Synthesis of α,α-Disubstituted α-Amino Acid Derivatives in Enantiopure Form via Stereoselective Addition of Grignard Reagents to a Chiral Acyclic Nitrone Derived from L-Erythrulose

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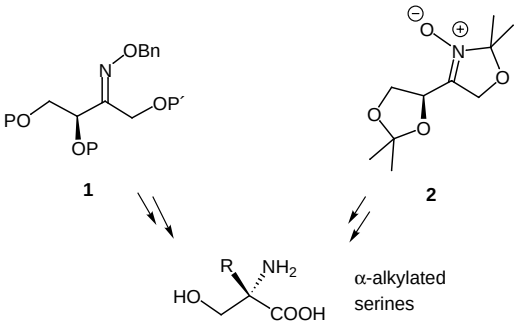
Abstract: The additions of various Grignard reagents to a chiral nitrone prepared from L-erythrulose take place with variable diastereoselectivity. The degree and strength of the facial selectivity can be modified if the reaction is performed in the presence of Lewis acidic additives: zinc bromide enhances attack to the *si* face whereas diethyl aluminum chloride promotes attack to the *re* side. The obtained adducts can be then efficiently transformed into protected *N*-hydroxy α,α-disubstituted α-amino acid derivatives as well as into the corresponding α,α-disubstituted α-amino acids.

Key words: Grignard reagents, chiral nitrone, erythrulose, α,α-disubstituted α-aminoacids, *N*-hydroxy aminoacids



Scheme 1

The addition of carbon nucleophiles to C=N bonds[1] is a synthetically important method of preparing many types of biologically relevant nitrogen-containing compounds, among them non-proteinogenic amino acids. These are used, for example, for the synthesis of non-natural peptides.[2] One important class of non-proteinogenic amino acids are α,α-disubstituted α-amino carboxylic acids.[3] Another class, also interesting as synthetic targets, are *N*-hydroxy amino acids.[4] In relation with these synthetic goals, we described a few years ago the stereoselective additions of organolithium reagents to the C=N bond of chiral *E* oximes **1** (P, P′ = protecting groups),[5] prepared from the four-carbon monosaccharide L-erythrulose[6] (Scheme 1). The obtained adducts were then transformed into various α-substituted serine derivatives. As an alternative approach to the same targets, we later reported on the stereoselective additions of lithium and magnesium organometallics to the C=N bond of the chiral keto nitrone[7] **2**, also prepared from L-erythrulose.[8]

Even though the nucleophilic additions to the C=N bond took place in both cases with an excellent diastereoselectivity (diastereomeric ratios, dr, > 95:5 in many cases), the overall efficiency of the process suffered from insatisfactory yields in the preparation of precursors **1** and **2**.[9] We thus looked for another chiral nitrone which should be obtained from L-erythrulose with a good yield and show a good diastereoselectivity in its reactions with carbon nucleophiles. After due experimentation, we found that the reaction of a known silylated erythrulose derivative[6] with *N*-benzyl hydroxyl amine gave rise to nitrone **3** in a good yield (Scheme 2). The compound was an oil and thus not amenable to X-ray diffraction analysis but NOE measurements permitted us to assign the configuration of the C=N bond as *Z*.[10,11]

The results of the reactions of nitrone **3**[12] with several Grignard reagents in THF to yield a mixture of the diastereoisomeric adducts **4** and **5** (Scheme 2) are indicated in the Table.[13] Various mechanistic models have been proposed to explain the stereochemical outcome of such additions, which have in most cases been performed on functionalized nitrones derived from aldehydes.[14] For instance, the formation of either **4** or **5** can be rationalized within the mechanistic frame of Cram's α-chelated (→ **4**) vs. Felkin–Anh's nonchelated (→ **5**) transition states[5a] (MLn = MgBr in Scheme 2). According to our experience with organometallic additions to various types of erythrulose derivatives[5a,15] a β-chelated TS, which should also lead to stereoisomer **5**, seems less likely here (see also below). Variable dr were observed in THF,[13] with the additions of allyl and phenyl Grignard reagents being particularly stereoselective (entries 5 and 6). Stereoisomer **4** was the major or almost exclusive component of the mixture except in the case of allylmagnesium bromide, where **5** was the only isomer detected. Whether this differential behavior of the allyl reagent may be related to a different aggregation state of the reagent, to an intrinsic

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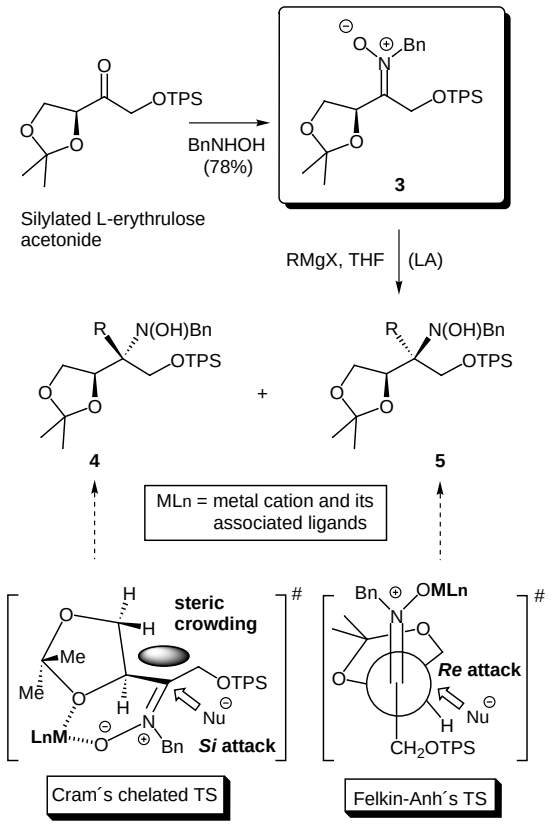


Scheme 2

preference for a non-chelated cyclic transition state of the metallo-ene type[16] or to another cause is unclear.

Interestingly, addition in the presence of $ZnBr_2$ (1 equiv) led to an increase in the proportion of **4**, in some cases to synthetically useful values (entries 1 and 2). The addition of the phenyl Grignard reagent was already very stereoselective without Lewis acid additive (entry 6) and remained so after adding $ZnBr_2$. These results may be explained if we assume that the bidentate Lewis acid $ZnBr_2$ binds to the substrate as the chelating species (MLn = ZnBr in Scheme 2) more tightly that the magnesium salt present in the reaction mixture. In contrast with this, addition of Et_2AlCl (1 equiv) to the reaction mixture caused consistently a marked increase in the proportion of the Felkin–Anh isomer **5** (except for entry 5). However, the stereochemical bias imposed by this Lewis acid was not strong enough to cause a complete reversal of the stereoselectivity except in the case of vinyl magnesium bromide, which proved highly stereoselective in the presence of Et_2AlCl (entry 4) and yielded only **5**.

Table Dr (ratio **4**:**5**) in the Reactions of **3** with Grignard Reagents RMgCl in THF[a]

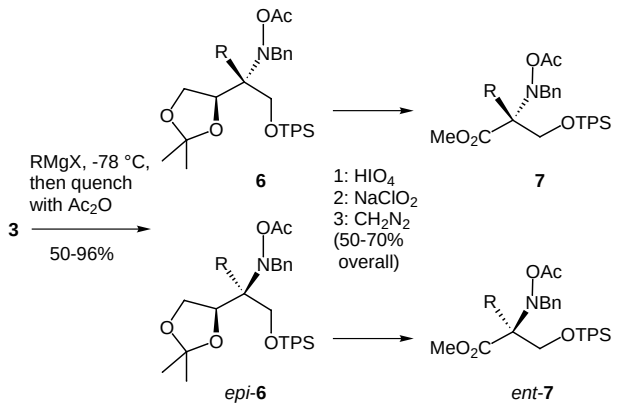
Entry	R	Lewis Acid Additive (LA, 1 equiv added)		
		None	$ZnBr_2$	Et_2AlCl[c]
1	Me	85:15 (63%)	> **95:5** (72%)	54:46 (69%)
2	Et[b]	85:15 (74%)	**93:7** (79%)	47:53 (85%)
3	*n*-Bu	83:17 (75%)	88:12 (75%)	50:50 (74%)
4	vinyl[b]	80:20 (75%)	85:15 (80%)	< **5:95** (78%)
5	allyl[b]	< **5:95** (84%)	80:20 (80%)	15:85 (80%)
6	Ph	> **95:5** (90%)	> **95:5** (85%)	70:30 (60%)

[a] Dr values (measured by high field ^1H and ^{13}C NMR) are followed by chemical yields in parentheses (dr > 95:5 or < 5:95 means that the minor stereoisomer was not detected). When the same reactions were performed in Et_2O, the dr were markedly lower.
[b] RMgBr instead of RMgCl.
[c] With 2.5 equiv of Et_2AlCl the results changed only slightly.

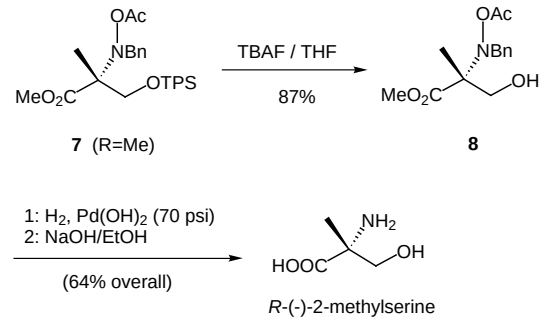
Findings of this type have previously been observed in the additions of organometallics to α-oxygenated nitrones.[4d,14b] In order to explain such results, it has been proposed that Et_2AlCl acts as monodentate Lewis acid which coordinates only with the negatively charged oxygen atom of the nitrone, thus leading to a Felkin–Anh-type transition state. It is worth mentioning here that Evans and co-workers have shown that Me_2AlCl and $MeAlCl_2$ are exceptionally strong chelating species if added in an excess of 2–2.5 equivalents.[17] However, the results presented in the Table were essentialy the same, no matter whether 1 or 2.5 equivalents of Et_2AlCl were added to the reaction mixture. This and the preferent formation of stereoisomer **5** do not lend support to the idea that chelates are formed here in the presence of this Lewis acid. Perhaps the negatively charged oxygen atom of the nitrone displaces the chlorine atom and forms a $C{=}N^+{-}OAlEt_2$ species, where the aluminum atom is possibly not enough Lewis acidic to coordinate with the ketal oxygen atom.

We have also investigated the conversion of the obtained adducts into derivatives of non-proteinogenic amino acids of the type mentioned in the introduction. For synthetic purposes, it proved better to quench the Grignard reaction mixture with acetic anhydride at –78 °C instead of the aqueous work-up.[13] This yielded N-acetoxy derivatives **6** (and/or their epimers *epi*-**6**) which were both more stable and easier to purify by means of chromatography (Scheme 3). Subsequent functional manipulations transformed **6** (*epi*-**6**) into the *N*-acetoxy α-amino esters **7** (*ent*-**7**), which constitute a protected form of *N*-hydroxy α,α-disubstituted α-amino acids.

The α,α-disubstituted α-amino acids themselves can also be made available by means of this methodology, as shown in Scheme 4 in the case of 2-methyl serine. Compound **7** (R = Me) was first desilylated with TBAF in THF and then subjected to hydrogenolysis in the presence of Pearlman's catalyst. This caused both debenzylation and reductive cleavage of the N–O bond to yield 2-methyl serine methyl ester, which was then uneventfully hydrolyzed to *R*-(–)-2-methyl serine.[5b] Further amino acids with other α-substituents may also be prepared through desilylation of the TPS group and nucleophilic substitution of the hydroxyl function.



Scheme 3



Scheme 4

In summary, we have reported a convenient method for the preparation of two types of non-proteinogenic amino acids in enantiopure form. Application of this method to the synthesis not only of amino acids but also of various nitrogenated natural products of pharmacological interest is being currently developed within our group and will be reported in due course.

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References

(1) (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Adams, J. P.; Box, D. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 749.

(2) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.

(3) (a) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (b) Cativiela, C.; Díaz de Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (c) Cativiela, C.; Díaz de Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.

(4) For a general review on this class of compounds, see: (a) Ottenheijm, H. C. J.; Herscheid, J. D. M. *Chem. Rev.* **1986**, *86*, 697. (b) See also: Kolasa, T.; Sharma, S. K.; Miller, M. J. *Tetrahedron* **1988**, *44*, 5431. (c) Jin, Y.; Kim, D. H. *Tetrahedron: Asymmetry* **1997**, *8*, 3699. (d) Merino, P.; Castillo, E.; Franco, S.; Merchán, S. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 2371. (e) *N*-Hydroxy amino acids have been found as components of depsipeptide antibiotics: Lorca, M.; Kurosu, M. *Tetrahedron Lett.* **2001**, 2431. (f) Another N-hydroxy compound which displays useful pharmacological properties is the 5-lipoxygenase inhibitor Zileuton: Brooks, D. W.; Bell, R. L.; Carter, G. W.; Dube, L. M.; Rubin, P. D. *Drugs Future* **1993**, *18*, 616.

(5) (a) Marco, J. A.; Carda, M.; Murga, J.; Rodríguez, S.; Falomir, E.; Oliva, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1679. (b) Carda, M.; Murga, J.; Rodríguez, S.; González, F.; Castillo, E.; Marco, J. A. *Tetrahedron: Asymmetry* **1998**, *9*, 1703.

(6) (a) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996**, 1801. (b) Carda, M.; Rodríguez, S.; Murga, J.; Falomir, E.; Marco, J. A.; Röper, H. *Synth. Commun.* **1999**, *29*, 2601.

(7) (a) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: , **1988**. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1. (c) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

(8) (a) Marco, J. A.; Carda, M.; Murga, J.; Portolés, R.; Falomir, E.; Lex, J. *Tetrahedron Lett.* **1998**, 3237. (b) 1,3-Dipolar cycloadditions of this nitrone have also been investigated: Carda, M.; Portolés, R.; Murga, J.; Uriel, S.; Marco, J. A.; Domingo, L. R.; Zaragozá, R. J.; Röper, H. *J. Org. Chem.* **2000**, *65*, 7000.

(9) The oximes **1** were obtained as *E*/*Z* mixtures,[5] from which only the *E* isomers showed a good stereoselectivity. Moreover, nitrone **2** was obtained together with a structurally close dioxazine,[8] which was, however, unreactive towards organometallics..

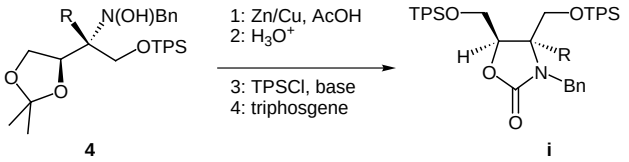
(10) A distinct NOE was detected between the N-benzylic hydrogens and the methylene protons of the CH_2OTPS group.

(11) We have studied the formation of the nitrone with the aid of quantum-mechanical ab initio methods. The non-isolated *E* nitrone was found to be more stable than the *Z* isomer by more than 3 kcal/mol. This indicates that the formation of the *Z* nitrone is subjected to kinetic control. Preliminary results of studies on possible transition states suggest that that leading to the isolated *Z* nitrone is lower in energy than the alternative transition state leading to the *E* isomer (unpublished results with S. Safont).

(12) **Preparation of Nitrone 3**. 1-*O*-*t*-butyldiphenylsilyl-3,4-*O*-isopropylidene-L-erythrulose[6] (19.93 g, 50 mmol) and *N*-benzyl hydroxylamine (6.16 g, 50 mmol) were dissolved in CH_2Cl_2 (150 mL). Anhyd $MgSO_4$ (10 g) was added to the mixture and the suspension was stirred under Ar for 48 h at r.t. The reaction mixture was then filtered through Celite, and the Celite pad was subsequently washed twice with CH_2Cl_2 (2 × 30 mL). After complete solvent removal in vacuo, the oily residue was chromatographed on silica gel (hexanes–EtOAc, 7:3). This furnished nitrone **3** as a dense oil (19.65 g, 78%), which could not be induced to crystallize: $[\alpha]_D^{25}$ –20.6 ($CHCl_3$, *c* 3.7). IR ν_{max}(film): 3052, 2986, 2934, 2892, 2860, 1577, 1472, 1455, 1428, 1382, 1266, 1212, 1181, 1154, 1112, 1058, 738, 704 cm^{-1}. HRMS (EI): *m/z* (rel. int.) = 503.2504 (0.5) [M^+], 488(10) [M^+ – Me], 446(16) [M^+ – *t*-Bu], 388(45), 341(88), 199(100), 101(96). Calcd for $C_{30}H_{37}NO_4Si$, M = 503.2492. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.80–7.20 (15 H, m), 5.27 (1 H, t, *J* = 7 Hz), 5.06 (2 H,

AB system, J = 11 Hz), 4.53 (1 H, dd, J = 8.5 and 7 Hz), 4.46 (2 H, AB system, J = 12.5 Hz), 3.77 (1 H, dd, J = 8.5 and 7 Hz), 1.35 (3 H, s), 1.29 (3 H, s), 1.10 (9 H, s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.1, 133.2, 132.3, 132.2, 109.7, 19.3 (C), 135.7, 135.6, 135.5, 130.0, 129.1, 128.8, 128.6, 128.5, 128.3, 128.2, 127.8, 127.7, 73.2 (CH), 68.3, 64.5, 56.3 (CH_2), 27.0, 26.0, 24.7 (CH_3).

(13) **General Reaction Conditions for Grignard Additions to Nitrone 3 with Aqueous Work-up**. A solution of **3** (1 mmol) in THF (5 mL) was cooled under Ar to –78 °C and treated with the appropriate Grignard reagent (5 mmol of a commercial solution in THF). After stirring for 5 h at the same temperature, the reaction mixture was quenched with sat. aq NH_4Cl (2 mL); the reaction mixture was stirred for further 5 min, poured into brine and extracted with EtOAc. The organic layers were then dried on anhyd Na_2SO_4 and concentrated in vacuo. Column chromatography of the oily residue on silica gel (hexane–EtOAc mixtures) afforded the corresponding adducts (Table). Additions in the presence of Lewis acid additives were performed in the same way except that the Lewis acid (1 mmol) was added to an ice-cooled solution of **3**; the solution was then stirred for 15 min and cooled to –78 °C, prior to addition of the Grignard reagent. **Grignard Additions to Nitrone 3 with acetylating Work-up**. For the preparation of amino acid derivatives, the reaction was performed as above except that acetic anhydride (190 μL, 2 mmol) was added dropwise at –78 °C to the reaction mixture. The cooling bath was removed and the mixture was stirred for 30 min at r.t. After quenching with sat. aq NH_4Cl (2 mL), the reaction mixture was stirred for further 15 min, poured into brine and worked up as above.
The configuration of the newly formed stereogenic center was determined by straightforward conversion of adducts **4** into oxazolidinones **i** (Scheme 5) and observation of suitable NOE's in the latter. Additional support was given by X-ray diffraction analyses of **4** (R = Et), **4** (R = allyl) and **6** (R = Ph). The crystallographic data of these three compounds have been deposited at the Cambridge Crystallographic Data Centre (deposition numbers, CCDC-177985 to CCDC–177987).



4 **i**

Scheme 5

(14) See, for example: (a) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464. (b) Dondoni, A.; Franco, S.; Merchán, S. L.; Merino, P.; Tejero, T. *Synlett* **1993**, 78. (c) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103. (d) Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem.–Eur. J.* **1995**, *1*, 505. (e) Merino, P.; Lanaspa, A.; Merchán, F. L.; Tejero, T. *J. Org. Chem.* **1996**, *61*, 9028. (f) Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M. D.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475.

(15) (a) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, J. *J. Org. Chem.* **1998**, *63*, 698. (b) Carda, M.; Castillo, E.; Rodríguez, S.; González, F.; Marco, J. A. *Tetrahedron: Asymmetry* **2001**, *12*, 1417.

(16) Oppolzer, W. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: Oxford, **1991**, Chap. 1.2.

(17) (a) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840. (b) The strong chelating ability of Me_2AlCl is attributed to a bimolecular interchange where the anion $(Me_2AlCl_2)^-$ is formed together with formal transfer of the chelating, highly Lewis acidic species Me_2Al^+ to the substrate. Obviously, two equivalents of Me_2AlCl are required.