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Asymmetric Synthesis of Functionalized Nitrocompounds Through Michael Addition of Formaldehyde SAMP Hydrazone to Nitroolefins.

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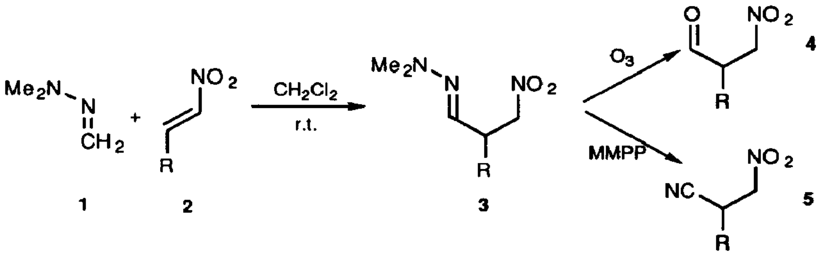
Abstract: Chiral β-nitrohydrazones **7** can be easily prepared in good yields and diastereoselectivities by non catalyzed Michael addition of formaldehyde SAMP hydrazone **6** to simple nitroolefins.

Enantioselective carbon-carbon bond-forming reactions with introduction of versatile functional groups are of utmost relevance for the preparation of target molecules containing numerous centres of chirality and branched skeleton. Among the reactions that can be used to create a new carbon-carbon bond, those processes involving nitrocompounds are of increasing importance in synthesis due to the remarkable versatility of nitro derivatives in their conversion into a variety of organic functional groups[1]. The synthetic utility of functionalized nitro derivatives should increase markedly if they are readily available in chiral form[2]. One approach to this kind of compounds consists in the Michael addition reaction involving carbon nucleophiles and good electrophiles as nitroolefins [1a,3]. We have recently demonstrated that formaldehyde dimethylhydrazone (FDMH, **1**) readily adds to nitroolefins **2**, without any need of base or catalyst, acting as a low-energy carbanion[4]. The corresponding Michael adducts **3** have been successfully transformed into β-nitroaldehydes **4** by ozonolysis of the azomethinic C=N double bond, and in β-cyanonitro derivatives **5** by treatment with MMPP[5] (Scheme 1). In this way, FDMH **1** behaves as a new formyl or cyano equivalent, introducing a functionalized carbon unit β to the nitro group of the nitroalkene.



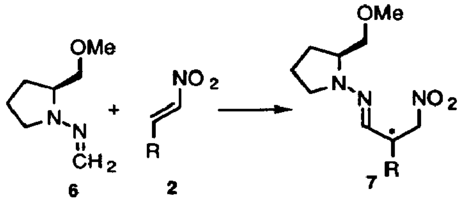
Scheme 1

Owing to the synthetic potential of this formylation or cyanation protocol, we have envisaged testing enantiomerically pure formaldehyde *N,N*-dialkylhydrazones with the aim of creating new C-C bonds in an asymmetric way. We now report on the *chiral version* of this process using the formaldehyde hydrazone of (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (FSAMPH, **6**)[6]. The synthetic utility of α-metalated-SAMP hydrazones of carbonyl compounds has been previously established by Enders and coworkers in alkylation reactions[7], but there is no precedent of the use of the simplest SAMP hydrazone in Michael addition to nitroolefins.

We have investigated the reaction of **6** with nitroolefins **2** which leads to chiral β-nitrohydrazones **7**[8]. The process takes place cleanly, under neutral conditions with good chemical yield and stereoselectivity both for aliphatic and aromatic nitroolefins (Scheme 2). Results are collected in the Table.

Table. Formation of β–nitrohydrazones 7

Comp.	R	Yield (%)[8,9]	D.e.[10]
7a	Me	81	87:13
7b	^{i}Pr	75	89:11
7c	*n*-C_6H_{13}	80	90:10
7d	*Cyclo*-C_6H_{11}	88	90:10
7e	Ph	61	78:22
7f	*p*-C_6H_4-Cl	81	80:20



Scheme 2

The mildness of the reaction conditions togheter with the good chemical and stereochemical yields observed for the addition of FSAMPH **6** to simple nitroolefins makes this methodology attractive for the construction of branched carbon skeleton. Additionally, the hydrazone moiety and the nitro group of adducts **7** can be easily transformed into aldehyde, hydroxymethyl, aminomethyl, cyano, etc., which would give rise to an ample variety of bifunctional derivatives. Moreover, the *R* isomer of the chiral hydrazone (FRAMPH) is also easily available, which would afford both enriched enantiomers of nitro derivatives with a functionalized carbon unit at β position.

We are presently employing different hydrazones derived from optically active *N,N*-dialkylhydrazines in order to improve the stereoselectivity and elucidate the stereochemistry of the addition products as well as applying this reaction to other Michael acceptors with the aim of exploring the synthetic potential of chiral formaldehyde hydrazones in the field of natural products. The results will be reported in due course.

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8. All new compounds were fully characterized by ^{1}Hnmr, ^{13}Cnmr, ir and high resolution mass spectroscopy and/or combustion analysis.
9. Yields of pure **7** after column chromatography of the reaction crude.
10. Diastereomeric excesses have been evaluated by ^{13}C and ^{1}Hnmr at 500 MHz.

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