

Diastereoselective Addition of Lithiated *N,N*-Diethyl-*o*-Tolamide to Chiral Isopropylidene Glyceraldehyde Imines. Asymmetric Synthesis of 3-Substituted 3,4-Dihydro-1(2*H*)-isoquinolones

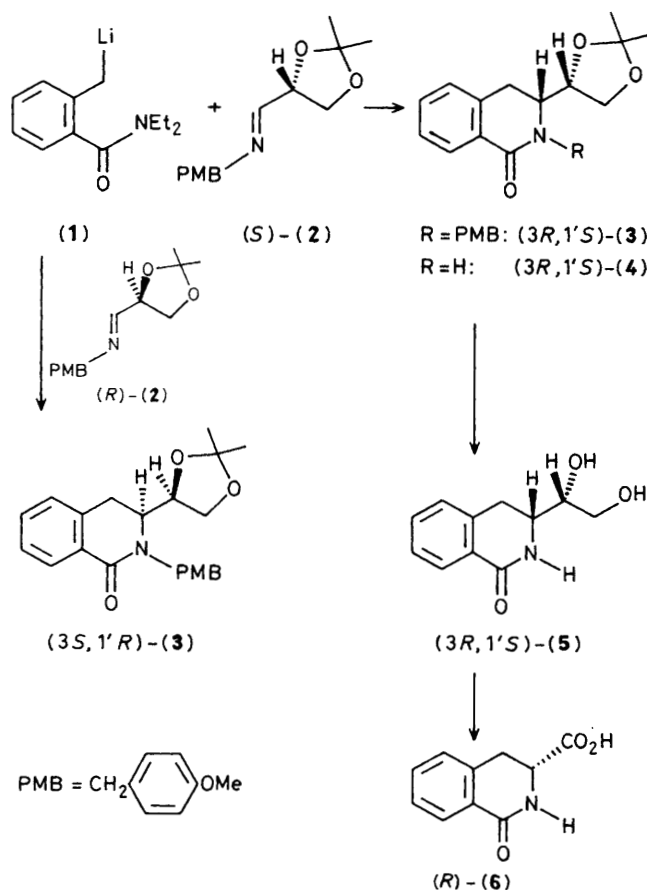
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The lithio derivative of *N,N*-diethyl-*o*-tolamide adds regiospecifically to (*R*)- and (*S*)-glyceraldehyde acetonide *p*-methoxybenzyl imines to afford the Cram-chelation controlled products (3*S*,1'*R*)-(3) and (3*R*,1'*S*)-(3), respectively.

Although a wealth of literature exists on the stereoselectivity of addition of organometallic reagents to α - and β -substituted aldehydes,¹ few examples of additions to α - and β -alkoxy imines have been reported.² This reflects the numerous problems inherent with imines, including low electrophilicity and their tendency to undergo α -deprotonation rather than addition.³ One notable success in this area has been the addition of allylic organometallic reagents to α -alkoxy imines. Allyl Grignard and allyl triethylaluminium–Grignard reagents afforded predominantly Cram-chelation control products⁴ while non-chelation products were obtained with allyl-9-borabicyclo[3.3.1]nonane (9-BBN).^{2a} Other successful approaches include addition of diethylzinc to 2,3-dialkoxy phenylsulpheneimines⁵ and addition of organolithium reagents to α -alkoxy aldehyde dimethylhydrazones.⁶ We now report an apparently unprecedented example of the addition of an organolithium reagent to a chiral 2,3-alkoxy imine which affords a product which can be rationalized by a Cram-chelation controlled process.

We have previously reported that addition of lithio species (1) to imines (primarily benzylidene imines) affords 3,4-dihydro-1(2*H*)-isoquinolines.⁷ In an extension of this work, condensation of (1) with the *p*-methoxybenzyl (PMB) imine of (*R*)-glyceraldehyde acetonide (*S*)-(2)⁸ was investigated. Thus, addition of (*S*)-(2) (1 equiv.) to a tetrahydrofuran (THF) solution at -78°C of (1) (1 equiv.; generated with lithium di-isopropylamide) afforded the single diastereoisomer† (3*R*,1'*S*)-(3) in 50% yield‡ {m.p. $151\text{--}153^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} -188^\circ$ (c 0.45, CHCl_3)} (Scheme 1).



Scheme 1

† Based on ^1H n.m.r. analysis at 500 MHz.

‡ The moderate (unoptimized) yield is due in part to dimerization of lithio species (1).

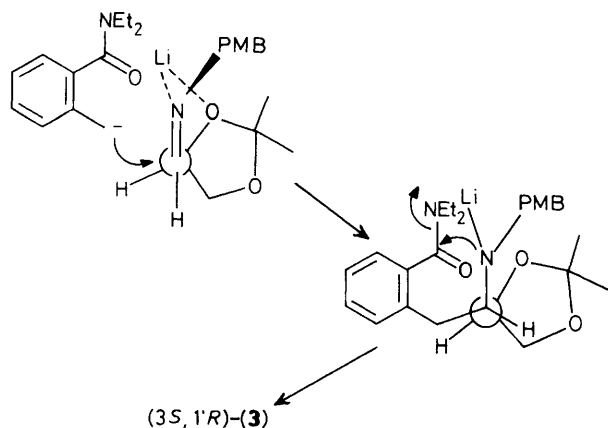


Figure 1. Proposed transition state for addition of (1) to (R)-(2).

The corresponding reaction with (R)-(2)⁹ gave (3S,1'R)-(3) also in 50% yield {m.p. 151–153 °C; $[\alpha]_D^{25} + 193^\circ$ (c 0.48 CHCl₃)}. Both antipodes were determined to be enantiomerically pure (>99%) by h.p.l.c. analysis. §

The absolute stereochemistry of C-3 of these products was determined by correlation with the known optically active 3-carboxy dihydroisocarbostyrils derived from D- and L-phenylalanine.¹⁰ Removal of the PMB group from (3R,1'S)-(3) by treatment with cerium(IV) ammonium nitrate (CAN)¹¹ in aqueous acetonitrile gave (3R,1'S)-(4) {50%, m.p. 97–99 °C; $[\alpha]_D^{25} + 62^\circ$ (c 1.6, CHCl₃)}. Hydrolysis with aqueous 5% HCl afforded diol (3R,1'S)-(5) {57%, m.p. 129–131 °C; $[\alpha]_D^{25} + 47^\circ$ (c 1.6, MeOH)} which was oxidized with ruthenium trichloride–periodic acid¹² to the known (R)-(6) {m.p. 234–236 °C, lit.¹⁰ m.p. 232.5–234 °C; $[\alpha]_D^{25} - 44^\circ$ (c 1.4, MeOH), lit.¹⁰ $[\alpha]_D - 45.2^\circ$ (c 1.5, MeOH)}.

The formation of (3R,1'S)-(3) and (3S,1'R)-(3) is notable for several reasons. The stereochemistry of these diastereoisomers can be rationalized by the Cram cyclic model of asymmetric induction⁴ in which lithium is co-ordinated between the imine nitrogen and the 2-alkoxy group (Figure 1). This is unusual since 5-membered chelation of lithium is not a general phenomenon.^{6,13} It is also of interest that α -epimerization of the imine (2) was not observed. The products (3) should be useful intermediates for further elaboration to

functionalized, optically pure 3-substituted 3,4-dihydro-1(2H)-isoquinolones¹⁴ and 1,2,3,4-tetrahydroisoquinolines.

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§ Analysis was on an alpha-1 glycoprotein Chiral AGP (ChromTech) column with an IPA-phosphate buffer mobile phase. Retention times for (3S,1'R)-(3) and (3R,1'S)-(3) were 6.6 and 14.3 min, respectively.