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Chiral Phosphoric Acid-Catalyzed Oxidative Kinetic Resolution of Indolines Based on Transfer Hydrogenation to Imines

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Supporting Information

ABSTRACT: The oxidative kinetic resolution of 2-substituted indoline derivatives was achieved by hydrogen transfer to imines by means of a chiral phosphoric acid catalyst. The oxidative kinetic resolution was applicable to racemic alkyl- or aryl-substituted indolines, and the remaining indolines were obtained in good yields with excellent enantioselectivities.

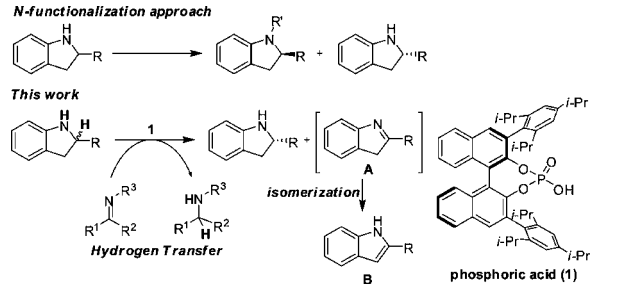
Enantiomerically pure compounds are key components of pharmaceuticals and agrochemicals.[1] The development of new methods for the asymmetric synthesis of chiral skeletons has therefore captured the attention of synthetic organic chemists.[2] Kinetic resolution of racemic starting materials using either chemical reagents or biotechnological approaches[3] is one of the most important methods to afford chiral compounds. Catalytic nonenzymatic methodologies for the kinetic resolution of amines are much less developed than those of alcohols.

Kinetic resolution via dehydrogenation of secondary alcohols to produce prochiral ketones is known as oxidative kinetic resolution (OKR), and various methods have been developed using transition-metal catalysts.[4] In contrast, OKR of secondary amines accompanied by oxidation to imines poses a number of challenges, mainly because (1) the N atom is generally susceptible to oxidation and (2) Lewis basic amine substrates generally deactivate transition-metal catalysts. Because of those difficulties, OKR of amines is limited to amine substrates bearing electron-withdrawing groups[5a] and tertiary amines,[5b−d] and there are no reports of OKR of secondary amines based on dehydrogenative oxidation of amines to imines.

2-Substituted indolines occur frequently in a variety of natural and biologically active products.[6] Nevertheless, there are few reports of catalytic synthetic methods for the construction of indolines in a highly enantioselective manner based on kinetic resolution.[7] Fu's group was the first to report the kinetic resolution of indolines by using bulky acylation reagents catalytically generated from O-acylated oxazolones with planar-chiral 4-(pyrrolidino)pyridine complexes.[7a] Hou and Zheng[7b] also demonstrated the kinetic resolution of indolines by Pd-catalyzed asymmetric allylic amination and obtained N-allylated products and the remaining starting materials with good enantioselectivities. Those two methods are based on functionalization of the indoline N atom (Scheme 1 top).

Our OKR-based approach to obtain chiral indolines[8] involves hydrogen transfer from the indoline to an imine by means of a chiral phosphoric acid (PA) catalyst (Scheme 1 bottom). The chiral PA contains a Brønsted acidic part (P−OH) and a Lewis basic part (P═O) and can therefore act as a bifunctional activator.[9] We hypothesized that the interaction of P−OH and P═O with an imine and the −NH group of an indoline, respectively, would result in enantioselective hydrogen transfer from the indoline to the imine.[10,11] One enantiomer of the indoline would preferentially participate in this hydrogen transfer reaction and be converted to cyclic imine **A**, which would immediately isomerize to the stable indole **B**, thereby achieving kinetic resolution. We report herein the Brønsted acid-catalyzed asymmetric hydrogen transfer reaction of indolines employing imines as hydrogen acceptors, which represents the first example of an efficient OKR of secondary amines.

Scheme 1



At the outset, we selected racemic 2-phenylindoline (*rac*-**2a**) as the model substrate and treated it with 0.5 equiv of aldimine **3a** in the presence of a catalytic amount of phosphoric acid (*R*)-**1**[12] at 50 °C (Table 1). Transfer hydrogenation from (*R*)-**2a** to **3a** proceeded smoothly to furnish 2-phenylindole and recovered (*S*)-**2a** in 55% yield with 23% ee (entry 1). Encouraged by this result, we examined the electronic effect of the imine *N*-aryl group. When imine **3b** containing an electron-deficient *N*-aryl group was subjected to the reaction, the enantioselectivity was lower (entry 2). Employing ketimine **3c** significantly improved the enantioselectivity to 93% ee with efficient conversion. The use of 1.0 equiv of ketimine **3d**, prepared from acetophenone and 3,4,5-trimethoxyaniline, further improved the enantioselectivity to >99% ee with 64% conversion (entry 4). Finally, the optimum reaction conditions were established as follows: 5 mol % (*R*)-**1**,

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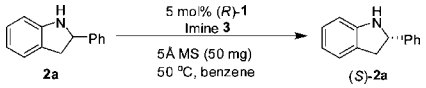
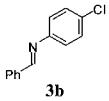
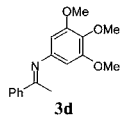
Table 1. Screening of Imines for Catalytic Kinetic Resolution

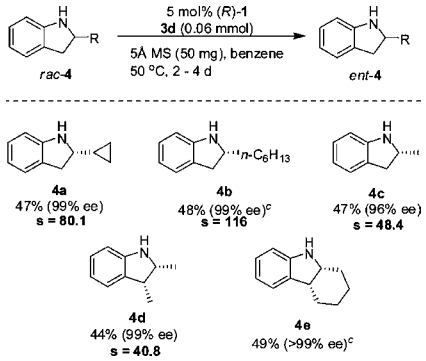


Entry	Imine	Imine (mmol)	Yield (%)[a]	ee (%)[b]
1	 **3a**	0.05	55	23
2	 **3b**	0.05	54	9
3	 **3c**	0.1	52	93
4	 **3d**	0.1	36	>99
5	**3d**	0.06	49 (48)[c]	>99

Resolutions were carried out on a 0.1 mmol scale with *rac*-**2a** (0.1 mmol), **3** (0.05 or 0.1 mmol), (*R*)-**1** (5 mol %), and 5 Å MS (50 mg) in benzene (0.1 M) at 50 °C for 19 h, unless otherwise noted. [a]Isolated yields. [b]Determined by chiral HPLC analysis. [c]1 mmol scale with *rac*-**2a** (1.0 mmol), **3d** (0.60 mmol), (*R*)-**1** (5 mol %), and 5 Å MS (0.50 g) in benzene (7 mL) at 50 °C for 19 h.

ketimine **3d** (0.6 equiv), and 5 Å molecular sieves (MS) in benzene at 50 °C (entry 5).[13,14]

Scheme 2. [a,b]

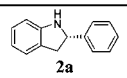
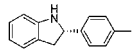
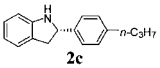
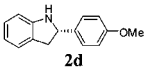
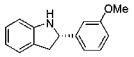
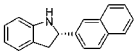
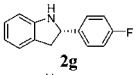
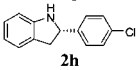
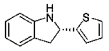
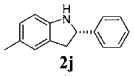
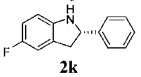
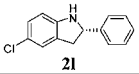


Resolutions were carried out on a 0.1 mmol scale with *rac*-**4** (0.1 mmol), **3d** (0.06 mmol), (*R*)-**1** (5 mol %), and 5 Å MS (50 mg) in benzene (0.1 M) at 50 °C for 2−4 days (see the SI for details). [a]Isolated yields are shown. [b]The ee's were determined by chiral HPLC analysis. [c]**3d** (0.07 mmol) was used.

To examine the scope of this reaction, a range of 2-substituted indolines **2a**−**i** were subjected to the optimized reaction conditions (Table 2). All of them reacted smoothly to afford the corresponding chiral indolines in high yields with excellent enantioselectivities. Indolines **2j**−**l** bearing electron-donating or -withdrawing groups at the 5-position were also suitable substrates, giving the corresponding chiral indolines in high yields with excellent enantioselectivities. It is noted that these 2-aryl-substituted indolines bearing a nonprotecting group on the N atom are not accessible using previously reported asymmetric hydrogen transfer reactions.[8f−i]

Indolines **4a**−**c** having sterically less-hindered alkyl substituents at the 2-position were also converted under the reaction

Table 2. Catalytic Kinetic Resolution of Indolines

Entry	Indoline	Time (h)	Yield (%)[a]	ee (%)[b]
1	 **2a**	19	49	>99
2	 **2b**	20	50	>99
3	 **2c**	20	50	>99
4	 **2d**	13	48	>99
5	 **2e**	20	50	>99
6	 **2f**	13	50	>99
7	 **2g**	20	46	>99
8	 **2h**	20	49	>99
9	 **2i**	20	43	>99
10	 **2j**	19	46	>99
11	 **2k**	20	48	>99
12	 **2l**	20	46	>99

Resolutions were carried out on a 0.1 mmol scale with *rac*-**2** (0.1 mmol), **3d** (0.06 mmol), (*R*)-**1** (5 mol %), and 5 Å MS (50 mg) in benzene (0.1 M) for the indicated time at 50 °C. [a]Isolated yields. [b]Determined by chiral HPLC analysis.

conditions, albeit with longer reaction times, and the target products were obtained with excellent selectivity factors (Scheme 2).[15] *cis*-2,3-Dimethylindoline (**4d**) was also kinetically resolved in this reaction, furnishing the remaining indoline with high efficiency and selectivity (s = 40.8).[16] Cis-fused tricyclic skeleton **4e** was also a good substrate for this OKR, and high enantioselectivity was realized with high conversion efficiency. In particular, the efficient kinetic resolution of 2,3-disubstituted indolines is of enormous significance because these indolines are difficult to obtain using asymmetric hydrogenation procedures.[8a,b] The applicability of this method to the kinetic resolution of both 2-aryl- and 2-alkyl-substituted indolines is noteworthy because the previously reported catalytic nonenzymatic methods are limited to either 2-aryl- or 2-alkylindolines.[7a,b]

To elucidate the reaction mechanism and the major factors contributing to the asymmetric induction through the present kinetic resolution, control experiments and DFT calculations were carried out [computational details are provided in the Supporting Information (SI)]. A remarkable difference in the reactivities of the enantiomers (*R*)- and (*S*)-**2a** was observed (Scheme 3). Compared with (*R*)-**2a**, which efficiently underwent the hydrogen transfer to ketimine **3d** (0.6 equiv) in 19 h to afford recovered (*R*)-**2a** in 38% yield with >99% ee and the corresponding amine **5d** in quantitative yield with >99% ee, the reaction of (*S*)-**2a** was much slower: (*S*)-**2a** was recovered in 96% yield without racemization, and amine **5d** was obtained in a

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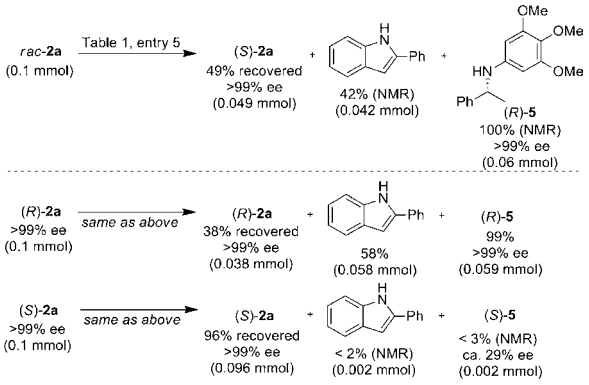
Scheme 3



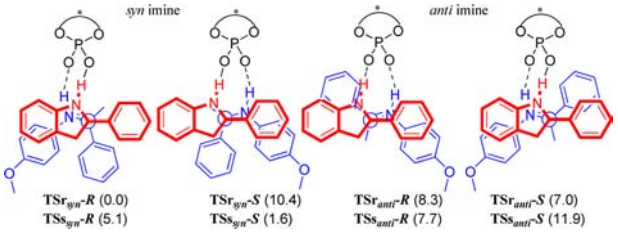


Figure 1. Schematic **TSr** structures and relative energies (kcal/mol) of the eight possible transition states.

very low yield (<3%) with low enantioselectivity (ca. 29% ee). These results confirmed that one enantiomer has much higher reactivity with chiral PA **1**. In addition, we investigated the reactions of N-protected substrates: when *N*-methyl- and *N*-acetyl-2-phenylindoline were subjected to the same reaction conditions as for **2a**, no reaction took place (see the SI). These results clearly showed that hydrogen bonding of the indoline N–H with the phosphoryl oxygen of the PA catalyst plays a significant role in the transition state (TS).[9,17]

On the basis of the bifunctional nature of the PA, the preliminary mechanistic study (see the SI), and the experimental results for N-substituted indolines, the dicoordinated cyclic TS was addressed. Whereas the Brønsted acidic proton activates the ketimine, the Lewis basic phosphoryl oxygen coordinates to the indoline N–H. Eight possible TS structures can be obtained from the two absolute configurations of indoline **2a** (*R* and *S*; **TSr** and **TSs**), the two geometric conformations of the imino group (*anti* and *syn* conformations with respect to the two aryl groups; $\mathbf{TS}_{anti}$ and $\mathbf{TS}_{syn}$), and the enantiofacial selection of the ketimine leading to *R* and *S* enantiomers of **5** (**TS-*R*** and **TS-*S***) The four **TSr** structures and the relative energies of the **TSr** and **TSs** structures are shown in Figure 1. In spite of the thermodynamic stability of the *anti* ketimine, the most energetically favored transition structures for both **TSr** and **TSs** include the sterically compact *syn* ketimine ($\mathbf{TSr}_{syn}$-***R*** and $\mathbf{TSs}_{syn}$-***S***), which can fit into the relatively small chiral space of the BINOL-type PA. There is a matched or mismatched pair between the absolute configuration of **2a** and the enantiofacial selection of the ketimine, depending on the geometric conformation of the ketimine. Whereas (*R*)-**2a** in **TS-*R*** or (*S*)-**2a** in **TS-*S*** is a matched pair for the *syn* ketimine (e.g., $\mathbf{TSr}_{syn}$-***R*** and $\mathbf{TSs}_{syn}$-***S***), the reverse tendency is found in the matched configurations of **2a** for the *anti* ketimine (e.g., $\mathbf{TSr}_{anti}$-***S*** and $\mathbf{TSs}_{anti}$-***R***). It is noted that $\mathbf{TSs}_{syn}$-***S*** is 1.6 kcal/mol higher in energy than $\mathbf{TSr}_{syn}$-***R***. This result is consistent with the experimental result that (*S*)-**2a** and (*R*)-**5** were obtained with

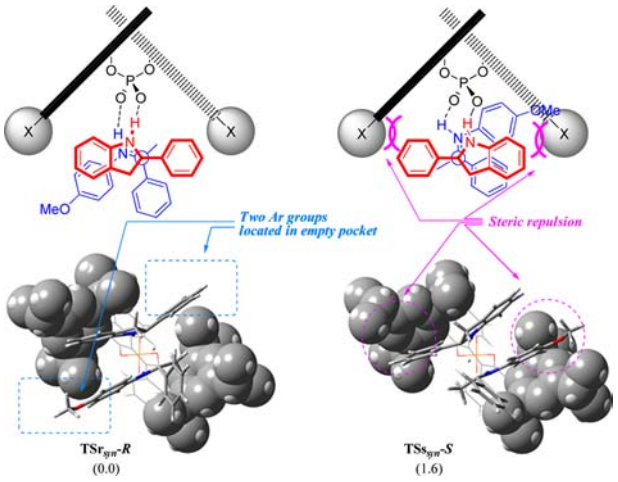


Figure 2. 3D structures and schematic representation models of $\mathbf{TSr}_{syn}$-***R*** and $\mathbf{TSs}_{syn}$-***S*** (PA 3,3′-substituents, ball model; substrates, tube model). Relative energies (kcal/mol) are shown in parentheses.

high enantioselectivities. A similar relative stability of the transition structures was found in the chiral-PA-catalyzed hydrogenation of imines using benzothiazoline.[18]

Structural analysis of $\mathbf{TSr}_{syn}$-***R*** and $\mathbf{TSs}_{syn}$-***S*** allowed us to identify the major factors contributing to the asymmetric induction. The *N*-aryl group of the ketimine and the 2-phenyl group of the indoline, which are located in the empty lower left-hand and upper right-hand quadrants, respectively, have no unfavorable steric interactions in $\mathbf{TSr}_{syn}$-***R*** (Figure 2). In contrast, the unfavorable steric interactions between the 3,3′-substituents of the chiral PA and the two aryl groups of the substrates (purple curve in Figure 2) are responsible for the destabilization of $\mathbf{TSs}_{syn}$-***S***. The C_2-symmetric space constructed by the 3,3′-substituents of the chiral PA would restrict the suitable absolute configuration of the indoline depending on the enantiofacial selection of the ketimine as an energetically favored matched pair. The use of ketimine **3d** derived from sterically more hindered 3,4,5-trimethoxyaniline achieved >99% ee irrespective of the indoline 2-substituent. This indicates that the steric repulsion between the *N*-aryl group of the ketimine and the 3,3′-substituents located in the lower right-hand quadrant is the main stereocontrolling factor.

In conclusion, we have developed a highly efficient kinetic resolution of indoline derivatives involving chiral-PA-catalyzed asymmetric transfer hydrogenation from indoline to imine. The kinetic resolution allows the synthesis of 2-substituted and 2,3-disubstituted indolines in high yields with excellent enantioselectivities. The method features a mild oxidative kinetic resolution using the hydrogen transfer reaction. Further investigations of the mechanistic insights and applications to the synthesis of more complex molecules are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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