Organic Process Research & Development **2007**, *11*, 215–222

Dynamic Biphasic Counterion Exchange in a Configurationally Stable Aziridinium Ion: Efficient Synthesis and Isolation of a Koga C_2-Symmetric Tetraamine Base

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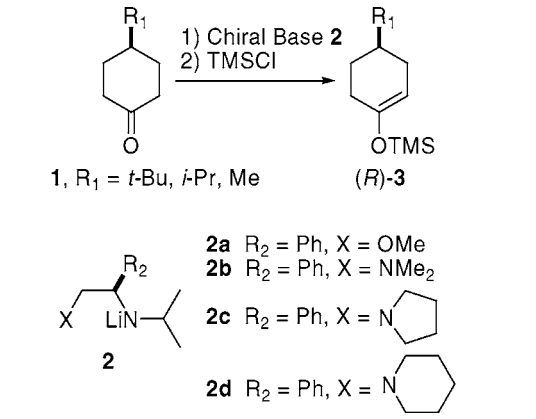
Abstract:

An efficient synthetic process for chiral tetraamine base (*R,R*)-5 is reported that leverages mechanistic understanding to enable control over key transformations. Specifically, a configurationally stable and observable aziridinium ion intermediate was found to undergo counterion exchange impacting the feasibility of the process. Mechanistic investigations revealed that both counterion exchange and trapping of the aziridinium ion were biphasic events and that the former could be suppressed at lower temperatures, facilitating the reaction on both small and large scales. The mechanistic insights gained have led to the development of an efficient one-pot process that enables preparation of multiple kilograms of (*R,R*)-5 as a crystalline solid without chromatography in excellent chemical and chiral purity.

In 1986, Koga et al. reported the use of chiral lithium amide bases (**2a**−**d**, Scheme 1) for the synthesis of chiral enolates from prochiral ketones via enantiotopic proton abstraction.[1] In a subsequent report, Koga demonstrated that a related chiral base ((*R,R*)-**5**) could also direct the approach of an electrophile to prochiral enolates (**4a** and **4b**) with the resulting alkylated α-tetralones (**6a** and **6b**) being isolated in high enantioselectivity.[2,3]

As part of an ongoing development program employing such an enantioselective alkylation, we required a means of preparing multi-kilogram quantities of tetraamine (*R,R*)-**5**. In 2001, O'Brien reported a general method for synthesis of Koga's chiral amines (Scheme 2).[4] The procedure involved thermal ring-opening of the appropriate antipode of styrene oxide (**7**) with piperidine to afford aminoalcohols **8a** and **8b**, which were isolated and then treated sequentially with mesyl chloride and the appropriate amine in diethyl ether to afford the desired Koga amine. Interestingly, displacement of the corresponding mesylates (**9a** and **9b**) was found to proceed at the benzylic carbon only and with net retention of stereochemistry, suggesting the intermediacy of aziridinium ion **10**. An acid/base extraction protocol afforded the desired Koga amines (e.g., (*R,R*)-**5**) with good purity. Given the apparent ease of this two-step protocol, we used this report as the starting point for our own investigations.

Scheme 1



Results and Discussion

In our hands, the reported procedure by O'Brien was functional. Ring-opening of (*R*)-**7** afforded a near 1:1 ratio of aminoalcohols **8a** and **8b**, which were carried through

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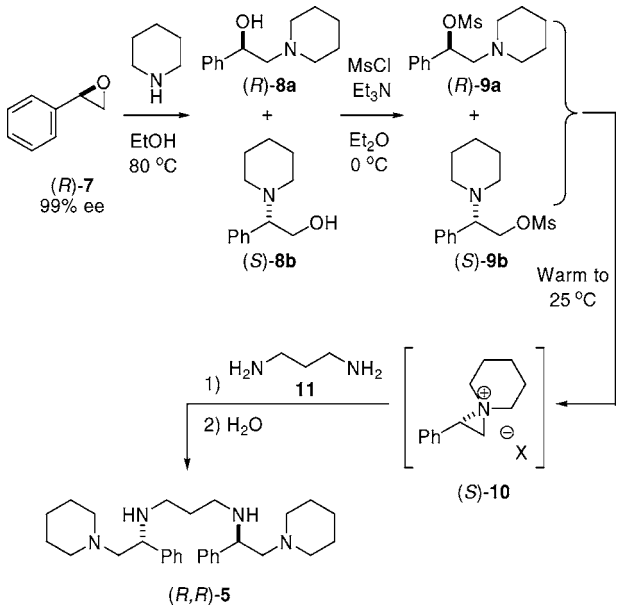
(1) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543.
(2) (a) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657. (b) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829. (c) Yamashita, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1999**, *40*, 2803.
(3) For reviews of asymmetric synthesis using chiral lithium amide bases, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. (b) O'Brien, P. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 1439. (c) Tomioka, K. *Synthesis* **1990**, 541. (d) Majewski, M. *Adv. Asymm. Synth.* **1998**, *3*, 39.
(4) (a) Poumellec, P.; O'Brien, P. *Tetrahedron Lett.* **1996**, *37*, 5619. (b) deSousa, S. E.; O'Brien, P.; Poumelec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483. (c) Cuthbertson, E.; O'Brien, P.; Towers, T. *Synthesis* **2001**, 693. (d) Towers, T. D.; O'Brien, P. *J. Org. Chem.* **2002**, *67*, 304.

10.1021/op0602371 CCC: $37.00
Published on Web 02/20/2007

Scheme 2



the mesylation step at 0 °C in MTBE. The mixture was warmed to room temperature and then treated with 1,3-propanediamine (**11**) and water. Koga amine (*R*,*R*)-**5** was isolated in 99% chiral purity, lending further credence to the intermediacy of aziridinium ion **10**.[5−7] There were, however, two noteworthy observations made during these initial experiments that would impact future efforts to scale the synthesis of (*R*,*R*)-**5** via the current procedure:

(1) As the reaction mixture was allowed to warm above 10 °C following mesylation and prior to charging **11**, a significant change in the reaction mixture consistency was observed. Specifically, the white, flocculent precipitate of $Et_3N{\cdot}HCl$ generated during the mesylation reaction, if the mixture were allowed to warm to ca. 10 °C, changed rapidly to a thick, gummy material that quickly settled to the bottom of the reactor and seized the agitator.[8] This stirring difficulty was observed in a number of ether solvents as well as in aromatic hydrocarbon solvents such as benzene and toluene. Addition of 1,3-diaminopropane (**11**) was followed by addition of water, which dissolved the gum and enabled stirring to be resumed. However, on larger scales, even temporary agitator seizure could be damaging to equipment and chemistry, and thus a means of maintaining agitation throughout the entire reaction would be necessary.

(2) Although reported by both Koga and O'Brien to be a colorless oil, Koga amine (*R*,*R*)-**5** solidified upon standing to a hard, amorphous solid that was very difficult to break up. To ease isolation and handling, a means of crystallizing (*R*,*R*)-**5** to a flowing, manageable solid would be required.

Our efforts to resolve the agitator seizure problem initially focused on characterizing the reactivity that was the source of the stirring difficulty. Isolation and characterization of the thick, gummy precipitate revealed its identity to be $Et_3NH{\cdot}$OMs. This suggested that formation of aziridinium ion **10** did not take place gradually, but rather was a rapid event at 10−20 °C, and that the mesylate anion liberated by the aziridinium formation underwent counterion exchange with $Et_3N{\cdot}HCl$. To confirm that such a counterion exchange event was operative under these conditions, an experiment was performed wherein (*R*)-**8a** and (*S*)-**8b** were treated with 1.1 equiv of MsCl at −10 °C. The supernatant reaction solution was sampled following complete MsCl addition at −10 °C and at intervals while warming to 22 °C, and the resulting aliquots were analyzed rapidly by ^{1}H NMR. As can be seen from Figure 1, initially both regioisomeric mesylates **9a** and **9b** are observed (Spectrum **A** in Figure 1). As the reaction progresses, both sets of mesylate signals are observed to converge to a single isomeric β-chloroamine **12** (Spectrum **B**), which is ultimately the sole constituent of the supernatant solution (Spectrum **C**). This outcome revealed not only that aziridinium ion **10a** did undergo mesylate-to-chloride counterion exchange but also that the chloride counterion was sufficiently nucleophilic to attack the aziridinium ion at the more reactive benzylic position, alleviating ring strain and establishing a covalent bond (Scheme 3). When held at −10 °C, mesylates **9a** and **9b** remained as stable covalent species with no chloride **12** visible even after 3 h, demonstrating that conversion of **9a**/**9b** to **12** via aziridinium ion **10a** could be suppressed at lower temperatures.

Further insight into the mechanism and driving force for the counterion exchange was gained by evaluating the solubilities of the reacting partners in the MTBE phase. As can be seen from Table 1, these studies revealed that, while β-chloroamine **12** was soluble in MTBE to 115 mg/mL, aziridinium mesylate **10a** was only soluble to 5 mg/mL[9] and $Et_3N{\cdot}HCl$ was soluble to less than 0.1 mg/mL. These data point to a biphasic process wherein counterion exchange occurs upon precipitation of **10a** and β-chloroamine **12** is re-extracted into the MTBE phase (Scheme 4). Importantly, the equilibrium between covalently bound mesylates **9a**/**9b** and **10a** was determined to lie extensively in favor of **10a** at room temperature when **9a** and **9b** were prepared using methanesulfonic anhydride (to eliminate the possibility of counterion exchange).[9] This equilibrium, coupled with the solubility-driven equilibrium between the aziridinium chlo-

(5) For examples of aziridinium ions in synthesis, see: (a) Liu, Q.; Marchington, A. P.; Rayner, C. M. *Tetrahedron* **1997**, *53*, 15729. (b) Rayner C. M. *Synlett* **1997**, 11. (c) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585. (d) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766. (e) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670. (f) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (g) Rosen, T.; Fesik, S. W.; Chu, D. T. W.; Pernet, A. G. *Synthesis* **1988**, 40. (h) Kametani, T.; Honda, T. *Adv. Heterocycl. Chem.* **1986**, *39*, 181. (i) Couterier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183.

(6) Chiral purity is reported relative to both the opposite enantiomer ((*S*,*S*)-**5**) and the meso isomer (*meso*-**5**). Analytical standards of both (*S*,*S*)-**5** and *meso*-**5** were obtained.

(7) For a review of Neighboring Group Participation in organic reactions, see: Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum Press: New York, 1976.

(8) O'Brien also reported stirring difficulty at lower temperatures due to the formation of $Et_3N{\cdot}HCl$. Using mechanical agitation, stirring was easily maintained with the initial precipitate of $Et_3N{\cdot}HCl$. The pronounced change in the form of the precipitate on warming was the event that seized the agitator in our case.

(9) An authentic ^{1}H NMR spectrum of aziridinium ion **10a** is available as Supporting Information. For NMR data of an unrelated aziridinium ion, see: Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511.

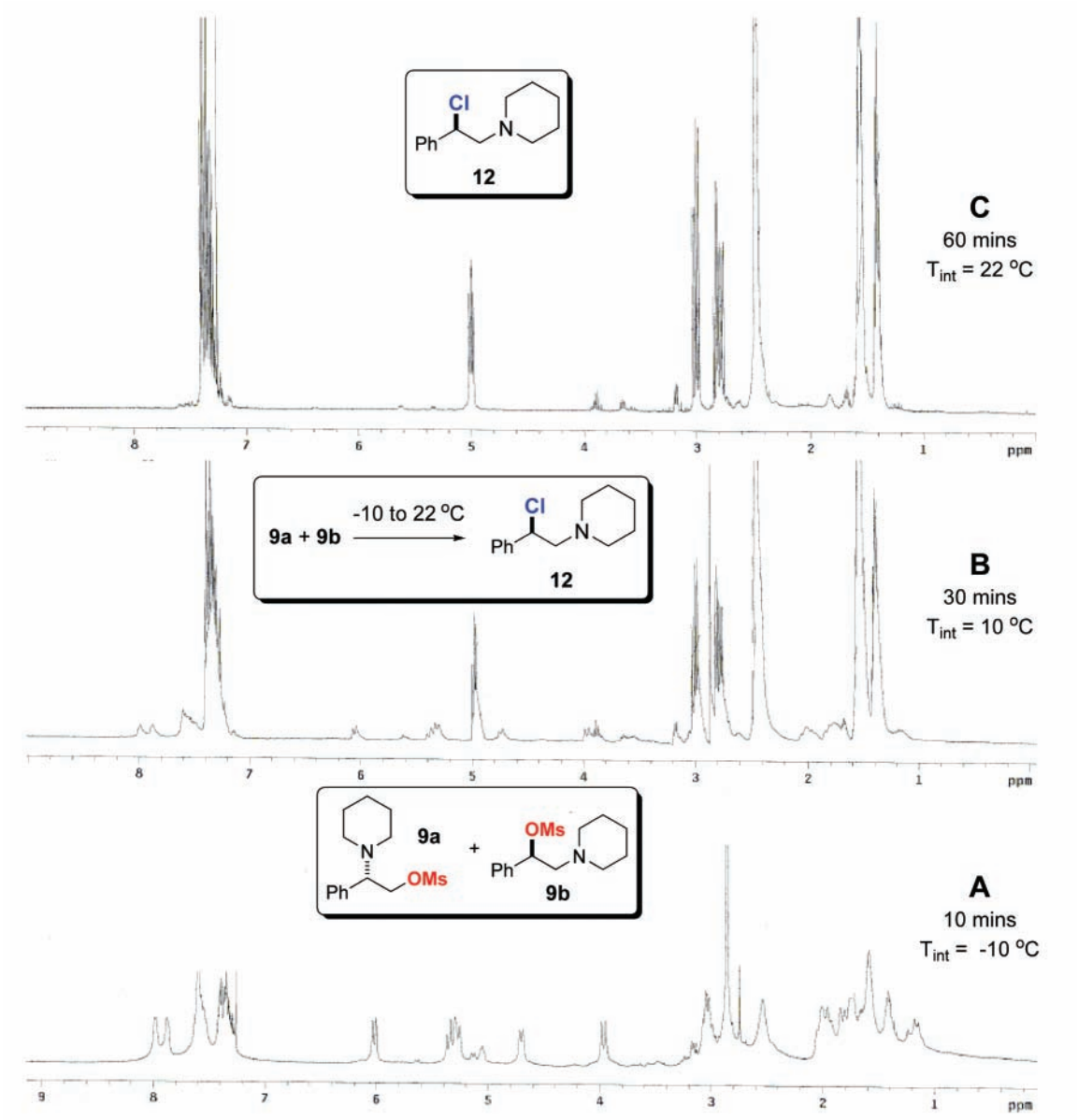


Figure 1. **Conversion of mesylates 9a and 9b to β-chloroamine 12 as observed by ^{1}H NMR ($CDCl_3$).**

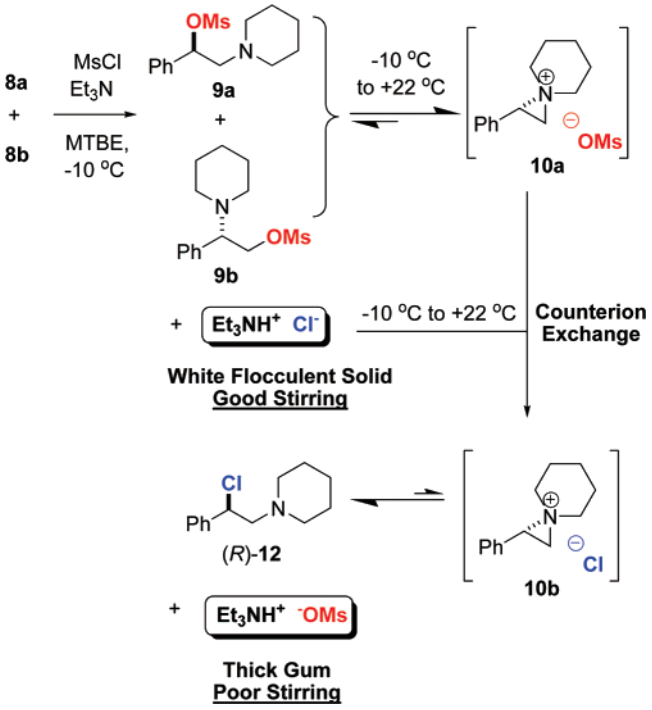
ride **10b** and **12**, presumably drives the counterion exchange towards the chloride.[10]

Having characterized the counterion exchange process, efforts focused on maintaining agitation throughout the mesylation and subsequent aziridinium formation reactions. Given that the aziridinium ion formation with subsequent conversion to chloroamine **12** was observed to occur upon warming, studies focused on maintaining the temperature in the range −10 to −8 °C during the mesylation step to maintain stirrability. It was expected based on the above NMR studies that lower temperatures would suppress aziridinium ion formation, maintaining the covalent mesylate intermediates **9a** and **9b**. Once mesylation was complete, 1,3-diaminopropane (**11**) and water would be added and the mixture warmed only once all reacting components were present. Key to the success of this approach would be the rapid formation and subsequent trapping of the incipient aziridinium ion **10** by 1,3-diaminopropane (**11**). However, it was recognized that one potential liability of this approach might be competing reactivities between the aziridinium ion (**10**) and mesylates (**9a** and **9b**) which would lead to mixtures of regioisomers and stereoisomers.

To assess the feasibility of this approach, a study of the composition of the biphasic reaction mixture was carried out (Table 2). These studies revealed that 1,3-diaminopropane (**11**) was located in the lower aqueous phase within the limits of detection. Monoadduct **13** also had substantial concentration in the aqueous phase, while the product Koga amine (**5**) was found to reside almost exclusively in the upper

(10) The intermediate β-chloroamine **12** derived from mesylates (*R*)-**9a** and (*S*)-**9b** via aziridinium ion **10a** gives rise to (*R*,*R*)-**5** under the reaction conditions reported by O'Brien. Thus, reversion of **12** to the aziridinium ion prior to amine trapping is required for stereochemical competence. The formation of **12** from **9a**/**9b** has been observed previously; however neither the time course and temperature sensitivity of this interconversion nor its mechanism of formation were reported. See: Anderson, S. R.; Ayers, J. T.; DeVries, K. M.; Ito, F.; Mendenhall, D.; Vanderplas, B. C. *Tetrahedron: Asymmetry* **1999**, *10*, 2655.

Scheme 3

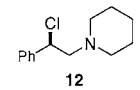
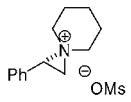
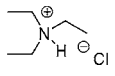


MTBE phase. These data suggested that aziridinium trapping would occur principally in the aqueous phase where 1,3-diaminopropane (**11**) resides and monoadduct **13** concentrations are significant. The final Koga amine product is then extracted back into the MTBE layer. Given such a mechanism, displacement of the mesylate by **11** in the organic phase would not be competitive.

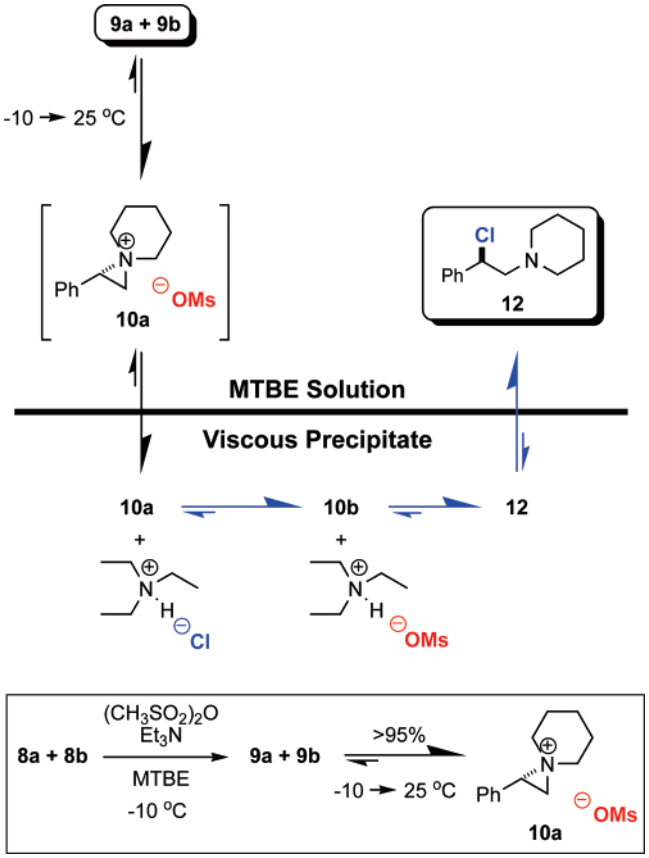
In the event, mesylation proceeded smoothly at −10 °C, preserving the white, flocculent precipitate of $Et_3N{\cdot}HCl$ throughout the mesylation process. Once complete, 1,3-diaminopropane (**11**) and water were added and the biphasic mixture was warmed to 25 °C. Proceeding through the acid/base workup utilized thus far afforded Koga amine (*R*,*R*)-**5** in equivalent yield and chemical and chiral purity to those obtained previously.

Having gained control over the counterion exchange process that led to the agitator seizure issue, attention was turned towards controlling the form of the final product. To facilitate isolation on-scale, a means of crystallizing Koga

Table 1. **Solubility of reacting species in MTBE phase at 22 °C**

Species	Solubility in MTBE Phase (mg/mL)
 **12**	115
 **10a**	5
	< 0.1

Scheme 4



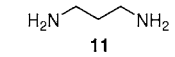
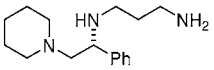
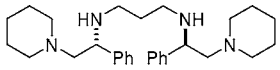
amine (*R*,*R*)-**5** as a flowing, filterable solid was essential. Current batches were isolated by rotary evaporation as a thick, yellow oil that slowly solidified into a very hard solid mass. Crystallization studies focused on solvent/antisolvent combinations. Several combinations were screened, the majority of which led to the precipitation of an oily species. Ultimately, a protocol was established wherein crude (*R*,*R*)-**5** was dissolved in IPA (5 mL/gram of crude solid). The resulting solution was cooled to 0 °C, and the cold solution was seeded with pure (*R*,*R*)-**5** (0.1% w/w). This resulted in the formation of a sizable seed bed to which water (0.9 × IPA volume) was charged.[11] The formation of a seed bed prior to antisolvent charge was critical to obtaining a crystalline solid rather than an oil. The thick product slurry was warmed to room temperature, filtered, and washed with 1.1:1 IPA/water to afford (*R*,*R*)-**5** as a white, crystalline solid in 99.9% chiral purity and 99.7 A% chemical purity by HPLC.[12]

Analysis of the mother liquor by GC/MS revealed that no (*R*,*R*)-**5** remained in the mother liquor following crystallization (see Figure 3). This was further confirmed by a spiking experiment wherein **1c** was added to the mother liquor prior to GC/MS analysis. Identification of the major

(11) Water was charged portionwise. An exotherm of ca. 9 °C was observed following each addition, and the mixture temperature was allowed to return to 0 °C between additions.

(12) A% refers to the HPLC peak area % of the desired material versus all other visible impurity peaks in the appropriate assay. Chiral purity refers to the HPLC peak area % of the desired isomer (i.e., (*R*,*R*)-**5**) versus the enantiomer ((*S*,*S*)-**5**) and the *meso*-isomer (*meso*-**5**).

Table 2. **Species partitioning between MTBE and aqueous phases**[a]

Species	Peak Area MTBE Phase	Peak Area Aqueous Phase	% in MTBE Phase	% in Aqueous Phase
 **11**	ND[b]	27087	<0.5%	>99.5%
 (*R*)-**13**	3667	2095	64%	36%
 (*R,R*)-**5**	160673	1158	99.3%	0.7%

[a] Layer content determined by gas chromatography. See Supporting Information for details. [b] ND = not detected.

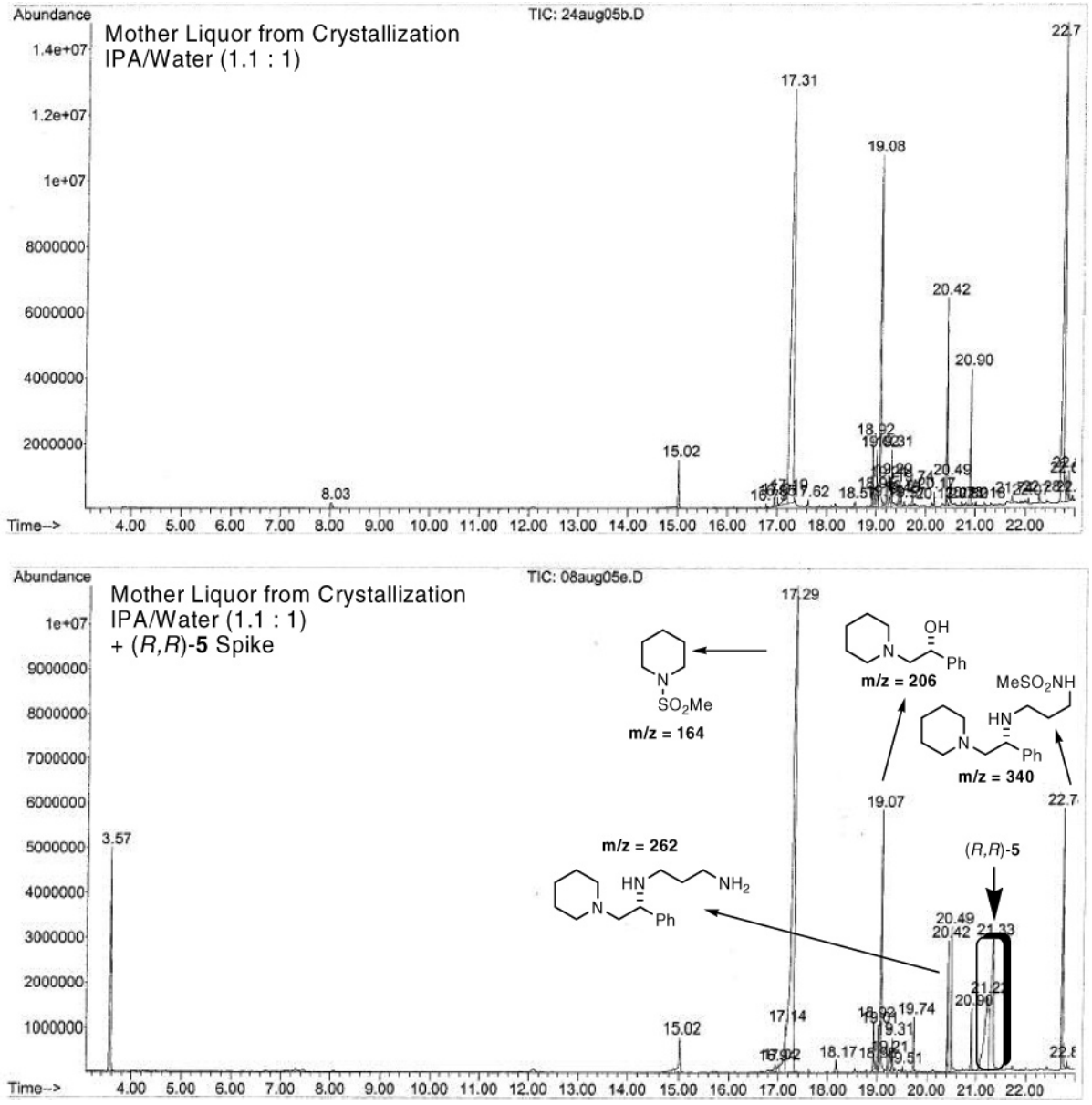
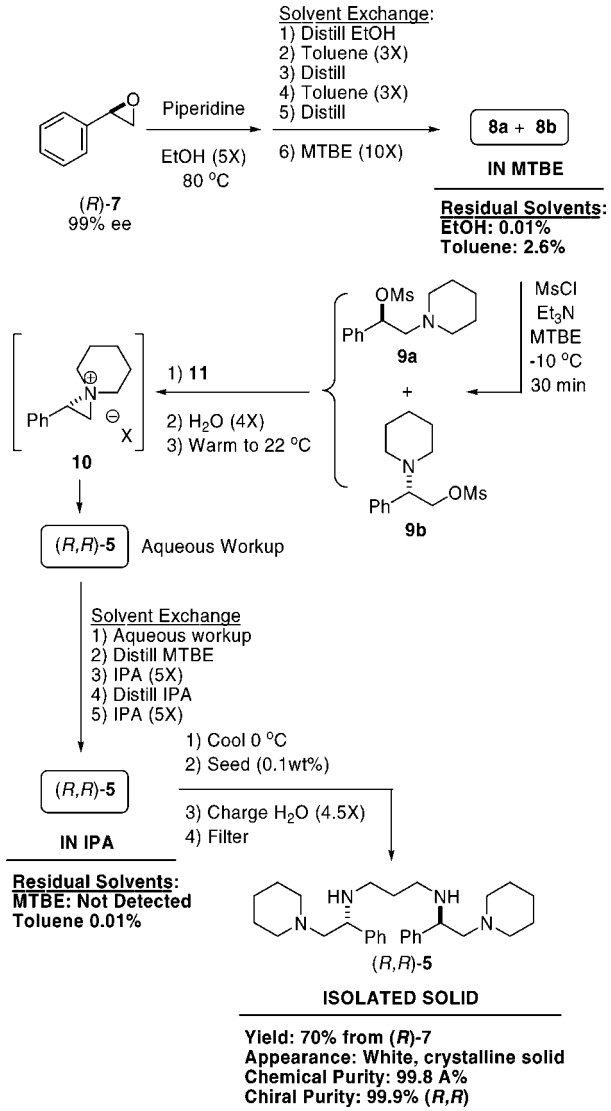


Figure 2. **GC/MS traces of crystallization mother liquor and mother liquor spiked with (*R,R*)-5.**

impurities was also accomplished, and their structures are indicated in Figure 2.

Efforts next focused on merging the two steps into a one-pot protocol. Scheme 5 describes the through-process that

Scheme 5



resulted from these efforts. Conversion of (*R*)-Styrene oxide ((*R*)-**7**) to aminoalcohols **8a** and **8b** proceeded smoothly at 80 °C in 3 h. To ensure the success of the subsequent mesylation step, thorough ethanol removal would need to be accomplished. Thus, a solvent exchange protocol was performed by first distilling the bulk of the ethanol and then performing two azeotropic distillations with toluene. Following the second toluene distillation, MTBE was added. Analysis of the resulting solution for residual solvents revealed very low (0.01 wt %) ethanol content and acceptable (2.6 wt %) toluene content. The mesylation step was conducted at −10 °C to preserve the mesylate and suppress aziridinium ion formation in accord with earlier experiments (see above). As expected, mesylation proceeded smoothly with no agitator interference due to the formation of $Et_3NH{\cdot}OMs$. Warming of the reaction mixture was performed only after both diamine **11** and water had been added.

The biphasic nature of the aziridinium-opening/Koga amine-formation step (i.e., **10**→**5**, Scheme 5) posed an analytical challenge in determining the degree of reaction completion. Since the bulk of the reaction appears to proceed

Table 3. **Change in concentration of (*R,R*)-5 in MTBE phase versus time**

time (h)	concentration of (*R,R*)-**5** (mg/mL)	concentration change/time (mg/mL/h)
1.5	64.5	0.0
2.5	69.0	4.5
3.5	70.8	1.8
4.5	71.9	1.1
21	79.8	0.48
23.5	79.2	−0.24

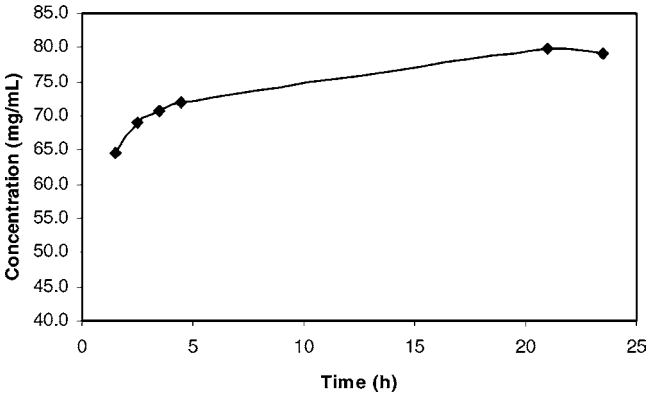


Figure 3. **Plot of concentration of (*R,R*)-5 in MTBE phase versus time**

in the aqueous phase and the product is extracted into the organic phase, obtaining a representative sample of the reaction mixture that would contain consistent levels of starting materials and product was not possible. To monitor the progress of the reaction, we developed a protocol wherein the concentration of (*R,R*)-**5** in the organic phase was monitored. The endpoint of the reaction was signaled by a plateau in product concentration in the MTBE phase. Concentration data collected during a representative 1 kg reaction and the corresponding plot of concentration versus time are provided in Table 3 and Figure 3, respectively.

Once complete, the reaction mixture was allowed to settle to two phases and subjected to an aqueous workup consisting of an ammonium chloride wash and brine wash. Solvent exchange to IPA proceeded smoothly in two rounds of addition and distillation. Residual solvent analysis revealed that the resulting IPA solution contained an undetectable level of MTBE and an acceptable level (0.01 wt %) of toluene. Cooling to 0 °C and seeding (0.1 wt %) resulted in the expected seed bed to which was charged water (4.5×) to accomplish complete crystallization. Filtration afforded a 70% overall yield of (*R,R*)-**5** as a white, crystalline solid (99.9 wt %, 99.8 A% chiral purity).

In conclusion, we have developed an efficient one pot process for the synthesis of Koga tetraamine (*R,R*)-**5** as a crystalline solid in excellent chemical and chiral purity. Importantly, the developed process leverages mechanistic understanding regarding the intermediacy of aziridinium ion **10a** and the counterion exchange process that takes place with this configurationally stable and observable intermediate to enable efficient control over both of these events.

Experimental Section

Materials and Methods. The vessel used was a 50 L nonjacketed glass reactor containing an internal Teflon-coated copper coil connected to a circulating chiller (operating range −60 to 150 °C). The 7-port reactor head with a 4 in. reagent charging port was fitted with a high efficiency condenser (operating at −5 °C), a temperature probe, a nitrogen gas inlet, an off-gas outlet connected to an oil bubbler, and a glass stir-shaft equipped with two paddles. The reactor was verified clean prior to operation and was placed under an atmosphere of nitrogen gas for 15 min prior to charging. All commercially obtained reagents were used as received. High performance liquid chromatography (HPLC) was performed using Agilent 1100 systems. Gas chromatography (GC) was performed using Agilent 6890 systems. ^{1}H and ^{13}C NMR chemical shifts are reported as δ values relative to internal chloroform (^{1}H δ 7.27 ppm, ^{13}C δ 77.0 ppm)

One-Pot Synthesis of Koga Amine (*R*,*R*)-5. To a 50 L reactor was charged ethanol (Absolute, 2.0 L), and stirring was commenced (ca. 200 rpm). (*R*)-Styrene oxide ((*R*)-**7**, 1.017 kg, 8.46 mol) was charged. Ethanol (2 × 1.0 L) was used to rinse the residual (*R*)-**7** from the container, and each rinse was charged. Piperidine (1.00 L, 10.16 mol, 1.2 equiv) was then charged to the reactor in a single portion. Ethanol (2 × 500 mL) was used to rinse residual piperidine into the reactor. The contents of the reactor were then heated to an internal temperature of 80 °C ± 2 °C and held at this temperature for 5 h. An analytical sample was pulled following the 5 h reflux period and subjected to HPLC analysis which showed 99.1% conversion to aminoalcohols **8a** and **8b**. The reactor was cooled to 22 °C and equipped with a batch concentration receiver flask. The reactor was placed under a vacuum (ca. 20 Torr) and then heated to an internal temperature of 45 °C ± 2 °C, and distillate was collected. The reaction mixture was concentrated until approximately a 2.0 L total volume was obtained. Toluene (3.0 L) was charged, and the mixture again was heated to an internal temperature of 45 °C ± 2 °C. Distillate was collected, and the batch again was concentrated to approximately a 2.0 L total volume (slurry). The reactor was cooled to 22 °C, and additional toluene (3.0 L) was charged. A second azeotropic distillation was performed. The reactor was cooled to 22 °C, and MTBE (9.0 L) was charged. An analytical sample was pulled and analyzed for residual solvents which showed residual ethanol at 0.01% (Pass: ≤ 0.5%) and residual toluene at 2.6%. To the MTBE solution of aminoalcohols **8a** and **8b** was added triethylamine (4.37 L, 31.4 mol, 3.7 equiv). Stirring was commenced, and no further additions to the reactor were made until the solids had dissolved (ca. 10 min). The batch was cooled to −10 °C, and upon reaching this temperature, mesyl chloride (790 mL, 10.2 mol, 1.2 equiv) was charged to the batch from a self-equilibrating glass dropping funnel at a rate of approximately 3.3 mL/min.

NOTE: Addition rate and chiller temperature were regulated such that the internal temperature of the reaction mixture was maintained between −8 and −10 °C during the addition. Total addition time was 50 min.

CAUTION: This is an exothermic reaction. Do not exceed an internal reaction temperature of −10 °C to −8 °C during this addition to maintain adequate stirring.

After the addition was complete the batch was stirred for 30 min at −10 °C. Adequate agitation was maintained by keeping the temperature at or near −10 °C. An analytical sample was pulled, and analysis indicated 98.6% conversion of aminoalcohols **8a** and **8b** to mesylates **9a** and **9b**. Next, 1,3-diaminopropane (**11**, 354 mL, 4.2 mol, 0.50 equiv) was charged from a clean self-equilibrating glass dropping funnel followed by deionized water (4.1 L). The reaction mixture was warmed to 20 °C over 1 h, during which time the precipitated triethylamine salt dissolved. The mixture was stirred at 20 °C for 18 h. Analytical samples were pulled at 1, 2, 5, and 18 h time points by halting agitation, allowing the layers to settle, and sampling the upper (MTBE) layer. Agitation was then reinitiated. HPLC analysis at each time point provided the data in Table 3. Once deemed complete, stirring was halted to allow phase separation (ca. 10 min). The lower aqueous phase was drained. The remaining organic fraction was washed with saturated ammonium chloride solution (3.5 L) by agitating for 20 min followed by phase separation. The lower aqueous layer was drained. The remaining organic fraction was washed with brine (3.5 L) by agitating for 20 min followed by phase separation. The lower aqueous layer was drained. The reactor containing the organic phase was fitted with a batch concentration receiver flask. The reactor was placed under a vacuum (ca. 20 Torr), and the internal temperature was increased to 30 °C. Distillate was collected, and the reaction mixture was concentrated to a total volume of ca. 3.5−4.0 L. Isopropyl alcohol (5.0 L) was charged to the reactor, and the mixture stirred to homogeneity. A sample was pulled to determine the residual solvent levels which showed residual MTBE at 3.33% (Pass: ≤ 0.1%) and residual toluene at 0.13% (Pass: ≤ 0.1%). The reactor was again placed under a house vacuum (ca. 20 Torr), and the internal temperature was increased to 50 °C. Some forerun was observed at distillate temperature 29 °C (MTBE). Once the forerun ceased, distillate was collected and the batch was concentrated to a volume of ca. 3.5 L (semiviscous oil). The reactor was again cooled to 22 °C and vented with nitrogen to atmospheric pressure. Additional isopropyl alcohol (5.0 L) was charged to the reactor, and the mixture was stirred to homogeneity. A sample was again pulled to determine residual solvent levels which showed residual MTBE below detectable levels and residual toluene at 0.01% (Pass: ≤ 0.1%). The internal temperature was cooled to 0 °C, and seed (*R*,*R*)-**5** (2.0 g) was charged to the reactor. After 45 min, a thick seed bed was present and water (4.5 L) was charged portionwise to the reactor, allowing the internal temperature to return to 0 °C following each water charge. The fluid temperature was set to −20 °C to control/abate the exotherms. Once internal temperature reached 0 °C following the final water charge, the mixture was held at 0 °C for 30 min and then warmed to 22 °C and stirred for 12 h at 22 °C. The resulting mixture was filtered through a medium-porosity sintered glass funnel. The remaining solid in the reactor was rinsed out with 1.1:

1.0 IPA/water solution (2 × 850 mL), and this was applied as a wash of the isolated solid on the funnel. The wet cake was allowed to dry on the funnel for 3 h, after which it was transferred to a vacuum oven and dried at 50 °C and 15 Torr for 24 h with a nitrogen bleed to afford 1330 g of dried (*R*,*R*)-**5** (70% yield based on styrene oxide, 99.9% chiral purity). Mp 63−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.35 (m, 10H), 3.71 (dd, J = 3.5, 10.9 Hz, 2 H), 2.21−2.54 (m, 18H), 1.39−1.68 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 128.2, 127.3, 126.9, 66.6, 60.1, 54.5, 46.2, 30.4, 26.1, 24.4; IR (thin film/NaCl) 3310 (w), 2929 (m), 2787 (m), 1452 (m), 1150 (m), 1116 (m), 914 (w), 748 (s). HRMS (EI) *m*/*z* found: 449.3639 [calcd for $C_{24}H_{45}N_4$ (M + H): 449.3644. Anal. Calcd for $C_{24}H_{44}N_4$: C, 77.63; H, 9.88; N, 12.49. Found: C, 77.66; H, 10.08; N, 12.46. $[\alpha]_D^{20}$ −112 (*c* 5.45, $CHCl_3$).

Acknowledgment

The authors wish to thank Dr. M. Bhupathy and Ms. RoseAnn Price for assistance with raw material procurement and logistics.

Supporting Information Available

Analytical methods for each step including methods for residual solvents and analytical data for intermediates, as well as procedures and NMR data/spectra for intermediates. This information is available free of charge via the Internet at http://pubs.acs.org.

Received for review November 15, 2006.

OP0602371