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.† The development of new methods for the asymmetric synthesis of chiral skeletons has therefore captured the attention of synthetic organic chemists.‡ Kinetic resolution of racemic starting materials using either chemical reagents or biotechnological approaches§ 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.¶ 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-donating groups and tertiary amines, 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.© Nevertheless, there are few reports of catalytic synthetic methods for the construction of indolines in a highly enantioselective manner based on kinetic resolution.‖ 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.¶ Hou and Zheng 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 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 Bronsted acidic part (P=O) and a Lewis basic part (P=O) and can therefore act as a bifunctional activator.§ We hypothesized that the interaction of P=O 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.† 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 Bronsted 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.

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.¶ 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 3c, 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,
ketimine 3d (0.6 equiv), and 5 Å molecular sieves (MS) in benzene at 50 °C (entry 5).\textsuperscript{13,14}

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.\textsuperscript{8f−i}

Indolines 4a−c having sterically less-hindered alkyl substituents at the 2-position were also converted under the reaction conditions, albeit with longer reaction times, and the target products were obtained with excellent selectivity factors (Scheme 2).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{7a,b}

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Table 1. Screening of Imines for Catalytic Kinetic Resolution

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imines</th>
<th>Imines (mmol)</th>
<th>Yield (%)\textsuperscript{a}</th>
<th>ee (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>0.05</td>
<td>55</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>0.05</td>
<td>54</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>0.1</td>
<td>52</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>0.1</td>
<td>36</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>0.06</td>
<td>49 (48)%</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

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. \textsuperscript{a}Isolated yields. \textsuperscript{b}Determined by chiral HPLC analysis. 

Scheme 2. \textsuperscript{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). \textsuperscript{a}Isolated yields are shown. \textsuperscript{b}The ee’s were determined by chiral HPLC analysis. \textsuperscript{c}3d (0.07 mmol) was used.

Table 2. Catalytic Kinetic Resolution of Indolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indoline</th>
<th>Time(h)</th>
<th>Yield (%)\textsuperscript{a}</th>
<th>ee (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>20</td>
<td>50</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>20</td>
<td>50</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>19</td>
<td>46</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>20</td>
<td>46</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>19</td>
<td>46</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

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. \textsuperscript{a}Isolated yields. \textsuperscript{b}Determined by chiral HPLC analysis.
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).

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 2-substituent. This indicates that the steric hindrance of the 3,3′-aryl group of the ketimine and the 2-phenyl group of the indoline 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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(10) An intramolecular hydride transfer reaction of indolines has been reported by: Mao, H.; Xu, R.; Wan, J.; Jiang, Z.; Sun, C.; Pan, Y. Chem.—Eur. J. 2010, 16, 13352.


(13) The absolute configuration of the recovered enantiomeriched 2a was determined to be S by X-ray analysis of the N-p-bromobenzoyl derivative of 2a (see the SI) and the fact that the specific rotation of our sample of (S)-2a exhibited a negative value. Although the absolute configuration and specific rotation had been already reported, they reported that the S conformer exhibited a positive specific rotation in ref. 7c. Also see: Stangello, E. M.; Liblikas, I.; Mudalige, A.; Törnroos, K. W.; Norby, P.-O.; Unelius, C. R. Eur. J. Org. Chem. 2008, 5915.

(14) The absolute configuration of amine 3d resulting from hydrogen transfer to imine 3d was determined to be R by optical rotation and HPLC analysis of the N-acetyl derivative of the amine obtained by removal of the trimethoxysilyl group (see the SI).


(16) trans,2,3-Dimethylindoline reacted very slowly and with moderate selectivity under the same reaction conditions.


NOTE ADDED AFTER ASPAP PUBLICATION

The acknowledgment and author addresses were updated on July 26, 2013.