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Diastereo- and Regioselectivity in the Reactions of Dilithiated Allylic Secondary Amides with Cyclopent-2-enone

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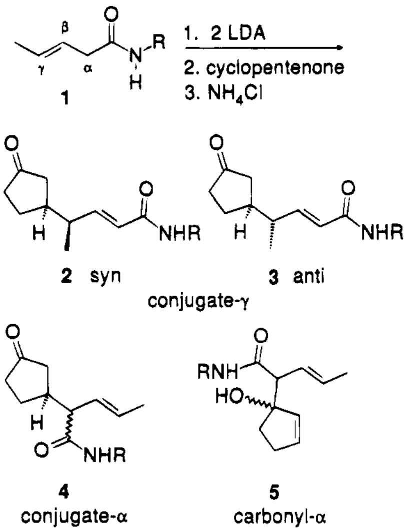
The conjugate (or Michael) addition is one of the most important reactions in organic synthesis for the construction of carbon−carbon bonds and is one of the most amenable to stereocontrol.[1] In this context, the conjugate additions of lithiated allylic systems stabilized by heteroatoms have been extensively examined.[2,3] In our case, we have shown that lithiated (*E*)- and (*Z*)-2-butenylphosphine oxides undergo highly diastereoselective conjugate addition to cyclopentenones in THF to give syn- and anti-vinylic phosphine oxides respectively.[4] An evident synthetic advantage would, however, accrue if we were able to utilize charge-stabilizing groups not attached to the allylic system by a heteroatom, but which confer the same high diastereo- and regioselectivity. In this respect, it is of interest to note that the dilithiated dienolate of sorbic acid was reported to react with cyclopentenone to provide adducts arising from reaction through C-γ (C-4),[5] a regiochemistry which corresponds to that of the lithiated phosphine oxides. However, under conditions of low temperature addition and quenching,[4] we found that the dilithiated dienolate of (*E*)-3-pentenoic acid, and lithiated allylic ester, thioester, and tertiary amide and thioamide derivatives gave largely products of conjugate addition through C-α (C-2).[6] Nevertheless, one class of pentenoic acid derivative, the secondary amides, upon dilithiation and reaction with cyclopentenone, was found to provide varying amounts of products arising from reaction through C-γ (C-4), that is, these reactions were tending to proceed in the same regiochemical sense as those of the lithiated phosphine oxides. However, the degree to which the dilithiated secondary amides behave like phosphine oxides or sulfoxides is dependent upon the nature of the *N*-substituent. Our findings are now presented.

Scheme 1



Deprotonation of a series of (*E*)-3-butenamides[7] with LDA (2.2 equiv) in THF according to Table 1 followed by treatment with cyclopentenone gave product mixtures which were fractionated by flash chromatography on silica. Results are presented in Table 1. The following points are noted. Although *N*-phenyl, *N*-benzyl, and *N*-(*p*-fluorophenyl)butenamides (**1a**, **1b**, **1e**, respectively) gave carbonyl-α- (**5**) (44−45%) and conjugate-α- (**4**) (5−14%) products in addition to the conjugate-γ-products **2** and **3**, the last were formed with good diastereoselectivities (90:10 to 95:5) in favor of the syn-isomer **3** (Scheme 1). Amides bearing an alkyl or phenylethyl group displayed poor regioselectivities. However, *N*-aryl amides bearing *ortho*-coordinating groups (**1d**, **1g**, **1h**)[8] and the trityl amide **1i** reacted with significantly enhanced regioselectivities in favor of the syn products.

Ratios of syn (**2**) and anti (**3**) conjugate-γ-adducts were determined by integration of the signals due to H2 (vinylic) in the ^{1}H NMR spectra (400 MHz). This was easily carried out, as the signal due to H2 in the syn product appeared consistently downfield of the signal H2 in the minor diastereomer **3**. Confirmation of the structure was made by X-ray crystallographic analysis of **2h** and **2i**.[9]

In line with the well-known structural features possessed by lithium enolates,[10] lithium ester enolates,[11] and lithiated tertiary amides,[12] dilithiated secondary amides are expected to be planar, with N−Li and O−Li contacts. While lithiated tertiary amides have (*Z*)-geometry, that

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(1) (a) Oare, D. A.; Heathcock, C. H. *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. 19, pp 227−407. (b) Oare, D. A.; Heathcock, C. H. *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1991; Vol. 20, pp 87−170. (c) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 199−236. (d) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon press: Oxford, 1992; (e) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (f) D'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron Asymmetry* **1992**, *3*, 459.

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(4) (a) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411. (b) Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423. For an explanation of the usage of the syn/anti nomenclature see ref 4a (footnote 14 therein).

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(6) King, L. M. Ph. D. Thesis, The University of Sydney, 1992.

(7) (3*E*)-Pentenoic acid was treated with thionyl chloride (1.1 equiv) at 60 °C for 30 min. The crude acid chloride was cooled to room temperature, dissolved in dichloromethane, to give a 1−3 M solution and treated, dropwise, with a solution of the amine (1−2 equiv; *ca.* 1 M in dichloromethane). After being stirred for a further 5 min, the reaction was quenched with a saturated solution of K_2CO_3, and the product was extracted into diethyl ether. The combined extracts were washed with saturated K_2CO_3 solution and HCl (2 M) and dried ($CaCl_2$), and the solvent was removed by evaporation under reduced pressure. In each case the crude amides were recrystallized from petroleum ether (bp 60−70 °C) to geometric purity (>95% *E*-isomer as indicated by NMR analysis) and in 50−60% overall yield.

(8) While fluorine is not known to form strong complexes with lithiated species, "complexed induced proximity effects" are attributed to increased stabilization in the transition state: van Eikema Hommes, N, J. R.; von Ragué Schleyer, P. *Tetrahedron* **1994**, *50*, 5903.

(9) Full X-ray crystallographic data will be reported elsewhere.

(10) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617.

(11) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

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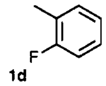
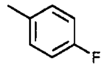
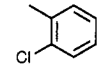
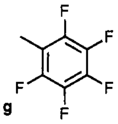
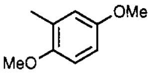
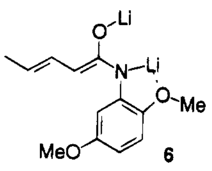
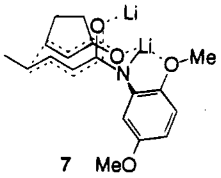
Table 1. Products Arising from the Reactions of Dilithiated Allylic Amides 1 with Cyclopentenone

R group	**2** and **3** (% yield) (**2**:**3**)	**4** (% yield)	**5** (% yield) (diastereomer ratio)	recovered starting amide (% yield)	reaction condns i. deprotonation[a] ii. with enone[b]
1a –Ph	40 (95:5)	5	42 (80:20)	0	i. –70 °C/5 min ii. –70 °C/5 min
1b –CH_2Ph	40 (90:10)	7	43 (50:50)	0	i. –70 °C/15 min ii. –70 °C/15 min
1c –$(CH_2)_2Ph$	40 (85:15)	10	35	1	i. –50 °C/15 min ii. –60 °C/10 min
 **1d**	58 (90:10)	10	14 (70:30)	11	i. –30 °C/15 min ii. –20 – 0 °C/4 h
 **1e**	37 (90:10)	14	44	0	i. –70 °C/10 min ii. –70 °C/10 min
 **1f**	39 (90:10)	12	8 (70:30)	30	i. –50 °C/15 min ii. –20 °C/2 h
 **1g**	72 (96:4)	0	0	20	i. –50 °C/15 min ii. –70 °C/4 h
 **1h**	72 (95:5)	12	0	8	i. –30 °C/15 min ii. –15 – 0 °C/4 h
1i –$C(Ph)_3$	80 (75:25)	0	0	19	i. –70 °C/15 min ii. –70 °C/1 h
1j –*t*-Bu	56 (75:25)	11	33 (50:50)	0	i. –50 °C/15 min ii. –40 °C/15 min
1k –*n*-Bu	18 (80:20)	8	20	2	i. –40 °C/15 min ii. –40 °C/30 min

[a] The allylic amide (*ca.* 0.5 M in THF) was deprotonated by addition to LDA (2.2 equiv; *ca.* 0.1–0.15 M in THF). [b] The enone was added as a solution in THF (*ca.* 0.5 M).





of dilithiated secondary amides is unknown. Nevertheless, we believe this to be (*Z*)[12] and in the special case of the allylic amides of the current work, we are dealing with (1*Z*,3*E*)-"dienolates" such as **6**. In view of the extended *trans*-decalyl transition state previously invoked for the phosphine oxide reactions, we can posit analogous "endo" orientation of the dienolate to the enone, as in **7**, with the nitrogen atom incorporated within the cycle.[13] Such a representation will account for formation of the syn products from the (*E*)-amides and for the fact that lithiated tertiary allylic amides with (1*Z*,3*E*)-dienolate geometry are unable to undergo conjugate-γ-addition. Nevertheless, it is not clear from this model how the anti-γ-addition products **3** are formed, as the starting secondary amides are geometrically pure (*E*)-isomers. Alternative extended transition state models such as one involving "exo" orientation of the dianion to the enone so as to afford a *cis*-decalyl or "cis-boat–boat-like"[4b] arrangement may account for formation of **3**. Enhanced rigidity through lithium coordination in the case of the aryl amides bearing *ortho*-coordinating groups must favor the γ-addition mode over other regiochemical pathways. This is nicely illustrated by comparing the reaction of the (*o*-fluorophenyl)amide **1d** with that of the (*p*-fluorophenyl)amide **1e**, in which the latter displays very poor regioselectivity. In the case of the trityl amide **1i** steric bulk in the vicinity of Cα is tentatively suggested to overwhelm the electronic tendency, in the absence of a coordinating group, for these amides to react through Cα. The same *trend* is reflected in the reactions of the *tert*-butylamide **1j** as compared to the *n*-butylamide **1k**. However, the effects are not nearly as marked.

In summary, dilithiated allylic secondary amides undergo diastereoselective conjugate addition to cyclopentenone. The nature of the coordination to lithium and its role in the proposed transition state both provide a means of fine-tuning the reaction and potentially enable the design of chiral amides that can undergo enantioselective reactions. Work in this direction is currently underway.

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Supporting Information Available: Experimental procedures for reactions of amides **1** with cyclopentenone and characterization data for all new compounds; ORTEP plots of **2h** and **2i** (18 pages).

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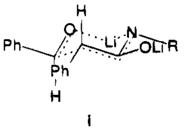
(13) This assumption is based on our finding that dilithiated *N*-ethyl alkylamides and -thioamides react with identical stereoselectivities with benzaldehyde to give exclusively anti products: Haynes, R. K.; Gordon, P. A.; Potter, L. B. Unpublished work; see also: von Schriltz, D. M.; Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1967**, *32*, 2610. Tamura, Y.; Amino, Y.; Furukawa, Y.; Kagotani, M.; Yoshida, Z. *J. Am. Chem. Soc.* **1982**, *104*, 4018. Formation of the anti product in both cases is rationalized in terms of six-membered Zimmerman–Traxler transition states **i** involving N–Li, rather than O–Li or S–Li, in the cycle.



i