Control of the Enantiochemistry of Electrophilic Substitutions of *N*-Pivaloyl-α-lithio-*o*-ethylaniline: Stereoinformation Transfer Based on the Method of Organolithium Formation

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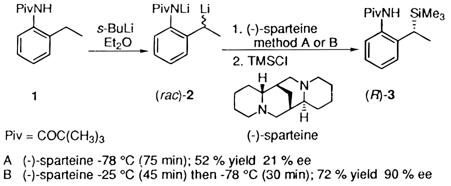
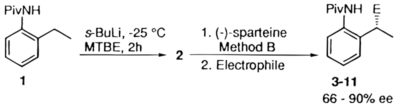
Enantioselective reactions of organolithium reagents in the presence of (−)-sparteine have been the focus of a number of recent synthetic and mechanistic investigations.[1−4] Factors that have been demonstrated to affect, and even invert, the sense of enantioselection include subtle modifications in the structure of the organolithium species, directing group, chiral ligand, solvent, and choice of electrophile.[1−3] Effects of temperature, where reported, involve decreasing selectivities with increasing temperature, as expected.[1c,4] The enantiochemistry has also been independent of the method of generation of the organolithium intermediate.[5] We now wish to report an investigation of the lateral lithiation of *N*-pivaloyl-*o*-ethylaniline (**1**) to give **2**. Subsequent electrophilic substitution of **2** affords the products **3**−**10** with good enantioselectivities in the presence of (−)-sparteine.[6] *We are able to induce high enantioselectivities in the substitutions by employing a warm−cool protocol and to invert the sense of enantioselectivity by changing the method of formation of the organolithium intermediate.* We provide data which show that these observations can be ascribed to diastereomeric complexes of **2**/(−)-sparteine which can equilibrate at −25 °C but are nonequilibrating at −78 °C with respect to the rate of reaction with the electrophiles.

Treatment of the anilide **1** with *sec*-butyllithium (*s*-BuLi) at −25 °C for 2 h generates the dilithio intermediate **2**, which upon cooling to −78 °C, followed by subsequent additions of (−)-sparteine and TMSCl, affords the product (*R*)-**3** in 52% yield with 21% enantiomeric excess (ee).[7] However, if the sparteine is added at −25 °C and the solution allowed to stir at this temperature for 45 min prior to cooling to −78 °C and subsequent addition of TMSCl, (*R*)-**3** is obtained in 72% yield with 90% ee. The induction of high enantioselectivities by a −25 °C to −78 °C sequence for a reaction which gives modest selectivities under the usual −78 °C conditions suggests that a warm−cool protocol should be investigated for other reactions which afford low enantioselectivities.



The dianion **2** has been reacted in the prescence of (−)-sparteine with a variety of electrophiles, including activated alkyl halides, carbonyl compounds, and stannylating and silylating agents using the warm−cool sequence of method B. Good yields and enantioselectivities are obtained (Table 1). Absolute configurations of products **4** and **11** were determined by comparison with products of known configuration obtained by independent syntheses.[8] Assignments of absolute stereochemistry to **3** and **5**−**10** are based on their correspondence to (*R*)-**4** and (*S*)-**11** as the more retained isomers on the (*S*,*S*)-Whelk-O chiral stationary phase HPLC column and the chiral recognition models proposed by Pirkle.[9] Deoxygenation of the benzaldehyde adduct **7** afforded (*S*)-**9**, indicating that the organolithium reagent **2** reacts with carbonyl electrophiles and alkyl halides with the same stereochemical sense at the benzylic carbon.[10]



Since Still's seminal report in 1980, lithiodestannylation of organostannanes of known configuration has served as a useful probe of organolithium configurational stability.[12] Transmetalation of (*R*)-**5** (70% ee) in both the absence and the presence of TMEDA, followed by reaction with TMSCl, affords essentially racemic **3** in both cases. However, lithiodestannylation of enantioenriched (*R*)-**5** (66% ee) with *s*-BuLi in the presence of (−)-sparteine, followed by reactions with TMSCl or cyclo-

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[1] (a) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (b) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516. (c) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

[2] (a) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158. (b) Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323. (c) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (d) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski,. S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479. (e) Personal communication by M. Schlosser, June 1995. Apparently, M. Schlosser and D. Limat were the first to observe a pronounced inversion of steroselectivities when switching from hexane or Et_2O to THF as the solvent for the (−)-sparteine-mediated lithiation/substitution of Boc-*N*-methyl benzyl amine. Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342.

[3] Lautens, M.; Gajda, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193. Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797. Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. Muci, A.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

[4] For studies on the effect of temperature on the configurational stability of related organolithium species, see: Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *56*, 6077. Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *56*, 6089. Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51. Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809.

[5] The two most common methods are deprotonation and tin/lithium exchange (lithiodestannylation).

[6] For a review of the directed lateral lithation, see: Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.

[7] That a dilithio species is generated prior to addition of the diamine or electrophile has been independently determined by quenching the reaction at this point with MeOD. The product with deuterium incorporated at the benzylic position was obtained in 98% yield and 94% deuterium incorporation as determined by ^1H, ^{13}C NMR, and mass spectral analysis.

[8] The organosilane **4** was subject to a Tamao−Fleming oxidation to afford the hydroxy amide. The oxidation has been shown to proceed with retention of configuration, even at a benzylic position. Fleming, I.; Henning, R.; Parker, D. C.; Plant, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317. Oppolzer, W.; Mills, R. J.; Pachinger, W.; Stevenson, T. *Helv. Chim. Acta* **1986**, *69*, 1542. This was correlated with a sample of the enantioenriched alcohol independently prepared from commercially available (*S*)-(−)-2-bromo-α-methylbenzyl alcohol. The MOM-protected bromo alcohol was electrophilically aminated using Trost's azidomethyl phenyl sulfide methodology. Subsequent hydrolysis of the triazoline and acylation of the resultant aniline, followed by deprotection of the MOM ether, afforded (*S*)-**14** in 86% ee. Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 2483. The absolute configuration of **11** was determined through independent chemical synthesis from (*R*)-3-phenylbutyric acid. The sequence involves reduction of the acid to the alcohol and activation as the tosylate, followed by a one-carbon homologation with methylmagnesium bromide in the presence of the Tamura−Kochi catalyst. Nitration of the alkane, followed by reduction and pivaloylation, affords the desired product. See supporting information for full experimental details.

[9] Pirkle, W. H.; Welch, C. J.; Lamm, B. *J. Org. Chem.* **1992**, *57*, 3854.

[10] Preparation of the methyl oxalate ester of **7**, followed by deoxygenation with Bu_3SnH, afforded (*S*)-**9** in 82% ee. Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588.

[11] While the initial work was conducted in Et_2O, a subsequent solvent study revealed that MTBE afforded higher yields with little effect on the enantioselectivities.

[12] (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Aggarwal, V. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 175 and references cited therein.

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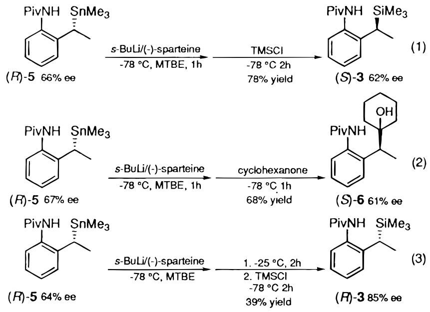
Table 1. Yields and Enantioselectivities for Products **3**−**11** from the Electrophilic Substitution of **2** in the Presence of (−)-Sparteine in MTBE via the Warm−Cool Protocol[11]

electrophile	E	product	yield (%)	ee (%)
Me_3SiCl[a]	Me_3Si	(*R*)-**3**	72	90
$PhMe_2SiCl$[a]	$PhMe_2Si$	(*R*)-**4**	6[b]	79
Me_3SnCl	Me_3Sn	(*R*)-**5**	77	66
cyclohexanone	$(CH_2)_5C(OH)$	(*R*)-**6**	80	77
benzaldehyde	PhCH(OH)	(*R*)-**7**	67[c]	82[d]
allyl bromide[e]	$CH_2{=}CHCH_2$	(*S*)-**8**[f]	67	82
benzyl bromide	$PhCH_2$	(*S*)-**9**[f]	56	84
iodoundecane	$CH_3(CH_2)_{10}$	(*S*)-**10**[f]	62	78
allyl bromide	$CH_3CH_2CH_2$[g]	(S)-**11**[f]	100[h]	84

[a] Reaction conducted in Et_2O. [b] The yield of unpurified product, as determined by GC, is 85%. However, separation of **4** from **1** chromatographically proved difficult, accounting for the low yield. [c] A 2:1 ratio of unseparated diastereomers. [d] See footnote 10. [e] Reaction conducted in ether/pentane (1/1 v/v). [f] The designation of (*S*)-configuration is a consequence of a change in substituent priority assignments. [g] Prepared via hydrogenation of (*S*)-**8**. [h] Yield of hydrogenation reaction.

hexanone, afforded (*S*)-**3** (62% ee) and (*S*)-**6** (61% ee) with virtually complete inversion of configuration (eqs 1 and 2). Lithiodestannylation of (*R*)-**5**, followed by warming of the reaction mixture to −25 °C for 2 h prior to cooling to −78 °C and subsequent reaction with TMSCl, provides (*R*)-**3** (85% ee) (eq 3). Thus, either enantiomer of **3** and **6** can be obtained from **1** by controlling the reaction conditions.



Two limiting mechanisms have been postulated to rationalize the observed stereoselectivities of the asymmetric substitution process.[1,2] The first involves the preferential formation of one diastereomer of the putative organolithium/(−)-sparteine complex which reacts with an electrophile stereoselectively. This requires configurational stability of the organolithium/chiral ligand complex on the time scale of reaction with electrophiles. A selective crystallization of one diastereomeric complex has been reported by Hoppe.[2b,c] The second mechanism involves diastereomeric complexes which are rapidly equilibrating on the time scale of the reaction, with enantioselection arising as a function of the energy difference between diastereomeric transition states. In this case, the organolithium intermediate is configurationally labile.[13]

If the substitution proceeded via rapidly equilibrating diastereomeric complexes, the stereochemical outcome should be independent of the method of organolithium formation, since a common intermediate would be formed. As this is not observed, we suggest that the reaction proceeds through the electrophilic substitution of two diastereomeric complexes, which can be formed under nonequilibrating (−78 °C) or equilibrating (−25 °C) conditions. At −25 °C, the complexes equilibrate to a thermodynamic ratio, which can be maintained by rapid cooling to −78 °C. At −78 °C, the ratio of diastereomeric complexes is established by the method of generation and subsequently remains invariant. Thus, the operation of these two pathways for stereoinformation transfer, along with the ability to transmetalate an enantioenriched organostannane derivative, allows access to both enantiomers with good enantioselection.

Our mechanistic hypothesis is consistent with the observation that the dianion must be stirred in the presence of the ligand at −25 °C for 45 min to obtain high asymmetric induction, allowing sufficient time for equilibration of the diastereomeric complexes to occur.[14] If the (−)-sparteine is added at −25 °C but allowed to stir for only 5 min before cooling to −78 °C and subsequent addition of TMSCl, (*R*)-**3** is obtained with only 39% ee.

We presume by analogy that the lithiodestannylation of **5** occurs with retention of configuration to generate a complex which is configurationally stable at −78 °C.[12] Electrophilic substitution must then occur with inversion.[1a,15] Upon warming the reaction mixture to −25 °C (eq 3), the complexes equilibrate to generate the same ratio of diastereomeric complexes formed by method B, affording the same enantiomer upon electrophilic substitution.[16] The occurrence of enantioinversions from (*R*)-**5** at −78 °C with (−)-sparteine, but not with TMEDA, indicates that TMEDA is not effective as an achiral mimic of (−)-sparteine in this reaction sequence.[17]

In summary, the present results illustrate two ways in which the enantiochemistry of the electrophilic substitutions of a racemic benzylic organolithium reagent can be controlled. High enantioselectivities can be obtained by allowing the diastereomeric complexes to equilibrate at −25 °C prior to cooling to −78 °C. Lithiodestannylation of the enantioenriched organostannane at −78 °C, followed by electrophilic substitution, provides products which are enantiomeric to those obtained by the warm−cool protocol. Thus, enantiodivergent synthesis can be achieved by choosing the appropriate substitution sequence and reaction conditions. A warm−cool protocol may be useful for inducing enantioselectivity in other organolithium/chiral ligand reactions. We anticipate that a detailed investigation of the mechanism of enantioinversion will afford insight into the mechanism of the asymmetric substitution and provide avenues for further development.

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Supporting Information Available: Experimental procedures and characterization data for **1**, **3**−**11**, as well as procedures for enantioinversion experiments and determination of absolute configurations (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) Asymmetric induction at a stereocenter capable of epimerizing under the reaction conditions is an example of dynamic kinetic resolution. See: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

(14) The diastereoselectivity of the addition of benzaldehyde to a metalated isoquinoloyloxazoline has been reported to be higher at −65 °C than at −78 °C. Zhang, P.; Gawley, R. E. *Tetrahedron Lett.* **1992**, *33*, 2945. A related effect has been reported for the enantioselective amidocuprate-mediated conjugate addition to enones. Rossiter, B. E.; Miao, G.; Swingle, N. M.; Eguchi, M.; Hernandez, A. E.; Patterson, R. G. *Tetrahedron: Asymmetry* **1992**, *3*, 231. The work of Schlosser and Limat (ref 2d) also shows a time-dependent enantioselectivity, consistent with the formation of diastereomeric complexes with (−)-sparteine.

(15) As far as we know, there is no known case of a lithiodestannylation that proceeds with inversion of configuration at the tin-bearing carbon. On the other hand, there are sporadic reports in the literature of electrophilic substitutions that proceed with inversion of configuration, most notably recent reports by both Hoppe and Gawley. Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, 6097. Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.

(16) If (*rac*)-**5** is transmetalated at −78 °C in the presence of (−)-sparteine, trapping with TMSCl affords (*rac*)-**3**. This indicates that there is no kinetic resolution during the transmetalation step, consistent with the formation of two nonequilibrating diastereomeric complexes in equal ratios. However, if (*rac*)-**5** is transmetalated at −78 °C in the presence of (−)-sparteine and allowed to stir at −25 °C for 2 h prior to cooling to −78 °C and trapping with TMSCl, (*R*)-**3** is obtained with 85% ee.

(17) For a discussion of the effectiveness of TMEDA as a bidentate ligand for lithium, see: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.