Asymmetric Substitutions: High and Opposite **Enantioselective Alkylations of a Racemic** Organolithium Intermediate in the Presence of (-)-Sparteine

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Asymmetric substitutions in which a racemic organolithium intermediate complexed to a chiral ligand reacts with high enantioselectivity in carbon-carbon bond formation is a very promising approach for efficient asymmetric syntheses.<sup>1,2</sup> We report alkylations of racemic N,N-diisopropyl-o-(1'-lithioethyl)benzamide in the presence of (-)-sparteine which occur with high and opposite enantioselectivities with different leaving groups. The enantioselectivities are shown to be determined by the energy differences in the competitive diastereomeric transition states for the alkylations. The significant features of this work are the preparations of opposite enantiomers with high enantioenrichments with a single chiral ligand and the fact that the enantioselectivities are achieved at a carbanionic center that is equilibrating more rapidly than it reacts with the electrophile.

Treatment of N, N-diisopropyl-o-ethylbenzamide (1) with 1.1 equiv of sec-butyllithium (s-BuLi)/(-)-sparteine at -78 °C in pentane or in 1:1 pentane/tert-butyl methyl ether gives the laterally lithiated intermediate 2/(-)-sparteine.<sup>3</sup> Reactions of 2/(-)-sparteine with alkyl, silyl, and stannyl chlorides give the products 4-9 in the yields shown in Table 1. The enantiomeric excesses for 4, 5, 7, 8, and 9 with chloride electrophiles range from 80% to 92% while a 68% ee is obtained for 6 with benzyl chloride as the electrophile. The use of butyl bromide or butyl iodide as the electrophile affords 5 with 74% and 28% ee, respectively. The absolute configuration of the silyl compound is assigned to be (S)-9 because oxidation of the corresponding phenyldimethylsilyl compound, which is assumed to have the same configuration as 9, followed by ring closure provides (S)-3-methylphthalide.<sup>4</sup> The absolute configurations of 4-8 are provisionally assigned on the basis of their correspondence to 9 as the less retained isomer on the chiral HPLC column using models proposed by Pirkle for the controlling factors in chromatographic separations of enantiomers.<sup>5</sup>

Remarkable results are observed when alkyl tosylates are used as electrophiles for alkylations of 2/(-)-sparteine as shown in the first three entries in Table 2. Following lithiation of 1 with s-BuLi/ (-)-sparteine, reaction of 2/(-)-sparteine with allyl tosylate provides 4 with a configuration which is opposite to that obtained

(1) For pertinent reviews of asymmetric syntheses, see: Cox, P. J.; Simpkins N.S. Tetrahedron: Asymmetry 1991, 2, 1. Tomioka, K. Synthesis 1990, 541. Noyori, R.; Kitamura, M. Angew. Chem., Int. Ed. Engl. 1991, 30, 49. For recent articles on stereochemical aspects of organolithium reactions, see: Schlosser, M., Ed. Mechanistic Aspects of Polar Organometallic Chemistry. Tetrahedron 1994, 50, No. 20.

see: Beak, P.; Du, H. J. Am. Chem. Soc. 1993, 115, 2516.
(3) The amides 1 and 10–13 are prepared by lateral lithiation of N,N-diisopropyl-o-methylbenzamide (3). For a review of lateral lithiations, see: Clark, R. D.; Jahangir, A. Org. React. (N.Y.), in press.

(4) For assignments of configuration to 3-methylphthalide, see: Takahashi, H.; Tsubuki, T.; Higashiyama, K. Chem. Pharm. Bull. 1991, 39, 3136. The enantiomeric excess of 3-methylphthalide obtained in this sequence is 32% based on rotation. However, since we were unable to independently determine the enantiomeric excess of the phenyldimethylsilyl-substituted product by chromatographic methods, the reaction of 2/(-)-sparteine with phenyldimethylsilyl chloride was not optimized. Therefore, even though the extent of enrichment appears to be different than for trimethylsilyl chloride, the reaction is assumed to have the same sense of facial selectivity as 9.

(5) Pirkle, W. H.; McCune, J. E. J. Chromatogr. 1989, 471, 271.

Table 1.	Yields and	Enantioselectivities	for Sequential	Reactions of
N,N-Diiso	propyl-o-et	hylbenzamide (1) w	ith s-BuLi/(–)·	Sparteine
and Halid	e Electroph	iles	,	•

electrophile	product	yield (%)	ee (%)
H <sub>2</sub> C=CHCH <sub>2</sub> Cl	(R)-4	89	92
n-BuCl	(R)-5	95	80
n-BuBr	(R)- <b>5</b>	45	74
n-BuI	(R)-5	71	28
PhCH <sub>2</sub> Cl	(R)-6	52	68
p-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Cl	(R)-7	79	92
Bu <sub>3</sub> SnCl	(S)-8	78	87
Me <sub>3</sub> SiCl	(S)-9	79	92

Table 2. Yields and Enantioselectivities for Sequential Reactions of N,N-Diisopropyl-o-alkylbenzamides with s-BuLi/(-)-Sparteine and Alkyl Tosylates or Methyl Chloride

reactant	electrophile	product	yield (%)	ee (%) <sup>a</sup>
1	H <sub>2</sub> C=CHCH <sub>2</sub> OTs	(S)-4	46	-88
1	n-BuOTs	(S)- <b>5</b>	52	-97
1	PhCH <sub>2</sub> OTs	(S)-6	26	-77
10	CH <sub>3</sub> Cl	(S)-4	88	-70
11	CH₃Cl	(S)- <b>5</b>	75	68
12	CH <sub>3</sub> Cl	(S)-7	72	-67
13	CH <sub>3</sub> Cl	(R)- <b>9</b>	94	-70

<sup>a</sup> Negative values indicate an enantioenrichment opposite to those in Table 1.



with allyl chloride in an enantiomeric excess of -88%.<sup>6</sup> With n-butyl tosylate or benzyl tosylate as electrophiles, 5 and 6 are obtained with enantiomeric excesses of -97% and -77%, respectively.<sup>6</sup> Thus high and opposite enantioselectivities are obtained on alkylation of 2 in the presence of the same chiral ligand, (-)sparteine, simply by changing the leaving group.

The enantiomers of 4, 5, 7, and 9 also were prepared with -70% ee by lateral lithiation of the requisite ortho substituted benzamides 10-13 with s-BuLi/(-)-sparteine followed by reaction with methyl chloride as shown in the last four entries in Table 2.6 Since the ortho substituted reactants 1 and 10-13 are prepared by lateral lithiation and substitution beginning with N,Ndiisopropyl-o-methylbenzamide (3), varying the order of group introductions is a useful tactic to obtain both enantiomers.

The two different pathways for asymmetric replacement of a prochiral hydrogen which are possible for this sequence are asymmetric deprotonation and asymmetric substitution.<sup>2,7</sup> The observation of opposite enantioselectivities does not necessarily rule out a pathway of asymmetric deprotonation since electrophile dependent facial selectivities have been observed for reactions of

<sup>(2)</sup> For a recent case of asymmetric substitution and leading references,

<sup>(6)</sup> Negative values of the enantioenrichments indicate that the enriched enantiomer has a configuration opposite to that obtained by the reaction of 2/(-)-sparteine with alkyl, silyl, or stannyl chlorides.

<sup>(7)</sup> Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. J. Am. Chem. Soc. 1994, 116, 3231

enantioenriched organolithium intermediates.8 When enantioenriched N,N-diisopropyl-o-(1'-lithioethyl)benzamide (2) was prepared by tin-lithium exchange of 87% enantioenriched 8 with n-butyllithium or n-butyllithium/TMEDA followed by reaction with allyl chloride, 4 was obtained in 71% and 51% yields with 5% and 1% ee. When racemic N, N diisopropyl-o-(l'-lithioethyl)benzamide was generated by initial reaction of 1 or of racemic 8 with s-butyllithium followed by addition of (-)-sparteine and allyl chloride, the enantioenriched product 4 was obtained in 46% and 62% yields and with 88% and 87% ee, respectively.

The configurational stability of 2 has also been evaluated using Hoffmann's test of configurational stability.9 Lithiation of 1 to generate 2 followed by addition of the chiral electrophile 14 provides the diastereomeric products 15. Treatment of 2 with racemic 14 gives a diastereomeric ratio of 1:1.6 as determined by the integration of the benzylic methine protons in the <sup>1</sup>H NMR. Reaction of 2 with highly enantioenriched 14 also affords a diastereomeric ratio of 1:1.6.10



The above results of the reactions of 2 show that enantioenriched 2 does not maintain its configuration by itself or in the presence of TMEDA and that racemic 2 complexed to (-)-sparteine can afford high enantioselectivities on alkylation. The reactions of 2 with racemic and enantioenriched 14 which give the same ratio of diastereomers also reveal that the benzylic organolithium 2 itself is configurationally labile and effectively racemic with respect to reactions with the electrophiles as discussed by Hoffmann.<sup>9,10</sup> These results can be taken to rule out asymmetric deprotonation as the enantiodetermining step. They also show that these asymmetric substitutions do not occur from predominantly nonequilibrating diastereometic complexes of 2/(-)sparteine, which react with electrophile-controlled facial selectivity.<sup>8,11</sup> The enantioselectivities, therefore, must be established in the competing transition states for alkylation which are diastereomeric because of complexation with (-)-sparteine. Determination of the source of different facial selectivity between the reactions of the tosylates and the chlorides will require further investigation.<sup>12</sup> It should be noted that the inversion in enantiodifferentiation for allyl chloride vs allyl tosylate requires a swing of only  $\sim 2.3$  kcal/mol as the sum of the two transition state energy differences.

Enantioselective reactions have been observed previously for benzylic organolithium intermediates and chiral ligands initially by Nozaki and Noyori.<sup>2,9,13</sup> Reactions which give enantiomeric excesses comparable to those of the present work have been reported. Regan and Staunton observed an enantiomeric excess of 70% in a sequence of lateral lithiation of ethyl 2,4-dimethoxy-6-ethylbenzoate with a chiral lithium amide followed by addition to acetone, and we have reported high enantiomeric excesses for the reactions of 3-lithio-3-phenyl-N-lithio-N-methylpropionamide/(-)-sparteine with a number of electrophiles. $^{2,14,15}$ 

The present results establish that the formally racemic benzylic carbanion 2 on alkylation in the presence of (-)-sparteine gives products with high enantioselectivities established in the competing transition states for the alkylations. These results provide both enantiomers in synthetically useful sequences. The fact that the selectivity can be reversed significantly with the same enantioenriched ligand by a change in the leaving group of the electrophile is intriguing. Study of the structures and roles of the organometallic intermediate, the ligand, the electrophile and of the reaction conditions in these and related asymmetric substitutions should provide further methodology for direct, convenient, efficient asymmetric syntheses.

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Supplementary Material Available: Experimental details for the preparation and reactions of 1-15 (12 pages). This material is contained in many libraries in microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. See any current masthead page for ordering information.

(13) For earlier reports of enantioselective reactions at benzylic lithiation sites with (-)-sparteine, see: Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. Tetrahedron 1971, 27, 905. Papasergio, R. I.; Skelton, B. W.; Twiss, P.; White, A. H.; Raston, C. L. J. Chem. Soc., Dalton Trans. 1990, 1161 and references cited therein.

(14) Regan, A. C.; Staunton, J. J. Chem. Soc., Chem. Commun. 1987, 520

(15) A case in which the same chiral ligand affords high and opposite enantioselectivities was recently reported by Kobayashi and Ishitani for an enantioselective Diels-Alder reaction catalyzed by a single "chiral Yb triflate" with different achiral ligands. Kobayashi, S.; Ishitani, H. J. Am. Chem. Soc. 1994, 116, 4083.

<sup>(8)</sup> Hoppe, D.; Carstens, A.; Kramer, T. Angew. Chem., Int. Ed. Engl.

 <sup>(9)</sup> Hoppe, D., Carstens, A., Hoppe, D. Tetrahedron 1994, 50, 6097.
 (9) (a) Hirsch, R.; Hoffmann, R. W. Chem Ber. 1992, 125, 975. (b) Hoffmann, R. W.; Ruhl, T.; Harbach, J. Liebigs Ann. Chem. 1992, 725. (c) Klute, W.; Dress, R.; Hoffmann, R. W. J. Chem. Soc., Perkin Trans. 2 1993, 1202. 1409

<sup>(10)</sup> Reaction of 2 with a mixture of allyl chloride and 14 gives only the products 15, establishing that the configurational lability of 2 also is faster than the rate of reaction of 2 with ally chloride. We have also carried out the Hoffmann test with 2/(-)-sparteine with 1.0 and 0.1 equiv of enantioenriched 14 and obtained a 1:1.6 ratio of diastereomers. This result is consistent with a rapidly equilibrating carbanion, but does not rule out configurationally stable carbanions which have very similar energies of activation for reaction with the electrophile. Determination of the diastereometic ratio of 2/(-)-sparteine could decide the possibility.9c

<sup>(11)</sup> For discussion of the configurations of a benzylic organolithium species, see: Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. J. Org. Chem. 1991. 56, 4938 and references cited therein.

<sup>(12)</sup> Diastereoinversions as a function of the leaving group have been reported; e.g.: Meyers, A. I.; Knaus, G. J. Am. Chem. Soc. 1974, 96, 6508. Chassaing, G.; Lett, R.; Marquet, A. Tetrahedron Lett. 1978, 5, 471. For the present cases, it should be noted that tributyl phosphate as the electrophile with 2/(-)-sparteine affords racemic 5. Hence a rationale based on control of the enantioselectivity by the general type of leaving group does not appear sufficient.