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Double Addition of Grignard Reagents to *N*-Glycosyl Nitrones: A New Tool for the Construction of Enantiopure Azaheterocycles

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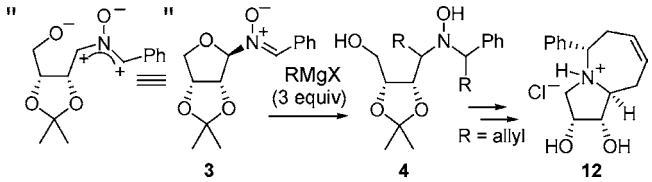
ABSTRACT



***C*-Phenyl-*N*-erythrosylnitrone 3 behaves as a C1,C1′ bis-electrophile, undergoing a double addition of Grignard reagents in a domino fashion to afford acyclic hydroxylamines 4. The reaction proceeds at 0 °C with variable degrees of diastereoselectivity, from moderate to good, mainly depending on the organomagnesium reagent used. The usefulness of compounds 4 has been exemplified with the synthesis of pyrroloazepine 12 through a ring closing metathesis key step.**

Nitrones are very useful tools for the construction of structurally complex molecules, and in particular, nitrogen-containing biologically active compounds. This is because of the high degree of diastereocontrol they often exhibit in their reactions with various reagents. Their most well-studied reactions, namely 1,3-dipolar cycloaddition[1] and the addition of organometallic reagents,[2] have yielded a number of extremely reliable synthetic procedures. Most recently, the involvement of nitrones in a promising SmI_2 mediated pinacol-type coupling with carbonyl and α,β-unsaturated carboxyl derivatives has also been disclosed.[3]

Considerable effort has also been devoted to the synthesis and applications of nonracemic chiral nitrones, because of their easy preparation and high versatility. Carbohydrate-derived nitrones have turned out to be particularly useful reagents for the synthesis of iminosugars and other hydroxylated compounds.[1d−h,2e−f,4] In this context, *N*-glycosylnitrones **1**, readily available from the corresponding hydroxylamines **2**,[5] have been extensively used, both in 1,3-dipolar cycloadditions[5,6] and nucleophilic additions,[7] for enantioselective syntheses, with the sugar moiety acting as a removable chiral

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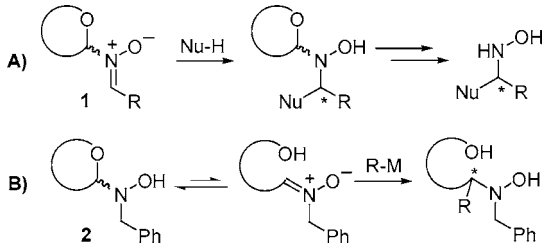
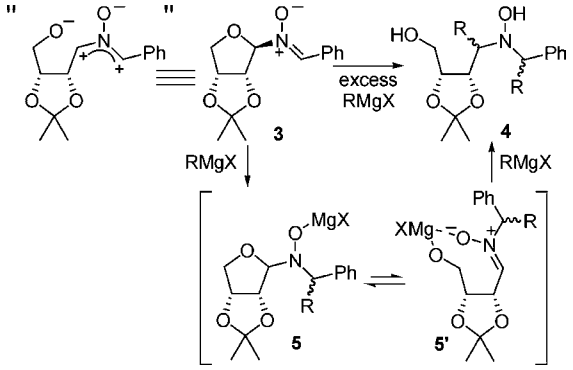
Scheme 1. Known Reactivity of **1** and **2**



auxiliary (Scheme 1, A). More recently, Dondoni has used *N*-glycosylhydroxylamines **2** as masked chiral nitrones in additions with organolithium and magnesium derivatives,[8] where the sugar framework remains embodied in the final adducts (Scheme 1, B).

In consideration of the above-described reactions, we envisaged the possibility of using *N*-glycosylnitrones **1** as synthetic equivalents of chiral C1,C1′ bis-nitrone (or dication) synthons in organometallic additions (Scheme 2). Indeed, intermediates such as **5** (formed from the first nucleophilic addition) should be in equilibrium with the open-chain nitrones **5′**, which can function as substrates for a further nucleophilic attack.[9] In this Letter, we report our findings

Scheme 2. Planned Domino Double Addition



on the domino double addition of Grignard reagents to a *N*-glycosylnitrone, and we show a synthetic application of a resulting bis-adduct.

As a model substrate for the methodological study we chose *C*-phenyl-*N*-erythrosylnitrone **3**.[5b] Treatment of an ice-cold THF solution of nitrone **3** with a 3-fold excess of a Grignard reagent afforded the bis-adducts **4** in good to excellent yields (Scheme 2 and Table 1).

Double addition at α,α′-positions[10] to nitrogen generates two new stereogenic centers (apart from addition of PhMgBr, entry 3, Table 1). Hence, formation of four diastereoisomers is possible. Taking into account the literature precedents which show that nucleophilic additions occur usually with good diastereoselection to both *N*-glycosylnitrones **1**[7] and *N*-glycosylhydroxylamines **2**,[8] we hoped that similar results would accrue in the double additions to nitrone **3**. In fact, a predominant adduct, whose configuration is depicted in Table 1, was generally obtained with diastereoselectivities from moderate to satisfactory. It is relevant that in all cases only two or three out of the four possible bis-adducts have been detected, which means that at least one of the two additions is particularly stereoselective. The major products of the additions from entries 1, 2, 5, and 6 show the (*R*,*S*) absolute configuration, respectively, at the C1,C1′ newly created stereogenic centers. Conversely, the major product of the addition of allylmagnesium chloride (entry 4, Table 1) turned out to have the opposite (*S*) configuration at C1, while the minor had the expected (*R*) configuration.

Complete stereochemical characterization of both the bis-adducts derived from the addition of allylmagnesium chloride (entry 4, Table 1) was achieved by nOe experiments on a derivative of the major adduct **4d** (compound **10**, see below). These results were confirmed by an X-ray structural determination, and by a single-crystal X-ray analysis of the minor adduct. The configuration of all the other major adducts **4** was also firmly ascertained. Single-crystal X-ray analyses were performed on the adduct **4a** and on the monoacetyl derivative (at the hydroxylamine oxygen atom, see Supporting Information) of **4e**. The configuration of adducts **4b** and

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(6) (a) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273−1295. (b) Vasella, A.; Voeffray, R. *J. Chem. Soc., Chem. Commun.* **1981**, 97−98. (c) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134−1144. (d) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1953−1964. (e) Vasella, A.; Voeffray, R.; Pless, J.; Huguenin, R. *Helv. Chim. Acta* **1983**, *66*, 1241−1252. (f) Kasahara, K.; Iida, H.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647−4648. (g) Mzengeza, S.; Whitney, R. A. *J. Org. Chem.* **1988**, *53*, 4074−4081. (h) Kasahara, K.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 2225−2233. (i) Machetti, F.; Cordero, F. M.; De Sarlo, F.; Guarna, A.; Brandi, A. *Tetrahedron Lett.* **1996**, *37*, 4205−4208. (j) Tamura, O.; Mita, N.; Kusaka, N.; Suzuki, H.; Sakamoto, M. *Tetrahedron Lett.* **1997**, *38*, 429−432. (k) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321−9327. (l) Chiacchio, U.; Rescifina, A.; Corsaro, A.; Pistarà, V.; Romeo, G.; Romeo, R. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2045−2048. (m) Tamura, O.; Kanoh, A.; Yamashita, M.; Ishibashi, H. *Tetrahedron* **2004**, *60*, 9997−10003. (n) Tamura, O.; Iyama, N.; Ishibashi, H. *J. Org. Chem.* **2004**, *69*, 1475−1480.

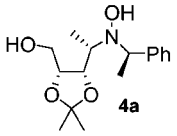
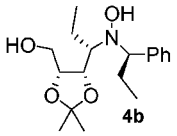
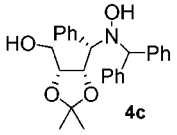
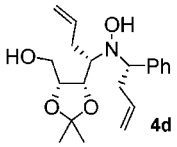
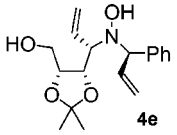
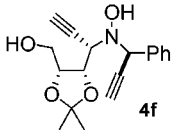
(7) Phosphites: (a) Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730−1747. (b) Bernet, B.; Krawczyk, E.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 2299−2311. (c) Huber, R.; Vasella, A. *Helv. Chim. Acta* **1987**, *70*, 1461−1476. (d) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33−58. Sulfoxonium ylides: (e) Lantos, I.; Flisak, J.; Liu, L.; Matsuoka, R.; Mendelson, W.; Stevenson, D.; Tubman, K.; Tucker, L.; Zhang, W.-Y.; Adams, J.; Sorenson, M.; Garigipati, R.; Erhardt, K.; Ross, S. *J. Org. Chem.* **1997**, *62*, 5385−5391. Trimethylsilyloxyfuran: (f) Mita, N.; Tamura, O.; Ishibashi, H.; Sakamoto, M. *Org. Lett.* **2002**, *4*, 1111−1114. Grignard reagents: (g) Mancini, F.; Piazza, M. G.; Trombini, C. *J. Org. Chem.* **1991**, *56*, 4246−4252. (h) Rohloff, J. C.; Alfredson, T. V.; Schwartz, M. A. *Tetrahedron Lett.* **1994**, *35*, 1011−1014. (i) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103−6106. Zinc acetylides: (j) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054−3056. (k) Patel, S. K.; Py, S.; Pandya, S. U.; Chavant, P. Y.; Vallée, Y. *Tetrahedron*: *Asymmetry* **2003**, *14*, 525−528.

(8) (a) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1999**, *40*, 9375−9378. (b) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203−7214. (c) Dondoni, A.; Perrone, D. *Tetrahedron* **2003**, *59*, 4261−4273.

(9) This hypothesis was supported by the observation reported, only in one of the previous studies (ref 7i), concerning the formation of a bis-adduct.

(10) We designate with α (or C1) and α′ (or C1′) the positions adjacent to phenyl and the dioxolane ring, respectively, following the sequential order of the two consecutive additions.

Table 1. Double Additions of Grignard Reagents to Nitrone **3**[a]

Entry	R	Major Product	Yield[b]	*dr*[c]
1	methyl	 **4a**	82% (55%)	70:18:12
2	ethyl	 **4b**	76%	52:27:21
3	phenyl	 **4c**	81% (55%)	65:35
4	allyl	 **4d**	98% (79%)	80:20
5	vinyl	 **4e**	87%	57:24:19
6	ethynyl	 **4f**	94% (75%)	80:20

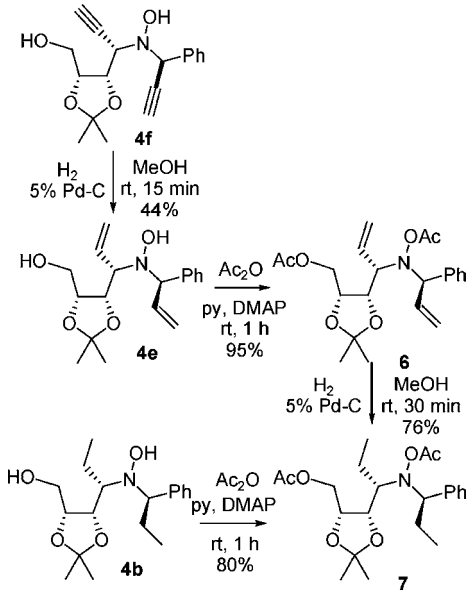
[a] Reactions were carried out in a 0.1 M solution of **3** in THF at 0 °C for 1 h. [b] Total yields considering all the adducts recovered after chromatography. Yields in parentheses are those of isolated major diastereoisomers. [c] Based on integration of ^{1}H NMR spectra of the crude reaction mixtures.

4f was determined to be the same as that for **4e** by chemical correlation, as reported in Scheme 3 (see Supporting Information for details). Only the configuration of compound **4c** was based on analogy.

The major bis-adducts **4a**, **4b**, **4e**, and **4f** appear to derive from preferential attack of the Grignard reagent at the *re* face of *N*-glycosylnitrone **3** (first attack) and the *si* face of open-chain nitrone **5′** (second attack). These preferred modes of approach were predicted according to the models proposed by Vasella for the nucleophilic addition to *N*-glycosylnitrones[7d] and Dondoni for those to *N*-glycosylhydroxylamines[8] (Figure 1). The second attack of phenylmagnesium bromide (entry 3, Table 1) is also in agreement with the latter model.

In the addition of allylmagnesium chloride, where only two bis-adducts were detected, whose configuration was established unequivocally, a further consideration can be inferred. Both adducts displayed the (*S*) configuration at C1′, thus showing that complete diastereofacial differentiation was attained in the second addition. This result is in agreement with the 96:4 diastereoselectivity observed for the addition of allylmagnesium bromide to *N*-erythrosyl-*N*-benzylhydroxylamine.[8c] A more strict diastereocontrol in the second addition seems to be operative in all additions.

Scheme 3. Interconversions for Chemical Correlation



The anomalous diastereoselection shown by allylmagnesium chloride is to be underlined. Possibly this is due to the peculiar nature of allyl metals. On the other hand, the precedent of an addition occurring with an opposite diastereofacial preference already has been reported.[7e] Furthermore, this result should be compared to those reported for the analogous addition (1 equiv) to a *N*-mannosyl nitrone,[7g] where only monoadducts were obtained, albeit in moderate yield, with a low 1.5 dr and with the same diastereofacial preference, while the D-mannosyl moiety should give the opposite induction.[5b]

The effects of varying the solvent and reagent concentrations and ratios and reaction temperature have been studied and are discussed in the Supporting Information.

From a practical point of view, it is interesting that the additions with unsaturated Grignard reagents (entries 4−6,

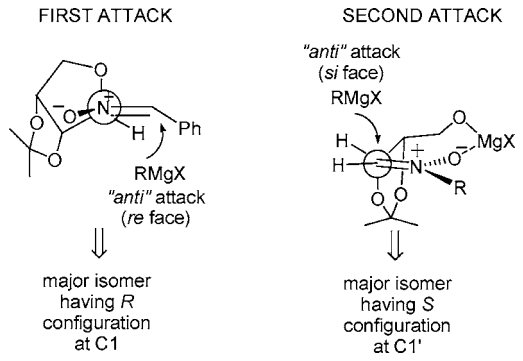
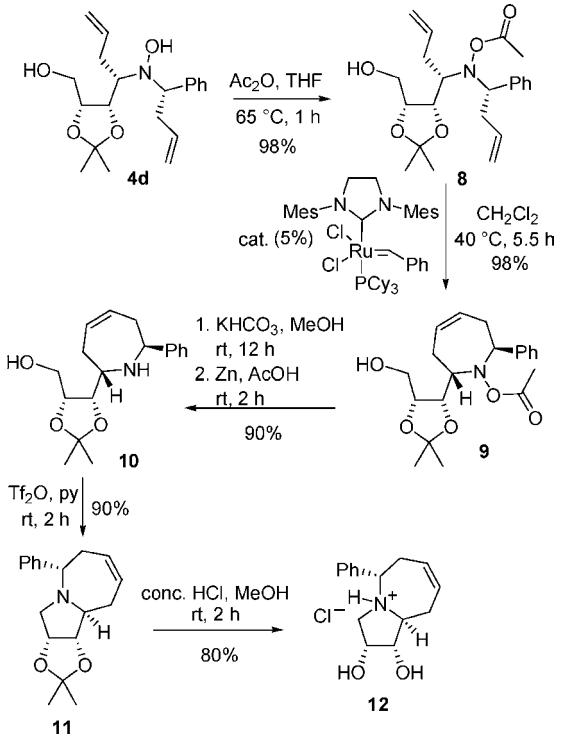


Figure 1. Preferred transition state models for the two consecutive attacks of Grignard reagents to nitrone **3**.

Table 1), which furnish more synthetically useful products, occur with excellent yields and are also the most diastereoselective. To demonstrate the synthetic potential of this novel double addition procedure, hydroxylamine **4d** was transformed into pyrroloazepine **12** (Scheme 4), which displayed

Scheme 4. Synthesis of Pyrroloazepine **12** through a Key RCM



good inhibition of α-glucosidase from yeast (90% at 1 mM).[11] After acetylation of hydroxylamine **4d**, a ring-closing metathesis with the second generation Grubbs' catalyst gave **9** in nearly quantitative yield. The product was then deprotected in situ to the corresponding hydroxylamine, which was reduced with zinc dust to the azepine **10**. Cyclization to **11** was induced by treatment with triflic anhydride. Final deprotection of the hydroxy groups was achieved in an acid medium, which afforded the desired product as its ammonium salt **12** (Scheme 4).

In conclusion, our preliminary results demonstrate the feasibility of the bis-addition of Grignard reagents to *N*-glycosylnitrones. The reaction can be performed at 0 °C fairly rapidly and affords in nearly quantitative yield the desired bis-adducts with moderate to good diastereoselectivity. The usefulness of the method has been demonstrated by the construction of a biologically active polyhydroxylated azepine system. The present reaction seems to have high synthetic potential and versatility for a range of applications. In consideration of this, possible structural variation at the nitrone carbon atom, in the Grignard reagent, and in the glycosyl moiety makes the method especially attractive. Further studies are currently underway in our laboratory to extend the methodology along these lines and to improve the diastereoselectivity of the reaction.

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Supporting Information Available: Experimental procedures, analytical and spectroscopic characterization of all new compounds, ^{1}H and ^{13}C NMR spectra of compounds **4a**, **4c**, **4d**, **4d′** (minor isomer), **4f**, and **6**−**13**, and X-ray crystallographic data of compounds **4a**, **4d′**, monoacetylated **4e** (i.e. **13**), and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047691E

(11) Details will be given in a full paper. We thank Prof. P. Vogel (University of Lausanne) for enzyme inhibition experiments.