

Organic Process Research & Development

Subscriber access provided by American Chemical Society

[View the Full Text HTML](#)



ACS Publications
High quality. High impact.

Organic Process Research & Development is published by the American Chemical Society, 1155 Sixteenth Street N.W., Washington, DC 20036

Technology Reports

In Situ Recycling of Chiral Ligand and Surplus Nucleophile for a Noncatalytic Reaction: Amplification of Process Throughput in the Asymmetric Addition Step of Efavirenz (DMP 266)

Anusuya Choudhury,^{*,†} James R. Moore, Michael E. Pierce, Joseph M. Fortunak, Ioannis Valvis, and Pat N. Confalone

Chemical Process R&D Department, Process Research Facility, The DuPont Pharmaceuticals Company,[‡] Deepwater, New Jersey 08023-0999, U.S.A.

Abstract:

The synthesis of efavirenz (DMP 266) involves a highly enantioselective asymmetric reaction of ketone **2a** with lithium cyclopropylacetylde **3a** in the presence of (1*R*,2*S*)-pyrrolidinylnorephedrine (PNE) **4b** as the chiral mediator to produce **6b**, a key advance intermediate bearing a tetrasubstituted chiral carbon. The major drawback of this reaction is that it requires at least 2 mol of cyclopropylacetylene (CPA) **3b**, 2 mol of the chiral mediator **4b**, and 4 mol of an *n*-alkyllithium base to generate a 1 mol of addition product **6b**. In a program to improve the cost-effectiveness of the process, we have studied this asymmetric addition reaction to reduce the stoichiometry of the chiral moderator and CPA nucleophile. The initial experimental designs to improve the stoichiometry were based on the assumption that the second equivalent of lithium cyclopropylacetylde simply acted as a base to deprotonate the N–H of ketones **2a** or **2b**, leaving 1 equiv of unlithiated and presumably unreactive CPA. It was reasoned that if we lithiate this CPA in the postreaction mixture, it would complex with the already lithiated ligand in the reaction which could then be used to convert additional **2a** or **2b** into product thus improving the stoichiometry. After some trial experiments, a dramatic decrease in stoichiometry was achieved and it was found that by simply adding one more equivalent of an *n*-alkyllithium to the system after the first reaction cycle, it was possible to obtain at least a 14% throughput increase with just a 5% dilution of the reaction volume in this simple and more cost-efficient process. The chiral addition reactions could be run with multiple cycles in the same pot with the sequential addition of *n*-alkyllithium **5**, CPA **3b**, and ketone **2a**. However, after four cycles, there was some decrease in the enantioselectivities (90.8%) that ultimately places a practical limit on the number of recycles possible. The process throughput increase can be explained in the light of a recent mechanistic investigation by Collum and co-workers. We postulate that the introduction of an *n*-alkyllithium to the reaction mixture after the completion of the first cycle regenerates the reactive cubic

tetrameric aggregate **8** by structural reorganization of the product-incorporated inactive aggregate **9**.

Aggregation in lithium-based anion chemistry is an important phenomenon in organic synthesis, which has been exploited to achieve high facial selectivities observed in asymmetric reactions. However, such aggregative properties often become a liability due to high stoichiometric requirements when the product is incorporated as a ligand, resulting in the disruption of reactive aggregates. An example is the synthesis of efavirenz (**1**), a potent HIV-1 reverse transcriptase inhibitor,¹ which is designed around the key asymmetric reaction of ketone **2a** with lithium cyclopropylacetylde **3a** in the presence of (1*R*,2*S*)-pyrrolidinylnorephedrine (PNE) **4b** as the chiral mediator (Scheme 1).² The asymmetric addition step, which creates a chiral tetrasubstituted carbon, proceeds with exceptionally high enantioselectivity. The major drawback of this reaction is that it requires at least 2 mol of cyclopropylacetylene (CPA) **3b**, 2 mol of the chiral mediator **4b**, and 4 mol of an *n*-alkyllithium base to generate a 1 mol of addition product **6b**. These superstoichiometric requirements for asymmetric addition, which has been postulated to be aggregation related, greatly increase the cost of the drug, particularly for the use of a custom designed chiral auxiliary³ **4b** and the CPA as the

[†] Present address: Johnson&Johnson Process Research & Development/Drug Evaluation, Raritan, NJ 08869. Telephone: 908-704-4975. Fax: 908-231-7429. E-mail: achoudhu@prds.jnj.com.

[‡] Current name: Bristol–Myers Squibb Pharma Company.

- (1) (a) Romero, D. L. *Ann. Rep. Med. Chem.* **1994**, *29*, 123. (b) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Oleson, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, L.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602.
- (2) (a) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937. (b) Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgans, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.-Y.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536.
- (3) (a) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264. (b) Zhao, D.; Chen, C.-Y.; Tillyer, R. D.; Pierce, M. E.; Moore, J. R. *Org. Synth.* **1999**, *77*, 12.

Scheme 1

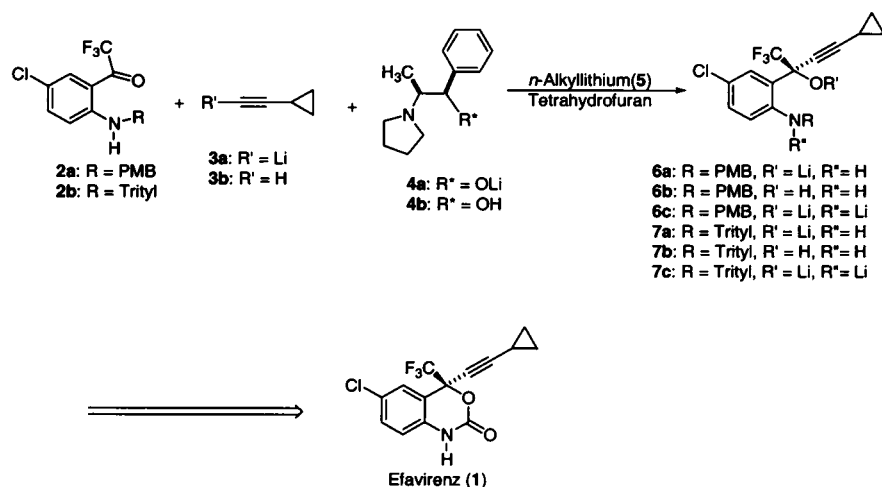


Table 1. Asymmetric Addition of Lithium Cyclopropylacetylide **3a** to Ketones **2a/2b** in the Presence of Chiral Ligand **4b**

entry	ketone (equiv in each cycle)	CPA (3b) (equiv)	<i>n</i> -hexyllithium (5) (equiv)	ligand 4b (equiv)	conversion ^a %, first cycle (overall)	% (<i>S</i>)-isomer ^b first cycle (overall)
1	2a (1)	2.15	4.4	2.3	>98	>98
2	2b (1)	2.15	4.4	2.3	>98	94
3	2a (1)	1.07	2.15	1.15	50	>98
4	2a (1 + 0.5)	2.2	4.8 + 1	2.6	92.7 (87)	99.4 (97.4)
5	2a (1 + 0.4)	2.3	4.4 + 1	2.1	97 (91)	(97.8)
6	2a (1 + 0.3)	2.36	4.44 + 1.07	2.3	>99 (100)	99 (99.03)
7	2a (1 + 1)	2.1 + 1.05	4.4 + 1.05	2.3	>99 (73)	99 (96.9)
8	2a (1 + 1)	2.1 + 1.05	4.4 + 1.5	2.3	98 (91)	97.9 (96)
9	2a (1 + 1)	3.33 ^c	4.33 + 2	2.3	>99 (99.0)	98.1 ^d
10	2a (1 + 1 + 1)	2.2 + 1 + 1	4.8 + 2 + 2	2.65	>96	94 ^e
11	2a (1 + 1 + 1 + 1)	2.2 + 1 + 1 + 1	4.8 + 2 + 2 + 2	2.65	>95	90.8

^a Conversion was monitored by HPLC. ^b Enantiomeric ratios were determined by chiral HPLC or chiral SFC. ^c The total amount of **3b** intended for a number of cycles can be introduced in the reaction flask from the beginning of the first cycle, but generation of **3a** in each cycle is controlled by sequential addition of hexyllithium, as shown in the column 4. ^d er of the isolated product; also see ref 7 for conversion. ^e An aliquot of the reaction was used to determine the er and % of conversion. The reaction was continued for the next cycle (see entry 11), which was subsequently quenched.

starting material. Although one can isolate and reuse most of the excess reagents, this additional processing and the high *n*-alkyllithium stoichiometry requirement still negatively impact the manufacturing cost. We have developed an alternate strategy where the chiral ligand **4a** and the nucleophile **3a** can be recycled in the same reaction pot, by in situ regeneration of the reactive aggregate, to amplify product generation with excellent enantiomeric purity and chemical yield for this super stoichiometric process.

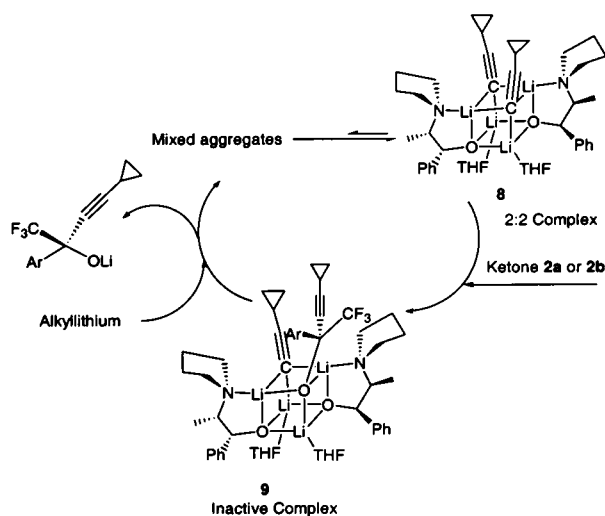
In a program to improve the cost-effectiveness of the process, we have been studying various aspects of this asymmetric addition reaction particularly in the direction of reducing the stoichiometry of the chiral moderator and CPA nucleophile. Our standard asymmetric addition procedure was to combine the components **3b**, **4b**, and an *n*-alkyllithium reagent **5** (2.15, 2.3, and 4.4 equiv, respectively) between -20 °C and 0 °C to allow complexation and then to cool the mixture below -40 °C followed by addition of either ketone **2a** or **2b** (1 equiv) while maintaining the temperature below -40 °C in order to avoid degradation of the lithiated intermediates **6a** or **7a**. Typically after 1 h, HPLC analysis showed 95–99% conversion and a 94–99% enantiomeric ratio (er) (see Table 1, entries 1 and 2). Workup resulted in

the enantiomerically enriched (>99% er) product **6b**. When the reaction was carried out under similar conditions but with stoichiometric ratios of **3a** and **4a**, only about 50% conversion was obtained (Table 1, entry 3).

Recently, Collum et al. have performed a spectroscopic investigation to elucidate the origin of the enantiofacial bias of this chiral addition reaction.⁴ On the basis of these studies, they proposed possible structures of the solution aggregates of the nucleophile and the chiral ligand, which explains the superstoichiometric requirements for this reaction. The salient features of their findings are as follows: (1) The N–H of the starting ketone **2a** or the product **6a** is unexpectedly not lithiated in the presence of 2 equiv of lithium cyclopropylacetylide **3a**. (2) A cubic tetrameric structure **8** (Scheme 2) comprised of **3a** and **4a** in a ratio of 2:2 is proposed as the reactive aggregate. (3) The origin of the 50% conversion (when **3a** and **4a** are used in stoichiometric ratios with respect to **2a**) has been postulated partly due to the tetrameric nature of the reactive aggregate and then the participation of product alkoxide **6a** in an aggregate of **3a:4a:6a** in a ratio of 1:2:1. The resulting complex **9** (Scheme 2) inhibits the reaction to

(4) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028.

Scheme 2



proceed further as it places the ketone **2a** and the nucleophile **3a** distal to each other in the transition structure.⁵ If the product-incorporated complex would have been the entire reason for inhibition of the reaction, then, with 1 equiv of **3a** and **4a** used, the yield could only be 33%.

Our initial experimental designs to improve the stoichiometry were carried out prior to mechanistic findings by Collum et al. and were based on the assumption that the second equivalent of lithium cyclopropylacetylide simply acted as a base to deprotonate the N–H of ketones **2a** or **2b** leaving 1 equiv of unlithiated and presumably unreactive CPA. We reasoned that if we lithiated this CPA in the postreaction mixture, it would complex with the already lithiated ligand in the reaction. Unless the product interferes, this assembly could then be used to convert additional **2a** or **2b** to product thus improving the stoichiometry.

This hypothesis was tested as follows: After completion of the reaction between 1.0 equiv of the PMB-protected ketone **2a** with the preformed chiral complex (at **3b**:**4b**:**5** = 2.2:2.6:4.8 equiv, respectively), an additional 0.5 equiv of PMB-protected ketone **2a** was introduced into the same reaction mixture. As expected, there was essentially no further reaction with continued aging at $-43\text{ }^{\circ}\text{C}$. On the other hand, when 0.5 equiv of **2a** was introduced after the addition of 1 equiv of *n*-hexyllithium **5** to the reaction mixture, an 87% additional product conversion with a 97.4% er (Table 1, entry 4) was obtained. Decreasing the amount of additionally charged **2a** to 0.4 equiv and 0.3 equiv (Table 1, entries 5 and 6, respectively) resulted in 91% and 100% conversions with 97.8% and 99.03% er's, respectively. This overall process is shown in Scheme 2.

The possibility of autostereoaugmentation⁶ by having the lithiated product (**6a**) acting as a chiral ligand in lieu of PNE was next examined. Analysis of the product of this reaction showed to have 70% ee favoring the wrong enantiomer. This “background” reaction must be insignificant in the presence

of PNE, since the enantiomeric ratio of the formed desired enantiomer is typically $>99\%$.

Three additional experiments were conducted to confirm that the postreaction mixture is giving extra enantio-pure product after the addition of 1 equiv of *n*-alkyllithium. Each of these experiments used 2.3 equiv of chiral ligand, 2.1 equiv of CPA, and 4.3 equiv of *n*-hexyllithium to generate the reactive tetrameric complex under our standard conditions, and the chiral additions were run at $-43\text{ }^{\circ}\text{C}$. The reactors, 1st, 2nd, and 3rd, each containing the tetrameric aggregate, were charged, respectively, with 1.3, 1, and 1 equiv of ketone **2a**. After 1 h at $-43\text{ }^{\circ}\text{C}$, the 1st reactor was left as such, 2nd reactor was charged with additional 0.3 equiv of **2a** and the 3rd reactor was charged with an additional 1 equiv of *n*-hexyllithium followed by 0.3 equiv of ketone **2a**. The reactions were quenched after another hour of aging. The enantiomeric ratios of all three reaction mixtures were experimentally the same, 98%. The significant finding was that the first two reactions gave a total of 1.1 equiv of product **6b**, but the third reaction gave a complete conversion (1.3 equiv) of product. Thus, by simply adding one more equivalent of an *n*-alkyllithium to the system after the first reaction cycle, it was possible to obtain at least a 14% throughput increase with just a 5% dilution of the reaction volume in this simple and more cost-efficient process.

We next focused on how to obtain 2 equiv of **6b** from a single pot (Table 1, entries 7, 8, and 9). Here, we added an extra 1 equiv of CPA, either before or after the first reaction cycle, followed by the addition of 1.05, 1.5, and 2 equiv of *n*-hexyllithium after the first reaction cycle, and then finally charged an additional 1 equiv of **2a**. These reactions gave 73, 91, and 99% additional conversions to product **6b**, respectively. A significant decrease in reaction rate⁷ was observed in the second reaction cycle, and the reaction showed a slight decrease in enantioselectivity compared to that of the first reaction cycle.

The chiral addition reactions could be run with multiple cycles in the same pot (Table 1, entries 10 and 11). The amounts of *n*-hexyllithium **5**, CPA **3b**, and ketone **2a** were adjusted at the end of each reaction cycle. After four cycles (entry 11), the overall stoichiometry of **2a**:**3b**:**4b**:**5** is 1:1.25:0.5:2.5 compared to 1:2:1:2.3:4 in the nonrecycled process. However, there was some further decrease in the enantioselectivities (90.8%) that ultimately places a practical limit on the number of recycles possible.

The process throughput increase can be explained in the light of recent mechanistic investigations by Collum and co-workers. We postulate that the introduction of an alkyllithium to the reaction mixture after the completion of the first cycle regenerates a reactive aggregate. As shown in Scheme 2, the aggregate **9** (**3a**:**4a**:**6a**)⁸ in a ratio of 1:2:1, which causes autoinhibition, undergoes structural reorganization in the

(5) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212.

(6) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471–472.

(7) This reaction was run in 0.579 mol scale in a 5 L reactor. For the initial chiral addition: at T1₃₀ conversion = 98.8%, at T1₆₀ conversion = 99.1%, er = 99.2%. For the second cycle reaction in the same pot: at T2₃₀ conversion = 93.8%, at T2₆₀ conversion = 97.6%, T2₉₀ conversion = 98.98%. T1 and T2 represent conversion times in minutes for original addition and the next iterative addition, respectively.

presence of an additional 1 equiv of alkyllithium.⁹ It might be possible that the product separates from the aggregate as a bis lithiated species **6c**.¹⁰ The remainder CPA-Li **3a** and ligand **4a** can reaggregate to generate **8** (or mixture of aggregates), which reacts with added ketone **2a** to generate additional product.

We postulate that the drop in enantiomeric ratios for the iterative addition cycles (Table 1, entries 10 and 11) could be due to the presence of an increased percentage of lithiated product **6b** (or **6c**) which was previously shown to lead to the opposite enantioselectivity.

In conclusion, we have demonstrated that the high stoichiometric requirement for the chiral ligand and the lithium cyclopropylacetylide in the enantioselective addition step of efavirenz can be significantly reduced and the product can be isolated with excellent enantiomeric purity. We have also demonstrated that multiple asymmetric reactions can be carried out in an iterative fashion in the same reaction pot, and with process throughput increased, controlling the amounts of subsequent charges of *n*-hexyllithium and the ketone **2a** at the end of each cycle.

Experimental Procedure:

Generation of 1.3 Equiv of Product (Table 1, Entry 6). A 5-L, four-neck round-bottom flask was equipped with a mechanical stirrer, Dean–Stark trap with condenser, nitrogen inlet, and thermocouple. The system was purged with nitrogen for 15 min, and a nitrogen atmosphere was maintained throughout the reaction. A stock solution of the ligand **4b** (693.83 g, 39.4 wt % in toluene, 779.6 mL, 2.3 equiv, 1.33 mol) was charged to the reactor followed by Ph₃CH (1.44 g, 0.0058 mol, 0.01 equiv, used as indicator). The reaction mixture was heated to boiling, and 82 mL of solvent was distilled off. The mixture was cooled to about room temperature, and anhydrous THF (827.3 mL) was charged. The reaction mixture was cooled to –20 °C, and *n*-hexyllithium (379.9 g, 32.2 wt % solution in hexanes, 1.327 mol, 2.29 equiv) was charged at such a rate as to maintain a temperature below 0 °C until the reaction mixture turned to an orange-red color. Additional *n*-hexyllithium (357.3 g, 32.2 wt % solution in hexanes, 1.248 mol, 2.157 equiv) was charged beyond this red point at such a rate as to maintain the temperature below 0 °C. Cyclopropylacetylene **3b** (90.36 g, 1.367 mol, 2.36 equiv) was added dropwise, keeping the temperature below 0 °C. The mixture was aged for 1 h at

–1 to –23 °C to give the tetrameric complex **8** and was cooled to –43 °C. The THF solution of the ketone (200 g, 99.5% pure, 0.5789 mol/250 mL of THF) was added to the complex, allowing the internal temperature to rise to –40 °C during the addition. The resulting red solution was aged at –43 ± 3 °C for 1 h. A half hour sample aliquot was quenched into 1 N HCl, and HPLC analysis showed >99% conversion of starting ketone to product. The reaction mass was aged for an additional 0.5 h. *n*-Hexyllithium (179.08 g, 32.2% solution in hexanes, 0.625 mol) was charged at –43 ± 3 °C, and the reaction mass was aged for 15 min. A THF solution of the ketone (60 g/90 mL of THF) was charged dropwise at –43 ± 3 °C. HPLC analysis of an aliquot after 0.5 h quenched into 1 N HCl showed a ratio of 99:1 product: starting ketone. The cooling bath was removed, and the reaction mixture was quenched into 1 N HCl (3.4 L). The organic layer was separated and was washed with 2 × 617 mL of 1 N HCl. The aqueous layers were combined and back extracted with 700 and 300 mL of toluene. The combined organic solution was washed with 750 mL of water and was concentrated under reduced pressure to 650 g. Toluene (208 mL) was charged, and the solution was heated to +65 °C and was aged for 0.5 h. *n*-Heptane (930 mL) was charged slowly at +65 °C to maintain a solvent ratio of 60:40 heptane:toluene and was aged for 0.5 h. The mixture was slowly cooled to –5 °C and aged for 0.5 h at that temperature to complete the crystallization. The solids were collected by filtration and washed with 700 mL of 60:40 heptane:toluene chilled to –1 °C. The product was dried at +50 °C with vacuum and nitrogen. The isolated yield of the product was 284 g: chemical yield 91.0%, 99.3 wt %, ep = 98.06, [α]_D²⁵ +8.07 (*c*, 1.006, methanol) (lit.^{2b} = 8.15).

Generation of 2 Equiv of Product (Table 1, Entry 9). A 5 L, 4-neck round-bottom flask was equipped with a mechanical stirrer, Dean–Stark trap with condenser, nitrogen inlet, and thermocouple. The system was purged with nitrogen for 15 min, and a nitrogen atmosphere was maintained throughout the reaction. A stock solution of the ligand **4b** (1872.4 g, 14.6 wt % solution in toluene, 2.1 L, 2.3 equiv) was charged to the reactor. Triphenylmethane (1.44 g, 0.0058 mol, 0.01 equiv, used as indicator) was charged to the reactor. The reaction mixture was heated to boiling, and 1.2 L of solvent was distilled off. The mixture was cooled to about room temperature, and anhydrous THF (884.6 mL) was charged. The reaction mixture was cooled to –20 °C and *n*-hexyllithium (552 mL, 385.96 g, 32.2 wt % solution in hexanes, 2.33 equiv) was charged at such a rate to maintain a temperature below 0 °C until the reaction mixture turns to a red color. Actual charge was 375.7 g. Additional *n*-hexyllithium (353.31 g, 32.2 wt % solution in hexanes) was charged beyond this red point at such a rate as to maintain the temperature below 0 °C. Cyclopropylacetylene (128.56 g, 1.947 mol, 3.36 equiv) was charged at such a rate as to maintain the temperature below 0 °C until the color changed from orange to yellow. The mixture was stirred at 0–10 °C and chilled to –40 °C. The ketone solution in THF (200 g/300 mL of THF, 99.5% pure, 0.5789 mol) was charged below –40 °C. The reaction mixture was

- (8) The monolithiated addition product **6a** decomposes at higher temperature. ¹H NMR analysis showed that the crude mixture appears to consist of a mixture of indolines as the major constituents.
- (9) For solution structures derived from *n*-butyllithium and vicinal amino alkoxides, see: Sun, X.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039. In this case, the addition of *n*-butyllithium to benzaldehyde seems to show no conversion dependence because the product separates out of the mixed aggregate, thus regenerating the C2-symmetric reactive aggregate.
- (10) It might be possible that the addition of *n*-hexyllithium causes the metalation of N–H possibly with a consequent formation of its own dianionic homoaggregate and regeneration of the reactive form (we thank reviewer 1 for this comment). However, if this would have been the reason, the original ee of the process (after multiple iterations) would have been restored. But some drop in enantiomeric ratio was observed (Table 1, entries 10 and 11) which implicated the involvement of another mechanism (possibly product acting as a competing ligand causing low enantioselectivity).

stirred at -43 ± 3 °C. A 0.5 h sample aliquot was withdrawn and quenched into 2 N HCl. The conversion was 98.8:1.2 (product:starting material). Another aliquot after 1 h of reaction showed a conversion of 99.1:0.9 (product:starting material) with a chiral purity of 99.2%. *n*-Hexyllithium was charged (347.81 g, 32.2% solution in hexane, 1.2156 mol, 2.099 equiv) to the reaction mixture at the chiral addition temperature. The mixture was stirred for 15 min at -43 ± 3 °C. A solution of the ketone (200 g/300 mL of THF) was charged slowly at -43 ± 3 °C. An aliquot withdrawn after 0.5 h of the reaction showed 93.8% product, whereas the 1 h sample showed 97.6% and 1.5 h sample showed 98.98% product being formed. The cooling bath was removed, and the reaction mixture was quenched into 1 N HCl (4.16 L). It was stirred for 20 min, and the layers were separated. The organic layer was extracted out and washed with 2×378 mL of 2 N HCl. The aqueous layers were combined and back extracted with 700 and 300 mL of toluene. The organics were combined and washed with 750 mL of H₂O. The organic layer was concentrated under reduced pressure to

have a toluene content of 954 mL. It was heated to 65 °C and was aged for 0.5 h. *n*-Heptane (1430 mL) was charged slowly at +65 °C to maintain a solvent ratio of 60:40 heptane:toluene and was aged for 0.5 h. The mixture was cooled to room temperature and aged for 1 h. The solids were collected by filtration and washed with 1000 mL of 60:40 heptanes:toluene. They were washed again with 200 mL of 60:40 heptanes:toluene. The wet cake was dried overnight at 50 °C with a nitrogen purge to generate 400.3 g (83.9%), 99.5 wt %, ep 96.9%, $[\alpha]_D^{25} +7.95$ (*c*, 1.006, methanol) (lit.^{2b} = 8.15).

Acknowledgment

We are thankful to Professor D. F. Taber for valuable suggestions and to Dr. Roger Stringham, Barbara Lord, and Bill Cummings for their analytical support.

Received for review September 17, 2002.

OP025595S