Communications to the Editor

Ligand Control and Asymmetric Michael Reactions of Enantioenriched Configurationally Stable *N*-Boc Anilino Benzylic and Allylic Organolithium Species

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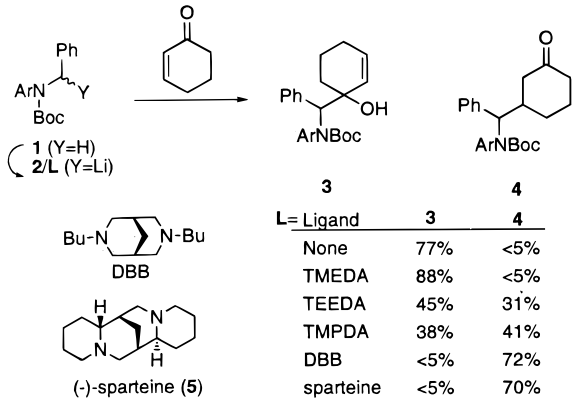
Reactions in which the formation of a new carbon−carbon bond provides two stereogenic centers with high enantioselectivity are of special interest for asymmetric synthesis. We report chiral ligand controlled Michael additions of organolithium species in which both termini of the new bond are formed with high levels of enantioselectivity.[1] This work is based on our discoveries that the regiochemistry of 1,2- vs 1,4-addition of an α-lithio-*N*-Boc benzylic and allylic aniline derivative can be ligand controlled and that the corresponding enantioenriched configurationally stable benzylic and allylic organolithiums, which are ligated to (−)-sparteine, give Michael addition products with high enantiointegrities.[2] Conjugate additions which have been reported to give high enantioenrichments at adjoining β- and γ-carbons are chiral ligand controlled additions of enolates and chiral auxiliary controlled additions of phosphine oxide, phosphonamide, phosphonate, oxazaphosphorinane 2-oxide, or sulfoximine allyl carbanions.[3,4] Chiral ligand and chiral auxillary controlled Michael additions which provide high enantioenrichments at β- or γ- carbons in diastereoselective conjugate additions have been reported.[5]

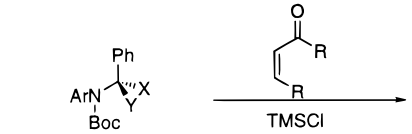
Lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine (**1**) with 1.1 equiv of *n*-BuLi/L complex in ether at −78 °C affords the dipole-stabilized carbanion **2/L** which reacts with 2-cyclohexenone to give the 1,2- and/or 1,4-addition products **3** and **4**, respectively.[2,6] In the absence of a ligand or with tetramethylethylenediamine (TMEDA) as the ligand, the 1,2-adduct **3** is obtained in a 1:1 diastereomeric ratio in 77 and 88% yields, respectively. In the presence of *N*′,*N*′,*N*,*N*-tetraethylethylene-



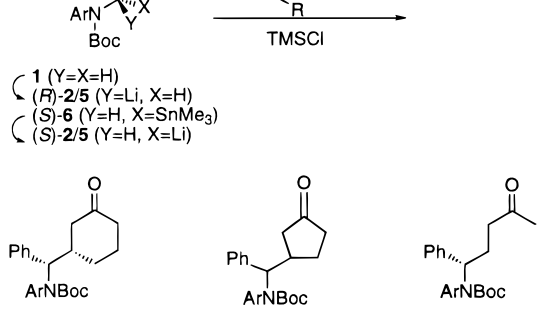
L= Ligand	3	4
None	77%	<5%
TMEDA	88%	<5%
TEEDA	45%	31%
TMPDA	38%	41%
DBB	<5%	72%
sparteine	<5%	70%

diamine (TEEDA), **3** and **4** are obtained in 45 and 31% yields, respectively. With *N*′,*N*′,*N*,*N*-tetramethyl-1,3-propanediamine (TMPDA) as the ligand, the yields of **3** and **4** are 38 and 41%. Reaction in the presence of *N*,*N*-dibutylbispidine (DBB), a ligand which was chosen because of its similarity to (−)-sparteine, provides the 1,4-adduct **4** in 72% yield.[7] In the presence of (−)-sparteine (**5**), **2** reacts with 2-cyclohexenone to provide **4** in 70% yield. The formation of 1,2- or 1,4-addition products from 2-cyclohexenone and **2/L** clearly can be controlled by selection of the ligand.[8]

Reactions of the configurationally stable enantioenriched benzylic lithiated intermediate (*R*)-**2/5**, conveniently generated by lithiation of **1** with *n*-BuLi/**5** in toluene, with 2-cyclohexenone, 2-cyclopentenone, and 2-butenone and trimethylsilyl chloride (TMSCl) give the highly enantioenriched products (*S*,*S*)-**4**, (*S*,*S*)-**7**, and (*S*)-**8** with >99:1 diastereoselectivities (dr) and >95:5 enantioselectivities in yields of 82, 86, and 63%, respectively. If trimethyltin chloride is used as the electrophile



1 (Y=X=H)
(*R*)-**2/5** (Y=Li, X=H)
(*S*)-**6** (Y=H, X=$SnMe_3$)
(*S*)-**2/5** (Y=H, X=Li)



and the product (*S*)-**6** is allowed to react with *n*-BuLi/(−)-sparteine followed by 2-cyclopentanone and TMSCl, (*R*,*R*)-**7**

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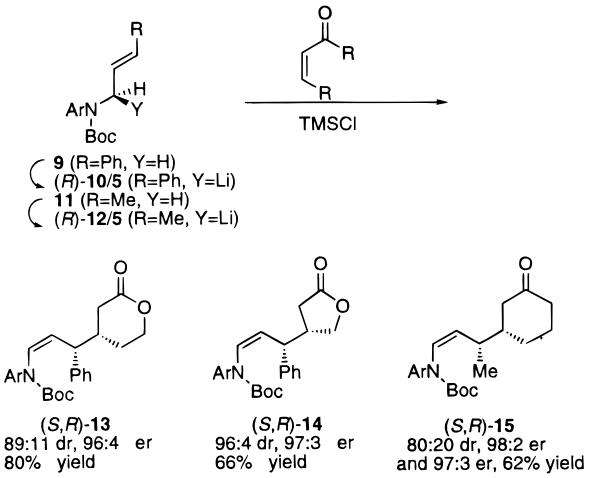
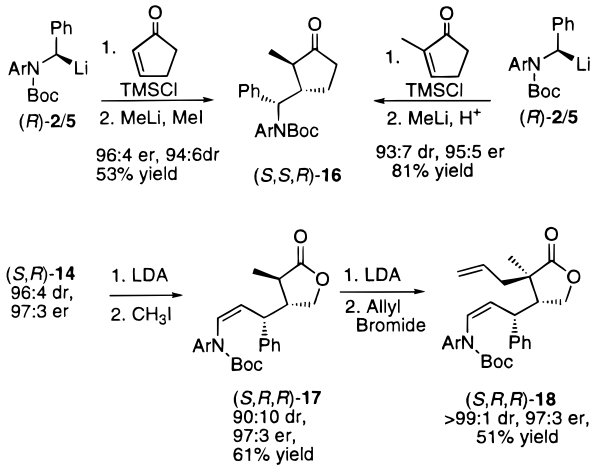
is obtained with a 98:2 er in 61% overall yield.[2,6] In the absence of TMSCl, the yields of the enantioenriched products decrease significantly.[9] The absolute configuration of (*S*,*S*)-**7** was assigned by X-ray crystallography of a (1*S*)-camphorsulfanamide derivative of deprotected (*S*,*S*)-**7**. The absolute configurations of **4** and **8** are assigned by analogy to (*S*,*S*)-**7**.

The methodology is applicable to configurationally stable α-lithio allylic aniline derivatives.[10] Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine (**9**) with 1.1 equiv of *n*-BuLi/**5** to provide (*R*)-**10/5** followed by addition of the Michael acceptors, 5,6-dihydro-2*H*-pyran-2-one or 2(5*H*)-furanone, along with TMSCl affords products (*S*,*R*)-**13** and (*S*,*R*)-**14** with 89:11 and 96:4 diastereoselectivities with 96:4 and 97:3 enantioselectivities, respectively. The diastereomers of (*S*,*R*)-



13 and (*S*,*R*)-**14** are separated by chromatography providing highly enantioenriched products. Reaction of *N*-Boc-*N*-(*p*-methoxyphenyl)crotylamine (**11**) with 1.1 equiv of *n*-BuLi/**5** at −78 °C in methyl *tert*-butyl ether (MTBE) affords (*R*)-**12/5** and addition of 2-cyclohexenone affords (*S*,*R*)-**15** in 62% yield with 80:20 dr and 98:2 er.[11] The absolute configurations of (*S*,*R*)-**13**, (*S*,*R*)-**14**, and (*S*,*R*)-**15** are assigned by analogy to (*S*,*S*)-**7**.[11]

Three contiguous asymmetric centers can be generated with high enantioselectivities by this methodology. With 2-methyl-2-cyclopentenone as the electrophile and (*R*)-**2/5**, the product (*S*,*S*,*R*)-**16** is obtained in 81% yield with 93:7 dr and 95:5 er. A one-pot reaction beginning with 2-cyclopentenone and alkylation of the intermediate silyl enol ether of (*S*,*S*)-**7** with methyl iodide gives (*S*,*S*,*R*)-**16** in 53% yield with 96:4 er and 94:6 dr.[12] Treatment of (*S*,*R*)-**14** with lithium diisopropylamide (LDA)



followed by addition of methyl iodide affords (*S*,*R*,*R*)-**17** in 61% yield with 97:3 er and 90:10 dr. Treatment of the major diastereomer of **17** with LDA followed by the addition of allyl bromide provides (*S*,*R*,*R*)-**18** diastereospecifically in 51% yield with 97:3 er.[12]

Understanding these reactions will require further work. The TMSCl can promote the Michael reaction and/or react with the initial enolate to prevent further reactions.[9] The inaccessability of the lithium in the RLi/L complexes may also be important in the regiocontrol. The 1,4-addition could be promoted because complexation of the carbonyl of the Michael acceptor with the substrate, which could favor 1,2-addition, is hindered by the ligand.[13] The hypothesis that lack of complexation promotes reaction with inversion at the carbanionic carbon has been previously suggested.[2,14]

In summary, the choice of the ligand can provide control of 1,2- vs 1,4-additions of organolithium species to α,β-unsaturated carbonyl substrates. With highly enantioenriched configurationally stable α-lithio benzylic and allylic amine derivatives and (−)-sparteine, (*R*)-**2/5**, (*S*)-**2/5**, (*R*)-**10/5,** and (*R*)-**12/5** participate in asymmetric Michael additions to give products with high enantioselectivities at both termini of the new β, γ bond.

The availability of either enantiomer of the organolithium nucleophiles **2**, **10**, and **12**, the facile subsequent conversions of the newly installed groups, and the convenience of the methodology recommends synthetic applications.[2,6,10] Control over additional stereogenic centers, extentions to related systems, and elucidation of the course of the reactions are under further study.[15]

Acknowledgment. We are grateful to the National Institutes of Health GM-18874 for the support of this work.

Supporting Information Available: Details of experimental procedures and spectroscopic, analytical, and X-ray crystallographic data (15 pages). See any current masthead page for ordering and Internet access instructions.

JA972333A

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(10) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218.

(11) The relative configuration of (*S*,*R*)-**13** is the same as that for (*S*,*S*)-**7** as determined by X-ray crystallography of (*S*,*R*)-**13**. With alkyl halides or trimethyltin chloride as electrophiles, the organolithium species (*R*)-**2/5** and (*R*)-**10/5** have been shown to provide products with the same absolute configurations.[10] The absolute configuration of the stannane derivatives previously provisionally assigned as (*R*) have determined by X-ray crystallography to be (*S*).[10]

(12) Analogy to previous studies, which show that the alkylations of related cyclopentanones give products with the new groups at C-2 *trans* to a C-3 substituent, are used to make these stereochemical assignments.[2a,b]

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