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In-Situ Generation of Ion-Paired Chiral Ligands: Rapid Identification of Optimal Ligand for Palladium-Catalyzed Asymmetric Allylation

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A method for the in-situ generation of ion-paired chiral ligands from simple salts of ammonium phosphines and chiral Brønsted acids under phase-transfer conditions is established. The exploitation of this method in combinatorial ligand screening enables the rapid identification of the optimal ion-paired chiral ligand for achieving a palladium-catalyzed asymmetric allylic alkylation of benzo[b]thiophen-2(3H)-ones.

Introduction

The discovery of a molecular catalyst that exerts high activity and stereoselectivity for target asymmetric transformation is often essential in various synthetic endeavors in academia and industry; yet it is usually a laborious task, relying to a great extent on trial and error. Despite rapid advances in theoretical chemistry, the rational design of chiral catalysts remains a formidable challenge because of the very small energy differences in the competing transition states leading to different enantiomers.1,2 In addition, the reactivity and selectivity profiles of catalytic asymmetric reactions are sensitive to both the steric and electronic nature of reactants; thus, an optimal catalyst for a particular substrate is not necessarily effective for other substrates with similar structures. Accordingly, a truly combinatorial approach to significantly accelerate the catalyst discovery process is much sought after.3–5

As a means for addressing this important issue, supramolecular chiral ligands and catalysts, spontaneously assembled from relatively simple molecular components through noncovalent interactions, have been introduced and successfully applied to the synthetically useful bond-forming reactions.6–9 The inherent modularity of supramolecular catalysts would allow the expeditious construction of structurally diverse and meaningful catalyst libraries. However, this possibility has rarely been exploited in the actual evaluation of the combinatorially formed mixtures of individual catalysts for rapidly identifying the best one. The pioneering study by Breit and the recent Reek’s contribution provide the only examples reported to date, which specifically focused on the identification of optimal bidentate ligands for asymmetric hydrogenation.10 This situation is largely due to the deficiency of reliable methods for generating sufficient libraries of chiral catalysts within a short time frame for efficient high-throughput screening; hence, the full potential of this powerful approach is yet to be realized, particularly in terms of solving synthetic problem such as the development of difficult-to-control asymmetric carbon–carbon bond formations.

Here, we report a new system for the combinatorial rapid ligand identification and its viability in developing an unprecedented palladium-catalyzed asymmetric allylic alkylation protocol. Our strategy is based on the establishment of a method for in-situ generation of ion-paired chiral ligands of type 311 (see Scheme for Table 1) from simple salts of ammonium phosphines and axially chiral phosphoric acids12–16 under phase-transfer conditions (Scheme 1). This method obviates the pre-preparation of the individual ion-paired ligands by the ion-exchange technique and thus enables its application to combinatorial ligand screening in palladium catalysis for achieving a highly enantioselective allylation of benzo[b]thiophen-2(3H)-ones.

## Scheme 1. Preparation of ion-paired chiral ligands.

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**In-situ generation of ion-paired chiral ligands**

**Previous system: pre-preparation of ion-paired chiral ligands**

**In-situ generation of ion-paired chiral ligands**

- **under liquid–liquid biphasic condition**
- **no need for tedious pre-preparation applicable to combinatorial screening**
**Results and discussion**

The conception of devising a practical method for the *in-situ* generation of ion-paired chiral ligand 3 and its analogues arose from our continued effort for taking full advantage of this multicomponent ligand, consisting of readily accessible ammonium phosphines and chiral phosphate ions, in synthetic reaction development. Because 3 was recently identified as an effective chiral ligand for the palladium-catalyzed, highly enantioselective bond formation between 3-benzylbenzofuranone 4 and allylic carbonate 5a by testing a series of each pre-prepared ion-paired ligand, we considered this allylation as an ideal benchmark to evaluate the feasibility of the *in-situ* generation of 3 through ion metathesis under phase-transfer conditions. After reconfirming the performance of pre-prepared 3 (entry 1 in Table 1), the initial trial was carried out by simply stirring an equimolar mixture of 4 and 5a with Pd₂(dba)₂·CHCl₃ (Pd 2.5 mol%), bromide salt of ammonium phosphine 1a·Br (5 mol%), and chiral phosphoric acid 2a (5 mol%) in toluene and an aqueous solution of K₂CO₃ (10 mol%) as the acid scavenger to facilitate the expected ion exchange at room temperature. Although the reaction proceeded smoothly, allylated product 6 was obtained with a negligible degree of enantioselectivity (entry 2). The observed lack of selectivity could be ascribed to the inefficiency of the ion exchange process between 1a·Br and 2a; thus, the reaction was mostly catalyzed by the palladium-1a·Br complex. We reasoned that the properties, such as basicity and hydrophilicity, of the anion moiety (X) would affect the capability of 1a·X both as an achiral ligand for palladium (nonstereoselective background reaction) and as a precursor for the generation of 3 through the requisite ion exchange with 2a under liquid–liquid biphasic conditions (stereoselective reaction). In fact, while the change of 1a·Br to ammonium phosphate with more lipophilic iodide ion (1a·I) failed to improve the reaction outcome (entry 3), the employment of hydrophilic acetate salt 1a·OAc yielded 6 quantitatively with dramatic enhancement of enantioselectivity (entry 4). Eventually, hydrogensulfate salt 1a·HSO₄ was found to be the most suitable precursor for the *in-situ* generation of ion-paired chiral ligand 3, allowing the isolation of 6 in 95% yield with 93% ee (entry 5). It should be noted that the attempted reaction with tris(4-chlorophenyl)phosphine as an achiral ligand instead of 1a·X under otherwise identical conditions afforded racemic 6 (entry 6), corroborating that the combined use of ammonium phosphate and the chiral acid is crucial for the stereocontrol.

Having established the system for the *in-situ* generation of ion-paired chiral ligands, we pursued its utilization for combinatorial ligand screening, particularly for the development of a new asymmetric palladium-catalyzed reaction. As a target transformation, we selected the asymmetric allylation of a sulfur analogue of benzofuran-2(3H)-one, 3-substituted benzo[b]thiophen-2(3H)-one, considering not only the relevance of C(3)-quaternary benzothiophenones as a core structure of potent pharmaceuticals, but also the presumed difficulty in rigorous stereocentrum using the ligand effective for the benzofuranone allylation despite the structural similarity. As anticipated, exposure of 3-benzylbenzothiophenone 7a to the optimized conditions for the allylation with *in-situ* generated ion-paired ligand 3 resulted in the quantitative formation of the desired product 8a, albeit with a markedly lower level of enantioselectivity (Scheme 2). This observation represents an obstacle often encountered in expanding the scope of the asymmetric catalysis of prominent ligand-transition metal complexes and emphasizes the importance of a high-throughput screening strategy as a viable solution to surmount it.

### Table 1. *In-situ* generation of ion-paired chiral ligand 3 for Pd-catalyzed asymmetric allylation of 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphate</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1a·Br</td>
<td>78</td>
<td>-11</td>
</tr>
<tr>
<td>3</td>
<td>1a·I</td>
<td>26</td>
<td>-5</td>
</tr>
<tr>
<td>4</td>
<td>1a·OAc</td>
<td>99</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>1a·HSO₄</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>Pd₄(C₄H₈)</td>
<td>40</td>
<td>-1</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, reactions were carried out with 0.10 mmol of 4 and 0.10 mmol of 5a in the presence of Pd₄(dba)₂·CHCl₃ (Pd 2.5 mol%), phosphine (5 mol%), 2a (5 mol%), and K₂CO₃ (10 mol%) in toluene (1.0 mL)/H₂O (0.05 mL) at room temperature. Isolated yield of 6. Enantiomeric excess of 6 was determined by chiral HPLC analysis. The reaction was carried out without chiral acid 2a and K₂CO₃.*

### Scheme 2. Asymmetric allylation of 3-benzylbenzothiophenone 7a with 5a under the conditions optimized for the reaction of 4 with *in-situ* generated 3.

To rapidly identify an optimal ion-paired chiral ligand for the palladium-catalyzed asymmetric allylation of benzothiophenones 7 by exploiting the *in-situ* generation system, we decided to adopt the iterative deconvolution strategy. For this purpose, we prepared 12 ammonium phosphines (1a-11) as a form of hydrogensulfate and 12 chiral phosphoric acids (2a-2i), from which 144 combinations of ion pairs could be generated (Figure 1). The 12 phosphines and 12 chiral acids were then divided into three groups (1a-1d, 1e-1h, and 1i-11) and two groups (2a-2f and 2g-2l), respectively. Each group of four ammonium phosphines 1·HSO₄ and each group of six chiral acids 2 were mixed in a single flask and subjected...
to the reaction of $7a$ with $5a$, where a total of 5 mol% phosphines and the same amount of a mixture of acids were used as the precursors of ion-paired chiral ligands. All six experiments were performed by combining the groups of phosphines with those of acids, and the results are summarized in Figure 2, Step 1. The catalyst activity was sufficient in all the cases, and the highest enantioselectivity was attained in the reaction with a mixture of the group of phosphines $1e$-$1h$ and the group of acids $2g$-$2l$. With this information in hand, we further divided phosphines $1e$-$1h$ and acids $2g$-$2l$ each into two groups as shown in Figure 2, Step 2. The similar experiments were then repeated by combining each group of two phosphines with each group of two acids, which revealed the combination of the group of ammonium phosphines $1g$, $1h$ and the group of phosphoric acids $2g$-$2i$ as the optimal candidate for ligand precursors. Finally, we evaluated the performance of the remaining six combinations of each ligand component (Figure 2, Step 3) and found that the combination of $1h$-$\text{HSO}_4$ and $2h$ allowed the generation of the ion-paired ligand that exerted excellent catalytic activity and stereocontrolling ability in this asymmetric allylation, leading to produce $8a$ quantitatively with 94% ee.

In general, a mixture of monodentate phosphines could generate the corresponding palladium complexes coordinated by two different monodentate phosphines, namely, hetero-complexes, as well as homo-complexes bearing the same two phosphines. Because these hetero-complexes would exhibit different stereoselectivity from the homo-complexes, it was uncertain if the iterative deconvolution of the in-situ prepared, monodentate ion-paired ligands led to the identification of the best combination of ammonium phosphate and chiral phosphoric acid. Therefore, although the optimal ligand

![Figure 1. Library of ammonium phosphines 1 and chiral acids 2.](image1)

![Figure 2. Combinatorial screening of ligand libraries.](image2)

![Figure 3. Individual evaluations of all the possible 144 combinations.](image3)

After a brief adjustment in the reaction temperature, which showed that even higher enantioselectivity could be attained at 0 °C (entry 1 in Table 2), further experiments were conducted to probe the substrate scope of the present asymmetric allylation of benzothiophenones $7$ using the newly identified, optimal combination of ammonium phosphate $1h$-$\text{HSO}_4$ with
chiral acid 2h. Significant structural variations in the 3-alkyl substituents of benzo thiophenones were well tolerated, and the corresponding allylated products were obtained with uniformly high enantioselectivities (entries 2–7). Benzothiophenones possessing methyl or chlorine at the C-5 position also appeared to be good substrates (entries 8 and 9). In addition, synthetically satisfactory levels of enantiocontrol were feasible with allylic carbonate having different electron-withdrawing groups such as methyl ester or phenyl ketone (entries 10 and 11).

#### Table 2. Substrate scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>R² (R³)</th>
<th>5 (R⁴)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a (Bn, H)</td>
<td>5a (CO₂Bu)</td>
<td>8a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>7b (Me, H)</td>
<td>5a</td>
<td>8b</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>7c (iBu, H)</td>
<td>5a</td>
<td>8c</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>7d (Pr, H)</td>
<td>5a</td>
<td>8d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>7e (Bu, H)</td>
<td>5a</td>
<td>8e</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>7f [(CH₃)₂CO, Me, H]</td>
<td>5a</td>
<td>8f</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>7g [(CH₃)₂Ph, H]</td>
<td>5a</td>
<td>8g</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>7h (Bn, Me)</td>
<td>5a</td>
<td>8h</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>7i (Bn, Cl)</td>
<td>5a</td>
<td>8i</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>7a</td>
<td>5e (CO₂Me)</td>
<td>8j</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>7a</td>
<td>5e (COPh)</td>
<td>8k</td>
<td>99</td>
</tr>
</tbody>
</table>

* Unless otherwise noted, the reactions were carried out with 0.10 mmol of 7 and 0.10 mmol of 5 in the presence of Pd₂(ba)₂Cl₂ (Pd 2.5 mol%), 1H- HS(=O)₂ (5 mol%), 2H (5 mol%), and K₂CO₃ (10 mol%) in toluene (1.0 mL)/H₂O (0.05 mL) at 0 °C for 24 h. * Isolated yield of 8. * Enantiomeric excess of 8 was determined by chiral HPLC analysis. The absolute configuration of 8a was established to be S by X-ray diffraction analysis, and the stereochemistry of the remaining examples were assumed by analogy. * Performed at –5 °C.

### Conclusions

In conclusion, we established a method for the in-situ generation of ion-paired chiral ligands from simple salts of ammonium phosphines and chiral Bronsted acids under phase-transfer conditions. This method was successfully utilized for the combinatorial ligand screening in palladium catalysis, which enabled the rapid identification of the optimal ion-paired ligand for achieving the first highly enantioselective alkylation of benzothiophenones. We believe that our approach based on the inherently combinatorial nature of the ion-paired chiral ligands paves the way for the development of hitherto difficult, transition-metal-catalyzed asymmetric bond-forming reactions.

### Acknowledgements

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### Notes and references


12 Chiral phosphoric acids have been widely used as efficient catalysts for asymmetric reactions. For reviews, see: (a) T. Akiyama, Chem. Rev. 2007, 107, 5744; (b) M. Terada, Chem. Commun. 2008, 4097; (c) M. Terada, Synthesis 2010, 1929.


18 For the catalytic activity of the complexes prepared from Pd(II)-dba·CHCl₃ and achiral ligands 1a-X, see Table S1 in the Supporting Information.


23 For more details, see the ESI (Table S2 in page S5).