asymmetric hydrogenation of azaarenes

quinalone  quinoxaline  indole  pyrrole  imidazole  oxazole

Reporter: Yajun REN
02/17/2014
IMPORTANCE & DEMAND of asymmetric hydrogenation of azaarenes

♫ Asymmetric hydrogenation is considered as a versatile method for the synthesis of new chiral compounds.

♫ The asymmetric hydrogenation of aromatic compounds will give the greatest number of potential chiral compounds.

♫ The asymmetric hydrogenation of azaarenes is a much less explored area.
Difficulties

- low activity of aromatic compounds
- harsh conditions are needed to destroy the aromaticity, which adversely affects the enantioselectivity
- nitrogen atom may poison and/or deactivate the chiral catalysts
early examples of homogeneous enantioselective hydrogenation of azaaromatic compounds


Fuchs, R. *European Patent Application* EP 803502, **1997**

strategies

catalyst activation

asymmetric hydrogenation of aromatic compounds

relay catalysis

substrate activation
**catalyst activation**

*low active catalyst*  
activator  
*high active catalyst*

Addition of additives or fine-tuning of steric and electronic effects of the chiral ligand.

**substrate activation**

*low active substrate*  
activator  
*high active substrate*

Introduction of activator to interact with the substrate and destroy the aromaticity partially, or as a secondary coordination group to assist coordination between substrate and catalyst.

**relay catalysis**

*aromatics*  
\( \xrightarrow{\text{cat. I}} \)  
*intermediates*  
\( \xrightarrow{\text{cat. II}} \)  
*products*

Partial hydrogenation  
Asymmetric hydrogenation
catalytic asymmetric hydrogenation

1. quinoline derivatives
2. quinoxaline derivatives
3. pyridine derivatives
4. indole derivatives
5. pyrrole derivatives
6. imidazoles and oxazoles
7. carbocyclic ring of quinoxalines

contents:
1. Catalytic asymmetric hydrogenation of quinoline derivatives

Scheme 1. Ir-catalyzed asymmetric hydrogenation of 2-substituted quinolines 1 with L1

Without iodine, only a trace amount of 2a were obtained with low ee

Reaction conditions: 1 mmol quinoline, [Ir(COD)Cl]2 (0.5%), chiral ligand (1.1%), I2 (10%), 5 mL solvent, under rt

Scheme 2. The proposed possible mechanism for Ir-catalyzed asymmetric hydrogenation of quinolines
Scheme 3. mechanism of Ir-Catalyzed hydrogenation of 2,3-disubstituted quinolines 5

![Scheme 3 diagram]

- High temperature and low hydrogen pressure (compared to rt, 700 psi) were employed to accelerate the isomerization and decelerate the hydrogenation.

more effective ligands with both high catalytic activity and enatioseselectivity.
Table 1 asymmetric hydrogenation of quinolines catalyzed by Ir-(P-Phos)\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R_1/R_2)</th>
<th>Yield (%)</th>
<th>ee(^b) (%)</th>
<th>Config.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me/H (1a)</td>
<td>97(98)(^d)</td>
<td>94(89)(^d)</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>Et/H (1b)</td>
<td>99(99)(^d)</td>
<td>92(90)(^e)</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>n-Pentyl/H (1c)</td>
<td>97 (2c)</td>
<td>91</td>
<td>(R)</td>
</tr>
<tr>
<td>4</td>
<td>Phenethyl/H (1d)</td>
<td>99 (2d)</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>5</td>
<td>Me/F (1e)</td>
<td>90(90)(^d)</td>
<td>90(88)(^d)</td>
<td>(S)</td>
</tr>
<tr>
<td>6</td>
<td>(1f)</td>
<td>99(99)(^d)</td>
<td>91(88)(^d)</td>
<td>(S)</td>
</tr>
<tr>
<td>7</td>
<td>(1g)</td>
<td>98 (2g)</td>
<td>90</td>
<td>(S)</td>
</tr>
</tbody>
</table>

\(\text{THF, r.t., } H_2 \text{ or DMPEG/hexane, r.t., } H_2\)

\(^a\) Reaction conditions: 0.5 mmol 1a, [Ir(COD)Cl]\(_2\) (0.0025 mmol), (R)-P-Phos (0.0055 mmol), I\(_2\) (0.025 mmol), 5 mL DMPEG/hexane (1/1), 700 psi \(H_2\), rt., 20 h.

**Air stable**


Scheme 5. Ir-catalyzed asymmetric hydrogenation of quinolines with diamine ligands

The reaction occurred smoothly in undegassed solvent with no need for inert gas protection.


Scheme 6. Ru-catalyzed asymmetric hydrogenation of quinolines 2a

The catalyst was stable in ionic liquid and showed the same activity and enantioselectivity after exposing to air for 30 days.

Scheme 7. activation of quinolines with chloroformates

- aromaticity was destroyed partially by the formation of quinolinium salts
- catalyst poison was avoided with the N-atom bonded by the activator
- COOR’ acted as a secondary coordination group, and thus is beneficial to the control of enantioselectivity

Scheme 8. asymmetric hydrogenation of quinolines 1 activated with chloroformates

Inconveniences:

- stoichiometric amount of ClCO₂Bn were used
- additional deprotection was needed for derivatives of hydrogenated products

Scheme 9. activation of quinolines with a catalytic amount of brønsted acid

Scheme 10. asymmetric hydrogenation of quinolines 1 activated with brønsted acid

2. catalytic asymmetric hydrogenation of quinoxaline derivatives

Scheme 12. Ir-catalyzed asymmetric hydrogenation of quinoxalines 20

![Scheme 12. Ir-catalyzed asymmetric hydrogenation of quinoxalines 20](image)

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21a</td>
<td>Me</td>
<td>H</td>
<td>93</td>
</tr>
<tr>
<td>21b</td>
<td>Et</td>
<td>H</td>
<td>89</td>
</tr>
<tr>
<td>21c</td>
<td>n-Bu</td>
<td>H</td>
<td>93</td>
</tr>
<tr>
<td>21d</td>
<td>i-Bu</td>
<td>H</td>
<td>94</td>
</tr>
<tr>
<td>21e</td>
<td>t-Bu</td>
<td>H</td>
<td>81</td>
</tr>
<tr>
<td>21f</td>
<td>Me</td>
<td>Me</td>
<td>87</td>
</tr>
<tr>
<td>21g</td>
<td>Et</td>
<td>Me</td>
<td>91</td>
</tr>
<tr>
<td>21h</td>
<td>Ph</td>
<td>H</td>
<td>85</td>
</tr>
<tr>
<td>21i</td>
<td>2-MeOC₆H₄</td>
<td>H</td>
<td>84</td>
</tr>
<tr>
<td>21j</td>
<td>PhCH₂=CH₂</td>
<td>H</td>
<td>97</td>
</tr>
<tr>
<td>21k</td>
<td>4-MeC₆H₄CH=CH</td>
<td>H</td>
<td>98</td>
</tr>
</tbody>
</table>

♫ The hydrogenation of 20a provided up to 5620/h TOF
(the highest TOF attained so far in the catalytic asymmetric HOAC)

Scheme 13. disproportionation of dihydroquinoxaline 4a

The first hydrogenation process catalyzed by Ru(II) complex is the rate-determining step.

The excellent enantioselectivity is attributed to the fact that $k_2$ is greater than undesired $k_3$. 

Scheme 14. proposed mechanism for the convergent asymmetric disproportionation of dihydroquinoxalines
3. Catalytic asymmetric hydrogenation of pypidine derivatives

**Approach 1**: Diastereoselective hydrogenation of a chiral precursor

**Approach 2**: The enantioselective hydrogenation of a prochiral substrate with a chiral catalyst

Substrate activation
Scheme 15. diastereoselective hydrogenation of pyridines 23 with Pd(OH)$_2$/C

This transformation unites the highly selective chirality transfer and nondestructive and traceless cleavage of the chiral auxiliary in one reaction.

AcOH not only activates the pyridine for hydrogenation but also suppresses the product piperidine to poison the catalyst.

Scheme 16. Brønsted acid-catalyzed enantioselective reduction of pyridines 28

♫ the first example of AOTH of trisubstituted pyridine using Hantzsch ester as hydrogen source

♫ the success attributed to the presence of the strong electron withdrawing substituents at 3-position of pyridines.

Scheme 17. Mechanistic proposal for enantioselective organocatalytic reduction of pyridines
4. catalytic asymmetric hydrogenation of indole derivatives

substrate activation and catalyst activation

Scheme 18. Rh-catalyzed asymmetric hydrogenation of N-Ac protected 2/3-substituted indoles 30/5

♫ trans-chelating bisphosphine ligand L41 was crucial for high enantioselective, other biphosphine ligand gave almost racemic products

♫ base additive was the other key factor for both reactivity and enantioselectivity

♫ The protecting group is pivotal for both reactivity and enantioselectivity

♫ unprotected simple indoles could not be hydrogenated under this catalytic system


a. Conditions: 0.25 mmol 36, Pd(OCOCF₃)₂ (2 mol%), (R)-H₈-BINAP (2.4 mol%), L-CSA (0.25 mmol), 3 mL solvent, 50 °C, 16–24 h. b. Determined by HPLC.
Scheme 19. isotopic labeling experiments using D$_2$ and d$^3$-TFE

In the former case:

♫ A reversible process of protonation and deprotonation existed
♫ The equilibrium is faster than hydrogenation

In the latter case:

♫ The indole was hydrogenated through the iminium intermediate activated by Bronsted acid
♫ The indole cannot be hydrogenated in the absence of acid.
5. catalytic asymmetric hydrogenation of pyrrole derivatives

Scheme 20. Pd-catalyzed asymmetric hydrogenation of simple pyrroles 47

♫1-pyrrolines were the sole products, no complete hydrogenation product pyrrolidine was observed

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Ar</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48a</td>
<td>Me</td>
<td>Ph</td>
<td>92</td>
</tr>
<tr>
<td>48b</td>
<td>Et</td>
<td>Ph</td>
<td>80</td>
</tr>
<tr>
<td>48c</td>
<td>n-Pr</td>
<td>Ph</td>
<td>81</td>
</tr>
<tr>
<td>48d</td>
<td>n-Pentyl</td>
<td>Ph</td>
<td>85</td>
</tr>
<tr>
<td>48e</td>
<td>i-Bu</td>
<td>Ph</td>
<td>86</td>
</tr>
<tr>
<td>48f</td>
<td>CyCH₂</td>
<td>Ph</td>
<td>86</td>
</tr>
<tr>
<td>48g</td>
<td>Bn</td>
<td>Ph</td>
<td>80</td>
</tr>
<tr>
<td>48h</td>
<td>Me</td>
<td>4-MeC₆H₄</td>
<td>81</td>
</tr>
<tr>
<td>48i</td>
<td>Me</td>
<td>3-MeC₆H₄</td>
<td>84</td>
</tr>
<tr>
<td>48j</td>
<td>Me</td>
<td>2-MeC₆H₄</td>
<td>85</td>
</tr>
<tr>
<td>48k</td>
<td>Me</td>
<td>4-CF₃C₆H₄</td>
<td>89</td>
</tr>
<tr>
<td>48l</td>
<td>Me</td>
<td>4-FC₆H₄</td>
<td>86</td>
</tr>
<tr>
<td>48m</td>
<td>Me</td>
<td>3,5-F₂C₆H₃</td>
<td>88</td>
</tr>
<tr>
<td>48n</td>
<td>Me</td>
<td>1-Naphthyl</td>
<td>90</td>
</tr>
</tbody>
</table>

Conditions: 47 (0.25 mmol), Pd(OCOCF₃)₂ (2 mol %), (R)-C4-TunePhos (2.4 mol %), EtSO₃H (0.375 mmol), solvent (3 mL), 60°C, 1624 h. b. isolated yields. c Determined by HPLC. d 1a (3.0 mmol), EtSO₃H (4.5 mmol), solvent (24 mL), 40 h.
Scheme 21. possible pathways for hydrogenation of pyrroles
B is more stable than A by 1.4 Kcal/mol ($\Delta G$ in CH$_2$Cl$_2$).

The calculation shows the hydride transfer barrier for A lower than that for B by 1.8 Kcal/mol.

B is more stable than A by 1.4 Kcal/mol ($\Delta G$ in CH$_2$Cl$_2$).

Figure 6. **Left:** optimized bond lengths (in angstroms) and charges (in parentheses) for intermediates A and B. **Right:** The structure of the transition state for hydride transfer with A (bond lengths in angstroms).
Scheme 22. process of pyrrole hydrogenation
6. asymmetric hydrogenation of imidazoles and oxazoles

Scheme 42. Ru-catalyzed asymmetric hydrogenation of imidazoles 49

Scheme 43. Ru-catalyzed asymmetric hydrogenation of 2,4 or 2,5-disubstituted oxazoles

<table>
<thead>
<tr>
<th>entry</th>
<th>R (4)</th>
<th>product</th>
<th>convn. (%)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Ph (4a)</td>
<td>5a</td>
<td>100</td>
<td>&gt;99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>2a</td>
<td>Ph (4a)</td>
<td>5a</td>
<td>100</td>
<td>86</td>
<td>98 (R)</td>
</tr>
<tr>
<td>3a</td>
<td>p-CH₃OC₆H₄ (4b)</td>
<td>5b</td>
<td>100</td>
<td>93</td>
<td>97 (R)</td>
</tr>
<tr>
<td>4a</td>
<td>p-FC₆H₄ (4c)</td>
<td>5c</td>
<td>100</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>5a</td>
<td>p-FC₆H₄ (4c)</td>
<td>5c</td>
<td>23</td>
<td>13</td>
<td>97</td>
</tr>
<tr>
<td>6a</td>
<td>p-CF₃OC₆H₄ (4d)</td>
<td>5d</td>
<td>100</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>7a</td>
<td>Me (4e)</td>
<td>5e</td>
<td>100</td>
<td>88</td>
<td>91 (R)</td>
</tr>
<tr>
<td>8a</td>
<td>Me (4e)</td>
<td>5e</td>
<td>23</td>
<td>—</td>
<td>84 (R)</td>
</tr>
<tr>
<td>9a</td>
<td>c-C₆H₁₁ (4f)</td>
<td>5f</td>
<td>100</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>10a</td>
<td>t-Bu (4g)</td>
<td>5g</td>
<td>5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11a</td>
<td>CO₂Me (4h)</td>
<td>5h</td>
<td>100</td>
<td>89</td>
<td>50 (S)</td>
</tr>
<tr>
<td>12a</td>
<td>Ph (4i)</td>
<td>5i</td>
<td>100</td>
<td>78</td>
<td>90 (S)</td>
</tr>
</tbody>
</table>

2014/2/17
7. **A bonus** -- asymmetric hydrogenation of carbocyclic ring of aromatic compounds

Scheme 44. Ru/NHC-catalyzed asymmetric hydrogenation of carbocyclic ring of quinoxalines

It is the first example of homogenous catalytic asymmetric hydrogenation of carbocyclic ring of aromatic compounds.

very high yields (12 examples 99%) with excellent regioselectivity ( > 99/1)

Scheme 45. Ligand-Controlled Regioselective Hydrogenation of Quinoxaline 18

♫ The regioselectivity of hydrogenation was completely controlled by the choice of NHC ligands

But how this reversion occurred? ongoing......
A number of effective catalytic systems including transition metal and organocatalysts have been successfully developed for the asymmetric hydrogenation of heteroarenes.

A breakthrough with asymmetric hydrogenation of carbocyclic ring of special quinoxaline substrates was also achieved.

Straightforward and facile access to a wide range of chiral compounds bearing cyclic skeleton with heteroatoms at the chiral center were offered.
Thank you for your attention