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# Synthesis of Highly Enantioenriched All-Carbon Quaternary Centers: Conjugate Additions of Chiral Organolithium Nucleophiles to α,α-Dinitrile *β*,*β*-Disubstituted Olefins

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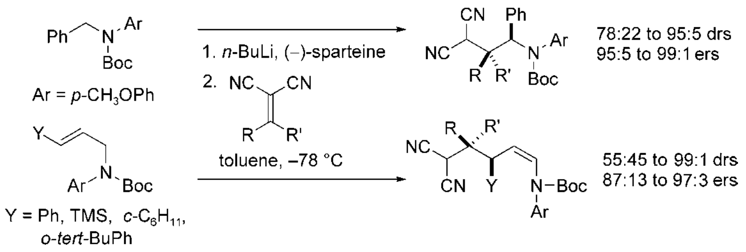
## ABSTRACT



**Highly enantioenriched quaternary centers are obtained by the reaction of chiral lithiated intermediates complexed to (−)-sparteine with tetrasubstituted, α,α-dinitrile activated olefins. Lithiated *N*-Boc-*N*-Aryl benzylamine furnishes products with drs from 78:22 to 95:5, with ers exceeding 94:6. Lithiated *N*-Boc-*N*-Aryl allylamine reactants provide enecarbamate products with drs from 55:45 to 99:1, with ers ranging from 87:13 to 97:3.**

Synthesis of highly enantioenriched all-carbon quaternary centers is a challenging task.[1−6] The development of one-step procedures not involving α-carbonyl compounds or α-heteroatoms has not experienced high levels of success. A conjugate addition strategy would be useful, but there are few precedents for highly diastereoselective *β*-additions that create all-carbon quaternary centers.[7,8] We now wish to report the development of conjugate additions to α,α-dinitrile *β*,*β*-disubstituted olefins by configurationally stable enantio-

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(1) Revews: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(2) A strategy that has had success is the addition of a tertiary enol or enolate to an electrophile in the presence of a chiral ligand or auxiliary.[1] Direct, one-step procedures not involving an enol derived or α-heteroatom nucleophiles that have been reported to give products with a wide range of drs and ers include alkylations,[3] allylations,[4] Diels−Alder cyclizations,[1b] Heck reactions,[5] and intramolecular rearrangements/cyclizations.[6]

(3) (a) Spino, C.; Beaulieu, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1930. (b) Beaulieu, C.; Spino, C. *Tetrahedron Lett.* **1999**, *40*, 1637. (c) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832.

(4) (a) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456. (b) Nakamura, M.; Inoue, T.; Sato, A.; Nakamura, E. *Org. Lett.* **2000**, *2*, 2193.

(5) (a) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737. (b) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 757. (c) Lebsak, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008.

(6) (a) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911. (b) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (c) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726. (d) Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229. (e) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193. (f) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026. (g) Lee, E.; Shin, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112*, 260.

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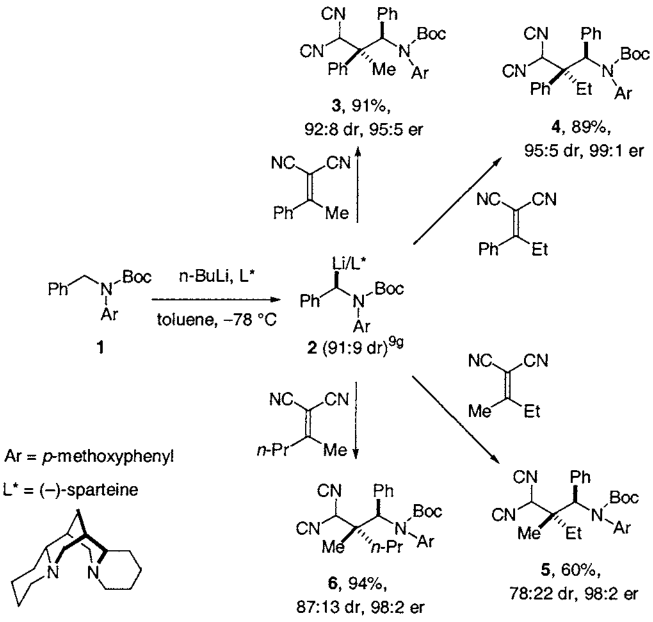
enriched benzylic and allylic organolithium species that are complexed to (−)-sparteine. The products have all-carbon quaternary centers at the $\beta$-position with a range of diastereomeric ratios and high enantiomeric ratios.[8]

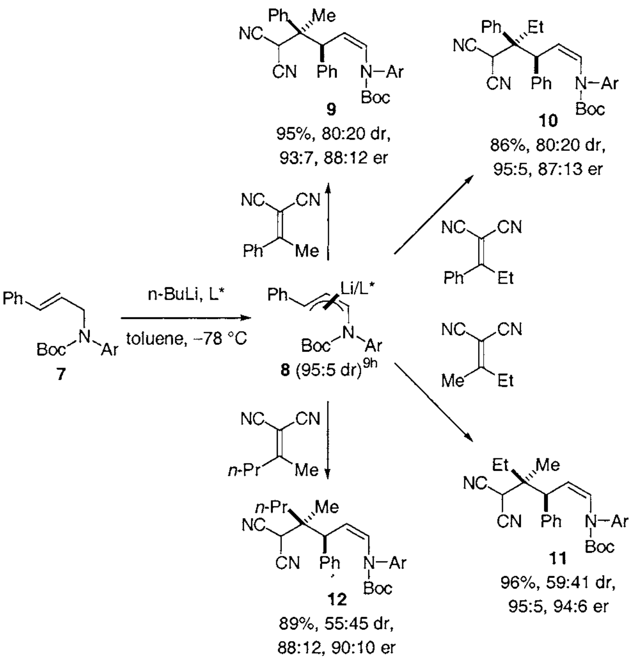
The lithiation of **1** with $n$-BuLi/(−)-sparteine to give **2**, followed by conjugate addition to a dinitrile tetrasubstituted olefin, provides **3** in high yield with a 92:8 dr and a 95:5 er as previously reported.[8a] The additions of **2** to other $\alpha$,$\alpha$-dinitrile $\beta$,$\beta$-aryl, alkyl- and alkyl, alkyl-substituted olefins proceed as shown to give products with drs that range from moderate to excellent and ers that are greater than 94:6 for the major diasteromers (Scheme 1). The lowest dr of 78:22 is obtained for the olefin in which the difference between the $\beta$-substituents is methyl vs ethyl. The diastereomeric ratios were determined from $^1$H NMR integrations, and the diastereomers for **5** and **6** were separated by preparative HPLC. The enantiomeric ratios were determined by chiral HPLC using racemic compounds as standards. The absolute configurations of **4**−**6** are assigned by analogy to that established for **3**.[8a]

**Scheme 1**



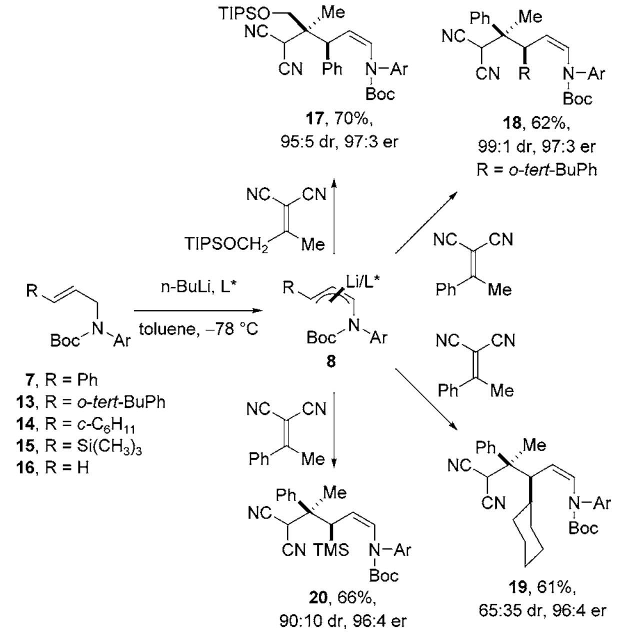
The asymmetric lithiation of **7** proceeds to give **8**, which on conjugate additions to $\alpha$,$\alpha$-dinitrile $\beta$,$\beta$-disubstituted olefins provides **9**,[8a] **10**, **11**, and **12** in high yields (86−96%) with moderate drs (55:45−80:20) and good ers (87:13−95:5) for each diastereomer (Scheme 2). The diastereomers were separated by HPLC, and the enantiomeric ratio of each diastereomer was established by chiral HPLC.

**Scheme 2**



The scope of this methodology has been investigated for substitutions on the allyl terminus and on the olefin. Lithiation of the allyl substrates **7** and **13**−**15** with $n$-BuLi/(−)-sparteine gives lithiated intermediates that, on addition of the activated olefins, provide **17**−**20**, respectively, in useful yields with a range of drs and excellent ers (Scheme 3).

**Scheme 3**



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(7) Diastereoselective conjugate additions to activated olefins with single substituents at the $\beta$-positions are being rapidly developed for the formation of highly enantioenriched tertiary centers. Reviews: (a) Sibi, M. P.; Mangem, S. *Tetrahedron* **2000**, *56*, 8033. (b) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, *2*, 171.

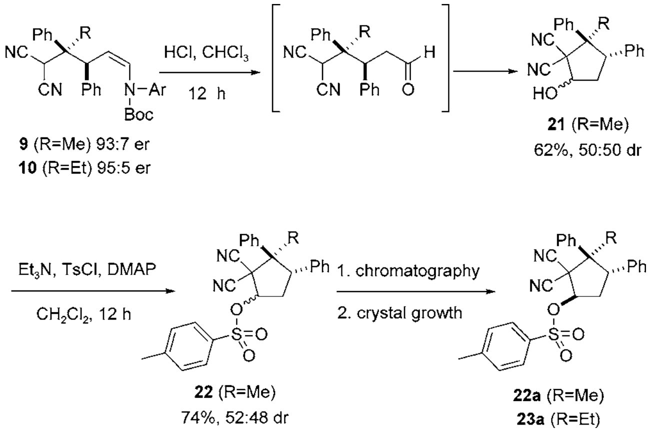
(8) The only cases we are aware of in which all-carbon quaternary centers are formed at $\beta$-positions in asymmetric syntheses by nucleophilic 1,4-additions to $\beta$,$\beta$- disubstituted olefins are: (a) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996. (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron* **1999**, *55*, 12045.

The formation of **17** provides a compound with a highly enantioenriched quaternary center that has orthogonal functionalities on three of the four carbons. The enecarbamate may be hydrolyzed to an aldehyde or reduced to an amine, and the dinitrile and protected alcohol functionalities are available for further synthetic elaborations. The preparation of **18** shows that ortho substitution by a large group on the aromatic ring of the allyl group does not reduce the enantiomeric ratio. The syntheses of **19** and **20** establish that an aryl group is not necessary for formation of the highly enantioenriched quaternary carbon center.

We have found that reaction of the unsubstituted allylamine **16** in this sequence gives products with low ers on additions to the $\beta,\beta$-phenyl methyl or $\beta,\beta$-*n*-propyl methyl-substituted dinitrile olefins. Apparently, a terminal substituent is necessary to achieve high enantioselectivities.

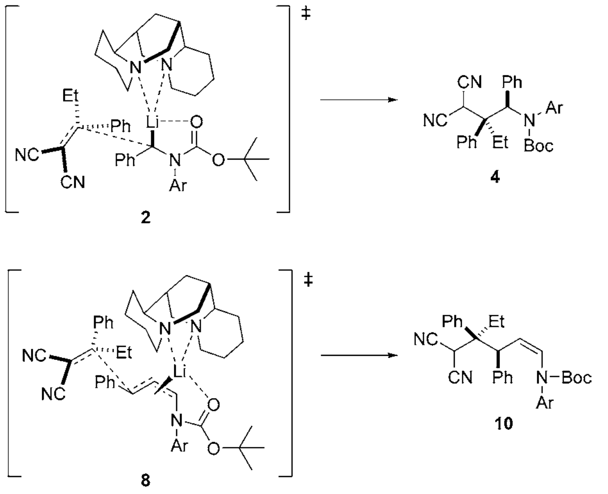
Hydrolyses of enecarbamates **9** and **10** have been used to establish the absolute configurations.[9] This sequence demonstrates application of the methodology to an asymmetric synthesis of substituted cyclopentanes. Acidic hydrolysis of **9** afforded a 50:50 diastereomeric mixture of cylopentanol **21** (Scheme 4). Tosylation of this mixture followed by separation of the diastereomers by chromatography gave **22**. Crystals suitable for X-ray analysis of **22a** were grown by liquid diffusion in $CH_2Cl_2$ and heptane, and the absolute configuration of the quaternary center was determined by X-ray crystallography of this sulfur-containing derivative.[10] The same sequence was carried out with **10** to provide **23a**.

**Scheme 4**



The reactions of both organolithium intermediates **2** and **8** proceed with inversion of configuration. The transition structures shown provide working rationales for the stereoselectivities (Scheme 5). The approach of the electrophile can be seen to take place from the sterically less encumbered bottom face, resulting in inversion of configuration to give the observed high enantioenrichments.

**Scheme 5**



A rationalization for the opposite sense of olefin orientation of **2** and **8** is not obvious. In the formation of **10**, the favored transition state requires reaction of the electrophile on the *re*-face. Reaction on the *si*-face leads to the formation of **4**.

X-ray crystal structure analysis of the Michael acceptor ((Ph)MeC=C(CN)$_2$) shows the phenyl ring to be out of the plane by 41° and sterically larger than the alkyl group. If this is maintained in the transition state leading to **4**, steric size appears to be more of an influence for **4** than in the transition state leading to **10**.

In summary, the formation of highly enantioenriched all-carbon quaternary centers can be carried out by conjugate additions of configurationally stable *N*-Aryl, *N*-Boc-substituted benzylic and allylic organolithium nucleophiles complexed to (−)-sparteine to α,α-dinitrile $\beta,\beta$-disubstituted olefins. The ers are high, and the drs range from low to high and appear to be electrophile dependent. Compounds with functionalities suitable for further elaboration can be prepared by this approach. Understanding the course of the reaction and developing the synthetic consequences of this methodology will require further investigation.

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**Supporting Information Available:** Experimental procedures, characterization data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (b) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574. (c) Kim, B. J.; Park, Y. S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1705. (d) Whisler, M. C.; Soli, E. D.; Beak, P. *Tetrahedron Lett.* **2000**, *41*, 9527. (e) Lim, S. H.; Curtis, M. D.; Beak, P. *Org. Lett.* **2001**, *5*, 711. (f) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056. (g) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. (h) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522.

(10) On the basis of these results, the absolute configuration of the quaternary center assigned to **9** is reassigned as the opposite of what we previously proposed by analogy.[8]