## Electronic Supplementary Material (ESI) for Chemical Science.

## Supporting Information

Integration of Aerobic Oxidation and Intramolecular Asymmetric aza-Friedel-Crafts Reaction with a Chiral Bifunctional Heterogeneous Catalyst<br>Hong-Gang Cheng, Javier Miguélez, Hiroyuki Miyamura, Woo-Jin Yoo and Shū Kobayashi*<br>Department of Chemistry, School of Science, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

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## 1. General Information

Unless otherwise noted, commercial reagents were purchase from Tokyo Chemical Industry Co. Ltd and purified by distillation or recrystallization before use. All organic solvents were purified by distillation under dry argon atmosphere or purchased as anhydrous solvent from Wako Pure Chemical Industries, Ltd. ${ }^{1} \mathrm{H},{ }^{13} \mathrm{C}$ and ${ }^{31} \mathrm{P}$ NMR spectra were recorded on a JEOL ECX-400, JEOL ECX-500 or JEOL ECX-600 in $\mathrm{CDCl}_{3}$. Chemical shifts of ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ were reported in parts per million ( ppm ) from tetramethylsilane using the solvent resonance as the internal standard $\left(\mathrm{CDCl}_{3}\right.$ : 7.24 ppm for ${ }^{1} \mathrm{H}$ NMR and 77.0 ppm for ${ }^{13} \mathrm{C}$ NMR). Chemical shifts of ${ }^{31} \mathrm{P}$ were reported in parts per million ( ppm ) from $\mathrm{H}_{3} \mathrm{PO}_{4}$ using triphenylphosphine oxide ( 23.0 ppm ) as the internal standard. IR spectra were measured on a JASCO FT/IR-610 spectrometer. High-resolution mass spectrometry was carried out using a JEOL JMS-T100TD (ESI and DART). Column chromatography and preparative thin-layer chromatography (PTLC) were carried out using Wako gel B-5F from Wako Pure Chemical Industries, Ltd. or Merck \& Co. (normal type). Enantiomeric ratios were determined by chiral HPLC with chiral columns (chiralpak AS-H column, chiralpak AD-H column, chiralpak OJ-H column, chiralpak IC-H column or chiralcel OD-H column) with hexane and ${ }^{i} \mathrm{PrOH}$ as solvents. Optical rotations were measured with a polarimeter. Inductively Coupled Plasma (ICP) analysis was performed on Shimadzu ICPS-7510 equipment.

## 2. Optimization of the Sequential Aerobic Oxidation-Asymmetric aza-Friedel Crafts Reaction Using a Homogeneous Phosphoric Acid Catalyst

In order to evaluate the possibility of integrating an aerobic oxidation process with a FC reaction, we examined the TOP between benzyl alcohol (1a) and $N$-aminoethylpyrrole 2a using PI/CB$\mathrm{Au} / \mathrm{Pd}$ and $p$-toluenesulfonic acid as co-catalysts (Scheme 1S, eqn 1).


Scheme 1S. Initial Attempt and Control Experiments for the Sequential Oxidation-FC Process
However, the desired product 3a was not observed. We performed control experiments and it was found that the aerobic oxidation of $\mathbf{1 a}$ occurs with a moderate yield (Scheme 1S, eqn 2 ) and the $a z a-$ FC reaction occurs in a good yield (Scheme 1S, eqn 3) under our initial reaction conditions. Since the individual steps occur under the initial reaction conditions, it was assumed that the starting reagents might not be compatible to the two catalysts used in the reaction system. As such, when the reaction was performed in a one-pot, stepwise manner, the desired cyclic amine 3a was obtained in a low yield (Scheme 1S, eqn 4). This result confirmed our initial suspicion and began the optimization process for this TOP.

Since we were able to obtain only moderate yield of the desire aldehyde 12a, we began by optimizing the aerobic oxidation step (Table 1S).

Table 1S. Optimization of the Aerobic Oxidation of $1 \mathbf{1 a}$ with $\mathrm{PI} / \mathrm{CB}-\mathrm{Au} / \mathrm{Pd}^{a}$


| Entry | Solvent | Temp. $\left({ }^{\circ} \mathrm{C}\right)$ | Conc. | Conv. $^{b}$ | ${\text { Yield }(\%)^{b}}^{\text {}}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | THF | 25 | 0.1 M | 30 | 25 |


| 2 | THF | 25 | 1.0 M | 49 | 45 |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 3 | THF | 60 | 1.0 M | 100 | 59 |
| 4 | THF:H2O (v:v = 1:1) | 25 | 1.0 M | 100 | 85 |
| $\mathbf{5}$ | $\mathbf{T H F}: \mathbf{H}_{\mathbf{2}} \mathbf{O}(\mathbf{v}: \mathbf{v}=\mathbf{9 : 1})$ | $\mathbf{2 5}$ | $\mathbf{1 . 0} \mathbf{M}$ | $\mathbf{9 9}$ | $\mathbf{8 5}$ |

It was found that by increasing the concentration of the solvent, in conjugation with using an aqueous THF solution provided the desired aldehyde 12a in an excellent yield (entry 5). Once we optimized the oxidation step of the sequential reaction, we focused on the TOP using (S)-TRIP as a CPA for the asymmetric $a z a$-FC reaction (Table 2 S ).

Table 2S. Optimization for the Tandem Aerobic Oxidation-Asymmetric $a z a$-FC Reaction with $(S)$ TRIP as the CPA Catalyst ${ }^{a}$


| Entry | Ratio (1a/2a) | Ratio (3a/3a' $\left.{ }^{6}\right)^{b}$ | $4 \AA \mathrm{MS}$ | Yield of 3a (\%) $^{c}$ | Ee of 3a (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $1.5: 1$ | $4: 1$ | 100 mg | 72 | 91 |
| 2 | $1.2: 1$ | $5.5: 1$ | 100 mg | 74 | 88 |
| 3 | $1: 1$ | $>95: 5$ | 100 mg | 75 | 84 |
| 4 | $1: 1.2$ | $>95: 5$ | 100 mg | 68 | 80 |
| 5 | $1: 1.5$ | $>95: 5$ | 100 mg | 70 | 75 |
| 6 | $1.5: 1$ | $3.3: 1$ | - | 70 | 90 |
| 7 | $\mathbf{1 . 5 : 1}$ | $\mathbf{4 . 5 : 1}$ | $\mathbf{2 0 0} \mathbf{m g}$ | $\mathbf{7 6}$ | $\mathbf{9 3}$ |
| ${ }^{a}$ |  |  |  |  |  |

${ }^{a}$ Unless otherwise noted, reactions were carried out with 1a ( $0.2-0.3 \mathrm{mmol}$ ), PI/CB-Au/Pd in THF: $\mathrm{H}_{2} \mathrm{O}(\mathrm{v}: \mathrm{v}=0.27: 0.03$ mL ) under a balloon of oxygen at $25^{\circ} \mathrm{C}$ for 24 h , (aerobic oxidation step). Then ( $\boldsymbol{S}$ )-TRIP ( $5 \mathrm{~mol} \%$ ), 2a ( $0.2-0.3 \mathrm{mmol}$ ), $4 \AA$ MS $(0-200 \mathrm{mg})$ and THF ( 1.7 mL ) were added under a balloon of Ar at $25^{\circ} \mathrm{C}$ for $24 \mathrm{~h}\left(a z a-\mathrm{FC}\right.$ step). ${ }^{b}$ Determined by crude ${ }^{1} \mathrm{H}$ NMR. ${ }^{c}$ Yield of isolated product. ${ }^{d}$ The ee values were determined by chiral HPLC analysis.

We examined the effect of the ratio of reagents and the use of molecular sieves, and we were able to determine using an excess of $\mathbf{1 a}$ and 200 mg of $4 \AA$ MS provided the desired product in good yield and excellent enantioselectivity (entry 7). While the yield of the asymmetric TOP was somewhat acceptable, we found that $\mathbf{3 a}$ can also undergo oxidation to generate the undesired by-product $\mathbf{3 a}^{\mathbf{a}}$. A hint to overcome this problem was revealed in our optimization studies. It was found that when an excess of the $N$-aminoethylpyrrole $\mathbf{2 a}$ was used, the formation of $\mathbf{3 a}$ ' was minimized (entries 35). Therefore, we hypothesized 2a may act as a catalyst poison to the $\mathrm{Au} / \mathrm{Pd} \mathrm{NPs}$ and we believed that the introduction of Lewis basic additives could improve the overall reaction. We tested this hypothesis by examining the effect of Lewis basic compounds for the oxidation of $\mathbf{3 a}$ (Table 3S) and found that both $\mathrm{PPh}_{3}$ (entry 4) and BnSMe (entry 6) could be used to completely suppress this oxidation process.

Table 3S. Effect of Lewis Basic Additives for the Conversion of 3a to 3a' ${ }^{a}$


| Entry | Additive | Conv. (\%) ${ }^{\text {b }}$ | Yield (\%) ${ }^{\text {b }}$ |
| :---: | :---: | :---: | :---: |
| 1 | Amine 2a | 0 | 0 |
| 2 | $\mathrm{PhCONH}_{2}$ | 32 | 24 |
| 3 | DMF | 25 | 19 |
| 4 | $\mathrm{PPh}_{3}$ | 0 | 0 |
| 5 | TMEDA | 11 | 7 |
| 6 | $\mathrm{BnSCH}_{3}$ | 0 | 0 |
| ${ }^{a}$ Unless otherwise noted, reactions were carried out with 3a ( 0.30 mmol ), PI/CB-Au/Pd ( $1 \mathrm{~mol} \%$ wrt Au ) in THF: $\mathrm{H}_{2} \mathrm{O}(\mathrm{v}: \mathrm{v}=2.7: 0.3 \mathrm{~mL})$ at $25{ }^{\circ} \mathrm{C}$ under a balloon of Ar. ${ }^{b}$ Determined by crude ${ }^{1} \mathrm{H}$ NMR. |  |  |  |

With these results in hand, we examined the effect of these two additives for the asymmetric TOP (Table 4S). It was found that both additives improved the yield of $\mathbf{3 a}$ significantly and minimized the formation of 3a'. However, we chose $\mathrm{BnSCH}_{3}$ as the additive since the use of $\mathrm{PPh}_{3}$ led to significant metal leaching (entry 2).

Table 4S. Sequential Aerobic Oxidation-Asymmetric aza-FC Reaction with Additives ${ }^{a}$


| Entry | Additive | Ratio (3a/3a' ${ }^{\text {b }}$ | Yield of 3a (\%) ${ }^{\text {c }}$ | Ee of 3a $\mathbf{( \% )}^{\text {d }}$ | Metal Leaching $(\mathrm{Au} / \mathrm{Pd})^{e}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathrm{PPh}_{3}$ | >95:5 | 91 | 93 | 8.4\%/5.5\% |
| 2 | $\mathrm{BnSCH}_{3}$ | >95:5 | 90 | 92 | $N D^{f} / 0.22 \%$ |

${ }^{a}$ Unless otherwise noted, reactions were carried out with $1 \mathbf{1 a}(0.3 \mathrm{mmol}), \mathbf{P I} / \mathbf{C B}-\mathbf{A u} / \mathbf{P d}(1.5 \mathrm{~mol} \% \mathrm{wrt} \mathrm{Au})$ in THF: $\mathrm{H}_{2} \mathrm{O}(\mathrm{v}: \mathrm{v}=0.27: 0.03 \mathrm{~mL})$ under a balloon of oxygen at $25^{\circ} \mathrm{C}$ for 24 h (aerobic oxidation step). Then ( S )-TRIP $(5 \mathrm{~mol} \%)$, 2a $(0.2 \mathrm{mmol}), 4 \AA \mathrm{MS}(200 \mathrm{mg})$, additive $(0.02 \mathrm{mmol})$ and THF $(1.7 \mathrm{~mL})$ were added under a balloon of Ar at $25{ }^{\circ} \mathrm{C}$ for 24 h (aza-FC step). ${ }^{b}$ Determined by crude ${ }^{1} \mathrm{H}$ NMR. ${ }^{c}$ Yield of isolated product. ${ }^{d}$ The ee values were determined by chiral HPLC analysis. ${ }^{e}$ Detected with ICP analysis. Detection limit: $\mathrm{Au} / \mathrm{Pd}=0.009 / 0.008 \mathrm{ppm} .{ }^{f} \mathrm{ND}=$ below the detection limit of the ICP equipment.

While we were able to determine the optimized reaction conditions for the asymmetric TOP using a homogeneous CPA as a co-catalyst, in our actual system using a bifunctional catalyst, we need to separate $4 \AA$ MS if we wish to recycle the heterogeneous catalyst. Therefore, we examined possible water-soluble dehydrating reagents as replacements for $4 \AA$ MS (Table 5S).

Table 5S. Investigation of Various Dehydrating Reagents for the $a z a$-FC Reaction ${ }^{a}$


| Entry | Additive | Yield (\%) ${ }^{b}$ | Ee (\%) ${ }^{c}$ |
| :---: | :---: | :---: | :---: |
| 1 | $4 \AA \mathrm{MS}$ | 90 | 93 |
| 2 | $\mathrm{Na}_{2} \mathrm{SO}_{4}$ | 87 | 89 |
| 3 | $\mathrm{MgSO}_{4}$ | 89 | 90 |
| 4 | $\mathrm{CaCl}_{2}$ | 92 | 57 |
| $5^{d}$ | $\mathrm{MgSO}_{4}$ | 88 | 91 |
| $\mathbf{6}$ | $\boldsymbol{C a S O}_{4}$ | $\mathbf{9 4}$ | $\mathbf{9 2}$ |

${ }^{a}$ Unless otherwise noted, reactions were carried out with 2a ( 0.2 mmol ), 12a ( 0.3 mmol ), ( $\boldsymbol{S}$ )-TRIP ( $5 \mathrm{~mol} \%$ ), additive ( 200 mg ) in THF: $\mathrm{H}_{2} \mathrm{O}(\mathrm{v}: \mathrm{v}=1.97: 0.03 \mathrm{~mL})$ at $25{ }^{\circ} \mathrm{C}$ under a balloon of Ar. ${ }^{b}$ Isolated yield. ${ }^{c}$ The ee values were determined by chiral HPLC analysis. ${ }^{d}$ Add 300 mg of $\mathrm{MgSO}_{4}$.

Among the various dehydrating reagents tested, $\mathrm{CaSO}_{4}$ provided the best result (entry 6) and was selected as an additive for the asymmetric TOP catalyzed by a chiral bifunctional heterogeneous catalyst.

In addition, we also examined the possibility of performing the tandem process using two separate solid catalysts, $\mathrm{PI} / \mathrm{CB}-\mathrm{Au} / \mathrm{Pd}$ and the immobilized $(S)$-TRIP (Scheme 2 S ). It was found that the tandem process occurs well to provide the desired amine in similar results to the bifunctional catalyst. However, it should be noted that our bifunctional heterogeneous catalyst may be more reliable for recycling the catalyst since the ratio of the $\mathrm{Au} / \mathrm{Pd}$ NPs and the CPA will be constant throughout the reuse and recovery cycle.


Scheme 2S. The Sequential Oxidation-asymmetric aza-FC Process by Utilizing Two Separate Immobilized Catalyst

## 3. Preparation and Characterization Data of the Chiral Bifunctional Heterogeneous Catalyst

### 3.1 General Procedure for the Preparation of the CPA Monomer



Scheme 3S. Synthesis of CPA Monomer 4
Compound $\mathbf{S}-\mathbf{1}^{1}$ and $p$-vinylphenylboronic acid ${ }^{2}$ were prepared according to literature procedures.

## Synthesis of Intermediate S-2

To a solution of diol $\mathbf{S}-1(1.6 \mathrm{~g}, 1.9 \mathrm{mmol})$ in THF $(15 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ was added $\mathrm{NaH}(55 \% \mathrm{w} / \mathrm{w}, 33$ $\mathrm{mg}, 0.76 \mathrm{mmol})$. The reaction mixture was stirred for 30 min at $0^{\circ} \mathrm{C}$, and then $\mathrm{MsCl}(400 \mu \mathrm{~L}, 5.7$ mmol ) was added. Next, the reaction mixture was stirred at $60^{\circ} \mathrm{C}$ for 12 h , then was allowed to cool to room temperature. The mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ solution, and then extracted with EtOAc. The combined organic fractions were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and finally concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (eluent: $10 \%$ DCM in hexane) to provide $\mathbf{S}-2$ as a yellow foam ( $83 \%$ ).

## Synthesis of Intermediate S-3

To a solution of aryl bromide $\mathbf{S - 2}(500 \mathrm{mg}, 0.50 \mathrm{mmol})$ in $\mathrm{MePh}(2 \mathrm{~mL})$ and $\mathrm{EtOH}(1 \mathrm{~mL})$ was added an aqueous solution of $\mathrm{Na}_{2} \mathrm{CO}_{3}(2 \mathrm{M}, 1 \mathrm{~mL})$, followed by the addition of $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}(60 \mathrm{mg}$, 0.05 mmol ) and $p$-vinylphenylboronic acid ( $400 \mathrm{mg}, 2.7 \mathrm{mmol}$ ). The reaction mixture was degassed, then heated at $100{ }^{\circ} \mathrm{C}$ for 24 h . After cooling to room temperature, the reaction mixture was extracted with DCM and the combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated under reduced pressure. The crude product was then dissolved in dioxane $(15 \mathrm{~mL})$ and a solution of $\mathrm{NaOH}(6 \mathrm{~N}, 15 \mathrm{~mL})$ was then added. After stirring the reaction mixture at $60^{\circ} \mathrm{C}$ overnight, the reaction was allowed to cool to room temperature. The reaction was quenched with $\mathrm{NaHCO}_{3}$ until the pH of the mixture was approximately 9, then was extracted with EtOAc, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: $5 \%$ DCM in hexane) to provide diol S-3 ( $60 \%$ over two steps).

## Synthesis of Intermediate S-4

In a flame-dried round bottom flask, monomeric diol $\mathbf{S - 3}(1.5 \mathrm{~g}, 1.67 \mathrm{mmol})$ was dissolved in pyridine ( 22 mL ) under an Ar atmosphere. To this solution was added phosphrous oxychloride $(1.28 \mathrm{~g}, 8.35 \mathrm{mmol})$ and the reaction mixture was stirred at $60^{\circ} \mathrm{C}$ for 15 h . After cooling to room temperature, $\mathrm{H}_{2} \mathrm{O}(11 \mathrm{~mL})$ was added and the resulting suspension was stirred at $60{ }^{\circ} \mathrm{C}$ for an additional 4 h . After cooling to room temperature, the reaction mixture was poured into aqueous $\mathrm{HCl}(6 \mathrm{~N}, 100 \mathrm{~mL})$ and extracted with DCM. The organic fraction was washed with aqueous HCl ( 6 N ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated under reduced pressure. The crude was purified by column chromatography (eluent: $1 \% \mathrm{MeOH}$ in DCM ) and the resulting white solid was dissolved in DCM , washed with aqueous $\mathrm{HCl}(6 \mathrm{~N})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated under reduced pressure to provide CPA monomer 4 (81\%).

### 3.2 Characterization Data


(1S,3's)-6,6'-Dibromo-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diyl dimethanesulfonate (S-2)
${ }^{1} \mathbf{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.87-7.86(\mathrm{~m}, 2 \mathrm{H}), 7.67(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 2 \mathrm{H})$, 7.39-7.36 (m, 2H), 7.22 (d, $J=1.3 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.13-7.09 (m, 4H), 3.79-3.64 (m, 6H), 2.92-2.90 (m, 6H), 2.47-2.39 (m, 24H), $2.36(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 6 \mathrm{H})$, 2.15-2.13 (m, 6H). ${ }^{13}$ C NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 149.88,148.53,148.13$, $145.42,134.03,132.68,131.65,131.28,131.01,130.20,129.92,129.15$, $127.14,121.27,121.02,120.76,38.02,34.39,30.69,30.56,26.78,25.25$, 24.17, 23.20, 23.09. MS (EI) $\mathrm{m} / \mathrm{z}=1004.2992$. HRMS (DART) calcd for $\mathrm{C}_{52} \mathrm{H}_{61} \mathrm{Br}_{2} \mathrm{O}_{6} \mathrm{~S}_{2}$ $([\mathrm{M}+\mathrm{H}])^{+}: 1003.2276$; found 1003.2272. IR $(\mathrm{KBr}) v=796,944,1163,1368,1465,2360,2874$, 2964, $3524 \mathrm{~cm}^{-1}$.

(1S,3's)-3,3'-Bis(2,4,6-triisopropylphenyl)-6,6'-bis(4-vinylphenyl)-[1,1'-binaphthalene]-2,2'-diol (S-3)
${ }^{1} \mathbf{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.00(\mathrm{~s}, 2 \mathrm{H}), 7.76(\mathrm{~s}, 2 \mathrm{H}), 7.60(\mathrm{~d}, J=$ $8.2 \mathrm{~Hz}, 4 \mathrm{H}), 7.54-7.52(\mathrm{~m}, 2 \mathrm{H}), 7.43(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 4 \mathrm{H}), 7.33(\mathrm{~d}, J=$ $8.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.09-7.07$ (m, 4H), 6.71-6.67 (m, 2H), 5.72 (d, $J=17.6$ $\mathrm{Hz}, 2 \mathrm{H}), 5.20(\mathrm{~d}, J=10.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.90(\mathrm{~s}, 2 \mathrm{H}), 2.90(\mathrm{dt}, J=13.7$, $6.8 \mathrm{~Hz}, 2 \mathrm{H}$ ), $2.82(\mathrm{dt}, J=13.7,6.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.66(\mathrm{dt}, J=13.5,6.7 \mathrm{~Hz}$, $2 \mathrm{H}), 1.25(\mathrm{~d}, J=6.9 \mathrm{~Hz}, 12 \mathrm{H}), 1.15(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 6 \mathrm{H}), 1.07-1.03$ $(\mathrm{m}, 12 \mathrm{H}), 0.98(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 6 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR $\left(150 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 150.72,149.29,147.85,147.79$, $140.43,136.44,136.39,136.17,132.71,130.84,130.07$, 129.60, 129.25, 127.32, 126.70, 126.14, $125.99,125.15,121.32,121.25,113.83,113.21,34.34,30.93,30.85,24.34,24.32,24.06,23.99$, 23.96, 23.74. HRMS (ESI) calcd for $\mathrm{C}_{66} \mathrm{H}_{69} \mathrm{O}_{2}[\mathrm{M}-\mathrm{H}]^{+}: 893.5298$; found 893.5295. IR (KBr) $v=740$, 824, 1439, 1496, 1604, 2961, $3519 \mathrm{~cm}^{-1}$.

(2s,11bS)-4-Hydroxy-2,6-bis(2,4,6-triisopropylphenyl)-9,14-bis(4-vinylphenyl)dinaphtho[2,1-d:1',2' f][1,3,2]dioxaphosphepine 4oxide (4)
${ }^{1} \mathbf{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.00(\mathrm{~s}, 2 \mathrm{H}), 7.81(\mathrm{~s}, 2 \mathrm{H}), 7.62(\mathrm{~d}, J=$ $8.2 \mathrm{~Hz}, 4 \mathrm{H}), 7.55(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.46(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 4 \mathrm{H}), 7.38$ (d, $J=8.8 \mathrm{~Hz}, 2 \mathrm{H}$ ), 6.89 (s, 4H), 6.71 (dd, $J=17.5,10.9 \mathrm{~Hz}, 2 \mathrm{H}$ ), 5.75 (d, $J=17.7 \mathrm{~Hz}, 2 \mathrm{H}), 5.23$ (d, $J=10.9 \mathrm{~Hz}, 2 \mathrm{H}), 2.80-2.76$ (m,
$2 \mathrm{H}), 2.56-2.53(\mathrm{~m}, 4 \mathrm{H}), 1.18-1.15(\mathrm{~m}, 12 \mathrm{H}), 1.01(\mathrm{~d}, J=5.7 \mathrm{~Hz}, 6 \mathrm{H}), 0.95(\mathrm{~d}, J=6.1 \mathrm{~Hz}, 6 \mathrm{H}), 0.86$ $(\mathrm{d}, J=6.7 \mathrm{~Hz}, 6 \mathrm{H}), 0.74(\mathrm{~s}, 6 \mathrm{H}){ }^{13} \mathbf{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 148.23,147.77,147.15,139.89$, $137.91,136.88,136.28,132.86,131.45,131.23,127.95,127.40,126.80,125.71,125.62,121.86$, $121.20,120.23,114.15,34.15,30.96,30.73,26.41,25.00,24.03,23.38,23.17 .{ }^{31} \mathbf{P}$ NMR (243 MHz, $\mathrm{CDCl}_{3}$ ) $\delta$ 2.11. HRMS (ESI) calcd for $\mathrm{C}_{66} \mathrm{H}_{68} \mathrm{O}_{4} \mathrm{P}[\mathrm{M}-\mathrm{H}]^{+}$:955.4855; found 955.4838. IR (KBr) $v=$ $743,764,1021,1265,1495,1605,2870,2930 \mathrm{~cm}^{-1}$.

### 3.3 General Procedure for the Preparation of the Chiral Bifunctional Catalyst

The polymer-incarcerated $\mathrm{Au} / \mathrm{M}$ NPs used in these studies were prepared according to known literature procedures. ${ }^{3}$

## Synthesis of IOC-PI/CB(Au/Pd) 8



In a 20 mL test tube, chiral monomer $4(191 \mathrm{mg}, 0.2 \mathrm{mmol})$, benzyl methacrylate $\mathbf{6}(423.0 \mathrm{mg}, 2.4$ $\mathrm{mmol})$, divinyl benzene $7(62.5 \mathrm{mg}, 0.48 \mathrm{mmol})$, $\mathrm{PI} / \mathrm{CB}-\mathrm{Au} / \mathrm{Pd}(\mathrm{Au} / \mathrm{Pd}: 0.234 / 0.218 \mathrm{mmol} / \mathrm{g}, 256.0$ $\mathrm{mg}, 0.06 \mathrm{mmol}$ ), poly(vinyl alcohol) ( 19.2 mg ) and 2,2'-azo bisisobutyronitrile (AIBN) ( 19.2 mg ) were dissolved/suspended in a $\mathrm{MePh}: \mathrm{H}_{2} \mathrm{O}$ solvent mixture ( $\mathrm{v}: \mathrm{v}=1.6: 3.2 \mathrm{~mL}$ ). The solution was degassed and heated to $90^{\circ} \mathrm{C}$ under an atmosphere of Ar. After 12 h , the suspension was allowed to cool to room temperature and the solid materials were collected by vacuum filtration. The crosslinked polymer was washed successively with water, MeOH , and DCM , and dried overnight under high vacuum to provide IOC-PI/CB $(\mathrm{Au} / \mathrm{Pd}) 8$ as a greyish black powder $(785.2 \mathrm{mg})$. The loadings of $\mathrm{Au}(0.063 \mathrm{mmol} / \mathrm{g}), \mathrm{Pd}(0.059 \mathrm{mmol} / \mathrm{g})$, and $\mathrm{P}(0.22 \mathrm{mmol} / \mathrm{g})$ were determined by ICP analysis.

## Polymer-supported CPA 9



In a 10 mL test tube, chiral monomer $4(48 \mathrm{mg}, 0.05 \mathrm{mmol})$, benzyl methacrylate $\mathbf{6}(106 \mathrm{mg}, 0.6$ mmol ), divinyl benzene $7(18 \mathrm{mg}, 0.12 \mathrm{mmol}$ ), poly(vinyl alcohol) ( 10 mg ) and 2,2'-azo bisisobutyronitrile (AIBN) ( 4.8 mg ) were dissolved/suspended in a $\mathrm{MePh}: \mathrm{H}_{2} \mathrm{O}$ solvent mixture ( $\mathrm{v}: \mathrm{v}$ $=1: 2 \mathrm{~mL}$ ). The solution was degassed and heated to $90^{\circ} \mathrm{C}$ under an atmosphere of Ar. After 12 h ,
the suspension was allowed to cool to room temperature and the solid materials were collected by vacuum filtration. The cross-linked polymer was washed successively with acetone and DCM, and dried overnight under high vacuum to provide CPA-based polymer 9 as a white powder ( 129 mg ). The loadings of $\mathrm{P}(0.27 \mathrm{mmol} / \mathrm{g})$ were determined by ICP analysis.

## Synthesis of PI(Au/Pd)-CO 10



To a solution of polymer $5(150 \mathrm{mg})$ in diglyme ( 5 mL ) was added carbon black ( 150 mg ) and $\mathrm{NaBH}_{4}(18 \mathrm{mg}, 0.48 \mathrm{mmol})$. After stirring for 5 min , a solution of $\mathrm{PPh}_{3} \mathrm{AuCl}(24 \mathrm{mg}, 0.048 \mathrm{mmol})$ and $\mathrm{Pd}(\mathrm{OAc})_{2}(11 \mathrm{mg}, 0.048 \mathrm{mmol})$ in THF $(1 \mathrm{~mL})$ was added dropwise and stirred for 12 h . Next, the CPA polymer $9(120 \mathrm{mg})$ was added to the NP solution and was allowed to stir for 1 h . Then, $\mathrm{Et}_{2} \mathrm{O}(50 \mathrm{~mL})$ was added dropwise and the resulting solid was filtered and washed with $\mathrm{Et}_{2} \mathrm{O}$. The collected material was dried under high vacuum for 1 h , then heated at $150{ }^{\circ} \mathrm{C}$ under an Ar atmosphere for 6 h . Next, the cross-linked polymer was suspended in THF ( 5 mL ) and $\mathrm{HCl}(3 \mathrm{~N}, 5$ mL ) and was stirred overnight at room temperature. The suspension was filtered and washed with water, THF, DCM, and acetone, and the resulting polymer was dried under high vacuum for 24 h to provide $\mathrm{PI}(\mathrm{Au} / \mathrm{Pd})$-CO $10(389 \mathrm{mg})$. The loadings of $\mathrm{Au}(0.099 \mathrm{mmol} / \mathrm{g})$, $\mathrm{Pd}(0.092 \mathrm{mmol} / \mathrm{g})$, and P ( $0.083 \mathrm{mmol} / \mathrm{g}$ ) were determined by ICP analysis.

## Synthesis of IOC-PI/CB(Au/Pt) 11



In a 20 mL test tube, chiral monomer $4(191 \mathrm{mg}, 0.2 \mathrm{mmol})$, benzyl methacrylate $\mathbf{6}(423.0 \mathrm{mg}, 2.4$ $\mathrm{mmol})$, divinyl benzene $7(62.5 \mathrm{mg}, 0.48 \mathrm{mmol})$, $\mathrm{PI} / \mathrm{CB}-\mathrm{Au} / \mathrm{Pt}(\mathrm{Au} / \mathrm{Pt}: 0.163 / 0.258 \mathrm{mmol} / \mathrm{g}, 368 \mathrm{mg}$, $0.06 \mathrm{mmol})$, poly(vinyl alcohol) ( 19.2 mg ) and 2,2'-azo bisisobutyronitrile (AIBN) ( 19.2 mg ) were dissolved/suspended in a $\mathrm{MePh}: \mathrm{H}_{2} \mathrm{O}$ solvent mixture ( $\mathrm{v}: \mathrm{v}=1.6: 3.2 \mathrm{~mL}$ ). The solution was degassed and heated to $90^{\circ} \mathrm{C}$ under an atmosphere of Ar. After 12 h , the suspension was allowed to cool to room temperature and the solid materials were collected by vacuum filtration. The cross-linked polymer was washed successively with water, MeOH , and DCM, and dried overnight under high vacuum to provide IOC-PI/CB $(\mathrm{Au} / \mathrm{Pt}) 11$ as a greyish black powder $(829 \mathrm{mg})$. The loadings of Au $(0.065 \mathrm{mmol} / \mathrm{g}), \mathrm{Pt}(0.103 \mathrm{mmol} / \mathrm{g})$, and $\mathrm{P}(0.19 \mathrm{mmol} / \mathrm{g})$ were determined by ICP analysis.

### 3.4 Optimization of Reaction Conditions with IOC-PI/CB $(\mathrm{Au} / \mathrm{Pd}) 8$

We examined the influence of the co-monomers for the asymmetric TOP and prepared various chiral bifunctional catalysts following the method described for IOC-PI/CB(Au/Pd) 8 (Table 6 S ). Based on these results, we further optimize the reaction conditions for the asymmetric TOP using IOC-PI/CB(Au/Pd) 8 .

Table 6S. Preparation and Evaluation of Chiral Bifunctional Catalysts ${ }^{a}$


| Entry | IOC-PI/CB(Au/Pd) | Loadings of $\mathrm{Au} / \mathrm{Pd} / \mathrm{P}(\mathrm{mmol} / \mathrm{g})$ | Co-monomer | Yield (\%) ${ }^{b}$ | Ee (\%) ${ }^{\text {c }}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 8 | 0.063/0.059/0.22 |  | 89 | 88 |
| 2 | 8' | 0.11/0.090/0.26 |  | 88 | 82 |
| 3 | 8' | 0.10/0.091/0.23 | 人 Ph | 65 | 70 |

${ }^{a}$ Unless otherwise noted, reactions were carried out with $1 \mathrm{a}(0.3 \mathrm{mmol})$, IOC-PI/CB(Au/Pd) $(1.5 \mathrm{~mol} \% \mathrm{wrt} \mathrm{Au})$ in THF: $\mathrm{H}_{2} \mathrm{O}(\mathrm{v}: \mathrm{v}=0.27: 0.03 \mathrm{~mL})$ under a balloon of oxygen at $25^{\circ} \mathrm{C}$ for 24 h (aerobic oxidation step). Then 2a ( 0.2 mmol ), $\mathrm{CaSO}_{4}(200 \mathrm{mg}), \mathrm{BnSCH}_{3}(2.8 \mathrm{mg})$ and THF $(1.7 \mathrm{~mL})$ were added under a balloon of Ar at $25^{\circ} \mathrm{C}$ for $24 \mathrm{~h}\left(a z a\right.$-FC step). ${ }^{b}$
Isolated yield. ${ }^{\text {c }}$ The ee values were determined by chiral HPLC analysis.
Since the yield and ee of chiral piperazine 3a using IOC-PI/CB(Au/Pd) 8 as a catalyst was slightly lower than the results obtained using PI/CB-Au/Pd and $(S)$-TRIP as co-catalysts, we optimized the reaction temperature for the $a z a$-FC step (Table 7S).

Table 7S. Screening of Temperature of Asymmetric $a z a$-Friedel-Crafts Reaction ${ }^{a}$


| Entry | Temp. ( ${ }^{\circ} \mathrm{C}$ ) | Yield (\%) ${ }^{\text {b }}$ | Ee (\%) ${ }^{\text {c }}$ |
| :---: | :---: | :---: | :---: |
| 1 | 35 | 88 | 84 |
| 2 | 30 | 90 | 87 |
| 3 | 25 | 88 | 89 |
| 4 | 20 | 88 | 90 |
| 5 | 15 | 89 | 91 |
| 6 | 10 | 90 | 91 |
| 7 | 5 | 87 | 83 |
| 8 | 0 | 84 | 77 |
| $9^{d}$ | 10 | 90 | 91 |
| $10^{d}$ | 5 | 91 | 90 |
| $11^{d}$ | 0 | 87 | 88 |
| ${ }^{a}$ Unless otherwise noted, reactions were carried out with $\mathbf{1 a}(0.3 \mathrm{mmol})$, IOC-PI/CB(Au/Pd) $8(1.5 \mathrm{~mol} \%$, wrt Au ) in THF: $\mathrm{H}_{2} \mathrm{O}(\mathrm{v}: \mathrm{v}=0.56: 0.04 \mathrm{~mL})$ under a balloon of oxygen at $25^{\circ} \mathrm{C}$ for 24 h (aerobic oxidation |  |  |  |

> step $)$. Then $2 \mathrm{a}(0.2 \mathrm{mmol}), \mathrm{CaSO}_{4}(200 \mathrm{mg}), \mathrm{BnSCH}_{3}(2.8 \mathrm{mg})$ and $\mathrm{THF}(1.4 \mathrm{~mL})$ were added under a balloon of Ar at the corresponding temp., for $24 \mathrm{~h}(a z a-\mathrm{FC}$ step $) .{ }^{b}$ Isolated yield based on 2 a and determined by weight of the isolated product $\mathbf{3 a} .{ }^{c}$ The ee values were determined by chiral HPLC analysis. ${ }^{d}$ Stirred at the corresponding temp. for $48 \mathrm{~h}($ aza-FC step $)$.

It was found that the temperature had obvious effect on the enantioselectivity. Generally speaking, when the reaction was conducted at a higher temperature, for example, $35^{\circ} \mathrm{C}$, some drop in the enantioselectivity was observed (entry 1). In contrast, when the reaction was conducted at a lower temperature, higher enantioselectivities were observed (entries 1-6). When the reaction was conducted at $10^{\circ} \mathrm{C}$, we can get the best enantioselectivity ( $91 \%$ ee, entry 6 ). However, when the reaction was conducted at 5 or $0^{\circ} \mathrm{C}$, only $83 \%$ and $77 \%$ ees were obtained, respectively (entries 7 8). We speculated that at lower temperatures, the $a z a-\mathrm{FC}$ reaction was slow, and during purification by chromatography, some background cyclization occurred to lower the observed enantioselectivity. To demonstrate this issue, we prolonged the reaction time to 48 h . It was found that, for the reaction that occurred at $10^{\circ} \mathrm{C}$, no difference was observed (entry 9 vs. entry 6 ). However, for the reactions at 5 or $0^{\circ} \mathrm{C}$, obvious increase in enantioselectivities were observed (entries $10-11$ vs. entries $7-8$ ).

### 3.5 STEM and EDS Images of IOC-PI/CB(Au/Pd) 8



Figure 1S. STEM and EDS Images of IOC-PI/CB(Au/Pd) 8


Figure 2S. STEM and EDS Images of the Recovered IOC-PI/CB(Au/Pd) 8

## 4. General Procedure for the Asymmetric TOP using the Chiral Bifunctional Catalyst

### 4.1 General Procedure for the Asymmetric TOP with IOC-PI/CB(Au/Pd) 8



To a Carousel tube was charged benzyl alcohol 1a ( $32.4 \mathrm{mg}, 0.30 \mathrm{mmol}$ ), IOC-PI/CB( $\mathrm{Au} / \mathrm{Pd}$ ) $\mathbf{8}$ ( $47.6 \mathrm{mg}, 0.003 \mathrm{mmol}$ wrt Au ), THF $(560 \mu \mathrm{~L})$ and $\mathrm{H}_{2} \mathrm{O}(40 \mu \mathrm{~L})$. The carousel tube was flushed with $\mathrm{O}_{2}$ gas and the reaction mixture was stirred at $25^{\circ} \mathrm{C}$ for 24 hours under a balloon pressure of $\mathrm{O}_{2}$. Then, $N$-aminoethylpyrrole 2a ( $22.0 \mathrm{mg}, 0.2 \mathrm{mmol}$ ), $\mathrm{CaSO}_{4}(200 \mathrm{mg}), \mathrm{BnSCH}_{3}(2.8 \mathrm{mg}, 0.02$ $\mathrm{mmol})$, and THF ( 1.4 mL ) were added in sequence. The carousel tube was then flushed with Ar gas and the mixture was stirred at $10^{\circ} \mathrm{C}$ for an additional 24 hours. After completion of the asymmetric TOP, the heterogeneous catalyst 8 and $\mathrm{CaSO}_{4}$ were separated via vacuum-filtration and subsequently washed with THF ( 20 mL ). All solvents were removed under reduced pressure and the crude reaction mixture was purified by PTLC using EtOAc as the eluent to provide chiral piperazine $\mathbf{3 a}$ ( $35.8 \mathrm{mg}, 90 \%$ yield, $91 \%$ ee) as a white solid.

### 4.2 General Procedure for the Asymmetric TOP with IOC-PI/CB(Au/Pt) 11

During the course of our studies, it was found that the asymmetric TOP could not be performed with IOC-PI/CB $(\mathrm{Au} / \mathrm{Pd}) 8$ with benzyl alcohols bearing electron-withdrawing substituents. The problem stem from the inability of $\mathbf{8}$ to efficiently mediate the aerobic oxidation. Thus, we reoptimized the aerobic oxidation reaction (Table 8S).

Table 8S. Optimization of the Aerobic Oxidation Reaction of 4-Fluorobenzyl Alcohol ${ }^{a}$


| Entry | PI/CB-Au/M | Solvent | Temp. ( ${ }^{\circ} \mathrm{C}$ ) | Time (h) | Conv. (\%) ${ }^{\text {b }}$ | Yield (\%) ${ }^{\text {b }}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | PI/CB-Au/Pd | THF: $\mathrm{H}_{2} \mathrm{O}$ | 25 | 24 | 31 | 23 |
| 2 | PI/CB-Au/Pd | THF: $\mathrm{H}_{2} \mathrm{O}$ | 60 | 24 | 100 | 53 |
| 3 | PI/CB-Au/Pt | THF: $\mathrm{H}_{2} \mathrm{O}$ | 60 | 24 | 100 | 75 |
| 4 | PI/CB-Au/Pd | DCM: $\mathrm{H}_{2} \mathrm{O}$ | 25 | 24 | 85 | 78 |
| 5 | PI/CB-Au/Pt | DCM: $\mathrm{H}_{2} \mathrm{O}$ | 25 | 24 | 96 | 89 |
| ${ }^{a}$ Unless otherwise noted, reactions were carried out with $\mathbf{1 i}(0.3 \mathrm{mmol}), \mathbf{P I} / \mathbf{C B}-\mathrm{Au} / \mathbf{M}(2 \mathrm{~mol} \%$, wrt Au) in THF or DCM: $\mathrm{H}_{2} \mathrm{O}(9: 1,0.6 \mathrm{~mL})$ under a balloon of oxygen for $24 \mathrm{~h} .{ }^{b}$ Determined by GC analysis, with dodecane as internal standard. |  |  |  |  |  |  |

It was found that by changing the solvent from THF to DCM, and the use of PI/CB-Au/Pt as a catalyst enabled the aerobic oxidation of benzyl alcohol 1 i in an efficient manner (entry 5). Thus, a new chiral bifunctional heterogeneous catalyst IOC-PI/CB(Au/Pt) 11 was prepared and evaluated for the asymmetric TOP with benzyl alcohols substituted with electron-withdrawing moieties.


To a Carousel tube was charged (4-fluorophenyl)methanol 1i ( $37.8 \mathrm{mg}, 0.30 \mathrm{mmol}$ ), IOC$\mathrm{PI} / \mathrm{CB}(\mathrm{Au} / \mathrm{Pt}) 11(92.3 \mathrm{mg}, 0.006 \mathrm{mmol}$ wrt Au$)$, $\mathrm{DCM}(540 \mu \mathrm{~L})$ and $\mathrm{H}_{2} \mathrm{O}(60 \mu \mathrm{~L})$. The carousel tube was flushed with $\mathrm{O}_{2}$ gas and the reaction mixture was stirred at $25^{\circ} \mathrm{C}$ for 24 hours under a balloon pressure of $\mathrm{O}_{2}$. Then, $N$-aminoethylpyrrole $2 \mathrm{a}(22.0 \mathrm{mg}, 0.2 \mathrm{mmol}), \mathrm{CaSO}_{4}(200 \mathrm{mg})$, $\mathrm{BnSCH}_{3}(5.6 \mathrm{mg}, 0.04 \mathrm{mmol})$, and THF ( 2.0 mL ) were added in sequence. The carousel tube was then flushed with Ar gas and the mixture was stirred at $10^{\circ} \mathrm{C}$ for an additional 24 hours. After completion of the asymmetric TOP, the heterogeneous catalyst 11 and $\mathrm{CaSO}_{4}$ were separated via vacuum-filtration and subsequently washed with THF ( 20 mL ). All solvents were removed under reduced pressure and the crude reaction mixture was purified by PTLC using EtOAc/hexane (1:1) as the eluent to provide chiral piperazine $\mathbf{3 i}(39.8 \mathrm{mg}, 92 \%$ yield, $91 \% \mathrm{ee})$ as a white solid.

### 4.3 Characterization Data

With the exception of compounds $\mathbf{3 e - g}, \mathbf{3 1}$, all chiral piperazines $\mathbf{3}$ (with the opposite enantiomer) are known compounds. ${ }^{4}$


## (S)-1-Phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3a)

White solid, $89 \%$ yield and $94 \%$ ee, determined by chiral HPLC analysis (Chiralcel
AD-H, hexane/isopropanol, $97: 3 \mathrm{v} / \mathrm{v}, 0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 254 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=22.801 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=25.777 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H} \mathbf{N M R}(600 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 7.40-7.39(\mathrm{~m}, 2 \mathrm{H}), 7.33(\mathrm{t}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.30-7.29(\mathrm{~m}, 1 \mathrm{H}), 6.59(\mathrm{~s}, 1 \mathrm{H}), 6.11(\mathrm{t}, J=$ $2.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.54(\mathrm{~d}, J=1.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.08(\mathrm{~s}, 1 \mathrm{H}), 4.10-4.05(\mathrm{~m}, 1 \mathrm{H}), 4.01-3.96(\mathrm{~m}, 1 \mathrm{H}), 3.37-3.33$ $(\mathrm{m}, 1 \mathrm{H}), 3.28-3.23(\mathrm{~m}, 1 \mathrm{H}), 1.86(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR $\left(150 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 142.9,130.6,128.3$, 127.7, 118.9, 107.6, 104.8, 59.0, 45.4, 43.1.


## (S)-1-(p-Tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3b)

White solid, $89 \%$ yield and $84 \%$ ee, determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $98: 2 \mathrm{v} / \mathrm{v}, 0.6 \mathrm{~mL} / \mathrm{min}, 25{ }^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=30.777 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=37.009 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.28(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.15(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 6.59(\mathrm{~s}, 1 \mathrm{H}), 6.10(\mathrm{t}$, $J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.55(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.05(\mathrm{~s}, 1 \mathrm{H}), 4.10-4.06(\mathrm{~m}, 1 \mathrm{H}), 4.02-3.97(\mathrm{~m}, 1 \mathrm{H}), 3.38-$ $3.34(\mathrm{~m}, 1 \mathrm{H})$, 3.28-3.24 (m, 1H), $2.35(\mathrm{~s}, 3 \mathrm{H}), 1.75(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 139.9$, 137.4, 130.9, 129.0, 128.2, 118.9, 107.6, 104.8, 58.8, 45.4, 43.1, 21.1.

(S)-1-(o-Tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3c)

White solid, m.p. $=74{ }^{\circ} \mathrm{C} 91 \%$ yield and $92 \%$ ee, $[\alpha]_{\mathrm{D}}{ }^{20}=-35.6\left(\mathrm{c}=0.1, \mathrm{CHCl}_{3}\right)$ determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $98: 2 \mathrm{v} / \mathrm{v}$,
$0.6 \mathrm{~mL} / \mathrm{min}, 25{ }^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=22.725 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=$ 23.939 min for $(R)$-isomer. ${ }^{1} \mathbf{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.32(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.21-7.20(\mathrm{~m}$, $2 \mathrm{H}), 7.18-7.15(\mathrm{~m}, 1 \mathrm{H}), 6.62(\mathrm{~s}, 1 \mathrm{H}), 6.13(\mathrm{t}, J=3.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.53-5.52(\mathrm{~m}, 1 \mathrm{H}), 5.33(\mathrm{~s}, 1 \mathrm{H}), 4.13-$ $4.07(\mathrm{~m}, 1 \mathrm{H}), ~ 4.03-3.99(\mathrm{~m}, 1 \mathrm{H}), 3.41-3.38(\mathrm{~m}, 1 \mathrm{H}), 3.31-3.26(\mathrm{~m}, 1 \mathrm{H}), 2.43(\mathrm{~s}, 3 \mathrm{H}), 1.82(\mathrm{bs}, 1 \mathrm{H})$. ${ }^{13} \mathbf{C}$ NMR $\left(150 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 140.8,136.3,130.6,130.4,128.5,127.4,125.9,118.8,107.6,104.3$, 55.9, 45.5, 43.3, 19.3. HRMS (ESI) calcd for $\mathrm{C}_{14} \mathrm{H}_{17} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}: 213.1386$; found 213.1389. IR $(\mathrm{KBr}) v=748,764,1073,1293,1488,2360,2953 \mathrm{~cm}^{-1}$.

(S)-1-(4-Methoxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3d)

White solid, $80 \%$ yield and $80 \%$ ee, determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $80: 20 \mathrm{v} / \mathrm{v}, ~ 0.60 \mathrm{~mL} / \mathrm{min}, 25{ }^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=13.530 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=16.402 \mathrm{~min}$ for $(R)$ isomer. ${ }^{1} \mathbf{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.31(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 6.87(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 6.59(\mathrm{~s}$, $1 \mathrm{H}), 6.11(\mathrm{t}, J=2.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.54(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.03(\mathrm{~s}, 1 \mathrm{H}), 4.10-4.05(\mathrm{~m}, 1 \mathrm{H}), 3.99-3.97$ $(\mathrm{m}, 1 \mathrm{H}), 3.81(\mathrm{~s}, 3 \mathrm{H}), 3.38-3.34(\mathrm{~m}, 1 \mathrm{H}), 3.28-3.23(\mathrm{~m}, 1 \mathrm{H}), 1.68(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( 150 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 159.2,135.1,131.1,129.4,118.9,113.7,107.6,104.8,58.5,55.3,45.4,43.2$.


## (S)-1-(3-Methoxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3e)

White solid, m.p. $=75{ }^{\circ} \mathrm{C}, 83 \%$ yield and $93 \% \mathrm{ee},[\alpha]_{\mathrm{D}}{ }^{20}=-72.5(\mathrm{c}=0.1$, $\mathrm{CHCl}_{3}$ ) determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $90: 10 \mathrm{v} / \mathrm{v}, 1.0 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 202 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=13.133 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=18.890 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H} \mathbf{N M R}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.26-7.24(\mathrm{~m}$, $1 \mathrm{H}), 6.99-6.96(\mathrm{~m}, 2 \mathrm{H}), 6.85-6.83(\mathrm{~m}, 1 \mathrm{H}), 6.59(\mathrm{~s}, 1 \mathrm{H}), 6.11(\mathrm{t}, J=3.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.59(\mathrm{~m}, 1 \mathrm{H}), 5.07$ $(\mathrm{s}, 1 \mathrm{H}), 4.09-4.05(\mathrm{~m}, 1 \mathrm{H}), 4.00-3.96(\mathrm{~m}, 1 \mathrm{H}), 3.79(\mathrm{~s}, 3 \mathrm{H}), 3.38-3.35(\mathrm{~m}, 1 \mathrm{H}), 3.28-3.25(\mathrm{~m}, 1 \mathrm{H})$, 1.79 (bs, 1H). ${ }^{13} \mathbf{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 159.7,144.4,130.4,129.3,120.6,118.9,113.7$, 113.3, 107.6, 104.9, 59.0, 55.2, 45.4, 43.1. HRMS (ESI) calcd for $\mathrm{C}_{14} \mathrm{H}_{15} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}-\mathrm{H}]^{+}: 227.1184$; found 227.1188. IR (KBr) $v=749,1040,1265,1284,1586,2360,2835,2942 \mathrm{~cm}^{-1}$.


## (S)-1-(2-Methoxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3f)

Light yellow solid, m.p. $=69^{\circ} \mathrm{C},[\alpha]_{\mathrm{D}}{ }^{20}=-97.5\left(\mathrm{c}=0.1, \mathrm{CHCl}_{3}\right) 85 \%$ yield and $91 \%$ ee, determined by chiral HPLC analysis (Chiralcel OD-H, hexane/isopropanol, $90: 10 \mathrm{v} / \mathrm{v}, 0.60 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=12.546 \mathrm{~min}$ for $(R)$-isomer, $\mathrm{t}_{\mathrm{r}}=18.642 \mathrm{~min}$ for $(S)$-isomer (major). ${ }^{1} \mathbf{H} \mathbf{N M R}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.26-7.23(\mathrm{~m}$, $1 \mathrm{H}), 7.12(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.92-6.86(\mathrm{~m}, 2 \mathrm{H}), 6.60(\mathrm{~d}, J=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.13(\mathrm{t}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H})$, $5.63(\mathrm{~m}, 1 \mathrm{H}), 5.55(\mathrm{~s}, 1 \mathrm{H}), 4.04-3.98(\mathrm{~m}, 2 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}), 3.28-3.25(\mathrm{~m}, 1 \mathrm{H}), 3.17-3.14(\mathrm{~m}, 1 \mathrm{H})$, $1.99(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR (150 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 157.1,131.2,129.6,129.4,128.7,120.4,118.7$, $110.5,107.55,104.5,55.5,52.3,45.5,41.8$. HRMS (ESI) calcd for $\mathrm{C}_{14} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 229.1335$; found 229.1336. IR $(\mathrm{KBr}) v=756,841,1027,1102,1242,1293,1490,1599,2835,2952 \mathrm{~cm}^{-1}$.

(S)-1-(Benzo[d][1,3]dioxol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3g)

White solid, m.p. $=66^{\circ} \mathrm{C},[\alpha]_{\mathrm{D}}{ }^{20}=-15.5\left(\mathrm{c}=0.1, \mathrm{CHCl}_{3}\right) 84 \%$ yield and $73 \% \mathrm{ee}$, determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, 98:2 $\mathrm{v} / \mathrm{v}$, $0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 254 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=60.189 \mathrm{~min}$ for $(R)$-isomer, $\mathrm{t}_{\mathrm{r}}=$
63.849 min for $(S)$-isomer (major). ${ }^{1} \mathbf{H} \mathbf{N M R}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.89-6.86(\mathrm{~m}, 2 \mathrm{H}), 6.77(\mathrm{~d}, J=$ $7.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.59(\mathrm{dt}, J=2.3,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.12-6.10(\mathrm{~m}, 1 \mathrm{H}), 5.94(\mathrm{~s}, 2 \mathrm{H}), 5.58-5.57(\mathrm{~m}, 1 \mathrm{H}), 5.01$ $(\mathrm{s}, 1 \mathrm{H}), 4.10-4.04(\mathrm{~m}, 1 \mathrm{H}), 3.99-3.95(\mathrm{~m}, 1 \mathrm{H}), 3.38-3.33(\mathrm{~m}, 1 \mathrm{H}), 3.28-3.22(\mathrm{~m}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 147.6,147.1,137.0,130.7,121.6,118.9,108.7,107.9,107.6,104.8,101.0$, 58.8, 45.4, 43.1. HRMS (ESI) calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{2}[\mathrm{M}+\mathrm{H}]^{+}: 243.1113$, found 243.1114. IR $(\mathrm{KBr}) v$ $=552,710,796,944,1100,1176,1360,1485,2878,2922,3431 \mathrm{~cm}^{-1}$.


## (S)-1-(Naphthalen-1-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3h)

White solid, $85 \%$ yield and $93 \%$ ee, determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $98: 2 \mathrm{v} / \mathrm{v}, 0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=43.761 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=50.844 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.21(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.88(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.86(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.50-7.46(\mathrm{~m}, 3 \mathrm{H}), 7.39(\mathrm{dd}, J=11.2,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.65(\mathrm{~s}, 1 \mathrm{H}), 6.11(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.87(\mathrm{~s}$, $1 \mathrm{H}), 5.55$ (dd, $J=3.1,1.2 \mathrm{~Hz}, 1 \mathrm{H})$, 4.18-4.13 (m, 1H), 4.07-4.03 (m, 1H), 3.41-3.37 (m, 1H), 3.33$3.28(\mathrm{~m}, 1 \mathrm{H}), 1.84(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $\left.150 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 138.4,134.1,131.5,130.1,128.8$, 128.3, 126.1, 126.0, 125.5, 125.2, 124.0, 118.9, 107.2, 104.9, 55.7, 45.6, 43.0.

(S)-1-(4-Fluorophenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3i)

White solid, $91 \%$ yield and $90 \%$ ee, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/isopropanol, $95: 5 \mathrm{v} / \mathrm{v}, 0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=17.957 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=22.329 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.38-7.36(\mathrm{~m}, 2 \mathrm{H}), 7.01(\mathrm{t}, J=8.6 \mathrm{~Hz}, 2 \mathrm{H}), 6.60(\mathrm{~s}, 1 \mathrm{H}), 6.11(\mathrm{t}, J=3.0$ $\mathrm{Hz}, 1 \mathrm{H}), 5.53-5.52(\mathrm{~m}, 1 \mathrm{H}), 5.07(\mathrm{~s}, 1 \mathrm{H}), 4.10-4.06(\mathrm{~m}, 1 \mathrm{H}), 4.00-3.97(\mathrm{~m}, 1 \mathrm{H}), 3.37-3.34(\mathrm{~m}, 1 \mathrm{H})$, 3.29-3.24 (m, 1H), $1.75(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 163.2,161.5,138.7,130.5,129.9$, 129.9, 119.1, 115.2, 115.1, 107.7, 104.9, 58.4, 45.4, 43.1.

## (S)-1-(2-Fluorophenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3j)

White solid, $88 \%$ yield and $91 \%$ ee, determined by chiral HPLC analysis (Chiralcel AS-H, hexane/isopropanol, $98: 2 \mathrm{v} / \mathrm{v}, 1.0 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=15.920 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=17.317 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H} \mathbf{N M R}(500 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 7.29-7.25(\mathrm{~m}, 2 \mathrm{H}), 7.09-7.06(\mathrm{~m}, 2 \mathrm{H}), 6.60(\mathrm{~s}, 1 \mathrm{H}), 6.13(\mathrm{dd}, 1 \mathrm{H}, J=5.0,5.0 \mathrm{~Hz}), 5.61(\mathrm{~m}$, $1 \mathrm{H}), 5.49(\mathrm{~s}, 1 \mathrm{H}), 4.09-4.04(\mathrm{~m}, 1 \mathrm{H}), 4.02-3.98(\mathrm{~m}, 1 \mathrm{H}), 3.36-3.32(\mathrm{~m}, 1 \mathrm{H}), 3.27-3.22(\mathrm{~m}, 1 \mathrm{H}), 1.86$ (bs, 1H). ${ }^{13} \mathbf{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 161.8,159.8,130.0,129.95,129.9,129.2,129.1,128.9$, 124.0, 124.0, 119.0, 115.4, 115.3, 111.9, 107.7, 104.6, 51.9, 45.4, 42.6 .

c। (S)-1-(4-chlorophenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3k)
Colorless oil, $83 \%$ yield and $90 \%$ ee, determined by chiral HPLC analysis (Chiralcel OD-H, hexane/isopropanol, $80: 20 \mathrm{v} / \mathrm{v}, 0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=11.151 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=13.046 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.34(\mathrm{~d}, 2 \mathrm{H}, J=12 \mathrm{~Hz}), 7.31(\mathrm{~d}, 2 \mathrm{H}, J=6 \mathrm{~Hz}), 6.60(\mathrm{t}, 1 \mathrm{H}, J=4.1 \mathrm{~Hz})$, 6.10-6.10 (m, 1H), 5.53-5.51 (m, 1H), 5.06 (s, 1H), 4.10-4.05 (m, 1H), 4.00-3.97 (m, 1H), 3.36-3.33 $(\mathrm{m}, 1 \mathrm{H}), 3.28-3.25(\mathrm{~m}, 1 \mathrm{H}), 1.77(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 141.4,133.4,130.1$, 129.7, 128.5, 119.1, 107.7, 104.9, 58.4, 45.4, 43.0.

(S)-1-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3I)

White solid, m.p. $=81{ }^{\circ} \mathrm{C}, 82 \%$ yield and $86 \%$ ee, $[\alpha]_{\mathrm{D}}{ }^{20}=-36.17\left(\mathrm{c}=0.1, \mathrm{CHCl}_{3}\right)$ determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $99: 1 \mathrm{v} / \mathrm{v}$, $0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=36.690 \mathrm{~min}$ for $(S)$-isomer (major), $\mathrm{t}_{\mathrm{r}}=60.913 \mathrm{~min}$ for $(R)$-isomer. ${ }^{1} \mathbf{H} \mathbf{N M R}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.59(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H})$, $7.52(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.61(\mathrm{~d}, J=1.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.12-6.11(\mathrm{~m}, 1 \mathrm{H}), 5.53(\mathrm{~m}, 1 \mathrm{H}), 5.15(\mathrm{~s}, 1 \mathrm{H})$, 4.11-4.05 (m, 1H), 4.01-3.98 (m, 1H), 3.37-3.34 (m, 1H), 3.30-3.26 (m, 1H), $1.89(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 146.9,129.9,129.6,128.6,125.4,125.33,123.27,119.3,107.8,105.1$, 58.5, 45.4, 42.9. HRMS (ESI) calcd for $\mathrm{C}_{14} \mathrm{H}_{12} \mathrm{~F}_{3} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}: 265.0953$; found 265.0957. IR ( KBr ) $v$ $=606,710,763,1066,1326,1620,2360,2823,3239 \mathrm{~cm}^{-1}$.


Yellow solid, m.p. $=78^{\circ} \mathrm{C}, 89 \%$ yield and $95 \%$ ee, $[\alpha]_{\mathrm{D}}{ }^{20}=-11.30\left(\mathrm{c}=0.1, \mathrm{CHCl}_{3}\right)$ determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $98: 2 \mathrm{v} / \mathrm{v}$, $0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 254 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=20.570 \mathrm{~min}$ for $(R)$-isomer, $\mathrm{t}_{\mathrm{r}}$ $=22.074 \mathrm{~min}$ for $(S)$-isomer (major). ${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.63(\mathrm{~d}, 2 \mathrm{H}, J=8.2 \mathrm{~Hz}), 7.53$ $(\mathrm{d}, 2 \mathrm{H}, J=8.2 \mathrm{~Hz}), 6.62(\mathrm{~s}, 1 \mathrm{H}), 6.12(\mathrm{t}, J=3.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.52-5.51(\mathrm{~m}, 1 \mathrm{H}), 5.15(\mathrm{~s}, 1 \mathrm{H}), 4.12-4.15$ $(\mathrm{m}, 1 \mathrm{H}), ~ 4.02-3.97(\mathrm{~m}, 1 \mathrm{H}), 3.36-3.24(\mathrm{~m}, 2 \mathrm{H}), 1.89(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 142.9$, 130.7, 128.4, 128.3, 127.7, 118.9, 107.6, 104.8, 59.1, 45.4, 43.1. HRMS (ESI) calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{~N}_{2}$ $[\mathrm{M}+\mathrm{H}]^{+}: 224.1192$, found 224.1188. $\operatorname{IR}(\mathrm{KBr}) \mathrm{v}=639,680,728,944,1163,1368,1465,2361,2874$, $3063,3228 \mathrm{~cm}^{-1}$.

(S)-Methyl 4-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-1-yl)benzoate (3n)

White solid, m.p. $=89^{\circ} \mathrm{C}, 84 \%$ yield and $90 \%$ ee, $[\alpha]_{\mathrm{D}}{ }^{20}=-3.91\left(\mathrm{c}=0.1, \mathrm{CHCl}_{3}\right)$ determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $90: 10 \mathrm{v} / \mathrm{v}, 0.60 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 250 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}=21.623 \mathrm{~min}$ for $(R)$-isomer, $\mathrm{t}_{\mathrm{r}}=28.753 \mathrm{~min}$ for $(S)$-isomer (major). ${ }^{1} \mathbf{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.01(\mathrm{~d}, J=$ $8.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.47(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.61(\mathrm{~s}, 1 \mathrm{H}), 6.11(\mathrm{t}, J=3.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.53(\mathrm{~m}, 1 \mathrm{H}), 5.2(\mathrm{~s}$, $1 \mathrm{H}), 4.11-4.07(\mathrm{~m}, 1 \mathrm{H}), 4.03-3.98(\mathrm{~m}, 1 \mathrm{H}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 3.38-3.34(\mathrm{~m}, 1 \mathrm{H}), 3.29-3.25(\mathrm{~m}, 1 \mathrm{H}), 1.83$ (bs, 1H). ${ }^{13} \mathbf{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 166.9,147.9,129.7,129.6,128.3,119.2,107.8,105.0$, 58.6, 52.1, 45.3, 43.0. HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}_{2}[\mathrm{M}+\mathrm{H}]^{+}$: 257.1285; found 257.1279. IR $(\mathrm{KBr}) v=738,767,1019,1115,1280,1436,1610,1720,2810,2952 \mathrm{~cm}^{-1}$.

(S)-6-Methyl-1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (30)

91\% yield and $85 \%$ ee, determined by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol, $97: 3 \mathrm{v} / \mathrm{v}, 0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 254 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}$ $=31.665 \mathrm{~min}$ for $(R)$-isomer, $\mathrm{t}_{\mathrm{r}}=41.309 \mathrm{~min}$ for $(S)$-isomer (major). ${ }^{1} \mathbf{H} \mathbf{N M R}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 7.40 (d, $J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.34-7.29(\mathrm{~m}, 3 \mathrm{H}), 5.81(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.43(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.05$ $(\mathrm{s}, 1 \mathrm{H}), 3.84-3.82(\mathrm{~m}, 2 \mathrm{H}), 3.40-3.38(\mathrm{~m}, 1 \mathrm{H}), 3.28-3.25(\mathrm{~m}, 1 \mathrm{H}), 2.21(\mathrm{~s}, 3 \mathrm{H}), 1.88(\mathrm{bs}, 1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 142.9,129.9,128.3,127.6,126.9,105.3,104.0,59.3,43.1,42.8,11.5$.


## (S)-6,8-Dimethyl-1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (3p)

83\% yield and 70\% ee, determined by chiral HPLC analysis (Chiralpak AD-H, hexane/isopropanol, $97: 3 \mathrm{v} / \mathrm{v}, 0.6 \mathrm{~mL} / \mathrm{min}, 25^{\circ} \mathrm{C}$, UV 254 nm ): Retention times: $\mathrm{t}_{\mathrm{r}}$ $=26.174 \mathrm{~min}$ for $(R)$-isomer, $\mathrm{t}_{\mathrm{r}}=35.222 \mathrm{~min}$ for $(S)$-isomer (major). ${ }^{1} \mathbf{H} \mathbf{~ N M R ~}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 7.31-7.26 (m, 5H), 5.72 ( $\mathrm{s}, 1 \mathrm{H}), 5.12(\mathrm{~s}, 1 \mathrm{H}), 3.83-3.72(\mathrm{~m}, 2 \mathrm{H}), 3.22-3.16(\mathrm{~m}, 1 \mathrm{H}), 3.14-3.08(\mathrm{~m}$, $1 \mathrm{H}), 2.20(\mathrm{~s}, 3 \mathrm{H}), 1.55(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathbf{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 143.1,128.3,127.3,126.1,123.6$, 113.1, 107.4, 56.9, 42.8, 40.7, 11.4, 11.3.

### 4.4 Recovery and Reuse Studies

The recovery and reuse studies were performed for the tandem aerobic oxidation-asymmetric $a z a$ FC reaction between $\mathbf{1 a}$ and $\mathbf{2 a}$ (Table 9 S ) using the following procedure.

At the end of the reaction, the solution/suspension was carefully vacuum filtered with 8 mm filter paper (made for the Kiriyama funnel) to separate the insoluble materials from the organic compounds. The collected solids were then washed several times with THF and DCM. Next, the separated solids were placed in 300 mL of water and sonicated for 20 minutes (to dissolve $\mathbf{C a S O}_{4}$ ). This treated solid was filtered and washed three times with water, THF, and DCM. The solid material was then treated with aqueous $\mathrm{H}_{2} \mathrm{O}_{2}$ in MeOH and stirred overnight (to oxidize $\mathbf{B n S C H}_{3}$ ). The resulting solid was then filtered and washed several time with water, THF, and DCM, and the recovered catalyst was heated at $170{ }^{\circ} \mathrm{C}$ for 5 h under an atmosphere of $\mathrm{H}_{2}$. Finally, the recovered catalyst was transferred to a new Carousel tube for the next run.

Table 9S. Recovery and Reuse of IOC-PI/CB(Au/Pd) 8


| Run | Yield 3a (\%) ${ }^{a}$ | Ee 3a (\%) ${ }^{\text {b }}$ | Leaching ( $\mathbf{A u} / \mathbf{P d} / \mathbf{P})^{c}$ | Detection Limit ( $\mathbf{A u / P d / P})^{\text {c }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | 92 | 89 | ND/0.49\%/ND | 0.006/0.013/0.026 ppm |
| 2 | 91 | 88 | ND/0.24\%/ND |  |
| 3 | 90 | 88 | ND/0.19\%/ND |  |
| 4 | 87 | 87 | ND/0.21\%/ND | 0.01/0.014/0.015 ppm |
| 5 | 88 | 88 | ND/0.35\%/ND |  |
| 6 | 85 | 84 | ND/0.78\%/ND | 0.0075/0.011/0.032 ppm |

${ }^{a}$ Yield was determined by isolation of $50 \% \mathrm{v} / \mathrm{v}$ of a crude sample. ${ }^{b}$ The ee values were determined by chiral HPLC analysis. ${ }^{c}$ Leaching was determined by ICP analysis from $50 \% \mathrm{v} / \mathrm{v}$ of a crude sample. ND = below the detection limit of the ICP equipment.

It should be noted that the scale of the reaction was adjusted according to the amount of the IOC$\mathrm{PI} / \mathrm{CB}(\mathrm{Au} / \mathrm{Pd}) \mathbf{8}$ recovered from each run.

The $\mathrm{Au} / \mathrm{Pd} / \mathrm{P}$ leaching during the recovery and reuse studies was determined using the following procedure.

The filtrate obtained from each run was concentrated and diluted with 10 mL of THF. Then $50 \%$ $\mathrm{v} / \mathrm{v}$ of the crude THF solution ( 5 mL ) was then passed through a membrane filter ( 0.25 or $0.45 \mu \mathrm{~m}$ ) into a new test tube. The solvent was then removed under reduced pressure. The solid obtained in the test tube was then heated to $200{ }^{\circ} \mathrm{C}$ and 1.0 mL of concentrated $\mathrm{H}_{2} \mathrm{SO}_{4}$ was added. After further heating for 15 min , drops of concentrated $\mathrm{HNO}_{3}$ were added at regular intervals ( $45 \sim 60 \mathrm{~min}$ ) until the resulting solution was lightly coloured (yellow or orange, but not brown) and clear. Brown fumes should not be observed at this point when additional $\mathrm{HNO}_{3}$ is added. If brown fumes are still observed, the addition of $\mathrm{HNO}_{3}$ at regular intervals should be continued. To the obtained cooled clear solution, 1.0 mL of aqua regia was added and the resulting mixture was shaken lightly at first and then more vigorously. It was then diluted to 50 mL with water and the resulting diluted solution was filtered into a vial to remove any remaining solids. The clear solution was then subjected to ICP analysis.

## 5. Copies of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR Spectra




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## S-3



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## 6. Copies of the HPLC Chromatograms


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PDA Ch1 250nm 4nm

| Peak\# | Ret. Time | Area | Height | Area\% |
| ---: | ---: | ---: | ---: | ---: |
| 1 | 11.151 | 98108 | 7944 | 6.262 |
| 2 | 13.046 | 1468611 | 100956 | 93.738 |


rac-3I
PDA Ch1 250nm 4nm

| Peak\# | Ret. Time | Area | Height | Area\% |
| ---: | ---: | ---: | ---: | ---: |
| 1 | 39.070 | 9843235 | 219246 | 50.551 |
| 2 | 63.883 | 9628802 | 138260 | 49.449 |



31
PDA Ch1 250nm 4nm

| Peak\# | Ret. Time | Area | Height | Area\% |
| ---: | ---: | ---: | ---: | ---: |
| 1 | 36.690 | 4363259 | 102596 | 7.113 |
| 2 | 60.913 | 56981355 | 784132 | 92.887 |


|  |  |  <br> PDA Ch1 250nm 4nm |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Peak\# | Ret. Time | Area | Height | Area\% |
|  |  | 1 | 20.765 | 8621724 | 336274 | 50.044 |
|  |  | 2 | 23.349 | 8606604 | 305166 | 49.956 |
|  |  |  <br> PDA Ch1 250nm 4nm |  |  |  |  |
|  |  | Peak \# | Ret. Time | Area | Height | Area\% |
|  |  | 1 | 20.570 | 7914 | 290 | 2.698 |
|  |  | 2 | 22.074 | 285406 | 11012 | 97.302 |
|  |  |  |  |  |  |  |
|  |  |  <br> PDA Ch1 250nm 4nm |  |  |  |  |
| - | - | Peak\# | Ret. Time | Area | Height | Area\% |
|  |  | 1 | 21.595 | 553750 | 22308 | 49.766 |
|  | 27.5 30.0 | 2 | 29.296 | 558953 | 11892 | 50.234 |
|  |  |  <br> PDA Ch1 250nm 4nm |  |  |  |  |
|  |  | Peak\# | Ret. Time | Area | Height | Area\% |
|  | $27.5 \quad 30.0$ | 1 | 21.623 | 3039523 | 121516 | 5.104 |
|  |  | 2 | 28.753 | 56508110 | 1672996 | 94.896 |



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