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DIASTEREOSELECTIVE ADDITION OF ORGANOMETALLIC REAGENTS TO CHIRAL IMINES AND 1,3-OXAZOLIDINES

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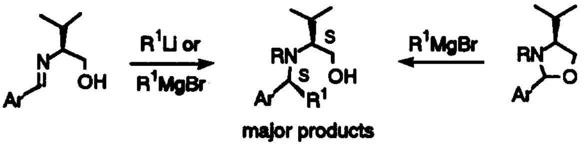
Summary: The reaction of MeLi or MeMgBr with chiral aromatic imines and 2-aryl-1,3-oxazolidines derived from (*R*)-phenylglycinol afforded with good diastereoselectivity (*R*,*R*)-amines from imines, but the (*R*,*S*)-amines from 1,3-oxazolidines, respectively.

Diastereoselective addition of organometallic reagents to the C=N bond of imines and their derivatives offers an attractive approach for asymmetric synthesis of amines.[1,2] Recent studies have shown that the diastereoselective addition of chiral imines and 1,3-oxazolidines derived from (*S*)-valinol with various organometallic reagents proceeds in highly diastereoselective manner, ultimately providing a route for generating chiral amines in high chemical and optical yields.[3]



As part of a program aimed at expanding the generality of this reaction we now report on the results of the diastereoselective addition of chiral imines and 1,3-oxazolidines derived from (*R*)-phenylglycinol with MeLi or MeMgBr.

The preparation of the requisite chiral imines and 1,3-oxazolidines followed the path described in Schem 1.

Condensation of aromatic aldehydes with (*R*)-phenylglycinol by heating in benzene with azeotropic removal of water gave chiral imines in good yield. However, these products were confirmed to be equilibrium mixture of imines(3a-e) and 2-aryl-1,3-oxazolidines(3'a-e) by ^{1}H-NMR spectra analysis.[4] The ratios of the mixture were determined to be 83:17—93:7 by peak-area measurement at 8.44—8.17ppm (N=CH) and 5.98—5.61ppm (NCHO).

Schem 1.

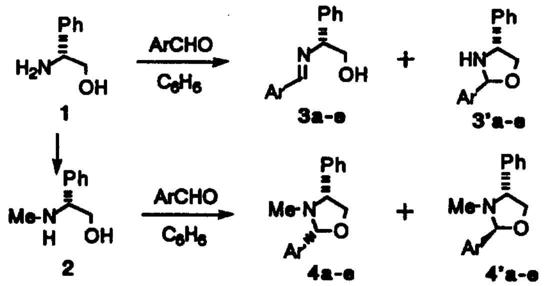


Table 1. Condensation of (*R*)-phenylglycinol and (*R*)-N-methylphenylglycinol with aromatic aldehydes

Compd.	Ar	3a-e yield[a] %	3a-e ratio 3:3'	$[\alpha]_D$[b]	4a-e yield[a] %	4a-e ratio 4:4'	$[\alpha]_D$[b]
a	phenyl	78	83:17	48.8	82	97: 3	-51.9
b	4-Methoxyphenyl	72	93: 7	110.7	96	>99: 1	-31.8
c	2-Furyl	88	94: 6	96.0	85	90:10	-65.6
d	2-Thienyl	98	94: 6	150.5	98	96: 4	-27.0
e	3-Thienyl	92	93: 7	51.5	89	99: 1	-47.7

a. Isolated yield. b. Specific rotations (c 0.9—1.3, $CHCl_3$)

In a similar manner, chiral 1,3-oxazolidines(4a-e) were synthesized by the condensation of (*R*)-N-methylphenylglycinol with aromatic aldehydes in quantitative yield. These products were confirmed to consist of thermodynamic mixtures,[5] depending on the asymmetric center at the 2-position of the 1,3-oxazolidine ring; the minor component amounted to less than 10% as judged from the ^{1}H-NMR(270MHz) spectra.

The reaction of chiral imines(3a-e) with MeLi(3equiv) in THF at low temperature(-55°C to room temp. over 15h) afforded pairs of the diastereomeric adducts(5a-e) in very high diastereoselectivities.[6] The isomer ratios were determined by analysis of their ^{1}H-NMR(270MHz).

The *R*,*R*-configuration of the major diastereomer(5a-e) have been determined by different method. The stereochemistry of 5a was established by ^{1}H-NMR(270MHz) spectral comparisons with an authentic sample.[7] On the other hand, since 5b was unknown, the major diastereomer was submitted to oxidative cleavage with lead tetraacetate, so affording known optically active (*R*)-(+)-(4-methoxyphenyl)ethylamine.[7,8] In the case of 5c and 5d, the structures were established by X-ray cristal structure analysis. The high degree of stereocontrol in this reaction may be attributed to a highly ordered transition state resulting from significant chelation of the alkoxy substituent and imino nitrogen to the lithium atom and then delivery of the other MeLi from the least hinderd face of the carbon-nitrogen double bond.[3a]

Schem 2.

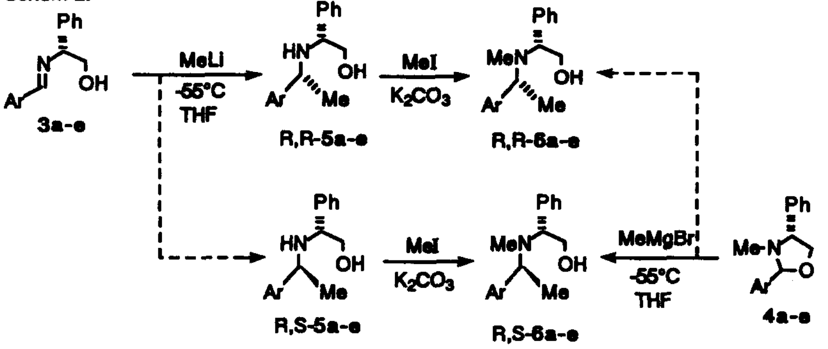


Table 2. Diastereoselective Reaction of 3a-e and 4a-e with MeLi or MeMgBr

Reactant	Reagent	Product	Yield%[a]	Ratio of Isomer[b] R,R : R,S
3a	MeLi	5a	82	97: 3
3b	"	5b	73	97: 3
3c	"	5c	62	95: 5
3d	"	5d	68	94: 6
3e	"	5e	62	>99: 1[c]
4a	MeMgBr	6a	86	34:66
4b	"	6b	93	18:82
4c	"	6c	64	9:91
4d	"	6d	69	9:91
4e	"	6e	68	9:91

a. Isolated yield. b. Estimated by ^{1}H-NMR(270MHz) spectral analysis.
c. The configuration of the tow diastereomers has not been determined.

Futher, these products were treated with MeI in DMF in the presence of anhydrous K_2CO_3 to give N-methyl compounds(6a-e) in quantitative yield.[9]

On the other hand, the reactions of chiral 1,3-oxazolidines(4a-e) with MeMgBr(2equiv) were curried out as described for the reaction of chiral imines(3a-e) to yield also the diastereomeric mixture(6a-e).

However, the major products(6a-e) of these reaction were identified with the minor products obtained from the reaction of chiral imines(3a-e). These experimental results are summarized in Table 2.

Thus, the proposed method seems to be of wide interest in the alkylation of imines since it can be applied to selective preparation of both asymmetric carbon atom from the single enantiomeric source. Further studies on the mechanistic and synthetic aspects of this stereoselective addition reaction are in progress.

References and notes.

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2. Enantioselective addition of organometallics to imines has been reported. K. Tomioka, I. Inoue, M. Shindo, and K. Koga, *Tetrahedron Lett.*, **1991**, *32*, 3095.
3. a) Y. Suzuki and H. Takahashi, *Chem. Pharm. Bull.*, **1983**, *31*, 2859. b) H. Takahashi, T. Kametani, and Y. Suzuki, *Heterocycles*, **1983**, *20*, 607.
4. M. B. Eleveld, H. Hogeveen, and E. P. Schudde, *J. Org. Chem.*, **1986**, *51*, 3635.
5. C. Agami and T. Pizk, *Tetrahedron*, **1985**, *41*, 537; A. H. Beckett and G. R. Jones, ibid, **1977**, *33*, 3313.
6. General procedure for the addition of MeLi to 3c is typical: MeLi in Et_2O (4.4ml, 6.6mmol) was added to a cold(-55°C) stirred solution of 3c(0.5g, 2.2mmol) in dry THF(30ml). After being stirred at room temperature for 15h, the reaction mixture was poured into sat. NH_4Cl and extracted with ether. The extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel(CH_2Cl_2:MeOH, 95:5) to give 5c (333.2mg, 62%). ^{1}H-NMR(270MHz) spectra analysis of a sample of the crude product showed a 95:5 ratio of ***R,R***-5c:***R,S***-5c.
7. H. Takahashi, B. C. Hsieh, and K. Higashiyama, *Chem. Pharm. Bull.*, **1990**, *38*, 2429.
8. M. Betti and G. del Rio, *Gass. Chim. Ital.*, **1912**, *42*, 283.
9. General procedure for N-methylation: To a stirred solution of amine (5a-e)(2mmol) in dry DMF(15ml) was added CH_3I(3mmol) in the presence of K_2CO_3(0.5g) at room temperature. After being stirred for 10h, the mixture was poured into water and extracted with ether. The extracts were washed with brine, dried over Na_2SO_4 and evaporated to leave the residue which was purified by bulb-to-bulb distillation to give the amines(6a-e).

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