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Diastereoselective Addition of Organolithiums to New Chiral Hydrazones. Enantioselective Synthesis of (*R*)- Coniine

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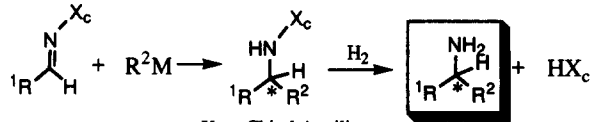
Abstract The reactions of organolithiums with the new chiral hydrazones derived from (*S*)-indoline-2-carboxylic acid afforded chiral hydrazines with high diastereoselectivities (up to 99% de) and the present method was utilized for the preparation of high optically pure (*R*)-coniine (94% ee).

The asymmetric additions of organometallic reagents to an imine and its derivatives (oximes and hydrazones) constitute an important method for the preparation of optically active amines. There are several reports concerning nucleophilic additions of chiral imines[1] and chiral hydrazones[2] bearing chiral auxiliaries. Enders' group described[2e] that the additions of organolithiums to a variety of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazones afforded the corresponding chiral hydrazines and the reductive cleavages of the adducts with Raney nickel catalyst gave enantiomerically enriched amines in 41-73% yield and 81- 93% enantiomeric excess (ee). Recently, Denmark and his coworkers[2f-2h] improved this method by using organocerium reagents instead of organolithiums, which are less basic and more nucleophilic than organolithiums and Grignard reagents.



X_c : Chiral Auxiliary
R^1, R^2 : aryl, alkyl

In this paper, we report that additions of organolithiums to (*S*)-1-amino-2-methoxymethylindoline (SAMI) hydrazones **1** derived from (*S*)-indoline-2-carboxylic acid afforded the corresponding chiral hydrazines **2** with extremely high diastereofacial selectivities and that the chiral auxiliary was smoothly removed by N-N bond cleavage in **2** utilizing $Pd(OH)_2$ at 20 °C under mild conditions. In general, the N-N bond cleavage of the hydrazines to amines and chiral auxiliary requires the rather harsh conditions: for instance SAMP-derived hydrazones need 375 psi at 60 °C for removal of chiral auxiliary and saturation of aromatic residues can become competitive.[2e,3] In contrast to this disadvantages from SAMP-hydrazones, the N-N bond of SAMI-derived hydrazines can be readily cleaved with $Pd(OH)_2$ at room temperature under mild conditions. Thus, our new method provides not only high diastereoselectivity but also an advantage to remove the chiral auxiliary of SAMI. Indoline-derived hydrazones were used for the synthesis of chiral α-

amino acids by Corey group.[4] Recently, we reported that (*S*)-indoline derivative catalysts resulted in high enantiomeric excess in asymmetric reduction of ketones to the corresponding secondary alcohols[5] and in asymmetric alkylation of the aldehydes to the secondary alcohols[6] , and that they also accomodate the chiral auxiliaries in asymmetric 1,3-dipolar cycloadditions[7] and the stereocontrolled additions of organometallics[8] and allylmetal regeants[9] to chiral α-ketoamides.

SAMI was prepared as following . (*S*)-Indoline-2-carboxylic acid was reduced with lithium aluminium hydride in tetrahydrofuran to give (*S*)-2-hydroxymethylindoline (80%), which was nitrosated with HNO_2 ($NaNO_2$-HCl) to the nitrosamine (90%). The nitrosamine was treated with NaH and iodomethane in THF (87%) followed by LAH reduction to afford SAMI (93%, $[\alpha]_D^{20}$ -15.5 ^{0}, c 0.66, $CHCl_3$, ≥ 99% ee[10]).

The chiral hydrazones **1** were prepared by condensation of aldehydes with SAMI in CH_3OH in 80 -85 % yield. The chiral hydrazone **1a** reacted with n-BuLi in THF at -78 ^{0}C to give a chiral hydrazine **2a** in good chemical yield (77%) and high diastereoselectivity (98 % de). In order to obtain the authentic sample and diastereomer of **2a**, **1b** reacted with PhLi in diethylether to give **2b** with high diastereoselectivity (96% de) and good chemical yield (87%). It is noteworthy that the same reaction did not proceed in tetrahydrofuran even at 20 ^{o}C : starting material remained totally (run 2). The addition of t-BuLi to **1a** resulted in extremely high diastereoselectivity (80% yield, >99% de). Diastereomeric ratios were determined by HPLC (LiChrosorb Si 60 (10 μm)) and ^{1}H NMR (300 MHz) analysis. In the case of alkyl hydrazones (**1b** and**1c**) containing α-hydrogen, enolization of substrates with α-hydrogens may be possible. A number of chiral imine derivatives resolve these problems by the use of less basic reagents. However most of these methods are limited to either aryl imines or hydrazones. As a genaral solution, organocerium reagent has been successfully used as a less basic reagent.[2f] Surprisingly, **1b** and **1c** reacted with PhLi or n-PrLi[11] to give high diastereoselectivities (run3 : *R*: *S* = 2: 98, run 5 : *R*: *S* = 97: 3, run 6 : *R*: *S*= 1: 99). The present method provides a highly general solution for the reactions of alkylhydrazones with both alkylmetal and arylmetal.

Scheme 1

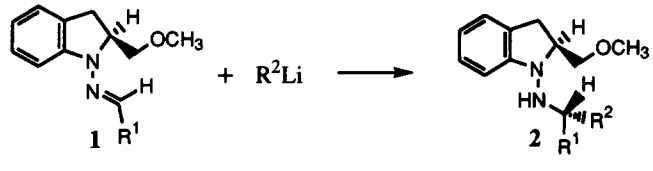


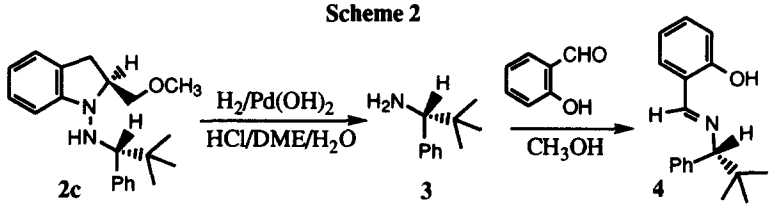
Table 1. Diastereoselective addition reactions of RLi to chiral hydrazones 1.

Run	Reactant	R^1	R^2Li[a]	Solvent	Temp (^{o} C)	Product	Yield[b] (%)	Ratio[c](*R* :*S*)
1	**1a**	Ph	n-BuLi	THF	-78	**2a**	77	99 : 1
2	**1b**	n-Bu	PhLi	THF	-78→rt	**2b**	-	-
3	**1b**	n-Bu	PhLi	Et_2O	-78	**2b**	87	2 : 98
4	**1a**	Ph	t-BuLi	THF	-78	**2c**	80	>99 : 1
5	**1c**	$(CH_2)_4OTHP$	n-PrLi	THF	-78	**2d**	84	97 : 3
6	**1c**	$(CH_2)_4OTHP$	PhLi	Et_2O	-78	**2e**	88	1 : 99

a. All reactions were carried out with 3 eq. of R^2Li for 30 min. b. Isolated Yield. c. Determined by HPLC (LiChrosorb Si 60 (10 μm)) and ^{1}H NMR analysis.

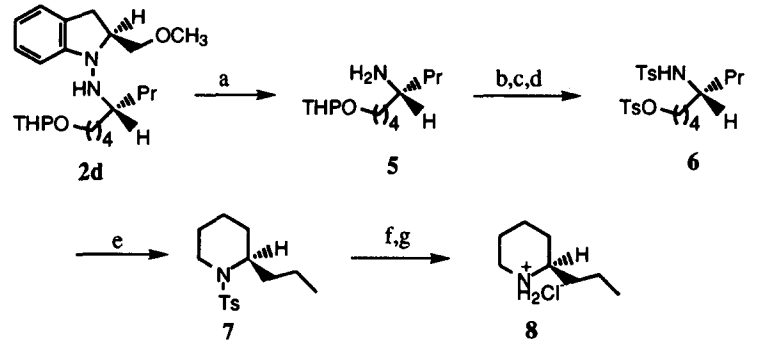
The absolute configuration of the newly induced chiral center in the adduct **2c** was determined by conversion to an optically active known N-salicylidene-α-phenylneopentylamine **4** (**Scheme 2**). The hydrogenation of **2c** gave an optically active amine **3**, following treatment with salicylaldehyde to provide **4** ($[\alpha]_D^{18}$ -246 (c 0.21, CH_3OH)), whose configuration was confirmed to be *R* form by comparison of its specific rotation with that from the known (*R*)-**4** (lit.[12] $[\alpha]_D^{18}$ -251 (c 0.99, CH_3OH)). The hydrogenation was carried at room temperature under atmosphere using $Pd(OH)_2/C$ catalyst in DME-H_2O containing hydrochloric acid and (*S*)-2-methoxymethylindoline used as chiral auxiliary was recovered in excellent yield (90 %) without any racemization.

Scheme 2



The construction of enantiometrically pure piperidine alkaloids has been intensively studied in the past years.[13] Our method was applied to the synthesis of the hemlock alkaloid (-)-coniine[14,15]as shown in **Scheme 3**. Hydrogenation of **2d** afforded a chiral amine **5** in 89% yield. Tosylation of **5** followed by deprotection of THP group and tosylation of NH_2 group gave ditosyl product **6** in 75% yield. Compound **6** was smoothly cyclized with NaH in DMF at 0 °C to give (*R*)-(-)-N-tosylconiine **7** ($[\alpha]_D^{22}$ -35.4 (c 0.67, C_6H_6))[15a] in 92% yield. Removal of the tosyl group from **7** with sodium naphthalide in THF at -78 °C followed by treatment with HCl in CH_3OH afforded (*R*)-(-) coniine hydrochloride **8** ($[\alpha]_D^{22}$ -5.5 (c 0.20, EtOH))[15b] in 85% yield. During the reactions the chirality on α-carbon of piperidine has been completely retained from **2d** (**2d** : 94% de, **8** : 94% ee).

Scheme 3



Reaction conditions: (a) 1 atm H_2, 20% $Pd(OH)_2$,1:1 DME/H_2O, HCl, RT (89%); (b) TsCl, NEt_3, CH_2Cl_2, 0 °C to RT; (c) TsOH, CH_3OH, 0 °C to RT; (d) TsCl, NEt_3, DMAP, CH_2Cl_2, 0 °C to RT (75% from **5**); (e) NaH, DMF, 0 °C (92%); (f) Na-Naphthalene, THF, -78 °C; (g) HCl in CH_3OH (85% from **7**).

In conclusion, the present method provides a useful way for the preparation of the optically active amines of both *R* and *S* configuration and has advantages that the additions of organolithiums to alkylhydrazones result in hydrazines with high diastereofacial selectivities, and that chiral auxiliary is easily recovered in excellent yield. Further studies on the mechanism and synthetic applications of this stereoselective addition reaction are in progress.

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