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

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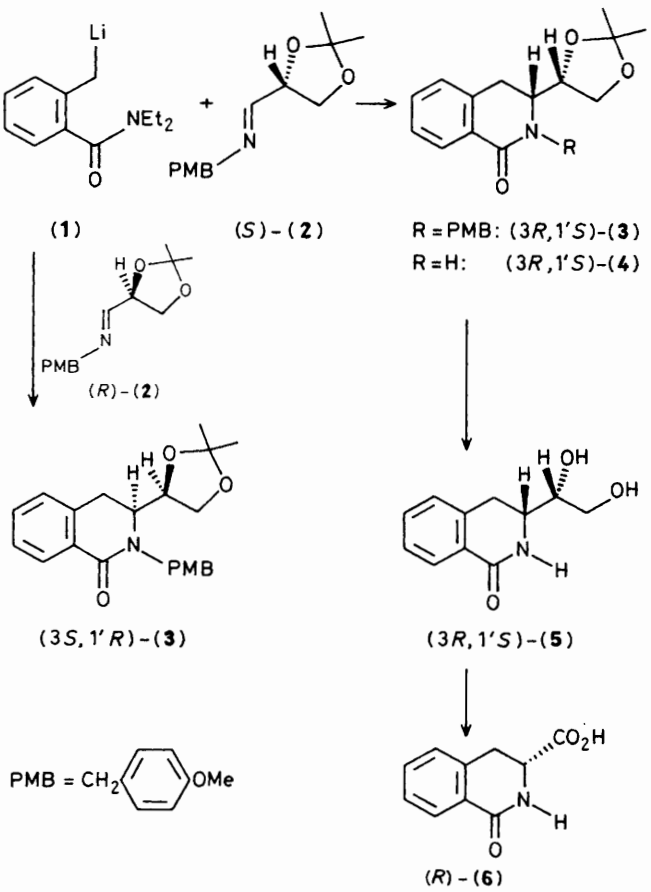
The lithio derivative of *N,N*-diethyl-*o*-toluamide adds regiospecifically to (*R*)- and (*S*)-glyceraldehyde acetonide *p*-methoxybenzyl imines to afford the Cram-chelation controlled products (3*S*,1′*R*)-(**3**) and (3*R*,1′*S*)-(**3**), respectively.

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 products[4] 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 phenylsulpheneimines[5] 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—153 °C; $[\alpha]_D^{25}$ −188° (*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**).

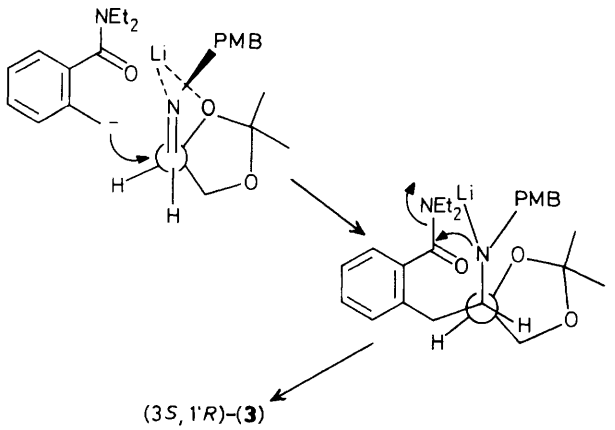


Figure 1. Proposed transition state for addition of (**1**) to (*R*)-(**2**).

The corresponding reaction with (*R*)-(**2**)[9] gave (3*S*,1′*R*)-(**3**) also in 50% yield {m.p. 151—153 °C; $[\alpha]_D^{25}$ + 193° (*c* 0.48 $CHCl_3$)}. 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 (3*R*,1′*S*)-(**3**) by treatment with cerium(IV) ammonium nitrate (CAN)[11] in aqueous acetonitrile gave (3*R*,1′*S*)-(**4**) {50%, m.p. 97—99 °C; $[\alpha]_D^{25}$ + 62° (*c* 1.6, $CHCl_3$)}. Hydrolysis with aqueous 5% HCl afforded diol (3*R*,1′*S*)-(**5**) {57%, m.p. 129—131 °C; $[\alpha]_D^{25}$ + 47° (*c* 1.6, MeOH)} which was oxidized with ruthenium trichloride–periodic acid[12] to the known (*R*)-(**6**) {m.p. 234—236 °C, lit.[10] m.p. 232.5—234 °C; $[\alpha]_D^{25}$ − 44° (*c* 1.4, MeOH), lit.[10] $[\alpha]_D$ − 45.2° (*c* 1.5, MeOH)}.

The formation of (3*R*,1′*S*)-(**3**) and (3*S*,1′*R*)-(**3**) is notable for several reasons. The stereochemistry of these diastereoisomers can be rationalized by the Cram cyclic model of asymmetric induction[4] 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(2*H*)-isoquinolones[14] and 1,2,3,4-tetrahydroisoquinolines.

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

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