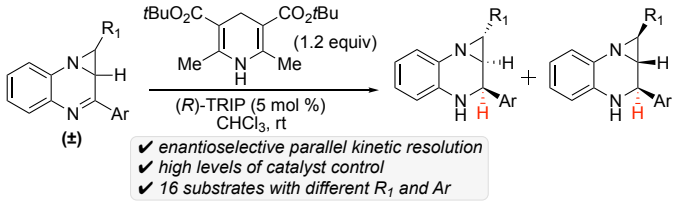
# Enantioselective Parallel Kinetic Resolution of Aziridine-Containing Quinoxalines via Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation

Yin-Jia Jhang,[†#] Oleksii Zhelavskyi,[†#] and Pavel Nagorny[†]*

[†]Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States

[#]These authors contributed equally to the manuscript

*Parallel Kinetic Resolution, Heterocycles, transfer hydrogenation, organocatalysis*

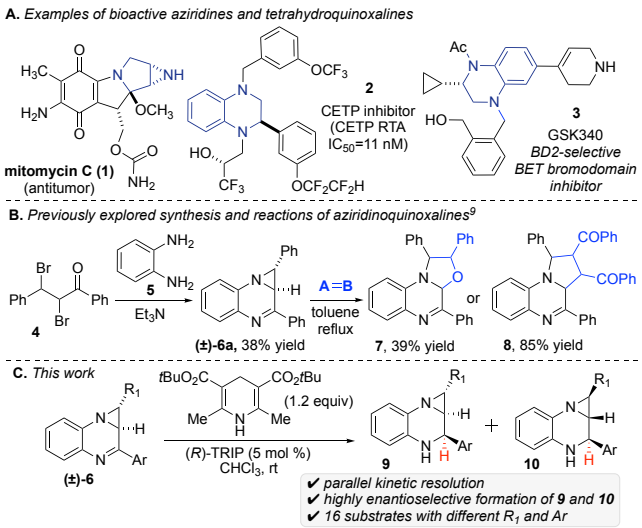



**ABSTRACT:** This manuscript describes asymmetric synthesis of chiral aziridinoquinoxalines using (*R*)-TRIP-catalyzed parallel kinetic resolution under transfer hydrogenation conditions. This resolution was successfully accomplished for 16 different substrates and led to highly enantioenriched diasteromers with (*R*)-configuration of the newly formed stereocenter (32-61% yield, 64-99% ee, for the (*R,R,R*)-diastereomers and 7-46% yield, 97-99% ee for the (*S,S,R*)-diastereomers). This process could be coupled with ring-opening of the (*S,S,R*)-diastereomer with thiophenol to produce chiral tetrahydroquinoxalines with three contiguous stereocenters.

Nitrogen-containing heterocycles are essential structural motifs present in a variety of biomolecules, natural products and pharmaceuticals.[1] Nitrogen-containing heterocycles have been of great importance to drug discovery, and their preparation and exploration has been a driving force for numerous recent studies in asymmetric synthesis and catalysis. The rich chemistry of the aziridine ring has attracted particular attention of the synthetic community.[2] The aziridine-containing substrates are key to the synthesis of nitrogen-containing compounds including cyclic and bicyclic nitrogen containing heterocycles, and numerous recent efforts have been focused on addressing various aspects associated with the synthesis and activation of the aziridine rings.[3]

In contrast to simple aziridines, only few asymmetric methods are available for the synthesis of the heterocyclic systems containing fused aziridine rings such as aziridinoquinoxaline **6** (Figure 1). The seminal studies by Gaunt and coworkers[4] have resulted in streamlined synthesis of fused aziridines via sp$^3$-C-H functionalization; however, no similar asymmetric methods are available for the synthesis of benzene ring-containing heterocycles such as **6**.[3,5] This is surprising considering that both the aziridine-containing compounds such as mitomycin C (**1**),[6] and compounds with tetrahydroquinoxaline motifs, such as the Merck CETP inhibitor **2**[7] and Glaxo-Smith-Klain BET bromodomain inhibitor GSK340 (**3**),[8] have been extensively explored in drug discovery (*cf.* Figure 1A). Although the racemic aziridinoquinaxoline (±)-**6** is readily accessible by a direct condensation of brominated chalcone **4** and 1,2-benzenediamine **5**, its reactivity is not well-defined, and only few reactions of **6** leading to cycloadducts such as **7** and **8** have been reported in the literature (Figure 1B).[9]

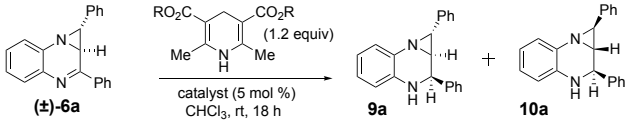
**Figure 1**



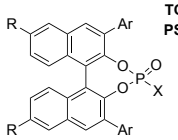

Our group has long-standing interest in developing asymmetric methods for accessing chiral oxygen- and

nitrogen-containing heterocyclic systems.[10] Our recent work highlighted the use of immobilized chiral phosphoric acid, PS-Ad-TRIP, for continuous flow asymmetric transfer hydrogenation of quinolines, 2*H*-1,4-benzoxazines, and 2*H*-1,4-benzoxazin-2-ones.[10d,11] Interested in extending these transformations to more complex heterocyclic systems **6**, we investigated the possibility of achieving asymmetric synthesis of chiral aziridinoquinoxalines **9** and **10** from the readily available racemic materials **(±)-6** via parallel kinetic resolution (Figure 1C). Chiral phosphoric acids have been previously used to achieve kinetic[12] and dynamic kinetic[13] resolutions; however, successful examples of utilizing these transformations for the CPA-catalyzed parallel kinetic resolution of racemic imines via transfer hydrogenation has not been realized. The aziridine ring present in **(±)-6** next to the prochiral center presents a significant obstacle for achieving catalyst-based control, and a successful parallel kinetic resolution protocol involving **(±)-6** requires overcoming this inherent challenge. This manuscript presents our development of highly selective parallel kinetic resolutions using commercially available catalyst (*R*)-TRIP. This process leads to novel chiral scaffolds **9** and **10** with excellent selectivities and could be used to produce complex quinoxaline derivatives **11** and **12** containing three contiguous stereocenters, which are not readily available by other methods.[14,15]

**Table 1. Catalyst evaluation for the parallel kinetic resolution of (±)-6a.**[a]




| entry | catalyst | R | d.r. | 9a, yield (%) | 9a, ee (%) |
|---|---|---|---|---|---|
| 1 | BPPA | Et | 34 :1 | 76 | 0 |
| 2 | BPPA | *t*-Bu | 14.4 :1 | 61 | 0 |
| 3 | (*R*)-**1a** | *t*-Bu | 1.0 : 0 | 49 | 19 |
| 4 | (*R*)-**1b** | *t*-Bu | 1.0 : 0 | 54 | 8 |
| 5[b] | (*S*)-**1c** | *t*-Bu | 1.0 : 0 | 36 | 12 |
| 6[b] | (*S*)-**1d** | *t*-Bu | 9.5 : 1 | 58 | 36 |
| 7 | (*R*)-TRIP | Et | 2.9 :1 | 61 | 85 |
| 8 | (*R*)-TRIP | *t*-Bu | 2.1 :1 | 46 | 93 |
| 9 | (*R*)-TCYP | *t*-Bu | 2.5 : 1 | 40 | 89 |
| 10 | (*R*)-PS-Ad-TRIP | *t*-Bu | 2.0 : 1 | 55 | 81 |
| 11 | (*R*)-**1e** | *t*-Bu | 2.3 : 1 | 42 | 78 |
| 12 | (*R*)-**1f** | *t*-Bu | 6.6 : 1 | 53 | 49 |

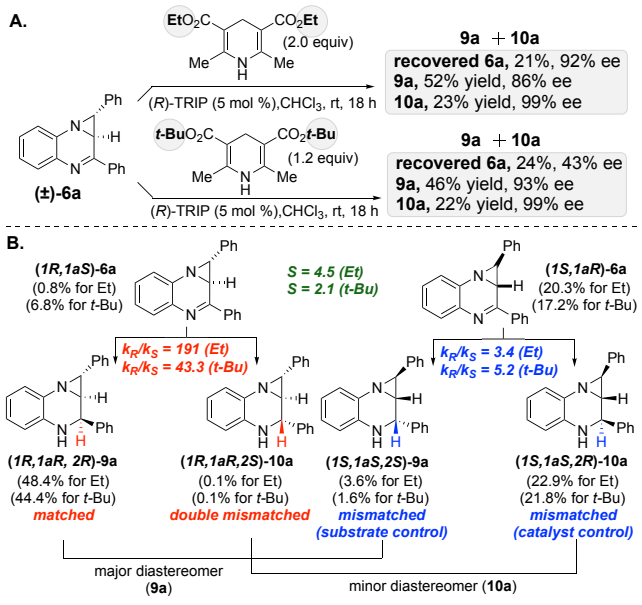



**TRIP**, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R = H, X = PO$_2$H
**TCYP**, Ar = 2,4,6-(Cy)$_3$C$_6$H$_2$, R = H, X = PO$_2$H
**PS-Ad-TRIP**, Ar = 2,6-(*i*-Pr)$_2$-4-(Ad)-C$_6$H$_2$, R = Styryl, X = PO$_2$H
**1a**, Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$, R = H, X = PO$_2$H
**1b**, Ar = 3,5-(*i*-Pr)$_2$C$_6$H$_3$, R = H, X = PO$_2$H
**1c**, Ar = 3,5-(*t*-Bu)$_2$C$_6$H$_3$, R = H, X = PO$_2$H
**1d**, Ar = C$_6$F$_5$, R = H, X = PO$_2$H
**1e**, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R = NO$_2$, X = PO$_2$H
**1f**, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R = H, X = PO(NHTf)

[a]All of the reactions were carried on 100 μmol scale in 2 mL of the solvent. The enantioselectivity was determined by chiral HPLC analysis. [b](*1S,1aS,2S*)-enantiomer of **9a** was favored.

Our studies commenced with subjecting known aziridinoquinoxaline **(±)-6a** to the standard ethyl- and *t*-butyl-substituted Hantzsch esters in the presence of 5 mol% of achiral biphenyl hydrogen phosphate (BPPA) as the catalyst at room temperature (entries 1 and 2, Table 1). Both reaction conditions led to highly diastereoselective reduction of **(±)-6a,** providing **9a** as the major product along with only trace amounts of **10a** (76% yield, 34:1 d.r. for R=Et, and 61% yield, 14.4:1 d.r. for X=*t*-Bu). These results suggested that there is a significant impact of the 3-membered ring situated next to the imine functionality, and that the reduction is inherently preferred from the face opposite to the aziridine moiety. Our subsequent studies were focused on exploring various chiral phosphoric acids as the catalysts that override this inherent substrate bias and dictate the reduction selectivity thus resulting in parallel kinetic resolution of two enantiomeric forms **6** leading to both **9** and **10**. The exploration of (*R*)-BINOL-based CPAs containing *meta*-substituted 3,3'-aryl groups with *t*-butyl substituted Hantzsch ester resulted in slow, but selective formation of **9a** and no diastereomer **10a** was observed (entries 3-5). The moderate enantioselectivities (19% ee for Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$, 8% ee for Ar = 3,5-(*i*-Pr)$_2$C$_6$H$_3$, and 12% ee for Ar = 3,5-(*t*-Bu)$_2$C$_6$H$_3$ coupled with the exclusive formation of **9a** indicate that these reductions proceed under substrate control and the catalyst chirality has little impact on the facial selectivity of the reduction. Similarly, the reaction with pentafluorophenyl substituted catalyst **1d** (entry 6) favored the formation of **9a** (9.5:1 d.r., 58% yield, 36% ee). In contrast, the exploration of (*R*)-TRIP CPA containing 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ groups at the 3,3'-positions of the BINOL scaffold led to the significant improvement in enantioselectivity of **9a** (entries 7 and 8). Thus, with (*R*)-TRIP as the catalyst, the reduction of **(±)-6a** with the ethyl-substituted Hatzsch ester produced **9a** in 85% ee, 61% yield and 2.9:1 d.r. (entry 7).

**Scheme 1. Detailed analysis of parallel kinetic resolution of (±)-6a leading to 9a and 10a.**



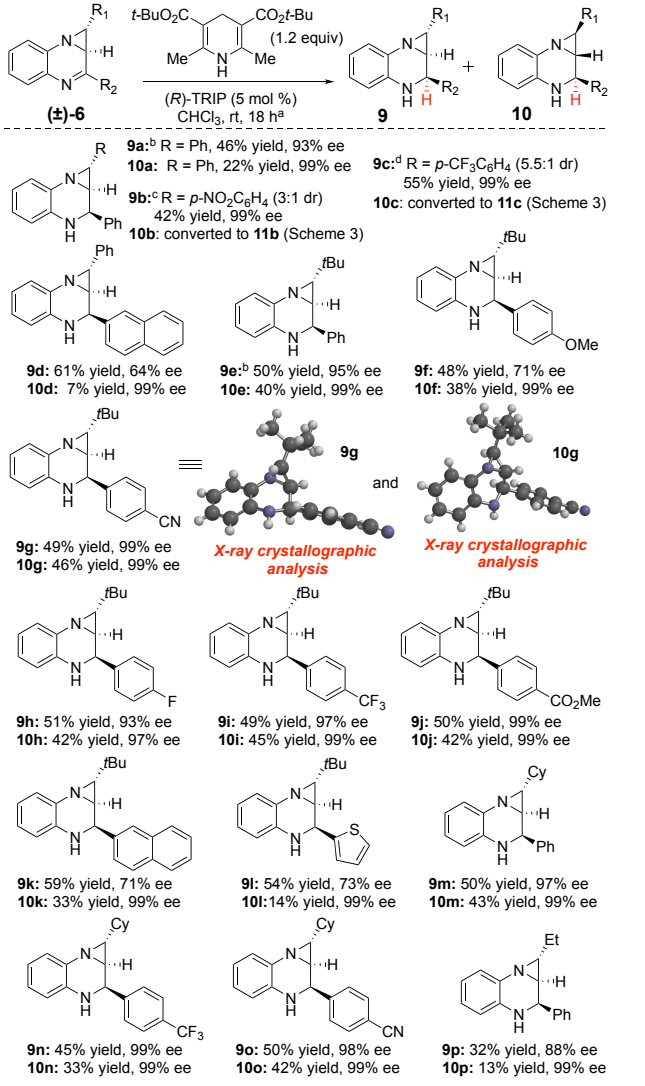

The use of *t*-butyl (instead of ethyl) Hantzsch ester has resulted in a slower, but more selective reaction yielding 46% of **9a** in 93% ee, and 2.1:1 d.r. (entry 8). With these results in hand, our further efforts focused on evaluating variants of TRIP (entries 9-12) that included using TCYP, PS-Ad-TRIP,[10e] 6,6'-dinitrosubstituted TRIP (**1e**) as well as *N*-triflyl phosphoramidate catalyst **1f**. These further attempts did not lead to the improvements in the enantioselectivity

of this reaction and the subsequent studies were carried out with standard TRIP catalyst.

The observed results for the (*R*)-TRIP-catalyzed reduction suggest that not only product **9a**, but also diastereomer **10a** and starting material **6a** may undergo enantioenrichment. Indeed, a more detailed analysis of the reaction mixture (*cf.* Scheme 1A) indicated that the reduction with ethyl substituted Hantzsch ester (2 equiv.) resulted in enantioenriched **6a** (21% yield, 92% ee), **9a** (52% yield, 86% ee) and **10a** (23% yield, 99% ee). Similarly, the use of the *t*-butyl substituted Hantzsch ester (1.2 equiv.) also resulted in enantioenriched **6a** (24% yield, 43% ee), **9a** (46% yield, 93% ee), and **10a** (22% yield, 99% ee). Based on the X-ray crystallographic analysis of the related derivatives **9g** and **10g** (Scheme 2), and prior observations for the transfer hydrogenation of quinolines and quinoxalines with (*R*)-enantiomer of CPA,[11,16] the stereoisomer distribution summarized in Scheme 1B was calculated. (*R*)-TRIP favors formation of (*R*)-configuration at the newly formed stereocenter. In the case of substrate **(*1R,1aS*)-6a**, the selectivity imposed by (*R*)-TRIP could be matched with the selectivity imposed by the aziridine ring, and the resultant product **(*1R,1aR,2R*)-9a** is expected to be the most favored product among the four potential stereoisomers formed in this reaction. In contrast, the reduction from the *Si*-face would provide a double mismatched product **(*1R,1aR,2S*)-10a**, which is observed in only trace quantities in both cases. Therefore, the formation of **(*1R,1aR,2R*)-9a** and **(*1R,1aR,2S*)-10a** from **(*1R,1aS*)-6a** proceeds with significant rate differences ($k_{(1R,1aR,2R)}$/ $k_{(1R,1aR,2S)}$ = 191 for ethyl and 43.3 for *t*-butyl Hantzsch esters). In contrast, the reduction of the enantiomer **(*1S,1aR*)-6a** has a mismatch between the catalyst-imposed and substrate-imposed selectivities. The observed selectivities suggest that the catalyst-controlled product **(*1S,1aS,2R*)-10a** formation is favored over the substrate-controlled formation of **(*1S,1aS,2S*)-9a** ($k_{(1S,1aS,2R)}$/ $k_{(1S,1aS,2S)}$ = 3.4 for ethyl and 5.2 for *t*-butyl Hantzsch esters). Consistent with this model, **(*1R,1aS*)-6a** enantiomer is more reactive than **(*1S,1aR*)-6a**, and kinetic resolution of these enantiomers is also observed under the reduction conditions (S = 4.5 for ethyl Hantzsch ester, and S = 2.1 for *t*-butyl Hantzsch ester).

Using the optimal conditions for the parallel kinetic resolution (entry 6, Table 1), our subsequent studies focused on exploring the substrate scope (Scheme 2). In addition to **9a/10a**, the reduction conditions could be used to produce *1a-p*-nitrophenyl-substituted products **9b/10b** and *1a-p*-trifluoromethyl-substituted products **9c/10c**. The mixtures of **9b/10b** and **9c/10c** could not be readily separated by flash chromatography, and one-pot functionalization protocol converting **10b** and **10c** to produce easily separable **11b** and **11c** was used to carry out the analysis (*cf.* Scheme 3). Remarkably, the introduction of electronwithdrawing groups resulted in significant enantioselectivity enhancement, and products **9b**, **11b**, and **9c** and **11c** were obtained with excellent enantioselectivities (99% ee). In contrast, the introduction of the C2-β-naphthyl substituent in substrate **6d** resulted in a significant selectivity erosion for the major diastereomeric product **9d** (61% yield, 64% ee). The formation of the diastereomer **10d** was slower, but still happened with excellent enantioselectivity (7% yield, 99% ee). The previously unknown substrates **6e-6l** carrying the *t*-butyl substitution at the aziridine ring were explored next. It is noteworthy that the significant steric bulk exhibited by the *t*-butyl group did not impact the balance between the catalyst vs. substrate control, and products **9** and **10** were obtained in excellent selectivities and yields and were readily separable by column chromatography for the subsequent analysis. Thus, C2-phenyl substituted products **9e** and **10e** were obtained in 50% yield (95% ee) and 40% yield (99% ee), correspondingly. The introduction of the *p*-methoxyphenyl substituent at the C2-position of the quinoxaline ring resulted in a significantly lower selectivity, and diastereomer **9f** was isolated in 48% yield, and 71% ee, while **10f** was formed in 38% yield and 99% ee.

**Scheme 2. Substrate scope for the parallel kinetic resolution of of (±)-8 leading to 9 and 10.**

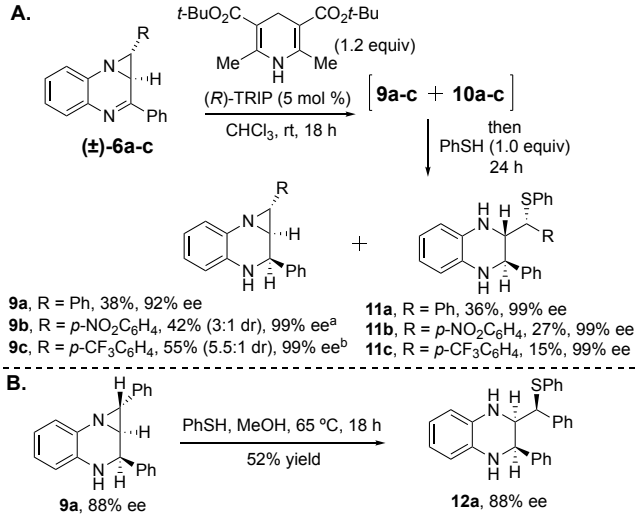



[a]The reactions were run on 100 μmol scale using Hatzsch ester (1.2 equiv) 5 mol% of (*R*)-TRIP in $CHCl_3$ for 18 h. [b]The reactions with **6a** and **6e** were performed on 1.0 mmol scale. [c]The inseparable crude mixture of **9b** and **10b** was subjected to one-pot resolution with PhSH (*cf.* Scheme 3A). The resultant product was obtained as a 3:1 mixture of **9b:10b** along with 27%, 99% ee of functionalized product **11b** resulting from **10b**. [d]The

inseparable crude mixture of **9c** and **10c** was subjected to one-pot reaction with PhSH (*cf.* Scheme 3A). The resultant product was obtained as a 5.5:1 mixture of **9c:10c** along with 15%, 99% ee of ring-opening product **11c** resulting from **10c**.

At the same time, the diastereomer **10e** was produced in 40% yield and excellent selectivity (99% ee). In contrast, placing electron-withdrawing groups such as cyano-, fluoro-, trifluoromethyl- or carbomethoxy onto the C2-phenyl substituent had a beneficial effect, and substrates **9g–9j** were obtained with good yields and excellent enantioselectivities (49%-51% yield, 93–99% ee). Similarly, minor diastereomers **10g–10j** were obtained in 42–46% yield and 97–99% ee. Importantly, the structures of the reduction products **9g** and **10g** were confirmed by the X-ray crystallographic analysis, and their absolute and relative configurations were consistent with the model depicted in Scheme 1. As in the case of substrate **6d**, changing the C2-substitution to the β-napthyl (**6k**) or 2-thiophenyl (**6l**) groups resulted in eroded selectivity for the formation of major diastereomers **9k** (59% yield, 71% ee), and **9l** (54% yield, 73% ee); however, **10k** and **10l** were still formed with excellent selectivity (99% ee). The use of previously unknown cyclohexyl-substituted substrates **6m-6o** resulted in excellent yields and selectivities for both diastereomers (45-50% yield, 97-99% ee for **9m-9o**, and 33-43% yield, 99% ee for **10m-10o**). Finally, subjecting ethyl-substituted substrate **6p** led to the formation of overlapping products **9p/10p** in good enantioselectivities (88% ee and 99% ee) and 32% yield and 13% yield, correspondingly. These results suggest that this resolution method is tolerant to the structural modifications at the aziridine ring; however, the selectivity for the formation of diastereomer **9** depended on the nature of the C2-substituent. At the same time, the selectivity for the formation of **10** was independent on the substitution, and all products **10** were obtained with excellent selectivities (97-99%).

**Scheme 3. Exploring the reactivity of 9 and 10 with thiophenol.**




The DFT studies of diastereomers **9a** and **10a** (*cf.* SI-section III), suggest that diastereomer **10a** carries excessive strain energy (1.5 kcal/mol) relative to **9a**. Surmising that this feature might be used to selectively functionalize **10** and thus simplify the purification of the mixtures of **9** and **10**, we investigated the possibility of a selective one-pot parallel kinetic resolution leading to **9** and **11** (Scheme 3A). Indeed, the aryl-substituted aziridines **10a-10c** were found to be significantly more reactive with thiophenol than their diastereomers **9a-9c**. Thus, simple addition of thiophenol to the reaction mixture at the end of the reduction leads to quantitative and selective formation of the ring-opened product **11a** in 99% ee. The resulting reaction mixture could be conveniently purified to separate **9** from **11**. It is also noteworthy that major diastereomer **9a** could also undergo a ring-opening reaction with thiophenol to produce diastereomeric product **12** (Scheme 3B); however, this is a significantly slower process that requires elevated temperature (65 ºC). To the best of our knowledge, this is the first example for the formation of chiral quinoxialines such as **11** or **12** and that contain three contiguous stereocenters, and our protocol offers a streamlined synthesis of such compounds from the readily available materials and catalysts.

In summary, a highly selective parallel kinetic resolution leading to valuable and previously unknown aziridinoquinoxalines **9** and **10** from readily available racemic fused heterocycles **6** has been developed. This resolution was achieved using transfer hydrogenation conditions with the Hantzsch ester and commercially available (*R*)-TRIP as the catalyst. The use of (*R*)-TRIP CPA was essential for overcoming the selectivity imposed by the aziridine ring. The detailed analysis of the product and starting material distribution suggests a complex interplay of the catalyst- and substrate-imposed factors effecting the enantio- and diastereoselectivities. Thus, a highly enantioselective formation of the diastereomer **10** (97-99% ee) was observed in all cases as the enantiomer **(*1R,1aR,2S*)-10** would result from a double mismatched reaction. Similarly, high enantioselectivities for **9** (64-99% ee) are due to the faster formation of the double-matched enantiomer **(*1R,1aR,2R*)-9** in comparison to the mismatched enantiomer **(*1S,1aS,2S*)-9**, which suffers from the opposing catalyst and substrate-dictated selectivities. The chiral aziridinoquinoxalines could be readily functionalized by reactions with thiophenol to produce previously inaccessible tetrahydroquinoxalines **11** and **12** containing three contiguous stereocenter.[17]

## ASSOCIATED CONTENT

**Data Availability Statement**. The data underlying this study are available in the published article and its supporting information.

**Supporting Information Statement**. The experimental procedures and crystallographic, computational and NMR data for starting materials and products are available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION


### Corresponding Author

* nagorny@umich.edu



### Funding Sources

P.N. is thankful to NSF grant CHE-1955069 and O.Z. is thankful to the Rackham Predoctoral Fellowship for supporting these studies.

## REFERENCES


1) Heravi, M. M.; Zadsirjan, V. "Prescribed drugs containing nitrogen heterocycles: an overview" *RSC Adv. Synth* **2020**, *10*, 44247.

2) (a) Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G. "Recent advances in the asymmetric synthesis of pharmacology-relevant nitrogen heterocycles via stereoselective aza-Michael reactions" *Org. Biomol. Chem*. **2019**, *17*, 3670; (b) Yu, J.; Chen, D.-F.; Gong, L.-Z. "Organocatalytic asymmetric synthesis of chiral nitrogenous heterocycles and natural products" *Pure Appl. Chem*. **2014**, *86*, 1217; (c) Magriotis, P. A. "Recent progress towards the asymmetric synthesis of carbon-substituted piperazine pharmacophores and oxidative related heterocycles" *RSC Med. Chem*. **2020**, *11*, 745.

3) (a) Salimi, F.; Karbakhshzade, A.; Salehi, N. "A review on recent approaches to the asymmetric synthesis of aziridine derivatives" *J. Chem. Lett.* **2021**, *2*, 56; (b) Degennaro, L.; Trinchera, P.; Luisi, R. "Recent advances in the stereoselective synthesis of aziridines" *Chem. Rev*. **2014**, *114*, 7881; (c) Singh, G. S. "Synthetic aziridines in medicinal chemistry: a mini-review" *Mini Rev. Med. Chem*. **2016**, *16*, 892.

4) (a) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. "Palladium-catalysed C-H activation of aliphatic amines to give strained nitrogen heterocycles" *Nature* **2014**, *510*, 129; (b) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. "Palladium-catalyzed enantioselective C-H activation of aliphatic amines using chiral anionic BINOL-phosphoric acid ligands" *J. Am. Chem. Soc.* **2017**, *139*, 1412.

5) (a) Zhang, M.; Wang, Q.; Peng, Y.; Chen, Z.; Wan, C.; Chen, J.; Zhao, Y.; Zhang, R.; Zhang, A. Q. "Transition metal-catalyzed $sp^3$ C-H activation and intramolecular C-N coupling to construct nitrogen heterocyclic scaffolds" *Chem. Commun.* **2019**, *55*, 13048; (b) Qiu, M.; Fu, X.; Fu, P.; Huang, J. "Construction of aziridine, azetidine, indole and quinoline-like heterocycles via Pd-mediated C-H activation/annulation strategies" *Org. Biomol. Chem*. **2022**, *20*, 1339.

6) Ismail, F. M. D.; Levitsky, D. O.; Dembitsky, V. M. "Aziridine alkaloids as potential therapeutic agents" *Eur. J. Med. Chem*. **2009**, *44*, 3373.

7) Wilson, J. E. et al. "Discovery of novel indoline cholesterol ester transfer protein inhibitors (CETP) through a structure-guided approach" *ACS Med. Chem. Lett*. **2016**, *7*, 261.

8) Law, R. P.; Atkinson, S. J.; Bamborough, P.; Chung, C.; Demont, E. H.; Gordon, L. J.; Lindon, M.; Prinjha, R. K.; Watson, A. J. B.; Hirst, D. J. "Discovery of tetrahydroquinoxalines as bromodomain and extra-terminal domain (BET) inhibitors with selectivity for the second bromodomain" *J. Med. Chem*. **2018**, *61*, 4317.

9) (a) Heine, H. W.; Henzel, R. P. "Aziridines. XXI. The 1,4-diazabicyclo[4.1.0]hept-4-enes and 1,1a-dihydro-1,2-diarylazirino[1,2-a]quinoxalines" *J. Org. Chem.* **1969**, *34*, 171; (b) Zbruyev, A. I.; Vashchenko, V. V.; Andryushchenko, A. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Chebanov, V. A. "Synthesis of polyarene derivatives of fused aziridines by Suzuki-Miyaura cross-coupling" *Tetrahedron* **2007**, *63*, 4297; (c) Orlov, V. D.; Vorob'eva, N. P.; Tishchenko, A. A.; Pikalev, O. M.; Popov, V. I.; Yaupol'skii, L. M. "Aziridinyl ketones and their cyclic anils. 11.* Fluorine-containing photochromes" *Chem. Heterocycl. Comp.* **1991**, *27*, 942; (d) Chebanov, V. A.; Zbruyev, A. I.; Desenko, S. M.; Orlov, V. D.; Yaremenko, F. G. "Three-membered azaheterocycles based on a,b-unsaturated ketones" *Curr. Org. Chem.* **2008**, *12*, 792; (e) Muzalevskiy, V. M.; Rulev, A. Y.; Kondrashov, E. V.; Romanov, A. R.; Ushakov, I. A.; Chertkov, V. A.; Nanajdenko, V. G. "Multichannel reactions of a-bromoenones with 1,2-diamines: synthesis of 1,4-diazabicyclo[4.1.0]hept-4-enes by reactions with N-unsubstituted 1,2-diamines" *Eur. J. Org. Chem*. **2016**, *8*, 11612.

10) (a) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. "Chiral phosphoric acid-catalyzed enantioselective and diastereoselective spiroketalizations" *J. Am. Chem. Soc.* **2012**, *134*, 8074; (b) Sun, Z.; Winschel, G. A.; Zimmerman, P. M.; Nagorny, P. "Enantioselective synthesis of piperidines through the formation of mixed chiral phosphoric acid acetals: experimental and theoretical studies" *Agew. Chem. Int. Ed.* **2014**, *53,* 11194; (c) Sun, S.; Nagorny, P.* "Exploration of chiral diastereomeric spiroketal (SPIROL)-based phosphinite ligands in asymmetric hydrogenation of heterocycles" *Chem. Commun.* **2020**, *56*, 8432; (d) Zhelavskyi, O.; Jhang, Y.-J.; Nagorny, P. "Asymmetric transfer hydrogenation of heterocyclic compounds in continuous flow using an immobilized chiral phosphoric acid as the catalyst" *Synthesis* **2023**, *55*, 2361.

11) For the original report refer to: Rueping, M.; Antonchick, A. P.; Theissmann, T. "A highly enantioselective Bronsted acid catalyzed cascade reaction: organocatalytic transfer hydrogenation of quinolines and their application in the synthesis of alkaloids" *Angew. Chem., Int. Ed*. **2006**, *45*, 3683.

12) Related kinetic resolutions: (a) Saito, K.; Shibata, Y.; Yamanaka, M.; Akiyama, T. "Chiral phosphoric acid-catalyzed oxidative kinetic resolution of indolines based on transfer hydrogenation to imines" *J. Am. Chem. Soc*. **2013**, *135*, 11740; (b) Saito, K.; Miyashita, H.; Akiyama, T. "Chiral phosphoric acid catalyzed oxidative kinetic resolution of cyclic secondary amine derivatives including tetrahydroquinolines by hydrogen transfer to imines" *Chem. Commun*. **2015**, *51*, 16648; (c) Wang, J.; Chen, M.-W.; Ji, Y.; Hu, S.-B.; Zhou, Y.-G. "Kinetic resolution of axially chiral 5- or 8-substituted quinolines via asymmetric transfer hydrogenation" *J. Am. Chem. Soc.* **2016**, *138,* 10413; (d) Saito, K.; Akiyama, T. "Chiral phosphoric acid catalyzed kinetic resolution of indolines based on a self-redox reaction" *Angew. Chem. Int. Ed*. **2016**, *55*, 3148.

13) Related transfer hydrogenation-based dynamic kinetic resolutions: (a) Han, Z.-Y.; Xiao, H.; Gong, L.-Z. "Dynamic kinetic asymmetric transfer hydrogenation of racemic 2,4-diaryl-2,3-dihydrobenzo[*b*][1,4]diazepines catalyzed by chiral phosphoric acids" *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3729; (b) Chen, M.-W.; Cai, X.-F.; Chen, Z.-P.; Shi, L.; Zhou, Y.-G. "Facile construction of three contiguous stereogenic centers via dynamic kinetic resolution in asymmetric transfer hydrogenation of quinolines" *Chem. Commun*. **2014**, *50*, 12526; (c) Horiguchi, K.; Yamamoto, E.; Saito, K.; Yamanaka, M.; Akiyama, T. "Dynamic kinetic resolution approach for the asymmetric synthesis of tetrahydrobenzodiazepines using transfer hydrogenation by chiral phosphoric acids" *Chem. Eur. J.* **2016**, *22*, 8078; (d) Mori, K.; Itakura, T.; Akiyama, T. "Enantiodivergent atroposelective synthesis of chiral biaryls by asymmetric transfer hydrogenation: chiral phosphoric acid catalyzed dynamic kinetic resolution" *Angew. Chem. Int. Ed.* **2016**, *55*, 11642.

14) (a) Zhang, Z.; Du, H. "A highly cis-selective and enantioselective metal-free hydrogenation of 2,3-disubstituted quinoxalines" *Angew. Chem. Int. Ed.* **2014**, *54*, 623; (b) Li, S.; Meng, W.; Du, H. "Asymmetric transfer hydrogenations of 2,3-disubstituted quinoxalines with ammonia borane" *Org. Lett.* **2017**, *19*, 2604; (c) Huang, J.; Li, G.; Yang, G.; Fu, D.; Nie, X.; Cui, X.; Zhao, J.; Tang, Z. "Catalytic asymmetric synthesis of N-substituted tetrahydroquinoxalines via regioselective Heyns rearrangement and stereoselective transfer hydrogenation in one pot". *Chem. Sci.* **2021**, *12*, 4789; (d) Luo, Z.; Li, Z.; Zhao, H.; Yang, J.; Xu, L.; Lei, M.; Fan, Q.; Walsh, P. J. "Borane-catalyzed tandem cyclization/hydrosilylation towards enantio- and diastereoselective construction of trans-2,3-disubstituted-1,2,3,4-tetahydroquinoxalines" *Angew. Chem. Int. Ed.* **2023**, *8*, e202305449; (e) Liu, C.; Liu, X.; Liu, Q. "Stereodivergent asymmetric hydrogenation of quinoxalines" *Chem* **2023**, *9*, 2585.

15) Asymmetric synthesis of related tricyclic derivatives: Chen, Y.; He, Y.-M.; Zhang, Miao, T.; Fan, Q.-H. "Rapid construction of structurally diverse quinolizidines, indolizidines, and their analogues via ruthenium-catalyzed asymmetric cascade" *Angew. Chem. Int. Ed.* **2018**, *58*, 3809.

16) Rueping, M.; Tato, F.; Schoepke, F. R. "The first general, efficient and highly enantioselective reduction of quinoxalines and quinoxalinones" *Chem. Eur. J*. **2010**, *16*, 2688.

17) A preprint of this manuscript has been available through ChemRxiv since September 21, 2023: Jhang, Y.-J.; Zhelavskyi, O.; Nagorny, P. "Enantioselective Parallel Kinetic Resolution of Aziridine-Containing Quinoxalines via Chiral Phosphoric Acid-Catalyzed Transfer Hydrogenation" *ChemRxiv* **2023**, DOI: 10.26434/chemrxiv-2023-gfwir