

Asymmetric addition of organometallic reagents to chiral α -alkoxy hydrazones[†]

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(Received 8 January 1997; accepted 6 February 1997)

Summary — The diastereoselective addition of organocerium and organolithium reagents to chiral α -alkoxy hydrazones is described. Three different alkoxy groups have been examined with three different types of nucleophilic reagents. With one exception, high yields and diastereoselectivities were observed with all combinations of reagents. While the chiral pyrrolidine auxiliary could be hydrogenolytically removed with Raney nickel, the resulting β -amino ethers suffered some epimerization.

asymmetric synthesis / diastereoselectivity / organocerium / organolithium / chiral α -alkoxy hydrazone / β -amino ether

Résumé — Addition asymétrique de réactifs organométalliques sur des α -alkoxyhydrazones chirales. Nous décrivons l'addition diastéréosélective de réactifs organocériques et organolithiés sur des α -alkoxyhydrazones chirales. Le comportement de trois différents groupes alkoxy vis-à-vis de trois types de réactifs nucléophiles a été examiné. À une exception près, les trois réactifs étudiés ont conduit à des rendements élevés et à de hautes diastéréosélectivités. L'auxiliaire chiral de type pyrrolidine a pu être récupéré par clivage hydrogénéolytique (nickel de Raney) de la liaison N–N. Les β -aminoéthers ainsi obtenus ont cependant subi une légère épimérisation.

synthèse asymétrique / diastéréosélectivité / organocérium / organolithium / α -alkoxyhydrazone chirale / β -aminoéther

Chiral β -amino ethers and β -amino alcohols are important classes of agents which have found widespread use as auxiliaries and as precursors for various types of catalysts [1]. Their preparation usually involves reduction of the corresponding α -amino acids either from natural sources or from asymmetric synthesis of unnatural congeners [2].

In continuing our investigation on the synthetic application of the cerium-mediated addition of organometallics to chiral hydrazones [3], we described the use of α,α -dialkoxy hydrazones derived from chiral hydrazines for the synthesis of α -amino acetals and aldehydes [4–6]. We have now extended this work in a brief survey of the additions of different organometallic nucleophiles [7, 8] to α -alkoxy hydrazones bearing various ether protecting groups.

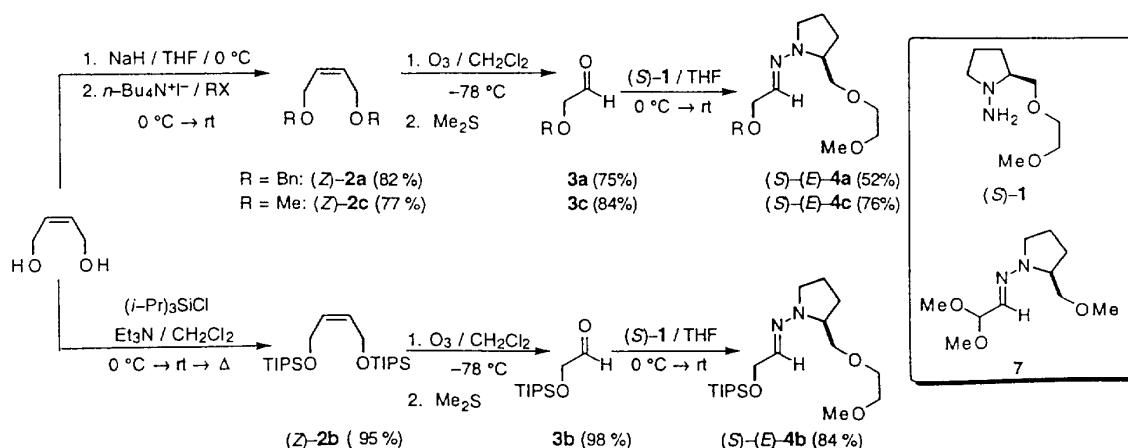
The chiral hydrazones examined in this study were all derived from (2*S*)-2-[(2-methoxyethoxy)methyl]pyrrolidin-1-amine (SAMEMP hydrazine), (*S*)-**1** [9], and were obtained by condensation with the desired alkoxy-acetaldehyde according to the standard procedure (scheme 1). The α -alkoxy aldehydes **3a–c** were prepared

in two steps from (*Z*)-but-2-ene-1,4-diol, ie, etherification followed by oxidative cleavage (scheme 1). Each of the three aldehydes, **3a–c**, was then treated with SAMEMP hydrazine, (*S*)-**1**, at 0 °C in THF. These condensation reactions were usually complete in less than one hour, using a slight excess amount of the aldehyde. The resulting chiral ether hydrazones (*S*)-(*E*)-**4a**, (*S*)-(*E*)-**4b**, and (*S*)-(*E*)-**4c** were easily obtained analytically pure in gram-quantities in 52%, 84%, and 76% isolated yield, respectively.

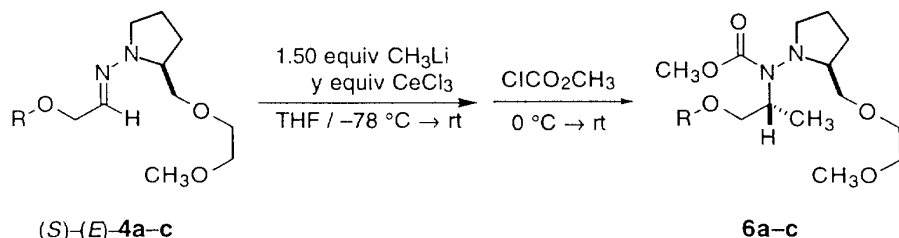
In view of the great deal of experimentation that was involved in the methylation of the chiral α,α -dialkoxy hydrazones [4, 6] (eg, **7**), the reactivity of these α -alkoxy hydrazones was tested with a methyl nucleophile. If the chelation of the organometallic nucleophile with the acetal oxygens of **7** would indeed be important for the observed selectivities, then hydrazone **4a** would be a suitable candidate. Indeed, there is a wealth of evidence for the strong chelating ability of benzyl ethers [10]. In contrast, hydrazone **4b** was prepared to test the reactivity of a substrate which could not chelate because of the steric bulk of the triisopropylsilyl (TIPS) group [11]. Finally, hydrazone **4c** was considered as a test-substrate

[†] Dedicated to Prof Henri Kagan, a pioneer in asymmetric organic reactions and organolanthanide chemistry, on the occasion of his 65th birthday.

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Scheme 1

Table I. Methylation of 4a-c with 1.5 equiv of available nucleophile^a.

Entry	Reagent nature and composition ^b CH ₃ Li/CeCl ₃ (equiv)	Product	Yield of 6 ^c (%)	de of 6 ^d (%)
4a R = PhCH ₂	1 Heterogeneous 1:1 (1.50)	6a	89	92
	2 Homogeneous 6:1 (0.25)	6a	90	88
	3 Cerium-free 1:0 (1.50)	6a	85	93
4b R = TIPS	4 Heterogeneous 1:1 (1.50)	6b	15 ^e	92
	5 Homogeneous 6:1 (0.25)	6b	89	90
	6 Cerium-free 1:0 (1.50)	6b	87 ^f	92
4c R = Me	7 Heterogeneous 1:1 (1.50)	6c	88	89
	8 Homogeneous 6:1 (0.25)	6c	90	85
	9 Cerium-free 1:0 (1.50)	6c	87	92
7	10 Heterogeneous 1:1 (2.00)	8	85	66
	11 Homogeneous 6:1 (0.33)	8	91	80
	12 Cerium-free 1:0 (2.00)	8	91	74

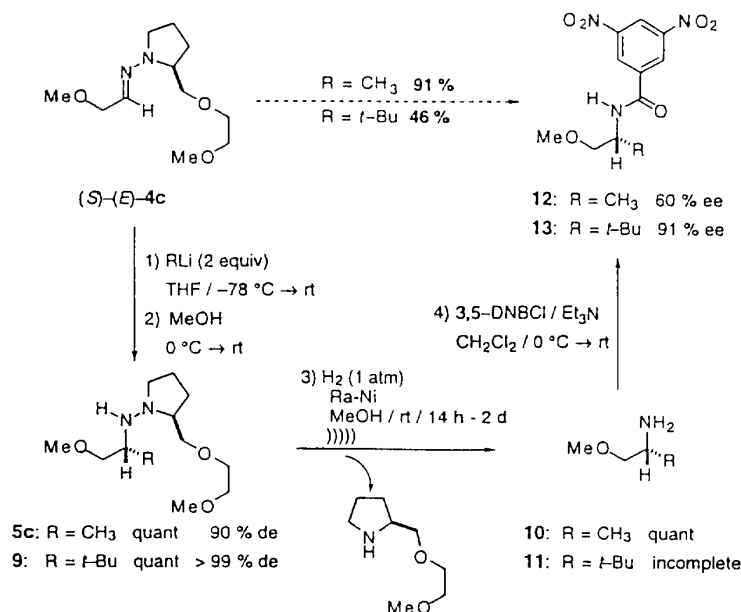
^a See [12]. ^b Heterogeneous 1:1 reagent: generated at -78 °C, and allowed to react from -78 °C to room temperature; homogeneous 6:1 reagent: generated at -78 °C, warmed to 0 °C, recooled to -78 °C, and allowed to react from -78 °C to room temperature. ^c Yield refers to chromatographically homogeneous material. ^d Determined by capillary GC analysis (HP-5 50-m); these values are given within an experimental error of ±2%. ^e Conversion determined by GC analysis.

^f Incomplete trapping with ClCO₂CH₃.

because of the wide utility of β-amino methyl ethers as chiral auxiliaries in asymmetric transformations [1c]. To compare the reactions of chiral acetal hydrazones, three methyl nucleophile-based systems were examined with the chiral ether hydrazones 4a-c: the *heterogeneous* 1:1 CH₃Li/CeCl₃ composition reagent; the *homogeneous* 6:1 CH₃Li/CeCl₃ composition reagent; and the Ce-free CH₃Li reagent [12]. The reactions were carried out using 1.5 equiv of available methyl, and the addition products

were isolated and analyzed as their methyl carbamates, 6a-c. The results of this study are presented in table I along with comparative data concerning the addition of methyl nucleophile (2 equiv) to dimethoxyacetaldehyde SAMEMP-hydrazone 7.

With the exception of the use of the 1:1 composition reagent with hydrazone 4b (entry 4), the data in table I indicate a comparable reactivity of ether hydrazones 4a-c and acetal hydrazone 7. However, it is



Scheme 2

important to note that longer reaction times were in general necessary for the completion of the reactions with ether hydrazones **4a–c**. For all three substrates, the use of the homogeneous 6:1 composition reagent afforded the highest yields of carbamates, demonstrating again the superior reactivity of this reagent (entries 2, 5, and 8) [12].

However, the difference of reactivity between this homogeneous reagent and other Ce-based reagents, such as the 1:1 composition reagent, was not as pronounced as that observed with the use of acetal hydrazones. Substrate **4b** was the least reactive and the greatest difference in reactivity was observed with the use of the 1:1 composition reagent (entry 4). With the other two reagents (6:1 and free CH_3Li), reaction with **4b** went to completion but the reaction times were the longest observed among all three hydrazones (entries 5 and 6). For all three substrates, the use of CH_3Li alone afforded good yields of the carbamates (entries 3, 6, and 9), just slightly lower than the 91% isolated yield recorded for the corresponding acetal hydrazone **7** (entry 12).

The most notable information to come out of this study were the high levels of diastereoselectivity reached in the nucleophilic addition to chiral α -alkoxy hydrazones. For all three substrates, the diastereoselectivities ranged from 85 to 93% de whereas the corresponding acetal hydrazone **7** afforded a significantly lower and wider range of values: 66–80% de (entries 10–12). In contrast to some observations made earlier, the results in the present study indicated quite similar selectivities obtained for Ce-mediated and Ce-free CH_3Li additions. Actually, the highest de's were recorded with the use of CH_3Li alone (entries 3, 6, and 9). For this reason, the use of Ce-free organolithium reagents was considered for the examination of the reactivity of hydrazone **4c** with other nucleophiles.

To access the target β -amino ethers in a straightforward fashion, an efficient N–N bond cleavage procedure for the resulting free hydrazines is required. The ultrasound-assisted hydrogenolytic N–N bond cleavage protocol, reported by Alexakis [13], appeared to be the method of choice. The feasibility of this overall synthetic transformation was first examined with methyl and *tert*-butyl as the nucleophiles and hydrazone **4c** to form the methyl ethers **5c** and **9**. As illustrated in scheme 2, the crude unprotected β -amino ethers **10** and **11** were transformed into their *N*-(3,5-dinitrobenzoyl) (3,5-DNB) derivatives **12** and **13** to facilitate their isolation, and subsequently determine their enantiomeric composition by chiral HPLC analysis.

The additions of methyllithium and *tert*-butyllithium alone to **4c** were carried out with 2 equiv of available nucleophile to afford the crude free hydrazines **5c** and **9**, respectively, in quantitative yields. The diastereomeric composition of **5c** and **9** could be determined by capillary GC analysis. The addition of CH_3Li to **4c** occurred in a highly diastereoselective fashion (90% de) and only one diastereomer could be detected from the addition of *t*-BuLi to **4c** (>99% de). The hydrogenolytic cleavage of the N–N bond in **5c** and **9** was then carried out as described by Alexakis [13]. While the reduction of the methyl adduct **5c** was completed in less than 14 h, a significant amount of *tert*-butyl adduct **9** was left unreacted after two days under the same reaction conditions. In both cases, the free β -amino ethers were isolated, and then were immediately converted to their 3,5-DNB derivatives **12** and **13** in 91 and 46% overall yields, respectively.

The chiral HPLC analysis of **12** indicated that the corresponding β -amino ether **10** was formed in 60% ee. A similar analysis of **13** revealed that the β -amino ether **11** was obtained in 91% ee. The assignment of the *R*

configuration to the major enantiomer for both compounds was established on the basis of previous preparations of these same compounds along with their enantiomeric purity determination. The loss of enantiomeric purity recorded in both cases was reproducible. This unfortunate outcome most likely arises from a redox process on the Raney nickel catalyst. This phenomenon finds a precedent in the epimerization of alcohols over Raney nickel [14]. The lithium/ammonia reduction procedure, although requiring an additional deprotection step, seemed to be suitable. Indeed, Li/ammonia reduction (4 equiv of Li) of **6c** afforded the *N*-protected β -amino methyl ether in ca 70% yield [15].

In conclusion, it should be noted that this two-step transformation (addition, cleavage) was attempted with other nucleophiles such as phenyl and 1-naphthyl. The Ce-mediated addition of PhLi to **4c** was highly selective (90% de) whereas that of PhLi alone afforded the adduct in less than 60% de. On the other hand, all attempts for 1-naphthyl addition to **4c** were unsuccessful.

Despite these problems in the use of chiral α -monoalkoxy hydrazones, this brief study was quite informative for a better understanding of the scope of organometallic additions to chiral hydrazones. In addition, the origin of the diastereoselectivity observed in the additions of organometallic reagents to these substrates still deserves further investigation.

Acknowledgment

We are grateful to the Pharmacia and Upjohn Company for generous financial support.

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