Enantioselective Syntheses of α-, *β*-, and *γ*-Aryl Amino Acids and Esters

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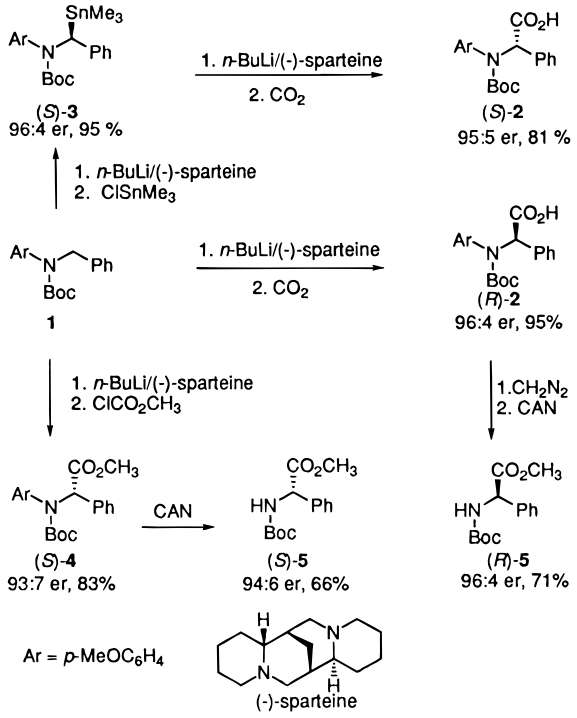
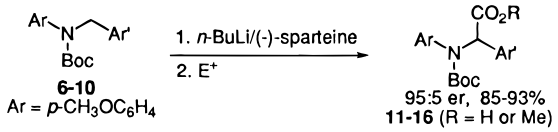
The importance of amino acids in medicinal and biological chemistry has made these compounds a focal point for asymmetric syntheses. Chiral pool-, chiral auxiliary-, and chiral ligand-based methods have been developed for syntheses of a variety of enantioenriched α and *β* amino acids and their derivatives.[1] We wish to report chiral ligand methodology that can provide either enantiomer of highly enantioenriched natural and unnatural α-, *β*-, and *γ*-aryl amino acids and esters from *N*-Boc-arylmethylamine derivatives by convenient lithiation substitution sequences.

The methodology is based on an asymmetric deprotonation and electrophilic substitution sequence that employs *n*-BuLi/(−)-sparteine as a chiral base.[2] The approach is illustrated for *N*-Boc-*N*-(*p*-methoxyphenyl)-benzylamine (**1**). Treatment of **1** with 1.1 equiv of



n-BuLi/(−)-sparteine at −78 °C in toluene for 8 h, with subsequent addition of CO_2, gives the highly enantioenriched phenylglycine derivative (*R*)-**2** with a 96:4 er (enantiomeric ratio) in 95% yield. If trimethyltin chloride is used as the electrophile and the product (*S*)-**3** is allowed to react with *n*-BuLi/(−)-sparteine followed by CO_2, (*S*)-**2** is obtained with a 95:5 er in 77% overall yield.[3] Lithiation of **1** with *n*-BuLi/(−)-sparteine followed by methyl chloroformate as the electrophile gives the α-amino acid derivative (*S*)-**4** with a 93:7 er in 83% yield. Thus, either enantiomer of a highly enantioenriched α-aryl amino acid derivative can be obtained by adding a stannylation transmetalation sequence or by changing the electrophile. Oxidative cleavage of the *p*-methoxyphenyl group of (*S*)-**4** with ceric ammonium nitrate (CAN) provides (*S*)-**5**, a highly enantioenriched amino acid ester. The preparation of (*R*)-**5** from **1** is accomplished by treatment of (*R*)-**2** with diazomethane and ceric ammonium nitrate.

Table 1. Enantioselective Reactions of 6−10 To Provide 11−16



reactant	Ar′	E^+	product	yield (%)	er[a]
6	2-naphthyl	CO_2	**11**	93	96:4 (*R*)
6	2-naphthyl	$ClCO_2Me$	**12**	90	6:94 (*S*)
7	*p*-CH_3Ph	CO_2	**13**	89	96:4 (*R*)
8	*m*-CH_3OPh	CO_2	**14**	90	95:5 (*R*)
9	*p*-FPh	CO_2	**15**	85	95:5 (*R*)
10	3-thienyl	CO_2	**16**	87	95:5 (*R*)

[a] The enantiomeric ratios of the acids were assigned by conversion to the methyl esters and analyses by CSP-HPLC.

As shown in Table 1, analogous lithiation−substitution reactions can be carried out with other *N*-Boc-*N*-(*p*-methoxyphenyl)arylmethylamines **6**−**10**. Treatment of each substrate with 1.1 equiv of *n*-BuLi/(−)-sparteine and carbon dioxide gives the (*R*)-α-amino acids **11** and **13**−**16** with 96:4−95:5 ers in 85−93% yields. When *N*-Boc-*N*-(*p*-methoxyphenyl)-2-naphthylmethylamine (**6**) is treated with methyl chloroformate, the α-amino acid derivative (*S*)-**12** is obtained with a 94:6 er in 90% yield. The absolute configurations of **11**−**16** are assigned by analogy to the formation of (*R*)-**2** and (*S*)-**4** and consistency in the CSP elution orders.

Highly enantioenriched *β*-aryl amino acid derivatives can also be obtained from **1**. Treatment of **1** with 1.1 equiv of *n*-BuLi/(−)-sparteine followed by 4-bromo-2-methyl-2-butene gives the α-substituted product in 95% yield. Subsequent oxidation with O_3 and Jones reagent provides the *β*-amino acid derivative (*S*)-**17** in 80% yield with a 93:7 er. If the initial lithiation of **1** is followed by reaction with trimethyltin chloride prior to a transmetalation with *n*-BuLi/(−)-sparteine, reaction with 4-bromo-2-methyl-2-butene, and oxidation, the opposite enantiomer (*R*)-**17** is obtained in 58% yield with a 89:11 er. Treatment of **1** with *n*-BuLi/(−)-sparteine followed by reaction with methyl bromoacetate gives the *β*-amino acid derivative (*R*)-**18** with a 92:8 er in 32% yield.[4] When carbomethoxymethyltrifluoromethane sulfonate is used

(1) Williams, R. M. *Syntheses of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. For recent reports see: Beaulieu, F.; Arora, J.; Veith, U.; Taylor, N. J.; Chapell, B. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 8727. Davies, S. G.; Walters, A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488. Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 4910. Davis, F.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y. *J. Org. Chem.* **1996**, *61*, 440. Pandey, G.; Reddy, P. Y.; Das, P. *Tetrahedron Lett.* **1996**, *37*, 3175. Cole, D. C. *Tetrahedron* **1994**, *51*, 9517. Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222. Seki, M.; Matsumoto, K. *Tetrahedron Lett.* **1996**, *37*, 3165. North, M. *Contemp. Org. Synth.* **1996**, *3*, 323 and references cited therein.

(2) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757.

(3) The absolute configuration is assigned to (*S*)-**3** on the basis of anomalous dispersions in the determination of the structure by X-ray crystallography. *Caution:* trimethyltin chloride is known to be toxic and should be used only with appropriate procedures. See: Sax, N. I.; Lewis, R. J. *Dangerous Properties of Industrial Materials*, 7th ed.; Van Nostrand Reinhold: New York, 1988; p 899.

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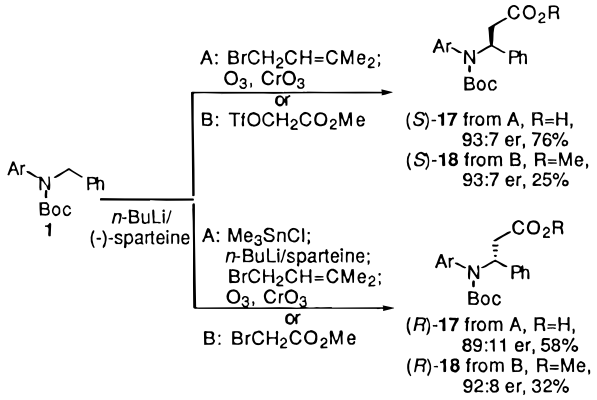
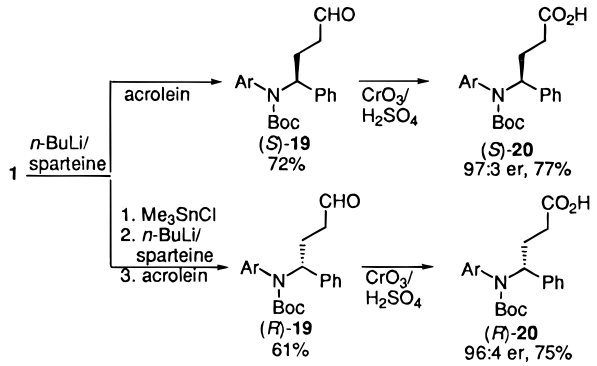
as an electrophile, (*S*)-**18** is obtained in 25% yield with 93:7 er. Thus, either enantiomer of highly enantioenriched β-amino acid derivatives can be obtained by this methodology.

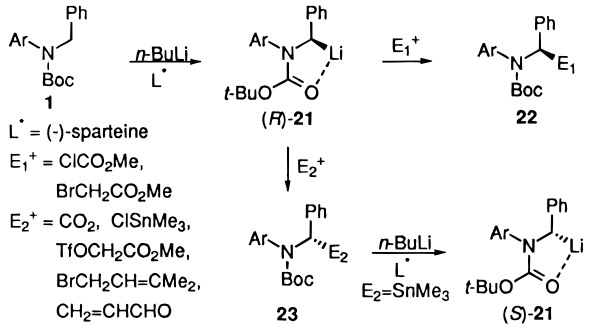


This methodology also can provide highly enantioenriched γ-aryl amino acids by lithiation of **1** with *n*-BuLi/(−)-sparteine followed by reaction with acrolein and a subsequent oxidation. When **1** is treated with *n*-BuLi/(−)-sparteine followed by reaction with acrolein, (*S*)-**19** is obtained in 72% yield. Oxidation with Jones reagent affords (*S*)-**20** in 77% yield with an er of 97:3.[5] When the lithiation−stannylation−transmetalation protocol is used (*vide supra*), (*R*)-**19** is obtained, and oxidation provides (*R*)-**20** in 46% overall yield with a 96:4 er.



A number of mechanistically interesting issues are embedded in these synthetically useful reactions. The *n*-BuLi/(−)-sparteine complex acts as a chiral base to effect an asymmetric deprotonation of **1**, which we suggest gives (*R*)-**21**. The assignment of the absolute configuration to (*R*)-**21** is based on the absolute configuration reported for (*S*)-**3** (*vide supra*) and the assumption of retentive transmetalation with *n*-BuLi/(−)-sparteine.[3,6] This absolute configuration is consistent with our original presumptive assignment, which we did provisionally change in a subsequent review.[2,7] The enantioenriched dipole-stabilized carbanion (*R*)-**21** maintains its configuration in the presence of (−)-sparteine before undergoing highly stereoselective reactions with electrophiles. Reactions of (*R*)-**21** with methyl chloroformate and methyl bromoacetate are considered to proceed with retention of configuration to give **22**. Reactions of (*R*)-**21** with CO_2, 4-bromo-2-methyl-2-butene, carbomethoxymethyl trifluoromethanesulfonate, trimethyltin chloride, and acrolein are considered to proceed with inversion of configuration to provide **23**. Our hypothesis is that the reactions of highly reactive or nonlithium coordinating electrophiles proceed with inversion, while less reactive and lithium coordinating electrophiles give retention.[8] To the best of our knowledge, the reactions of (*R*)- and (*S*)-**21** with acrolein provide the first case of a highly stereoselective Michael addition by an enantioenriched configurationally stable organolithium intermediate.

In addition to providing diastereoselectivity in the transition state for asymmetric deprotonation, (−)-sparteine influences the configurational stability of **21** and the regioselectivity of its reactions. If **21** is generated by tin−lithium exchange of enantioenriched tin derivative **23** of 95:5 er in the presence of TMEDA, subsequent reaction with methyl triflate provides the α-methyl-substituted product with an er of 70:30 as opposed to the er of 95:5 obtained in the presence of sparteine. Thus, TMEDA is less effective in maintaining the configuration of a chiral organolithium than is (−)-sparteine.[9] If the lithiation is carried out with TMEDA to give racemic **21**, subsequent reaction with acrolein gives the product of 1,2-addition in 83% yield with only a trace of the 1,4-adduct.



In summary, the lithiation−substitution of **1** under the influence of (−)-sparteine provides prototypical methodology for syntheses of highly enantioenriched α-, β-, and γ-aryl amino acids. Synthetic developments, assignments of absolute configurations of organolithium intermediates, and investigation of the reaction pathways are of future interest.

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for support of this work.

Supporting Information Available: Details of experimental procedures (13 pages).

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(4) The absolute configuration of (*R*)-**18** was assigned by removal of the *p*-methoxyphenyl group with CAN and comparison to the optical rotation of authentic compound. Alcon, M.; Canas, M.; Poch, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1995**, *35*, 1589.

(5) The sequence of reduction, mesylation of the resulting alcohol, removal of the *p*-methoxyphenyl group with CAN, and cyclization with sodium hydride gave (*S*)-*N*-Boc 2-phenylpyrrolidine in 45% yield with an er of 90:10, establishing the absolute configuration of (*S*)-**19**. Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.

(6) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. Aggarwal, V. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 175.

(7) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. We adopted the provisional assignment to give consistency with related reactions and note the present absolute configurations allow better assignments of retentive/invertive reactions than heretofore.

(8) For other cases of invertive and retentive reactions of organolithium intermediates, see: Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424. Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149. Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763. Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755.

(9) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575. Weisenburger, J.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218.