Communications

Complex-Induced Proximity Effects: Stereoselective Carbon−Carbon Bond Formation in Chiral Auxiliary Mediated *β*-Lithiation−Substitution Sequences of *β*-Substituted Secondary Carboxamides

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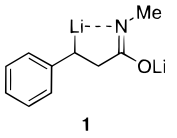
The central hypothesis of the complex-induced proximity effect (CIPE), that remote groups can influence the formation and reactivity of organolithium intermediates, has been demonstrated for a number of functional groups.[1,2] Reactions in which lithiated secondary amides provide CIPE control of regioselectivity and stereoselectivity have been a recurrent theme in this area.[3−5]

A recent investigation from our laboratories established by ^{6}Li, ^{13}C, and ^{15}N NMR that a lithium atom bridges the amide nitrogen and benzylic carbon in dilithiated intermediate **1**.[3c] This placement of the nitrogen proximal to the reactive carbanionic center suggests that a nitrogen-bound chiral auxiliary could influence the stereochemical course of *β*-lithiation−substitution sequences with derivatives of **1**. We now wish to report that the chiral homoenolate equivalents readily formed by dilithiation of **2**−**4** serve as nucleophiles for diastereoselective carbon−carbon bond-forming reactions. We demonstrate this approach for the synthesis of an enantiomerically pure 4-substituted dihydrocoumarin and provide evidence that favors a dynamic kinetic resolution as the diastereodetermining step.



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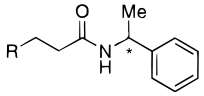
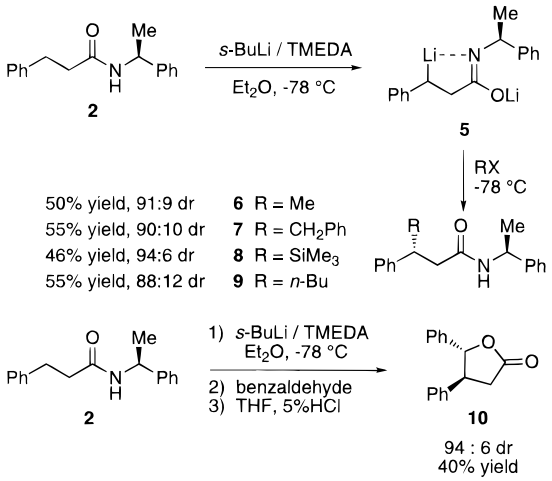
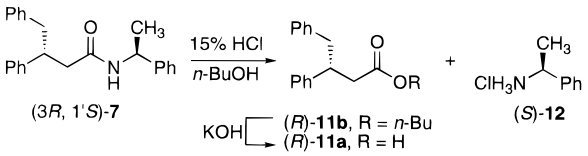


2, R = Ph
3, R = *o*-$OCH_3C_6H_4$
4, R = CH=CH-*c*-C_6H_{11}

Treatment of (*S*)-*N*-(1′-phenylethyl)-3-phenylpropionamide (**2**) in diethyl ether at −78 °C with 2.2 equiv of *s*-BuLi and TMEDA for 4.5 h followed by addition of an electrophile, stirring at −78 °C for 4 h, and addition of MeOH affords the products **6**−**9** in 46−55% yield and 88:12−94:6 diastereomeric ratios (dr). The absolute configurations of the major diastereomers for products arising from reactions with benzyl bromide and trimethylsilyl chloride electrophiles, **7** and **8**, were established by X-ray crystallography.[6] Reaction with benzaldehyde as the electrophile followed by cyclization provides (4*S*,5*R*)-**10** with an er of 77.73.[7] The configurations of **6** and **9** are assigned by analogy to **7** and **8**. It is notable that the carbonyl and alkyl halide electrophiles provide products with an opposite sense of configuration at the new carbon−carbon bond.[8]



The diastereomers are readily separated, and hydrolysis of the major diastereomer **7**, via ester **11b**, provides the enantiomerically pure carboxylic acid (*R*)-**11a** in 70% yield. The procedure also permits recovery of the chiral auxiliary as the hydrochloride (*S*)-**12**.



Both yields and selectivity increase when the *β*-substituent is an *o*-methoxy aryl group. Treatment of (*R*)-*N*-(1′-phenylethyl)-3-(*o*-methoxyphenyl)propionamide (**3**) with 2.2 equiv of *s*-BuLi and TMEDA in diethyl ether at −78 °C for 4 h followed by addition of the electrophile at −78 °C with warming to −10 °C over 4 h gives products **13**−**15** in 63−72% yield and 93:7−98:2 dr. The configuration for the major diastereomer (3*S*,1′*R*)-**15** was determined by X-ray crystallography;[6] configurations for **13** and **14** are based on analogy to **15**.

The amide **15** can be used for the preparation of the enantiomerically pure 4-substituted dihydrocoumarin (*S*)-**16**. Preparatory HPLC separation of (3*S*,1′*R*)-**15**, followed

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(2) Snieckus, V. *Chem. Rev. (Washington, D.C.)* **1990**, *90*, 879.

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(6) The authors have deposited atomic coordinates for structures **7**, **8**, **15**, and **17** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, U.K.

(7) Chang, C.-J.; Fang, J.-M.; Liao, L.-F. *J. Org. Chem.* **1993**, *58*, 1754.

(8) (a) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (b) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218 and references therein.

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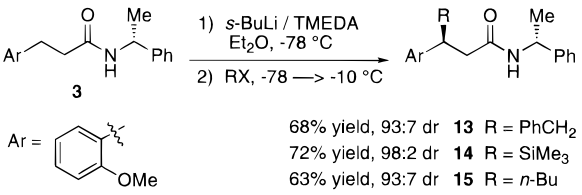

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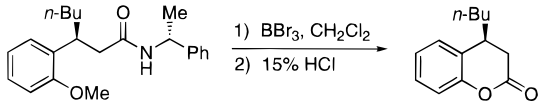
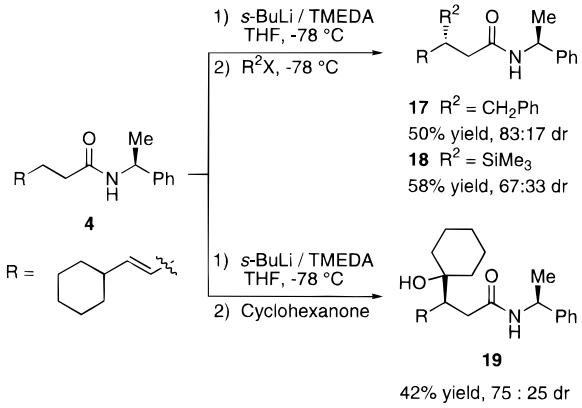
by demethylation and subsequent acid-catalyzed ring closure, gives (*S*)-4-*n*-butyldihydrocoumarin ((*S*)-**16**).[9]



(3*S*, 1′*R*)-**15**
dr > 99:1

(3*S*)-**16**
69% yield, er > 99:1

This lithiation−substitution methodology is also applicable to a derivative with a vinyl group at the β-position, albeit with lower diastereoselectivity. Reaction of (*S*)-*N*-(1′-phenylethyl)-5-cyclohexyl-4-(*E*)-pentenamide (**4**) with 2.2 equiv *s*-BuLi and TMEDA at −78 °C in THF for 4 h followed by reaction with an electrophile at −78 °C for an additional 4 h gives **16**−**18** in 42−58% yield with diastereomeric ratios from 67:33 to 83:17. The configuration of the major diastereomer (3*R*,1′*S*)-**17** is based on X-ray crystallography; configurations of **18** and **19** are assigned provisionally by analogy to **7** and **10**, respectively.[6]

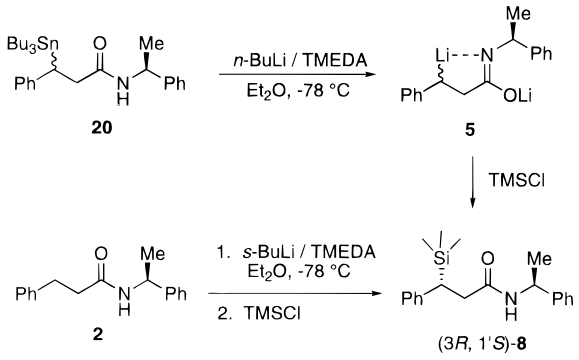


4

19
42% yield, 75 : 25 dr

The diastereodetermining step for these reactions could be an asymmetric deprotonation or an asymmetric substitution.[1b] The lithiated intermediate **5**, which is racemic at the β-position, was prepared from the reaction of **20** with *n*-BuLi. Addition of TMSCl gave the product **8** with a dr of 94:6. This is the same dr as obtained from direct dilithiation of **2**. These results establish that an asymmetric deprotonation is not the stereochemical-controlling step in the sequence.[10]

In an effort to determine if the lithiated intermediate **5** is configurationally stable on the time scale of reaction with the electrophile, a variation of Hoffmann's test for configurational stability was employed.[11] At −78 °C, **5** was generated from **2** in two parallel reactions. After cooling to −103 ± 2 °C, 3 equiv of TMSCl was added to one reaction and 0.1 equiv of TMSCl was added to the other. The product



20

5

2

(3*R*, 1′*S*)-**8**

substrate	temperature, eq TMSCl	yield	dr
20	-78 °C, 3.0	66%	94 : 6
2	-78 °C, 3.0	46%	94 : 6
2	-103 °C, 0.1	10%	97 : 3
2	-103 °C, 3.0	36%	97 : 3

diastereomeric ratios were determined to be 97:3 in both cases. This suggests that the diastereomeric intermediates are interconverting on the time scale of reaction with electrophile. The reaction appears to be under Curtin−Hammett control, and the process is presumed to be a dynamic kinetic resolution.[12]

In summary, the present work provides a synthetic equivalent for a chiral homoenolate of a carboxylate through a secondary amide chiral auxiliary. This approach affords an alternative to α-heteroatom allyllithium complexes, which have been shown to provide chiral homoenolate synthons in both chiral auxiliary and chiral ligand strategies.[7,8b,13] These results may be seen as a homologue of the work of Evans and of Myers who developed chiral amide auxiliaries for enolates.[14] More recent work by Magnus, which shows that secondary amide chiral auxiliaries, including α-methylbenzylamines, can exert diastereocontrol over substitutions at remote sulfone-activated carbanions, also appears to us to be related.[5b,c]

The commercial availability of both enantiomers of the chiral auxiliary and the relative ease in obtaining highly enantioenriched products suggests that this approach should be further developed.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**−**4** and **6**−**20**, experimental details for the mechanistic experiments, and ORTEP drawings for structures **7**, **8**, **15**, and **17** (27 pages).

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(9) The sense of optical rotation for (*S*)-**16** in conjunction with the X-ray crystal structure of (3*S*,1′*R*)-**15** corroborates a provisional literature assignment for (*R*)-**16**. Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250.

(10) These results do not rule out an initial asymmetric deprotonation to give configurationally labile lithiated intermediates.

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(12) This interpretation is provisional as it is possible that the diastereomeric intermediates are configurationally stable on the time scale of reaction with electrophile, but the activation energies for each diastereomer are not experimentally distinguished by this reaction.

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