JOC Article

On the Racemization of Chiral Imidazolines†

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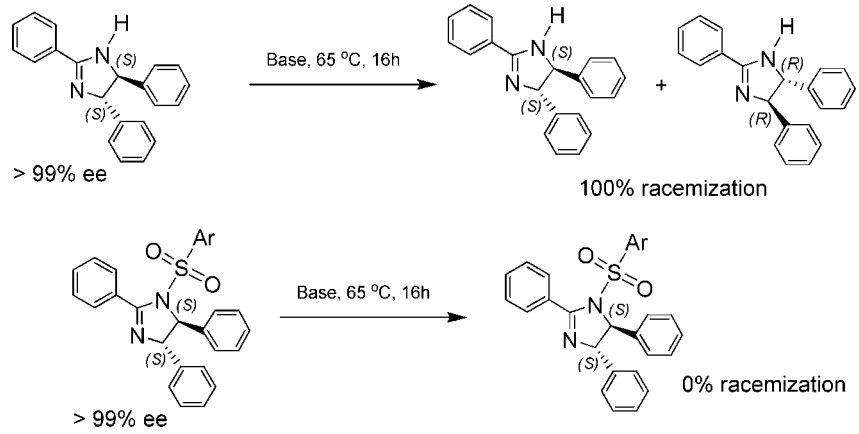


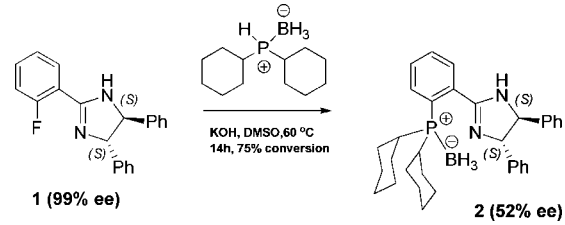
Racemization of chiral imidazolines with base has been studied for the first time following an unexpected finding in the synthesis of chiral imidazoline ligands. Amine bases do not cause racemization. Strong inorganic bases can induce racemization, yet this occurs only when the nitrogen is unsubstituted, in agreement with a symmetry-allowed thermal disrotatory ring opening and closure from a diazapentadienyl anion. Surprisingly, even with electron-withdrawing *N*-substituents, no racemization is observed. Conditions which allow for the racemization-free manipulations of this important compound class have been defined and developed.

Introduction

The synthesis and use of imidazolines has expanded dramatically in the past decade. This has been driven both by increased applications in catalysis[1] and especially by the development of imidazoline-based drugs for various therapeutic targets. Human imidazoline binding sites (IBS) have been identified, and the nature of these receptor subtypes and their preferred ligands have been explored in detail.[2] Imidazoline drugs are now in development for a remarkable array of disease states including oncology,[3] depression and neuroprotection,[4] hypertension,[5] inflammation,[6] and analgesia.[7,4a] Many of these molecules are chiral.

We have recently reported the development of chiral phosphinoimidazolines ligands (BIPI ligands) that perform asymmetric hydrogenations with near-perfect enantioselection.[1a] An unexpected finding was made during this research, namely extensive racemization which occurred in the phosphide borane S_NAr reaction. A typical result using dicyclohexylphosphine borane with KOH as base is shown in Scheme 1. We needed therefore to study the parameters which control this process and to gain an understanding of the mechanism involved.

SCHEME 1. Racemization in S_NAr Reaction



Results and Discussion

We repeated the S_NAr reaction of Scheme 1 using *t*-BuOK in DMSO. Aliquots were periodically removed, quenched with

† Dedicated to the memory of the late Professor Albert I. Meyers.

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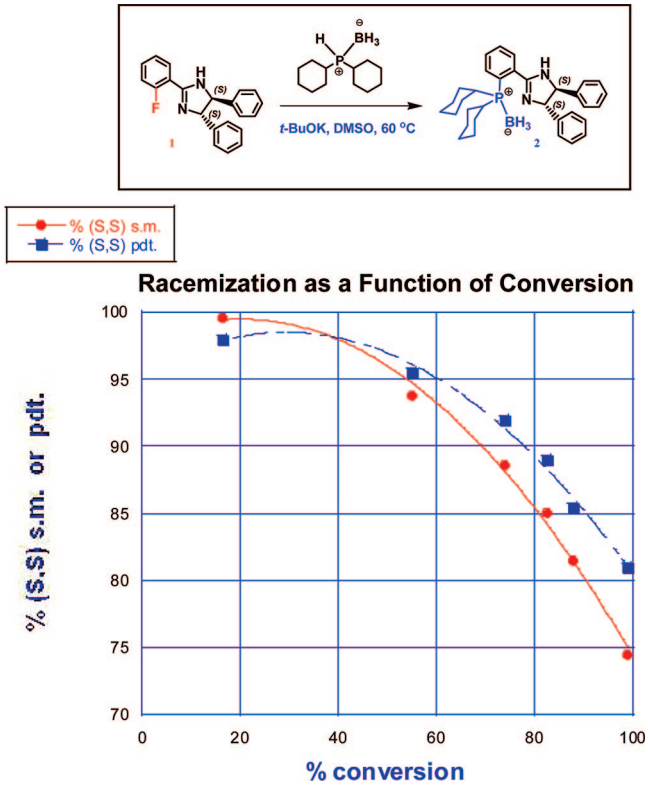

FIGURE 1. Racemization of reaction components.

acid, and chromatographed to isolate both unreacted starting material and product. The optical purities (% *S*,*S*) of each component were then determined by chiral HPLC, and the results were plotted as a function of conversion (Figure 1).

Both reaction components were observed to racemize and at similar rates. We had initially suspected that the phosphine borane functionality may have facilitated racemization if an equilibrium existed between **2** and a species in which the borane had transferred to the basic imidazoline nitrogen. There is clear precedent for increased acidity of hydrogens at the α center in such aminoboranes,[8] yet in fact, the phosphine borane is not required for racemization to occur, and we subsequently found that the parent, unsubstituted system behaves similarly. It is also clear from Figure 1 that if the S_NAr reaction is not quenched at the moment full conversion is reached, the ee of the isolated product from the basic reaction mixture will continue to erode. This fact then explained the range of optical purities we had observed in different S_NAr reactions prior to optimization.

Control experiments showed that the nucleophile in the S_NAr reactions, the phosphide borane anion, was also not a necessary requirement for racemization. Racemization in DMSO or DMAc with inorganic bases such as KOH, *t*-BuOK, or NaH themselves occurred readily. We also examined the amine bases triethylamine, DABCO, DMAP, and DBU. In no case did these bases lead to imidazoline racemization, even after 24 h at 60 °C. With the inorganic bases under these "superbasic"[9] conditions, however, the racemization which took place was always accompanied by a significant amount of decomposition that was not seen with the phosphide borane anion. We therefore employed the phosphide borane as base in all subsequent studies of the racemization. We chose to further simplify the system by employing the unsubstituted chiral imidazoline (*S*,*S*)-**3**. By removing the fluoro substituent, any substitution chemistry, which was now known to be irrelevant to the racemization process, could thus also be avoided.

Racemization of (*S*,*S*)-**3** was studied at 60 °C using the phosphide borane anion in DMSO, so that a baseline racemization rate for the parent system could be established. In order

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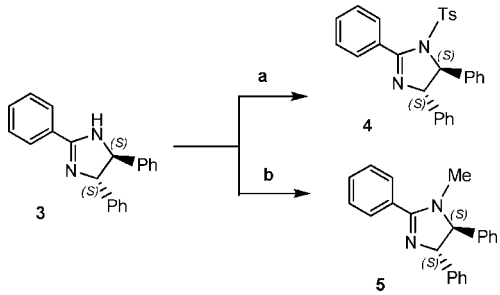
SCHEME 2. N-Substituted Imidazolines[a]



[a] Key: (a) TsCl, TEA, DCM, 64%; (b) KHMDS, MeI, 67%.

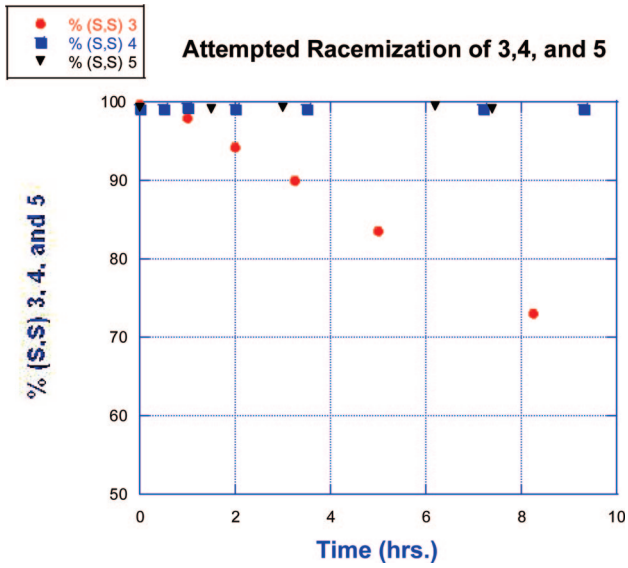


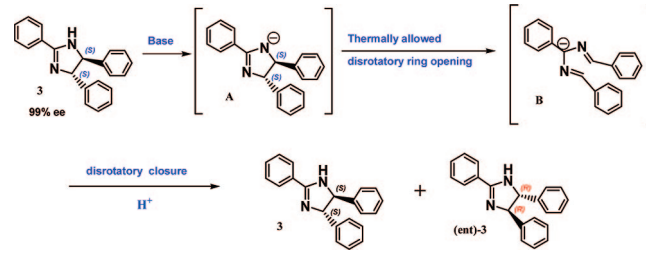
FIGURE 2. Racemization study of **3**−**5**.

to further understand the mechanism of racemization, two *N*-substituted chiral imidazolines, the sulfonamide **4** and methyl species **5**, were each prepared on one step (Scheme 2). Substrates **3**−**5** were then each independently subjected to the racemization conditions of the parent using the phosphide borane anion at 60 °C. Sulfonamide **4** suffered from some sulfonyl cleavage by phosphide borane under these conditions, yet the starting material was easily reisolated chromatographically for optical purity determination. The *N*-methyl species **5** did not degrade under the racemization conditions. The results for all three species are shown in Figure 2. Imidazoline **3** showed the expected time-dependent racemization, similar to the results in Figure 1. When the optical purities of isolated **4** and **5** were measured, we found that *these N-substituted species showed no racemization under the identical conditions used for* **3**.

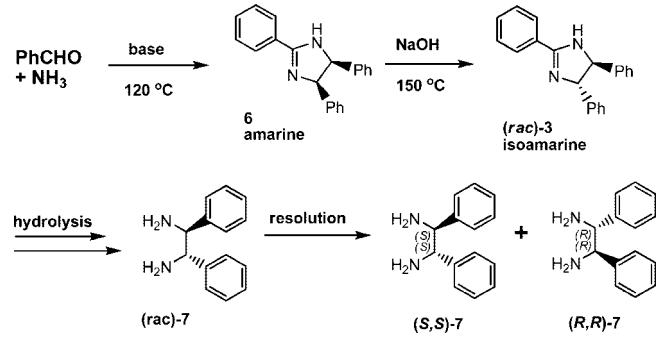
It was thus clear that introduction of any nitrogen substituent, even an electron-withdrawing one, completely suppressed the racemization process. Based on these results, we have therefore proposed the following symmetry-allowed process as a possible mechanism for imidazoline racemization (Scheme 3).

Deprotonation of imidazoline **3** by a strong base would produce anion **A**, which could lead to ring opening, generating diazadienyl anion **B** in a thermally allowed disrotatory process. This species would then undergo a disrotatory closure to furnish the observed mixture of enantiomers.[10a,d−f,11] Racemic **3** is also known as "isoamarine", and its synthesis starting with benzaldehyde and ammonia and proceeding through the *meso*-imidazoline **6** has been known for more than 150 years.[11h,i]

SCHEME 3. Proposed Racemization Mechanism



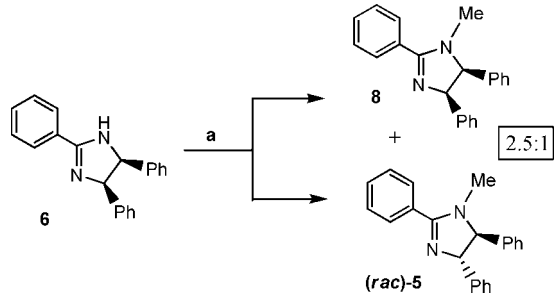
SCHEME 4. Route to DPEN, 7



Recent interest[10a,c,g,11g] in this venerable chemical reaction has focused not on the imidazoline as a target but on the hydrolysis of isoamarine to racemic 1,2-diphenylethylenediamine, **7** (DPEN, Scheme 4), as an inexpensive entry to this building block and its optical resolution. The kinetics and mechanism of formation of amarine have been studied in detail,[10d−f] and those results help drive our research as well. It was found that amarine, which is thermodynamically less stable than **3**, was formed under thermal conditions from an intermediate anion and that **3** was generated when the reaction was irradiated at 592 nm, the absorbance maximum of that anion. These results were found to be fully consistent with a thermally allowed disrotatory cyclization to give amarine and a photochemically allowed cyclization to give isoamarine.

This precedent certainly suggests that racemization of chiral imidazolines in the current work, which clearly requires anion formation to occur, likely involves the mechanistic reverse of the forward process. We had not, however, determined whether any of the *meso*-imidazoline **6** was generated in our racemization experiments. We thus prepared **6** from *meso*-DPEN and developed a chiral HPLC method capable of resolving (*S,S*)-**3**, (*R,R*)-**3**, and *meso*-**6**. We then repeated the time-dependent racemization experiment of Figure 2. No *meso*-**6** was observed at any time point, and spiking experiments showed that very low levels of **6** (<1%) could readily be quantitated. This result did not address the possibility that **6** had formed in the racemization experiment yet isomerized to *rac*-**3** too quickly to be observed, however. It was also unclear whether the isomerization process would be prevented by a *N*-substituent, as was observed with racemization. To address the latter, we alkylated *meso*-**6** with MeI, as shown in Scheme 5. A 2.5:1 mixture of desired *cis*-**8** to *rac*-**5** was formed, showing the ease with which isomerization can occur, even at ambient temperature. Heptane trituration of this 2.5:1 mixture afforded a 93:7 mixture, favoring *cis*-**8**. We next subjected both **6** and **8** (as the 93:7 mixture) to the identical conditions used in the racemization and plotted percent *meso* and *cis* as a function of time, as shown in Figure 3. The racemization data for (*S,S*)-**3** is included for comparison purposes. It can be seen that the isomerization of **6**

SCHEME 5. Synthesis of *cis*-8a



[a] Key: KHMDS, MeI, 20 °C, 99%.

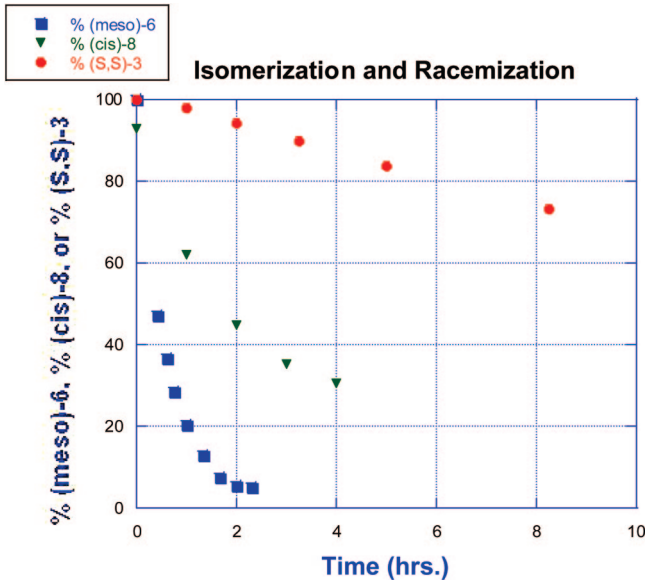
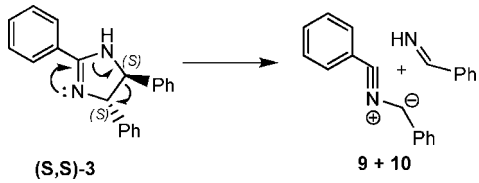


FIGURE 3. Isomerization of **6** and **8**.

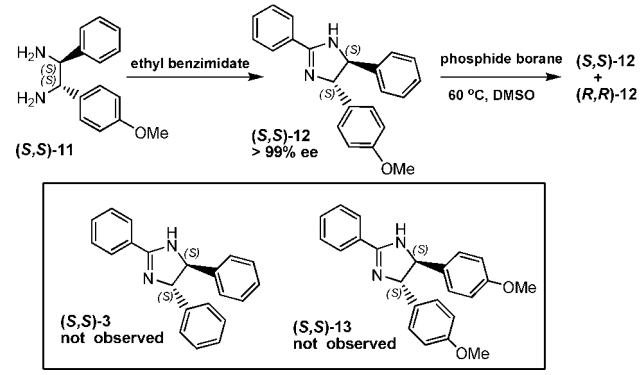
SCHEME 6. Nitrile Ylide Formation



from *cis* to *trans* with phosphide borane anion is more rapid than the racemization process, yet it is far from instantaneous. Fully 2 h was required to achieve complete isomerization. The *N*-alkylated species **8** isomerized at a similar rate. *Thus, isomerization, unlike racemization, takes place whether a N-substituent is present or not*. Therefore, these two processes are mechanistically distinct, and isomerization would not be expected to follow the apparent symmetry-controlled process of racemization. All of these results are therefore consistent with racemization proceeding by the symmetry-allowed process shown in Scheme 3.

Imidazolines have been prepared by cycloaddition of nitrile ylides with imine derivatives.[12] Fragmentation of the ring could thus conceivably occur as shown in Scheme 6. Recombination of fragments **9** and **10** might then lead to racemization. Another

SCHEME 7. Crossover Experiment



potential explanation for racemization can be imagined based on the known syntheses of diamines via imine dimerization. Alexakis,[13] Smith,[14] and Wotiz[15] have utilized the coupling of radical anions to make *N*,*N*′-disubstituted diamines from simple imines with low valent metals. Critically, it has been observed[14] that treatment of the dianions of these products, when the diamines are unsymmetric, leads to the "crossover" products, proving the intermediacy of radical anions. Any process such as this, or the one depicted in Scheme 5, that leads to complete scission of the imidazoline ring, should therefore be expected to yield crossover products in an unsymmetrical system.

We have previously described the synthesis of optically pure, non-C_2-symmetric diamines and their incorporation into chiral imidazolines.[1g] We therefore condensed one of these optically pure diamines, (*S,S*)-**11**, with ethyl benzimidate to furnish (*S,S*)-**12** as a stable, crystalline solid, as shown in Scheme 7. Our approach was to perform a crossover experiment with this nonsymmetric imidazoline and search for the crossover products **3** and **13**, the latter of which was readily prepared (one step) as an authentic standard. We subjected (*S,S*)-**12** to the identical racemization conditions previously described. After 12 h at 60 °C with the phosphide borane anion, the optical purity of (*S,S*)-**12** had been reduced to 30% ee. Analysis of the reaction mixture by both standard gradient C8 HPLC and chiral HPLC showed that absolutely none of the crossover imidazolines **3** or **13** were formed. These results, as well as all of those reported herein, are consistent with the symmetry-allowed process of Scheme 3.

With a working mechanistic model in place, we next examined the role of temperature on the racemization of imidazoline **3** with phosphide borane. The optical purities at six temperatures (25−65 °C) were determined under our standard conditions with phosphide borane in DMSO at two time points.

As shown in Table 1, there is an extreme temperature dependence on the racemization. At 65 °C, only 7 h exposure reduced the optical purity to 33%. When the reaction was held constant just above ambient temperature, at 25 °C, however, no decrease in optical purity was observed after 16 h. Opera-

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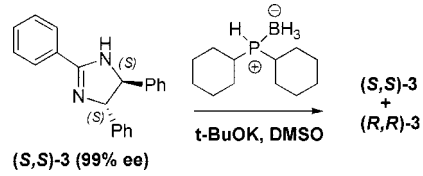
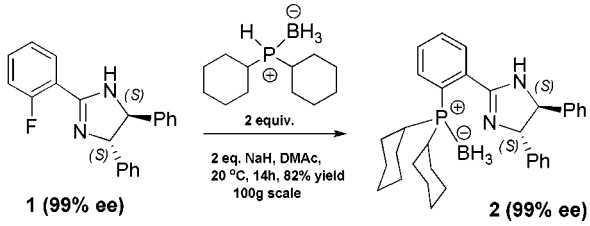
TABLE 1. Racemization of 3, 25−65 °C



entry	*T* (°C)	% ee	time (h)
1	25	99, 99	7, 16
2	45	85, 77	7, 16
3	50	72, 63	7, 16
4	55	64, 53	7, 16
5	60	47, 25	7, 16
6	65	33, 10	7, 16

SCHEME 8. Ambient Temperature S_NAr



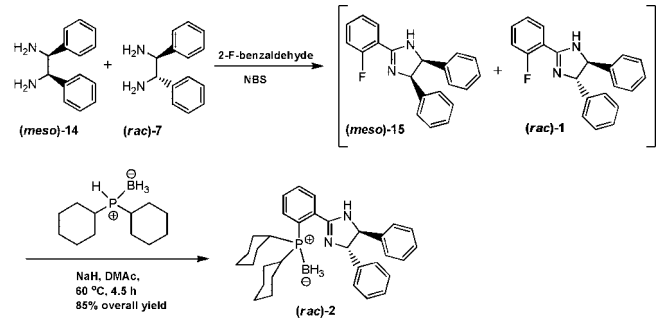
tionally then, only *brief* exposures at temperatures above ~30 °C can be tolerated.

These results proved critical to our subsequent development of a racemization-free S_NAr reaction.[1a] After some experimentation, we found we could carry out our desired phosphide borane S_NAr *at ambient temperature*, provided 2 equiv of the phosphide borane was employed (Scheme 8). In this way, more than 100 g of phosphine borane **2** were produced with 0% racemization, and S_NAr reactions on many different substrates have now been carried out successfully using this protocol, furnishing optically pure products.

One of the very significant advantages of the Alexakis[13] diamine syntheses is that the initial 1:1 mixture of *meso*- and *rac*-diamines produced is of no consequence, since the *meso*-diamine is efficiently isomerized to the *rac*-diamine by the low-valent metal. Simple resolution then provides the optically pure diamine. Although we believe our imidazoline syntheses to be mechanistically separate from the radical anion process, the Alexakis work and our racemization and isomerization results described here suggested an opportunity to effect a similar transformation. Optically pure 1,2-diphenylethylenediamine (DPEN) is readily available in bulk as both antipodes, and many optically pure diamines are now commercially available via the asymmetric diaza−Cope rearrangement of Chin.[16] However, many of these are not available in bulk, and more unusual chiral diamines are often not commercially available. By contrast, many diamines can be made as mixtures of *meso*- and *rac*- forms by inexpensive imine dimerization, as mentioned.[13a−c,17] We therefore felt that employing a mixture of *rac*- and *meso*-diamines in our imidazoline synthesis, followed by an S_NAr reaction that was deliberately performed at elevated temperature, should provide the pure (racemic) phosphine borane product.

As a test of this concept, we therefore first condensed equal quantities of *meso*-**14** and *rac*-**7** 1,2-diphenylethylendiamines

SCHEME 9. Utilization of Diamine Mixtures



with 2-fluorobenzaldehyde to generate the mixture of fluoroimidazolines *meso*-**15** + *rac*-**1** as shown in Scheme 9, using the procedure of Fujioka and Kita.[18] This mixture was then reacted with the phosphideborane anion at 60 °C and the reaction held at this temperature until substitution and isomerization were both complete by HPLC (4.5 h). As expected, racemic phosphinoimidazoline **2** was produced in high overall yield as a single geometric isomer. Optical resolution of this material by a number of methods could then furnish optically pure material.[10b,c] This methodology should prove particularly useful when ligands derived from diamines that are not commercially available, or are prohibitively expensive, are required, or when *both* enantiomeric ligands are needed for catalyst development.

Conclusions

In summary, the unexpected base-promoted racemization of optically pure imidazolines has been studied and found to depend principally on the base used and the reaction temperature. Amine bases cause no racemization, even at elevated temperatures, while inorganic bases in dipolar aprotic solvents such as DMSO and DMAc can lead to racemization. Chiral imidazolines can still be manipulated without racemization under these strongly basic conditions, provided that the temperature is ~30 °C or lower. Somewhat surprisingly, introduction of a substituent on the imidazoline nitrogen atom acts to protect the system from racemization, even at elevated temperature. These and other results are consistent with a racemization mechanism involving deprotonation followed by two symmetry-allowed disrotatory processes. An understanding of these mechanisms and the key process parameters surrounding racemization and isomerization have led to to the development of robust, racemization-free S_NAr reactions to produce the BIPI ligands, and these processes have been successfully demonstrated on multigram scale.

Experimental Section

Imidazoline (*S,S*)-3. A 250 mL flask was charged with 7.40 g of ethyl benzimidate (39.9 mmol, 1 equiv), 8.43 g of (*S,S*)-diamine DPEN (39.9 mmol, 1 eqiuv), and 50 mL of abs EtOH in the order given. The resulting slurry was stirred 1 h at rt and then heated to reflux. After 1 h, the mixture was cooled to rt, and then EtOH was removed in vacuo. To the resulting residue was added 100 mL of 1 N NaOH + 200 mL of EtOAc and the mixture stirred well for 5 min. The organic phase was washed with H_2O (1 × 100 mL) and then concentrated in vacuo to a light yellow solid. This solid was recrystallized from ~75 mL of boiling EtOAc. On cooling while

(17) For examples, see: (a) v. Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999. (b) Kise, N.; Ueda, N. *Tetrahedron Lett.* **2001**, *42*, 2365. For reviews, see: (c) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37* (19), 2580. (d) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

(18) (a) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63* (3), 638. (b) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46* (13), 2197.

standing, colorless needles were deposited. The solid was filtered, and air-dried on the frit for 20 min to give 9.10 g of imidazoline **3** (76% first crop yield) as a white, crystalline solid: mp 176−177 °C; $[\alpha]^{20}_D$ −31 (*c* 0.16, CH_2Cl_2); chiral HPLC (see below) shows >99% ee; ^{1}H (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2H), 7.72 (m, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.36−7.39 (m, 4H), 7.03−7.33 (m, 6H), 5.50 (br s, 1H), 4.91 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (s), 143.5 (s), 130.9 (d), 130.1 (s), 128.6 (d), 128.5 (d), 127.41(d), 127.35 (d), 126.5 (d), 74.4 (d); HRMS $[M + H]^+$ calcd for $C_{21}H_{18}N_2$ 299.1542, obsd 299.1550.

***N*-Tosylimidazoline (*S,S*)-4.** A three-neck 50 mL flask was charged with 1.00 g of (*S,S*)-**3** (3.35 mmol, 1 equiv), 639 mg of TsCl (3.35 mmol, 1 equiv), and 8.0 mL of CH_2Cl_2 in the order given. The resulting slurry was cooled to ∼5 °C, then 0.81 mL of TEA (6.70 mmol, 2 equiv) was added via syringe over ∼1 min, giving a thinner slurry. The bath was then removed, and the mixture allowed to warm to ambient temperature. After 4 h, HPLC showed 7% of **3** remained, so an additional 50 mg of TsCl was added. After 1 h, the volatiles were removed in vacuo and the residue partitioned between 50 mL of EtOAc and 25 mL of 0.5 N HCl. The organic phase was washed with satd NaCl (1 × 30 mL) and dried ($MgSO_4$), and the solvents were removed in vacuo to give a yellow oil. After standing for 24 h, the product crystallized. The solid was then recrystallized from boiling EtOAc. The solid thus obtained was filtered and air-dried on the frit for ∼20 min to give 0.96 g of (*S,S*)-**4** (64% recrystallized yield) as a white solid: mp 136−137 °C; $[\alpha]^{20}_D$ +151 (*c* 0.25, CH_2Cl_2); chiral HPLC (see below) shows >99% ee; ^{1}H (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.48 (m, 6H), 7.41 (m, 1H), 7.26 (m, 3H), 7.20 (t, J = 7.7 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 7.3 Hz, 2H), 5.15 (d, J = 4.5 Hz, 1H), 5.13 (d, J = 4.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6 (s), 144.5 (s), 142.4 (s), 141.7 (s), 134.9 (s), 131.1 (d), 130.5 (s), 129.8 (d), 129.5 (d), 129.1 (d), 128.6 (d), 128.2 (d), 127.8 (d), 127.7 (d), 127.3 (d), 126.0 (d), 125.9 (d), 77.3 (d), 72.4 (d), 21.5 (q); HRMS $[M + H]^+$ calcd for $C_{28}H_{24}N_2O_2S$ 453.1631, obsd 453.1649.

***N*-Methylimidazoline (*S,S*)-5.** A three-neck 100 mL flask was charged with 1.00 g of (*S,S*)-imidazoline **3** (3.36 mmol, 1 equiv) and then evacuated and Ar filled. Dry THF (15 mL) was then added via syringe, and the resulting solution was cooled to 5 °C under Ar. To this was added 7.06 mL of 0.5 M KHMDS/PhMe (3.53 mmol, 1.05 equiv) dropwise via syringe over ∼5 min. A thick slurry formed near the end of the addition. The bath was removed, and the mixture allowed to warm to rt. After 1.5 h at rt, a yellow slurry was present. MeI (0.22 mL, 3.53 mmol, 1.05 equiv) was added at once via syringe, causing a white slurry to form. After 2 h at rt, TLC (4:1 EtOAc/hexane) showed the reaction was complete to a more polar streak. The volatiles were then removed in vacuo under house vacuum to give a semisolid. These solids were then suspended in 25 mL of EtOAc, stirred vigorously for 5 min, and then filtered through a Celite pad to remove KI. The filtrate was evaporated under high vacuum to give 1.09 g of a yellow oil. This oil was chromatographed on silica gel eluting with EtOAc and then 10% MeOH/EtOAc to give 0.70 g of **5** (67%) as a yellow oil, which crystallized on standing: mp 60−61 °C; $[\alpha]^{20}_D$ +55 (c 0.14, CH_2Cl_2); chiral HPLC (see below) shows >99% ee; ^{1}H (500 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.50 (m, 3H), 7.31−7.43 (m, 10H), 5.01 (d, J = 9.8 Hz, 1H), 4.30 (d, J = 9.8 Hz, 1H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (s), 143.8 (s), 141.5 (s), 131.3 (s), 130.0 (d), 128.8 (d), 128.5 (d), 128.41 (d), 128.36 (d), 127.8 (d), 127.1 (d), 127.0 (d), 126.9 (d), 78.6 (d), 77.8 (d), 34.9 (q); HRMS $[M + H]^+$ calcd for $C_{22}H_{20}N_2$ 313.1699, obsd 313.1698.

Racemization Studies on (*S,S*)-3, (*S,S*)-4, and (*S,S*)-5 (Figure 2). A three-neck 100 mL flask containing a stir bar and equipped with a closable inert gas valve was charged with 467 mg of dicyclohexylphosphine borane (2.20 mmol, 2.2 equiv). The flask was then evacuated and Ar filled (3×), and then the gas valve was closed and the flask transferred to a N_2 glovebox. The flask was then charged with 248 mg of *t*-BuOK (2.20 mmol, 2.2 equiv), sealed, and removed from the glovebox. The flask was again evacuated and Ar filled (3×), and then 5.0 mL of DMSO was added via syringe. The resultant mixture was stirred for 30 min at ambient temperature, and then 298 mg of imidazoline (*S,S*)-**3** (1.00 mmol, 1 equiv), contained in a 1 dram vial, was added neat, at once, by quickly removing a septum. The flask was again evacuated and Ar filled (3×), then placed in a pre-equilibrated 60 °C oil bath under Ar. Aliquots (100 μL) were periodically removed via syringe and quenched into 1 mL 5 M NH_4Cl in 1 dram screw-cap vials. This mixture was then extracted with ∼2 mL of MTBE by brief shaking. The MTBE phase was then analyzed directly by chiral HPLC.

The identical stoichiometry, reaction concentration, and temperature were employed in the racemization studies using (*S,S*)-**4** and (*S,S*)-**5**. For the study with (*S,S*)-**5**, however, some sulfonamide hydrolysis occurred during the reaction. For this reason, further purification prior to the chiral HPLC analyses was required: The MTBE solution containing **5** was concentrated on the rotovap and then spotted heavily across the bottom of a standard 5 × 7 cm TLC plate and eluted in a TLC chamber using 1:1 hexane/EtOAc, like a "mini prep plate". The upper band (R_f 0.62), contained sulfonamide **5**, while the lower band (R_f 0.14) contained the cleavage product **3**. When the plate was dry, the upper band was scraped off with a razor blade and the silica extracted with ∼1 mL of MeOH by agitating in a 1 dram vial on a platform vibrator for several min. The resultant mixture was then filtered using a 0.5 μm syringe tip filter directly into an HPLC vial for analysis. Although dilute, chiral HPLC analyses were readily made by increasing the injection volume to 50 μL.

Chiral HPLC analysis of **3**: AGP, 4 × 150 mm, 5 μm particle size, 30 °C, 0.9 mL/min, isocratic with 80:20 A:B, where A = 0.1% HOAc in H_2O, buffered to pH 7 with NH_4OH using a digital pH meter, B = MeCN. Analysis wavelength 224 nm, 2 μL injection volume, retention times: (*R,R*)-**3**: 9.18 min, (*S,S*)-**3**: 10.86 min, *meso*-**6**: 10.15 min.

Chiral HPLC analysis of **4**: Chiralpak IA, 4.6 × 250 mm, 5 μm particle size, 20 °C, 1.0 mL/min, isocratic with 75:25 *n*-heptane/*i*-PrOH, analysis wavelength 220 nm, 5 μL injection volume, retention times: (*S,S*)-**4**: 9.24 min, (*R,R*)-**4**: 10.10 min.

Chiral HPLC analysis of **5**: Chiralpak AD-H, 4.6 × 250 mm, 5 μm particle size, 25 °C, 1.5 mL/min, isocratic with 90:10 A:B, where A = heptane, B = *n*-PrOH. Analysis wavelength 254 nm, 5.0 μL injection volume, retention times: (*R,R*)-**5**: 4.64 min, (*S,S*)-**5**: 5.69 min.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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