Asymmetric Carbon−Carbon Bond Formation in Michael Reactions: Conjugate Addition Reactions of Configurationally Stable Benzylic and Allylic Organolithium Species

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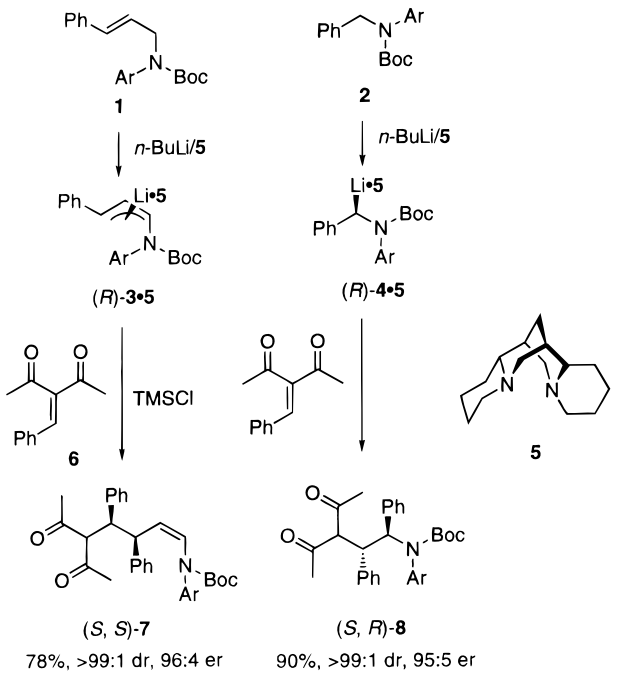
Asymmetric carbon−carbon bond formation under the control of a chiral ligand provides a direct strategic approach for efficient asymmetric syntheses. Enantioselective conjugate additions have been developed using a variety of chiral ligands with organozincates, metalloenolates, and most commonly mixed organocuprates.[1−4] Organolithium-based chiral ligand mediated conjugate additions, although uncommon, have been reported.[5−13] To the best of our knowledge only three laboratories have reported enantioselective Michael additions of organolithium species which provide products with two new contiguous stereogenic centers and good enantiomeric ratios.[8−13] Koga and co-workers reported stereoselective Michael additions of organolithium reagents to cyclic α,β-unsaturated aldimines in 1989.[8] More recently, Koga reported conjugate additions of lithioenolates to alkylidene diesters in the presence of a complex chiral tetraamine ligand which affords products in high yields, with high diastereo- and enatioselectivties.[9] Seebach reported stereoselective conjugate additions of lithioenolates to nitro olefins in the presence of various TADDOL chiral additives.[10] We recently reported conjugate addition reactions of configurationally stable benzylic and allylic organolithium species under the influence of (−)-sparteine to cyclic unsaturated ketones and esters which provide 1,4-addition products with generally high diastereomeric and enantiomeric ratios.[11−13] We are interested in developing a convenient, general methodology for conjugate additions of organolithium species to acyclic activated olefins with control of the new stereogenic centers at each carbon of the newly formed bond.

Scheme 1



We now wish to report that β-substituted doubly activated acyclic olefins and β-substituted nitro olefins afford conjugate addition products on reaction with enantioenriched benzylic and allylic organolithium species in good yields, with good diastereoselectivities and high enantioselectivities. Representative reactions are shown for **1** and **2**. Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine (**1**) with 1.1 equiv each of *n*-BuLi and (−)-sparteine (**5**) in toluene for 1 h provides (*R*)-**3·5**. Addition of benzylideneacetylacetone (**6**), in the presence of TMSCl, to (*R*)-**3·5** affords the *cis* enecarbamate (*S*,*S*)-**7** in 78% yield as a single diastereomer with an enantiomeric ratio (er) of 96:4. Employing the same reaction protocol with *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine (**2**) provides configurationally stable (*R*)-**4·5** which reacts with **6** to provide diastereomerically pure (*S*,*R*)-**8** in 90% yield with an er of 95:5 (Scheme 1).

Reaction of the η^3-organolithium species (*R*)-**3·5** with other activated olefins provides the enecarbamates **9**−**13** in good yields, with good diastereoselectivities and high enantioselectivities as shown in Table 1. Addition of diethyl ethylidenemalonate to (*R*)-**3·5** provides product (*S*,*S*)-**9** in 93%, with a dr of 80:20 and er's of 98:2 and 93:7 for the major and minor diastereomers, respectively (entry 1). A diester-activated olefin with a phenyl ring at the β position provides (*S*,*S*)-**10** with a dr of 94:6 and an er of 98:2 on reaction with (*R*)-**3·5** (entry 2). This methodology is also applicable to dicyano-activated olefins (entries 3 and 4). Reaction of (*R*)-**3·5** with a dinitrile trisubstituted olefin affords (*S*,*S*)-**11** in 80% yield with a dr of 66:34 and high er's of 94:6 and 95:5 for the major and minor diastereomers. The diastereomers can be separated by flash chromatography, providing highly enantioenriched products. Contiguous enantioenriched centers, one of which is a quaternary center, can be formed by this methodology as shown by the formation of (*S*,*S*)-**12** in 95% yield with a dr of 80:20 and er's of 93:7 and 88:12 for reaction of (*R*)-**3·5** with the tetrasubstituted dicyano olefin. Reaction of (*R*)-**3·5** with *trans* β-nitrostyrene gives (*S*,*R*)-**13** in 71% yield with a dr of 94:6 and an er of 96:4 (entry 5). The reaction conditions are also compatible with an aryl bromide as shown by reaction of (*R*)-**3·5** with *trans*-β-*p*-bromoni-

(1) For reviews on conjugate addition reactions, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.2. Leonard, J.; Diez-Barra, E. Merino, S. *Eur. J. Org. Chem.* **1998**, 2051.

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(3) For some examples of stereoselective conjugate additions of metalloenolates, see: Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666. Manickam, G.; Sandararajan, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2271. Bako, P.; Kiss, T.; Take, L. *Tetrahedron Lett.* **1997**, *38*, 7259. Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441. Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8223. Inagaki, K.; Noazaki, K.; Takaya, H. *Synlett* **1997**, 119. Kumamoto, T.; Aoki, S.; Nakajima, M.; Koga, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1431.

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(10) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.

(11) Park, Y.-S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574.

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(13) Pippel, D. J.; Weisenburger, G. A.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522.

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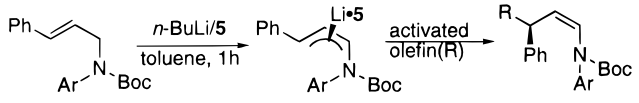
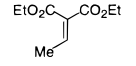
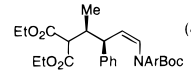
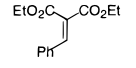
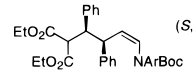
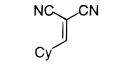
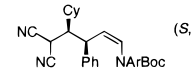
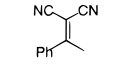
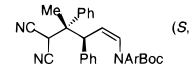
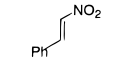
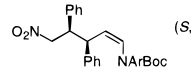
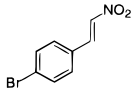
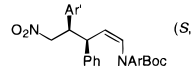
Table 1. Reaction of (*R*)-3·5 with Activated Olefins



Entry	Activated Olefin (E)	Product	Yield (%)	dr[a]	er(minor)[b]
1		 (*S, S*)-**9**	93	80:20	98:2 (93:7)
2		 (*S, S*)-**10**	86	94:6	98:2
3		 (*S, S*)-**11**	80	66:34	94:6 (95:5)
4		 (*S, S*)-**12**	95	80:20	93:7 (88:12)
5		 (*S, R*)-**13**	71	94:6	96:4
6		 (*S, R*)-**14**	78	90:10	98:2

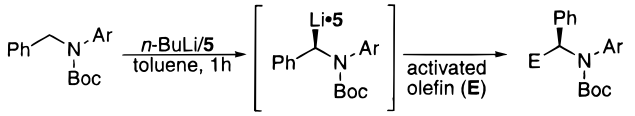
[a] Diastereomeric ratios determined by integration of the ^{1}H NMR spectrum. [b] Enantiomeric ratios determined by CSP HPLC.

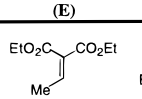
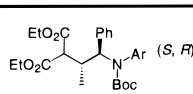
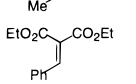
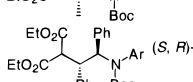
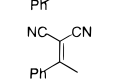
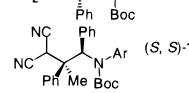
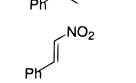
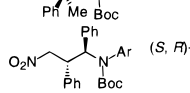
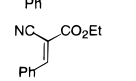
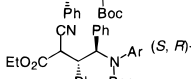
trostyrene to provide (*S*,*R*)-**14** in 78% yield with a dr of 90:10 and an er of 98:2 (entry 6). The absolute configurations of **7**,**9**−**14** are assigned by analogy to that of (*S*,*S*)-**10** which was unambiguously established by X-ray crystallography of an amide derivative.[14]

Reaction of (*R*)-**4·5** with several activated olefins provides the conjugate addition products **15**−**19** in good yields, with good to high diastereoselectivities and high enantioselectivities as shown in Table 2. Addition of diethyl ethylidenemalonate to (*R*)-**4·5** gives (*S*,*R*)-**15** in 92% yield with a dr of 80:20 and er's of 97:3 and 93:7 (entry 1). Reaction of diethyl benzylidenemalonate with (*R*)-**4·5** provides (*S*,*R*)-**16** in 72% yield as a single diastereomer with an er of 96:4 (entry 2). Reaction of (*R*)-**4·5** with the dicyano-tetrasubstituted olefin (entry 3) provides (*S*,*S*)-**17** with an enantiomerically enriched quaternary center in 91% yield with a dr of 92:8 and an er of 95:5 (entry 3). Reaction of *trans*-*β*-nitrostyrene with (*R*)-**4·5** gives (*S*,*R*)-**18** in 90% yield with a dr of 90:10 and an er of 97:3 (entry 4). Reaction with the mixed olefin, α-cyanoethyl cinnamate, introduces three new contiguous stereogenic centers on reaction with (*R*)-**4·5** (entry 5). Addition to the mixed olefin by (*R*)-**4·5** affords (*S*,*R*)-**19** in 85% yield as a 75:25 ratio of diastereomers epimeric at the carbon bearing the nitrile and ester groups.

The er of (*S*,*R*)-**19** was determined by CSP HPLC following hydrolysis, decarboxylation, nitrogen deprotection, and cyclization to the stereochemically pure butyrolactam (3*R*,4*S*)-**20** in 79% yield (Scheme 2). The absolute configuration of (3*R*,4*S*)-**20** was assigned unambiguously by X-ray crystallography of the brominated derivative (2*R*,3*R*,4*S*)-**21**.[14] The absolute configuration of (*S*,*S*)-**17** was also determined using the sequence described above while the absolute configurations of **8**, **15**, **16**, and **18** are assigned by analogy to (*S*,*S*)-**17** and (*S*,*R*)-**19**.[14]

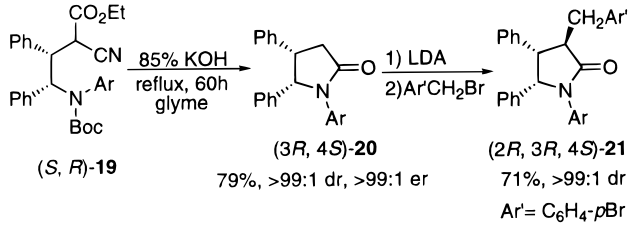
Table 2. Reaction of (*R*)-4·5 with Activated Olefins



Entry	Activated Olefin (E)	Product	Yield (%)	dr[a]	er(minor)[b]
1		 (*S, R*)-**15**	92	80:20	97:3 (93:7)
2		 (*S, R*)-**16**	72	>99:1	96:4
3		 (*S, S*)-**17**	91	92:8	95:5
4		 (*S, R*)-**18**	80	90:10	97:3
5		 (*S, R*)-**19**	85	75:25	>99:1[c]

[a] Diastereomeric ratios determined by integration of the ^{1}H NMR spectrum. [b] Enantiomeric ratios determined by CSP HPLC. [c] Enantiomeric ratio determined by CSP HPLC following hydrolysis and decarboxylation of **19** (see text).

Scheme 2



The observation of inversion of configuration for the reaction of (*R*)-**3·5** with diethyl benzylidenemalonate is opposite to the conjugate addition of (*R*)-**3·5** to a cyclic activated olefin.[13] Inversion of configuration at (*R*)-**4·5** is consistent with our previous working hypothesis.[11,12]

In summary, conjugate additions of the configurationally stable organolithium species (*R*)-**3·5** and (*R*)-**4·5** to doubly activated acyclic olefins, or nitro olefins, provide products in good yields with high enantioselectivities at both termini of the newly formed bond. The availability of both (*R*) and (*S*) epimers of **3·5** and **4·5** through a stannylation/lithiation sequence allows selection of the configuration on the donor organolithium species and thus either enantiomer of the product.[15,16] Products with enantioenriched contiguous tertiary/tertiary or tertiary/quaternary stereocenters can be formed using activated tri- and tetrasubstituted olefins, respectively. Useful transformations of these compounds can be envisioned, with the conversion of (*S*,*R*)-**19** into (2*R*,3*R*,4*S*)-**21** as an example. Extension of this methodology to other substrates, complete elucidation of the stereochemical course of the reactions, and evolution of a predictive model for the transition structure are areas of future interest.[17]

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 and analytical data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 115139−115141. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax (+44)1223-336-033; email deposit@ccdc.cam.ac.uk).

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

(17) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y.-S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.