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Dynamic Thermodynamic Resolution: Solvent Effects, Mechanism, and an Asymmetric 3,4,5-Substituted Benzazepine Synthesis

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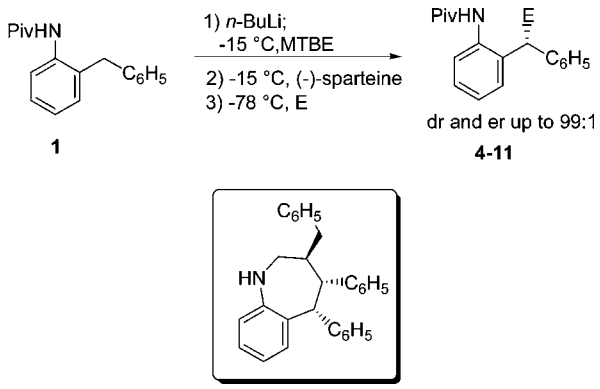
ABSTRACT



The resolution in the lithiation-substitution sequence from 1 to 4–11 in MTBE is shown to be under thermodynamic control in contrast to the previous report of kinetic control in diethyl ether. Diastereomeric equilibration of a soluble complex is shown to be controlling and an asymmetric synthesis of a 3,4,5-substituted benzazepine is reported.

Dynamic resolution under thermodynamic control can be used to transform a moderately asymmetric reaction into a highly asymmetric reaction by straightforward procedures.[1] Previous work has demonstrated that management of experimental conditions may offer control of the diastereomeric equilibrations which can drive dynamic thermodynamic resolutions (DTR) to provide significantly improved enantioselectivities. Protocols which use DTR have been shown to provide syntheses of either enantiomer and with thermal reequilibration to give enantioenrichments which are beyond that afforded by a single equilibration.[1,2] In this Letter, we demonstrate that a resolution which has been reported to be kinetically driven to give modest enantioenrichment can be transformed into a resolution that is thermodynamically driven and gives high enantioenrichment by solvent selection. The present work also shows that the resolution step is not necessarily driven by a selective crystallization and provides an asymmetric synthesis of a 3,4,5-substituted benzazepine.

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(1) (a) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (b) Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718. (c) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715.

(2) For examples see: (a) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Howard, S.; Vennall, G. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3887. (b) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340. (c) Clayden, J.; Mitjans, D.; Youssef, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 5266.

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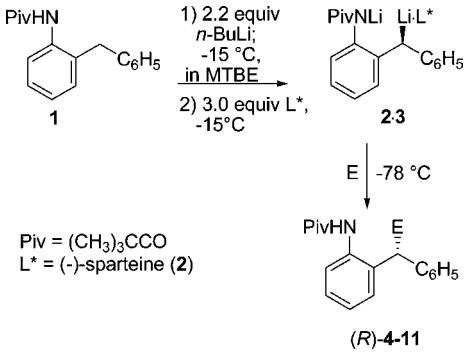
Treatment of *o*-benzyl pivanalide (**1**) with 2.2 equiv of *n*-BuLi at −15 °C in methyl *tert*-butyl ether (MTBE, 0.13 M) followed by 3.0 equiv of (−)-sparteine (**2**) at −15 °C, cooling to −78 °C, and addition of an electrophile provides the products (*R*)-**4**−**11** with the enantiomeric ratios shown in Table 1. The absolute configurations are assigned on the basis of the absolute configurations of **5** and a *N*-*p*-bromobenzoyl derivative of **11** as determined by X-ray crystallography and the assumption the other products conform to these absolute and relative configurations.[3] The configuration of **9** at the benzylic position was established by a deoxygenation sequence that provided **4**.

Table 1. Products from the Asymmetric Lithiation Substitution of **1**



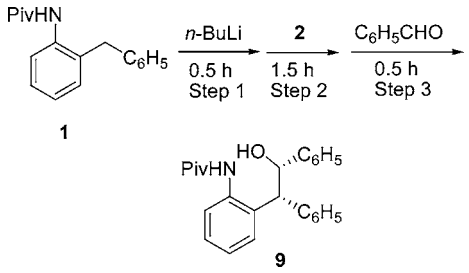
E	product	yield (%)	er
$C_6H_5CH_2$	**4**	80	93:7
p-$BrC_6H_4CH_2$	**5**	85	98:2
$CH_2{=}CHCH_2$	**6**	80	94:6
$(CH_3)_3Sn$	**7**	85	88:12
$C_6H_5(CH_3)_2Si$	**8**	77[a]	90:10
C_6H_5CHOH	**9**	95[b]	99:1; 90:10
p-BrC_6H_4CHOH	**10**	85[c]	98:2; 73:27
$(CH_3O_2C)_2CHCHCH_3$	**11**	66[d]	99:1; 89:11

[a] Base was *s*-BuLi. [b] dr is 81:19. [c] dr is 97:3. [d] dr is 92:8.

The lithiation substitution of **1** with *s*-BuLi and (−)-sparteine (**2**) in diethyl ether has been reported previously by Wilkinson et al.[4] Under a number of reaction conditions similar to those used for this work, that reaction was found to provide products with lower enantioenrichments than shown in Table 1. The conversion of **1** to **6** proceeded in 90−95% yields with er values of 85:15 to 88:12. The formation of **4** from **1** proceeded in 80% yield with an er of 73:27. The lithiation of **1** followed by the addition of **2** and reaction with 2-furaldehyde gave the expected alcohols with a dr of 50:50. Oxidative conversion of those alcohols gave the corresponding ketone with an er of 82:18. The authors tested the reaction for DTR and reasonably concluded it was not operable in diethyl ether under their conditions. They suggested the diastereomeric complexes of **2·3** to be rapidly equilibrating in diethyl ether, i.e., under kinetic control.

In MTBE, however, our investigation of the diastereoselectivity and enantioselectivities for the reaction sequence of **1** with benzaldehyde shows the reaction to give **9** in MTBE (Table 1) to be under thermodynamic control when a warm cool sequence is employed.[5] When the reaction is carried out totally at −78 °C, the alcohol **9** is obtained in 71% yield as a 50:50 mixture of diastereomers with er values of 75:25 and 77:23 as shown for the first two entries in Table 2.[6] With use of sequences with warming of the first and second steps or only the second step, major improvements in the product selectivities are observed as shown for the third and fourth entries in Table 2. With the reactants initially at −15 °C for the steps of lithiation and addition of **2** followed by cooling to −78 °C prior to the addition of benzaldehyde, the product **9** is obtained in 95% yield as an 81:19 mixture of diastereomers with er values of 99:1 and 10:90. With the warm−cool sequence the diastereoselectivity has been improved, as has the enantioselectivity of the major diastereomer. The enantioselectivity for the minor isomer is both improved and inverted. The fifth entry in the table shows the stereoselectivities to be relatively independent of the equivalents of benzaldehyde. Apparently the diastereomeric

Table 2. Temperature Variation for the Synthesis of **9** from **1**



temprature (°C)			yield		er	
step 1	step 2	step 3	(%)	dr	major	minor
−78		−78	71	49:51	75:25	77:23
−78	−78	−78	65	49:51	75:25	79:21
−78	−15	−78	87	83:17	98:2	24:76
−15	−15	−78	95	81:19	99:1	10:90
−15	−15	−78	5	80:20[a]	99:1	16:84
0	0	−78	91	77:33	98:2	21:79
25	25	−78	83	75:25	97:3	26:74

[a] 0.1 equiv of benzaldehyde.

(3) The absolute configuration is assigned to **2·3** based on analogy to the invertive course established for an analogous reaction. (a) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. (b) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537. (c) Weisenberger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522.

(4) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron*: *Asymmetry* **2004**, *15*, 3011.

(5) When *s*-BuLi was used for the sequence in MTBE, **4** was obtained in 54% yield with an er of 93:7 as opposed to the 80% yield and er of 73:27 in diethyl ether.[4]

(6) Since subsequent work shows the diastereomeric complexes to have similar reactivities toward benzaldehyde, the formation of nonracemic major and minor products in the first two entries is provisionally attributed to an asymmetric deprotonation.

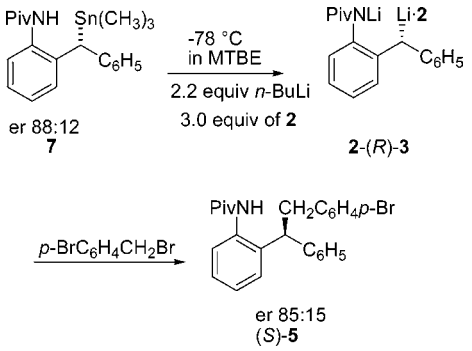
complexes do not have greatly different rates of reaction with this electrophile. The sixth and seventh entries in Table 2 show the range of improvements for different temperatures for the first two steps.

Thus an asymmetric lithiation substitution, which was reported to be under kinetic control in diethyl ether, can be transformed into a reaction that is under thermodynamic control when the reaction is carried out in MTBE. Significant improvement in both diastereoselectivity and enantioselectivities has easily been accomplished.

It is also significant that reactions of **1** in MTBE (0.03 M) at −15 °C remain homogeneous and give comparable results. This establishes that selective diastereomeric complexation in solution can be the driving force for a DTR.[7]

An advantage of thermodynamic over kinetic control of a resolution is that the formation of either enantiomer may be possible from one ligand. Tin lithium exchange of **7** (88:12 er) in MTBE at −78 °C provides **2**·(*R*)-**3**, which is configurationally stable under these conditions (Scheme 1). Addition of *p*-bromobenzyl bromide at −78 °C provides (*S*)-**5** (85:15 er), consistent with an invertive substitution.

Scheme 1

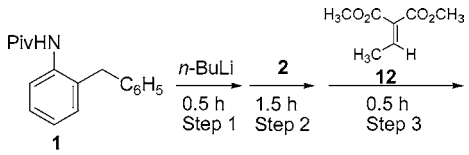


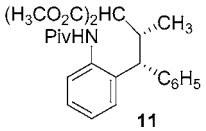
We have carried out reactions of **2**·(*S*)-**3** with **12** to probe the effect of solvent and temperature control in a conjugate addition. As shown in Table 3, the warm to cool sequence with MTBE is the protocol of choice although diethyl ether is also satisfactory in this case. The diastereoselectivity of 92:8 and enantioselectivities of >99:1 and 89:11 for entry 5 suggest this approach should be useful for synthesis. Toluene gives intermediate results while THF is ineffective.

The improvement in diastereomeric and enantiomeric ratios under DTR can offer an advantage for synthetic applications. This is demonstrated by the first asymmetric synthesis of a 3,4,5-substituted 1-benzazepine **19** (Scheme 2).[8,9] Lithiation of **1**, addition of **2**, and conjugate addition to **13** provides **14** in 67% yield with a dr of 98:2 and an er of 99:1. The absolute and relative configurations of **14** were assigned based on the formation of **11**. Hydrolysis of **14** to **15**, followed by cyclization provides **16** in a yield of 70%

(7) Since many DTRs are carried out at low temperatures with solid observable, it is possible that some cases do involve resolution by crystallization. In such cases, the favored crystallized diastereoisomer may redissolve but maintain its structure before reaction with an electrophile.

Table 3. Temperature Variation for the Synthesis of **11** from **1**



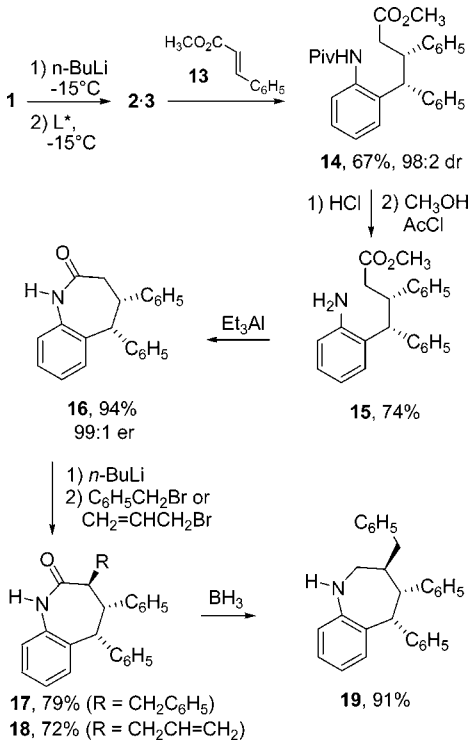


	temperature (°C)			yield		er	
solvent	step 1	step 2	step 3	(%)	dr	major	minor
toluene	−78	−78	−78	51	62:38	79:21	50:50
toluene	−15	−15	−78	90	76:24	96:4	75:25
ether	−78	−78	−78	31	66:34	90:10	75:25
ether	−15	−15	−78	64	88:12	>99:1	90:10
MTBE	−15	−15	−78	66	92:8	>99:1	89:11
THF	−15	−15	−78	70	54:46	57:43	55:45

with an er of 99:1. Further conversions by stereospecific lithiation−alkylation to **17** or **18**, respectively, and reduction of **17** to **19** complete the synthetic sequence.

In summary, the present work demonstrates that kinetic or thermodynamic control of a resolution can be determined

Scheme 2



by selection of the solvent. It is also established that crystallization is not a necessary condition for the operation

of dynamic thermodynamic resolution. In addition, the first asymmetric synthesis of a 3,4,5-substituted benzazepine has been reported. We recommend determination of the effect of temperature and solvent on any promising reaction, as this approach often may be more efficient for improving an asymmetric synthesis than the alternative of testing a number of different ligands or catalysts in a number of different experiments.

(8) Asymmetric syntheses of 5- and 4,5-substituted 1-benzazepines and 3,4-substituted 1-benzazepin-2-ones have been reported as drug candidates. (a) Matsubara, J.; Kitano, K.; Otsubo, K.; Kawano, Y.; Ohtani, T.; Bando, M.; Kido, M.; Uchida, M.; Tabusa, F. *Tetrahedron* **2000**, *56*, 4667. (b) Das, J.; Floyd, D. M.; Kimball, S. D.; Duff, K. J.; Vu, T. C.; Lago, M. W.; Moquim, R. V.; Lee, V. G.; Gougoutas, J. Z.; Malley, M. F.; Moreland, S.; Brittain, R. J.; Hedberg, S. A.; Cucinotta, G. G. *J. Med. Chem.* **1992**, *35*, 773.

(9) An asymmetric synthesis of 4,5,6- and 3,4,5,6-substituted azepanes by a conjugated addition of an *N*-Boc allyllithium (−)-sparteine complex and subsequent conversions has been reported recently. Lee, S. J.; Beak, P. *J. Am. Chem. Soc.* **2006**, *128*, 2178.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences GM-18874 and to funds provided by the James R. Eiszner chair for support of this work. Y.S.P. thanks Konkuk University for the support of this work in 2005.

Note Added in Proof: Wilkinson and co-workers have reported, based on further work, that equilibration of the diastereomeric complexes is not occuring at −78 in diethyl ether. Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833.

Supporting Information Available: All experimental procedure and spectroscopic data for new compounds, and crystallographic data for **5** and the *N*-*p*-bromobenzoyl derivative of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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