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Pathways for Stereoinformation Transfer: Enhanced Enantioselectivity via Diastereomeric Recycling of Organolithium/(−)-Sparteine Complexes

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Asymmetric synthesis with organolithium reagents in the presence of a chiral ligand is rapidly emerging as an efficient and powerful methodology.[1−3] Asymmetric induction in a lithiation−substitution sequence can occur in the lithiation or it can be introduced in the second step in a process we have termed asymmetric substitution.[3] Enantioselectivities in the sequence have been shown to be a function of not only the nucleofuge, ligand, reagent structure, and solvents but also the method and the temperature used for formation of the organolithium intermediate.[1] We now report that enantioselectivity can also be a function of the limiting electrophilic reagent. These results provide another approach for improving enantioselectivities and analyzing reaction pathways. The mechanistic framework that we use is derived from the elegant work of Hoffmann on the rates of equilibration of diastereomeric organolithium complexes.[4,5]

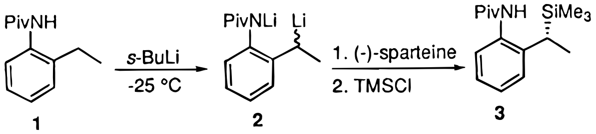
The pertinent experimental observations for the lithiation−substitution of *N*-pivaloyl-*o*-ethylaniline (**1**) via **2** to provide **3** in the presence of (−)-sparteine (**4**) are summarized in Table 1. As previously reported, the enantiomeric ratio (er) for the sequence is a function of temperature as seen by comparing the first and third entries.[1b] The er of 56:44 obtained at −78 °C is changed to 92:8 when **2** and (−)-sparteine are stirred at −25 °C for 45 min prior to cooling to −78 °C and addition of TMSCl. The requirement for a warm/cool cycle was postulated to arise as a consequence of diastereomeric complexes that are equilibrating at −25 °C and nonequilibrating at −78 °C.[1b] Consistent with that proposal is the fact that use of 0.1 equiv of TMSCl in the reaction that is carried out entirely at −78 °C provides **3** with an er of 91:9 (Table 1, entry 2). Moreover, as shown in entries 4 and 5 of Table 1, when complexation is carried out at −25 °C before cooling to −78 °C and the reaction is carried out with deficient amounts of electrophile, enantiomeric ratios of 99:1 and 98:2 are obtained.[6] These ratios are significantly higher than the 92:8 observed with excess TMSCl. Finally, if 0.9 equiv of TMSCl is added in 0.45 equiv batches with a warm/cool sequence after the first addition, an er of 97:3 is obtained, as shown in entry 6 of Table 1.

Table 1. Reactions of 2 with (−)-Sparteine Followed by TMSCl

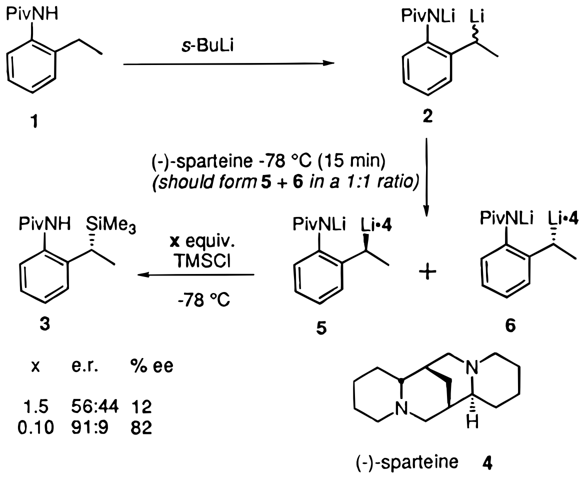
entry	exposure of **2** to **4** prior to addn of TMSCl	TMSCl (equiv)	er	% ee
1	−78 °C, 15 min[a]	2.3	56:44	12
2	−78 °C, 15 min[a]	0.10	91:9	82
3	−25 °C, 45 min then −78 °C, 30 min	2.1	92:8	84
4	−25 °C, 45 min then −78 °C, 30 min	0.10	99:1	98
5	−25 °C, 45 min then −78 °C, 30 min	0.50	98:2	96
6	−25 °C, 45 min then −78 °C, 30 min	0.45		
	−25 °C, 45 min then −78 °C, 30 min	0.45	97:3[b]	94

[a] The (−)-sparteine was precooled to −78 °C prior to addition. [b] After the first addition of 0.45 equiv of TMSCl a warm/cool cycle precedes the second addition of TMSCl.

Scheme 1



The reactions of two interconverting diastereomeric species that lead to different products can be quantitatively modeled by a Curtin−Hammett−Winstein−Holness analysis.[4−7] Qualitatively, for diastereomeric complexes that are configurationally stable on the time scale of reaction with an electrophile, the reaction with excess electrophile will provide an enantiomeric ratio that reflects the population of the diastereomeric complexes.[8] However, reaction of the same population of diastereomeric complexes with a deficient amount of electrophile will give rise to an enantiomeric ratio that reflects the difference in activation energies between the two diastereomeric complexes.[5,9]



The observation of an er of 56:44 for the reaction of entry 1 in Table 1 at −78 °C is indicative of the formation of the diastereomeric complexes **5** and **6** in an approximately 1:1 ratio. In the reaction with 0.1 equiv of TMSCl under these conditions, the observed er can be taken to correspond to the intrinsic energy difference between the transition state energies $\Delta G_6^{\ddagger}$ - $\Delta G_5^{\ddagger}$ for the reaction of each diastereomer. At −78 °C, this er of 91:9 corresponds to a difference in free energies of activation of 0.81 kcal/mol.[10] As seen previously, if the reaction is carried out with 0.1 equiv of TMSCl after the warm/cool sequence allows equilibration of the diastereomeric complexes, an er of 99:1 is observed. This corresponds to a free energy difference of 1.78 kcal/mol at −78 °C that is due to both the difference in activation energies and the difference in population of the diastereomeric complexes.

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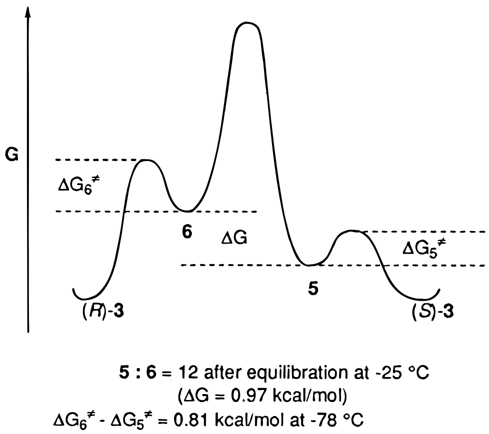
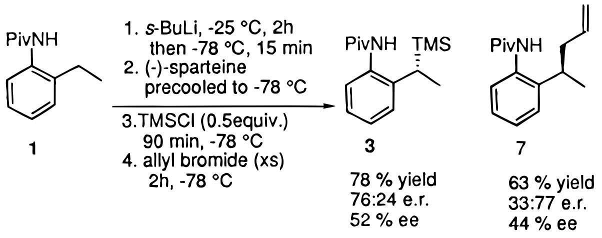


Figure 1.

Extraction of the latter value from the difference of 0.97 kcal/mol provides a ratio of 92:8 for the two diastereomeric complexes **5** and **6**. Treatment of the diastereomeric complexes derived from the warm/cool cycle with excess TMSCl affords the product with an er of 92:8 (Table 1, entry 3), consistent with this model.[11] These results are summarized in the energy diagram shown in Figure 1, which assumes the diastereomeric complexes undergo reaction with inversion of configuration.[1b,12]

The use of a limiting reagent in conjunction with temperature as an enantiocontrol element is illustrated by the reaction sequence of entry 6 (Table 1). The lithiation is conducted with the standard warm/cool sequence to allow equilibration of the diastereomeric complexes, but only 0.45 equiv of electrophile is added. After a period of time to allow for completion of the electrophilic substitution, the solution is warmed to allow reequilibration of the unreacted diastereomeric organolithium complexes. Upon subsequent cooling, the solution is then treated again with a deficiency of electrophile. This results in the formation of the product with 97:3 er (94% ee, 72% yield), as opposed to 92:8 er (84% ee, 63% yield) obtained when the substitution is carried out with excess electrophile. This "diastereomeric recycling" is conceptually analogous to a dynamic kinetic resolution,[13] with the difference that epimerization of the less reactive complex is induced by using a deficiency of electrophile and raising the reaction temperature to promote reequilibration.

The intrinsic energy difference between the activation energies for reactions of **5** and **6** can be used in a synthetically novel fashion to provide opposite enantiomers for two different products in a one-flask sequence, as shown below. Since the difference in the activation barriers for the reaction of **5** and **6** with TMSCl is sufficient to provide selectivity (0.81 kcal = 89:11 er, 78% ee), treatment of an equal amount of **5** and **6** with a deficient amount of electrophile allows for selective reaction with complex **5** to provide **3** and consequent enrichment of the remaining solution in the diastereomeric complex **6**. Subsequent reaction with a second electrophile provides the second product **7** enriched in the normally less favored enantiomer.[14]



In summary, we have described a method of kinetic resolution that allows determination of the energy difference between nonequilibrating diastereomeric complexes of organolithium reagents. A synthetic consequence of this approach is to provide products with amplified enantioselectivities by recycling the less reactive diastereomer via an asymmetric equilibration. In addition, enantiodivergent electrophilic substitution of a common organolithium intermediate that allows enrichment in the normally disfavored enantiomer is demonstrated.

To the best of our knowledge, this and the recent work of Klute, Krüger, and Hoffmann constitute the first reports of cases where the choice of limiting reagent controls the enantiochemistry and configuration of the products.[7,14] The use of substoichiometric amounts of reactant to probe the interconversion rates of diastereomeric intermediates is not restricted to the chemistry described herein and can be applied to a variety of stereoselective processes.

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Supporting Information Available: Calculations of free energy differences and procedures for lithiations/substitutions of **3** (4 pages).

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(7) When a racemic organometallic reagent is treated with a deficiency of a chiral electrophile, the product ratio obtained can be different than the ratio obtained with excess electrophile. This forms the basis for Hoffmann's test of configurational stability. See ref 4a and Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772. Gately and Norton have recently reported a study of equilibrating diastereomeric zirconium organometallic species in which product enantiomeric ratios increase as the equivalent of electrophile is increased from 2-fold excess to 60 equiv: Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 3479 and references cited therein. This is shown by kinetic analyses to be a consequence of the reaction with the electrophile becoming competitive with the rate of epimerization of the diastereomeric complexes.

(8) This a case of kinetic quenching, or boundary condition I in ref 6.

(9) If the diastereomeric complexes are configurationally labile with respect to the rate of reaction with the electrophile then the enantiomeric ratio observed in the both reactions will be the same, since the enantioselectivity is determined by $\Delta\Delta G^{\ddagger}$ in both reactions. This is a Curtin–Hammett situation, or boundary condition II in ref 6. A limitation of this test is that it can establish only configurational stability but not configurational lability. If the two experiments provide the same enantiomeric ratio, this can arise either as a result of configurational lability or accidental equivalence of the activation energies of configurationally stable complexes (see text).

(10) A correction of 0.09 kcal/mol has been incorporated to account for the observation of an er of 56:44 under the conditions of an experiment that should provide an er of 50:50.

(11) In general, the maximum error on all er values, as derived from chiral stationary phase HPLC anaylsis, is ±2%. The agreement of the experimental and predicted er values thus falls within our expected range of experimental error.

(12) This assumption does not affect the calculations or conclusions derived from our analysis.

(13) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

(14) Hoffmann and co-workers have recently reported a kinetic resolution of the enantiomers of a configurationally stable α-seleno Grignard reagent. The use of a deficient amount of a chiral electrophile enriches the reaction solution in one enantiomer, which is then reacted with an achiral electrophile. Klute, W.; Krüger, M.; Hoffmann, R. W. *Chem. Ber.* **1996**, *129*, 633.