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Kinetic Resolution of Racemic Lactones by Conjugate Additions of Allylic Organolithium Species: Direct Formation of Three Contiguous Centers with High Diastereo- and Enantioselectivities

Sung H. Lim and Peter Beak*

Department of Chemistry, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801

beak@scs.uiuc.edu

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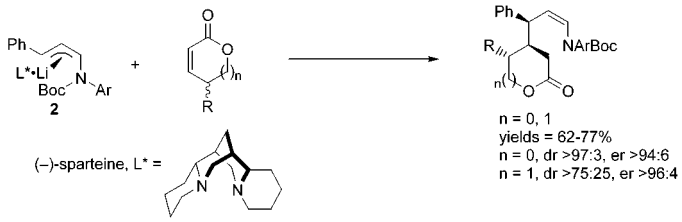
ABSTRACT



Kinetic resolution of racemic α,β-unsaturated lactones by the organolithium species produced from asymmetric lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine provides conjugate addition products with three contiguous stereogenic centers in yields of 62–77% with diastereomeric ratios from 75:25 to >99:1 and enantiomeric ratios for the major diastereomers from 94:6 to 98:2.

Conjugate carbon−carbon bond formations that generate a single asymmetric center via enantioselective 1,4-additions have been developed with organozincate, metalloenolate, organocuprate, and organolithium nucleophiles.[1,2] Stereoselective conjugate additions that provide control of two stereogenic carbons usually employ enol silanes or metalloenolates as nucleophiles.[3] Feringa has developed kinetic resolution of cyclohexenones via copper−phosphoramidite-catalyzed conjugate addition.[4] Buchwald has reported the kinetic resolution and dynamic kinetic resolution of racemic 3,5-dialkylcyclopentenones via asymmetric conjugate reduction.[5] We have reported organolithium-based (−)-sparteine-mediated conjugate addition reactions of configurationally stable allylic organolithium species to provide 1,4-addition products with high diastereomeric and enantiomeric ratios.[6] The products obtained from the conjugate addition reactions

(1) For reviews on conjugate addition reactions, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Pergamon Press: Oxford, 1992. (b) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. (c) Feringa, B. L. *Acc. Chem. Res*. **2000**, *33*, 346. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033 and references therein.

(2) For recent examples of asymmetric conjugate additions, see: (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984. (c) Barbas, C. F., III; Betancort, J. M. *Org. Lett.* **2001**, *3*, 3737. (d) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083. (e) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852. (f) Totani, K.; Nagatsuka, T.; Yamaguchi, S.; Takao, K.; Ohba, S.; Tadano, K. *J. Org. Chem.* **2001**, *66*, 5965.

(3) For leading references on asymmetric conjugate reactions with control of the two new stereogenic centers, see: (a) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, M.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271. (b) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921. (c) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 3531. (d) Evans, D. A.; Scheidt, K. A.; Johnson, J. S.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480 and references therein.

(4) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 927.

(5) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 2892.

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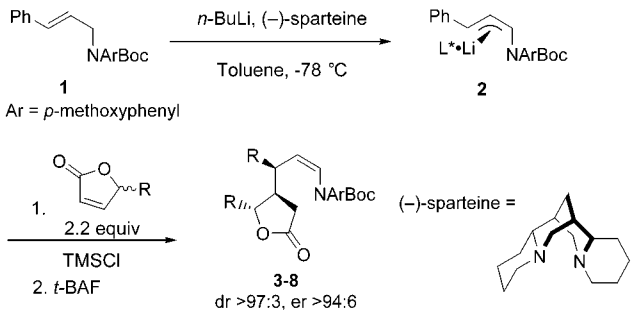
are precursors to a number of synthetically useful compounds, including substituted piperidines[6d] and bicarbocyclic compounds.[7] We now report kinetic resolution[8] of racemic α,β-unsaturated lactones with the organolithium species under the influence of (−)-sparteine to provide conjugate addition products with three contiguous stereogenic centers with high diastereo- and enantioselectivity in a single step.

Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine **1** with 1.1 equiv of *n*-BuLi in the presence of (−)-sparteine at −78 °C in toluene for 30 min generates the lithiated intermediate **2**.[6b] Addition of **2** to a premixed solution of trimethylsilyl chloride (TMSCl) and 2.5 equiv of 5-substituted 5*H*-furan-2-ones in toluene provides the 1,4-addition products **3**−**8** in good yields with high diastereo- and enantioselectivities as shown in Table 1. In the absence of TMSCl, the yield of the reaction decreases significantly. In all cases, the selectivity factors were >20.[9] With a phenyl at the 5-position, the 1,4-addition product was not obtained; the organolithium acted as a base to afford the isomerized electrophile.

Table 1. Kinetic Resolution of 5-Alkyl-Substituted 5*H*-Furan-2-ones



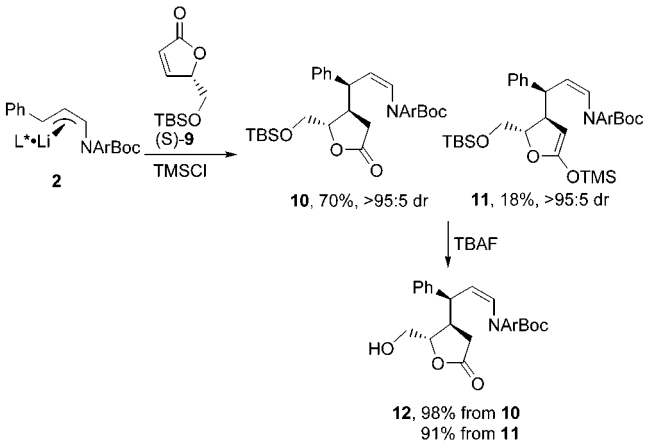
entry	R	product	% yield	dr	er[a]
1	H	**3**	71	97:3	97:3[b]
2	Me	**4**	77	97:3	94:6[c]
3	Et	**5**	62	>99:1	95:5[c]
4	Pr	**6**	62	>99:1	96:4
5	hex	**7**	69	>99:1	96:4
6	hex-3-enyl	**8**	75	>99:1	97:3
7	Ph	na	na	na	na

[a] Enantioselectivities were determined by CSP-HPLC analysis by comparison with authentic racemic material. [b] To **2** was added 1.3 equiv of electrophile. [c] Electrophile (2.5 equiv) was used.

The relative configuration of **5** has been determined by X-ray crystallographic analysis.[10] On the basis of the configuration of the recovered electrophile, (*S*)-5-ethyl-5*H*-furan-2-one, which was determined by comparing the optical rotation,[11] the absolute configuration is assigned as (3*R*,2′*R*,3′′*S*)-**5**. This result established that the reaction proceeds with the retention of the configuration relative to the organolithium, which is consistent with our previous results in which 5,6-dihydro-pyran-2-one reacts with the organolithium with retention to afford **13** (vide infra).[6b] The absolute configurations of the other products are assigned by analogy.

Two separate experiments were conducted to confirm that (*R*)-alkyl 5*H*-furan-2-ones have matched selectivity with the lithiated intermediate **2** (Scheme 1). With the (*S*)-5-(*tert*-butyldimethyl-silanyloxymethyl)-5*H*-furan-2-one **9** as the electrophile, the products **10** and **11** were obtained in 70 and 18% yields, respectively, with >95:5 dr.[12] Both **10** and **11** can be easily deprotected with tetrabutylammonium fluoride, TBAF, to afford the same isomer **12** in 98 and 91% yields, respectively. With (*R*)-**9** as the electrophile, only a trace of the 1,4-addition product was obtained. This set of experiments shows the (*R*)-alkyl 5*H*-furan-2-ones to have the matched stereochemistry for these highly stereoselective conjugate additions.

Scheme 1



The methodology can be extended to kinetic resolutions of 5-alkyl-5,6-dihydro-pyran-2-ones. The results are summarized in Table 2. The diastereoselectivities are lower than those for the 5-alkyl-5*H*-furan-2-ones. The diastereomers of **13** were separated by preparatory HPLC to afford a single diastereomer.[6a] The kinetic resolution products **14** and **15** were obtained as mixtures of diastereomers as shown in

(6) (a) Park, Y.-S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537. (b) Pippel, D. J.; Weisenburger, G. A.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522. (c) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996. (d) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004.

(7) Lim, S. H.; Curtis, M. D. Beak, P. *Org. Lett.* **2001**, *3*, 711.

(8) For leading references on kinetic resolution, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330. (b) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 489−526. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (d) Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 545.

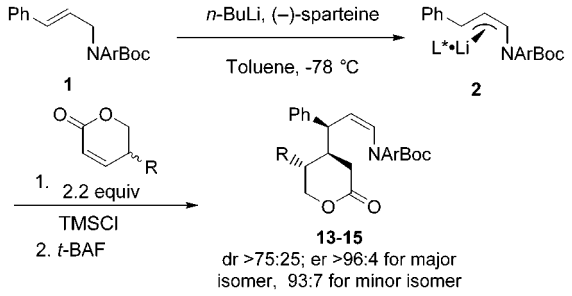
(9) The selectivity factor, $s = \ln [1 - C(1 + ee)]/[1 - C(1 - ee)]$, was calculated using the enantiomeric excess of the conjugate addition product. For each substrate, *s* was greater than 20.

(10) Crystallographic data for structure of **5** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 18373. Copies of the data can be obtained free of charge upon application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax (+44) 1223-336033; e-mail deposit@ccdc.cam.ac.uk).

(11) Tsuboi, S. *J. Org. Chem.* **1998**, *63*, 1102.

(12) The *R* and *S* designations of configuration change with **9** and **17** due to a change in priorities; the absolute configurations are as shown.

Table 2. Kinetic Resolution of 5-Alkyl-5,6-dihydro-pyran-2-one



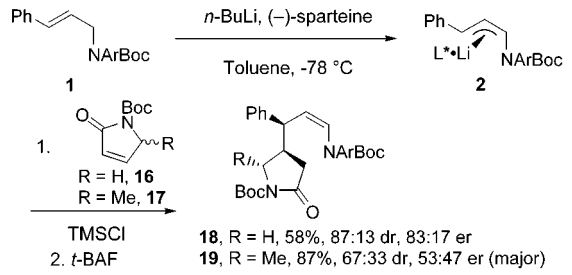
entry	R	product	% yield	dr	er (minor)[a]
1	H	**13**	85	89:11[b]	96:4[c]
2	Me	**14**	67	75:25	98:2 (93:7)
3	Et	**15**	65	80:20	98:2 (93:7)

[a] Enantioselectivities were determined by CSP-HPLC analysis in comparison with an authentic sample. [b] Diastereomerics were separated by HPLC. [c] To **2** was added 1.3 equiv of electrophile.

Table 2. For **14** and **15**, enantiomeric ratios of 98:2 er and 93:7 er were observed for the major and minor diastereomers, respectively.

The kinetic resolution of *N*-Boc-5-methyl-dihydropyrrol-2-one **17** was investigated (Scheme 2). First, treatment of

Scheme 2



the organolithium **2** with a premixed solution of **16** and TMSCl afforded **18** in 58% yields with 87:13 dr and 83:17 er. The diastereomers were separated using preparative HPLC to provide **18** as a single diastereomer. The kinetic resolution of the N-Me lactam **17** with **2** afforded **19** in good yield, but with a selectivity significantly lower than that observed for lactones. Recovered **17** had the (*S*)-configuration, which is consistent with the results with the 5-alkyl-5*H*-furan-2-ones.[12,13] With *N*,*N*,*N*′,*N*′-tetraethylethylenediamine, TEEDA, as the ligand, *rac*-**19** was obtained from **2** as a single diastereomer; the er of the minor diastereomer could not be determined.

A reasonable transition structure for the substitution reactions of the 5-alkyl-5*H*-furan-2-ones is depicted in Figure 2. Our working hypothesis is that the carbonyl group of α,*β*-unsaturated lactones complexes to the lithium atom of the

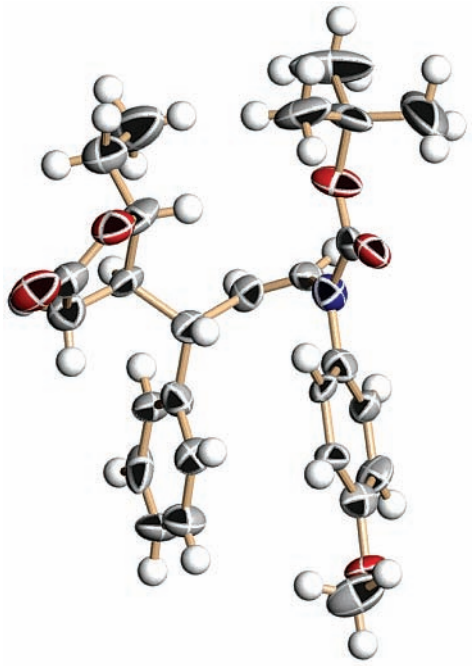


Figure 1. SHELXTL Crystal Structure of plots showing 35% probability circles for non-H atoms and circles of arbitrary size for H atoms.

organolithium species prior to retentive substitution.[14] Lactones with the R substituent located away from the Ph group on the allyllithium lead to the transition structure represented as **A** to avoid the steric interaction between the groups evident in **B**.

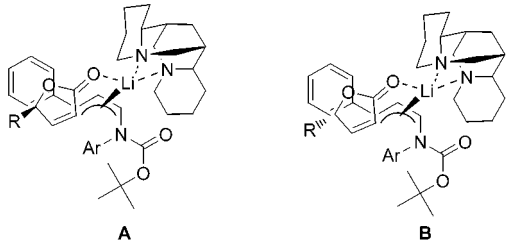


Figure 2. Proposed transition structure for reaction of the organolithium, (−)-sparteine, and the electrophile.

In summary, kinetic resolutions of racemic cyclic unsaturated esters with the organolithium intermediates derived from

(13) Cuiper, A. D.; Brzostowska, M.; Gawronski, J. K.; Smeets, W. J. J.; Spek, A. L.; Hiemstra, H.; Kellogg, R. M.; Feringa, B. L. *J. Org. Chem.* **1999**, *64*, 2567.

(14) Electrophiles such as alkyl halides and activated olefins[6c,d] react with inversion of configuration, as either their rate of reaction with the organolithium is faster than complexation or the molecule does not contain functionality that precoordinates to Li in the productive transition structures. The absolute configuration of the orgolithium has been established.[6,15]

(15) Pippel, D. J.; Weisenberger, G. A.; Fabish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919.

lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine with *n*-BuLi/(−)-sparteine provides 1,4-conjugate addition products in good yields with high diastereo- and enantioselectivity. The present methodology provides a conjugate addition approach that generates three contiguous stereogenic centers simultaneously with high stereoselectivities. Extension of this methodology to other substrates and synthetic application are areas of future interest.

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Supporting Information Available: Detailed experimental procedures, including spectroscopic and analytical data for the preparation of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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