield[e] (%)
1	**1**	PhMgBr	THF	none	**3**	73 : 27	84
2	**1**	PhMgBr	Et_2O	none	**3**	65 : 35	78
3	**1**	PhMgBr	toluene	none	**3**	70 : 30	81
4	**1**	PhMgBr	Et_2O	$ZnBr_2$	**3**	78 : 22	86
5	**1**	PhMgBr	THF	Et_2AlCl	**3**	29 : 71	83
6	**1**	PhMgBr	Et_2O	Et_2AlCl	**3**	15 : 85	78
7	**1**	MeMgBr	THF	none	**4**	70 : 30	81
8	**1**	MeMgBr	Et_2O	none	**4**	69 : 31	83
9	**1**	MeMgBr	Et_2O	$ZnBr_2$	**4**	82 : 18	80
10	**1**	MeMgBr	THF	Et_2AlCl	**4**	33 : 67	87
11	**1**	MeMgBr	Et_2O	Et_2AlCl	**4**	18 : 82	76
12	**1**	EtMgBr	THF	none	**5**	75 : 25	74
13	**1**	EtMgBr	Et_2O	$ZnBr_2$	**5**	78 : 22	71
14	**1**	EtMgBr	Et_2O	Et_2AlCl	**5**	30 : 70	81
15	**2**	PhMgBr	THF	none	**6**	93 : 7	84
16	**2**	PhMgBr	Et_2O	Et_2AlCl	**6**	35 : 65	82
17	**2**	EtMgBr	THF	none	**7**	80 : 20	83
18	**2**	EtMgBr	Et_2O	Et_2AlCl	**7**	26 : 74	86

[a] All reactions were carried out at -40 °C for 6 h. [b] 1.5 equiv. were used. [c] 1.1 equiv. were used. [d] Measured from the intensities of ^1H NMR signals. [e] Determined on isolated mixture of diastereomers

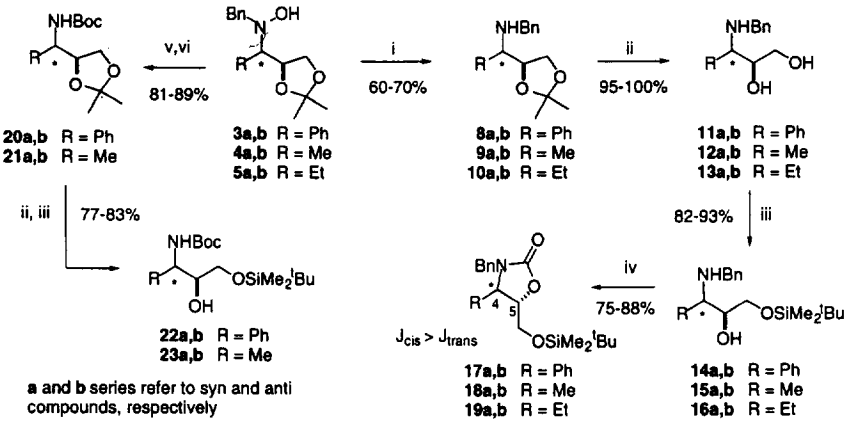
increased in all cases. By contrast, the use of diethylaluminum chloride as a precomplexing agent led to a complete reversal of the diastereofacial selectivity, thus obtaining the corresponding *anti* adducts (entries 5, 6, 10, 11 and 14). In order to extend the reactivity to other α-alkoxy nitrones, nitrone[8] **2** (derived from Mukaiyama's aldehyde) was also tested. Similar results were observed and whereas the *syn* adduct was obtained in the absence of any chelating agent (entries 15 and 17), the *anti* adduct was the major product when the nitrone was precomplexed with diethyl aluminum chloride (entries 16 and 18). In all cases the mixtures of *syn* and *anti* adducts could be separated by flash chromatography using hexane–diethyl ether mixture of solvents as eluents. The configurational assignments were made by analogy to previous reactions of hetaryl organometallic reagents with nitrones.[6e–g] This was put on a firm basis by conversion of the obtained α-alkoxy hydroxylamines into 1,3-oxazolidinones as described in Scheme 1.



Scheme 1.

The obtained *syn* and *anti* hydroxylamines **3–5** were easily deoxygenated by using the system Zn–$Cu(OAc)_2$ in acetic acid.[5b] Further acid-catalyzed hydrolysis of the acetonide group afforded 3-amino-1,2-diols **11–13** in almost quantitative yields. These diols were protected at the primary hydroxyl group as the corresponding tert-butyldimethylsilyl ethers **14–16**. Cyclization of these compounds by using imidazole dicarbonyl in THF as a solvent gave rise to oxazolidinones **17–19** (Scheme 2).[9] ^1H NMR analysis of compounds **17–19** served to confirm the stereochemistry of the addition reactions.[10] The trans isomers **17a–19a** showed $J_{4,5}$ values shorter than that of the cis isomers **17b–19b**. The data are consistent with dihedral angle values measured by using Chem3D® desktop molecular modelling package (125° for **17a–19a** and 5° for **17b–19b**) and are also in agreement with NMR data for related compounds.[11] Alternatively, hydroxylamines **3** and **4** were converted into protected 3-amino-1,2-diols **20** and **21**, respectively by catalytic hydrogenation (70 psi, r.t., 3 days) using $Pd(OH)_2$–C as a catalyst and further treatment with Boc_2O. Those compounds were further deprotected to the corresponding

diols which were isolated and characterized as the tert-butyldimethylsilyl ethers **22** and **23**. The optical and spectroscopic properties of **22** and **23** were in good agreement with those reported in the literature.[9]



Reagents and conditions. i, Zn-Cu(OAc)$_2$, AcOH, 70°C, 1 h. ii, p-TosOH(cat., MeOH,reflux, 4 h. iii, ^{t}BuMe$_2$SiCl, imidazole, DMF, r.t., 12 h. iv, Im$_2$CO, THF, r.t., 16 h. v, H_2, Pd(OH)$_2$-C, 70 psi, r.t., 3 days. vi, Boc$_2$O, dioxane, r.t., 16 h.

Scheme 2.

The stereochemical outcome of the addition reaction is best explained by chelate models considering an external organometallic reagent delivery. Whereas for the addition in the presence of $ZnBr_2$ an α-chelate could be considered (Figure 1, model **A**), β-chelation could be invoked for the addition in the presence of Et_2AlCl (Figure 1, model **B**). Semiempirical calculations (MOPAC 6.0) demonstrated that both conformers **A** and **B** are in the proximity of a minimum of energy, the electronic interactions with the most relevant conformers having been evaluated.[12] In addition the formation of the complexes between nitrone **1** and Lewis acids such as $ZnBr_2$ and Et_2AlCl has been well-demonstrated by previous NMR studies made in our laboratory,[6e] thus supporting the proposed models.

In conclusion we have shown that the nucleophilic addition of Grignard reagents to α,β-dialkoxy nitrones can be stereocontrolled by the appropriate use of Lewis acids. In addition the obtained α,β-dialkoxy hydroxylamines have been readily converted into 3-amino-1,2-diols of synthetic utility. Further efforts for natural product synthesis are underway.

Acknowledgements

Financial support from DGICYT (MEC, Madrid, Project PB94-0598) is gratefully acknowledged. The authors are also grateful to Prof. Pericas and his research group (University of Barcelona, Spain) for helpful discussions concerning the synthetic importance of 3-amino-1,2-diols.

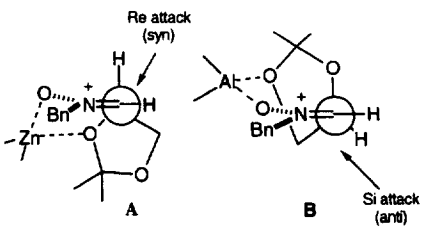


Figure 1. Proposed models for addition to **1**

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9. All new compounds exhibited consistent spectral (^{1}H and ^{13}C NMR) and analytical data. Optical rotations: 20±2°C (c 1.0, $CHCl_3$). Selected data: **3a**: $[\alpha]_D$ −6.5. **3b**: $[\alpha]_D$ −17.5. **4a**: $[\alpha]_D$ −19.8. **4b**: $[\alpha]_D$ −8.3. **5a**: $[\alpha]_D$ +24.9. **5b**: $[\alpha]_D$ −13.0. **6a**: $[\alpha]_D$ −28.9. **6b**: $[\alpha]_D$ −23.6. **7a**: $[\alpha]_D$ −14.5. **7b**: $[\alpha]_D$ −10.1. **22a**: $[\alpha]_D$ −3.1, lit.(for enantiomer)[7a] $[\alpha]_D$ +2.7. **22b**: $[\alpha]_D$ +23.9, lit.[7a] $[\alpha]_D$ +25.9. **23a**: $[\alpha]_D$ +10.1, lit.(for enantiomer)[7a] $[\alpha]_D$ −9.6. **23b**: $[\alpha]_D$ +1.5, lit.[7a] $[\alpha]_D$ +1.2.

10. Selected ^{1}H NMR (300 MHz, $CDCl_3$) data. **17a**: δ −0.23 (s, 3H), −0.16 (s, 3H), 0.74 (s, 9H), 3.21 (dd, 1H, J=10.7, 6.6 Hz), 3.50 (dd, 1H, J=10.7, 5.7 Hz), 3.60 (d, 1H, J=14.5 Hz), 4.55 (d, 1H, J=*8.3* Hz), 4.65 (ddd, 1H, J=*8.3*, 6.6, 5.7 Hz), 4.90 (d, 1H, J=14.5 Hz), 7.10–7.37 (m, 10H). **17b**: δ −0.22 (s, 3H), −0.14 (s, 3H), 0.78 (s, 9H), 3.64 (d, 1H, J=14.5 Hz), 3.64 (dd, 1H, J=11.5, 3.3 Hz), 3.76 (dd, 1H, J=11.5, 4.2 Hz), 4.27 (ddd, 1H, J=*6.4*, 4.2, 3.3 Hz), 4.47 (d, 1H, J=*6.4* Hz), 4.87 (d, 1H, J=14.5 Hz), 7.12–7.36 (m, 10H). **18a**: δ −0.01 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.22 (d, 3H, J=6.4 Hz), 3.74 (dq, 1H, J=*8.2*, 6.4 Hz), 3.80 (m, 2H), 4.07 (d, 1H, J=15.1 Hz), 4.40 (pseudo dt, 1H, J=*8.2*, 5.5 Hz), 4.78 (d, 1H, J=15.1 Hz), 7.24–7.33 (m, 5H). **18b**: δ −0.01 (s, 3H), 0.01 (s, 3H), 0.81 (s, 9H), 1.23 (d, 3H, J=6.3 Hz), 3.56 (dq, 1H, J=*6.3*, 6.3 Hz), 3.68 (m, 2H), 4.00 (dt, 1H, J=*6.3*, 4.3), 4.08 (d, 1H, J=15.3 Hz), 4.75 (d, 1H, J=15.3 Hz), 7.22–7.35 (m, 5H). **19a**: δ −0.03 (s, 3H), −0.01 (s, 3H), 0.81 (s, 9H), 0.83 (t (3H, J=7.3 Hz), 1.60 (m, 2H), 3.57 (ddd, 1H, J=*7.6*, 4.1, 2.6 Hz), 3.84 (m, 2H), 4.05 (d, 1H, J=15.0 Hz), 4.43 (dt, 1H, J=5.2, *7.6* Hz), 4.78 (d, 1H, J=15.0 Hz), 7.24–7.35 (m, 5H). **19b**: δ −0.03 (s, 3H), −0.01 (s, 3H), 0.81 (s, 9H), 0.90 (t, 3H, J=7.3 Hz), 1.50 (m, 2H), 3.45 (ddd, 1H, J=7.6, *4.6*, 3.2 Hz), 3.62 (m, 2H), 4.03 (d, 1H, J=15.0 Hz), 4.14 (pseudo quintuplet, 1H, J=*4.6* Hz), 4.79 (d, 1H, J=15.0 Hz), 7.24–7.35 (m, 5H).
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(Received in UK 21 March 1997)