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Pyrazolidinones and related 1,2-diaza-3-one heterocycles are highly desirable building blocks owing to the fact that they frequently set up the core framework of numerous pharmaceutically and agro-chemically active compounds. Particularly, apart from drug development, optically pure pyrazolidinones have also shown great advantages in synthetic methodology. For example, the chiral pyrazolidinones could act as efficient catalyst to promote Diels-Alder reactions, and catalyze kinetic resolution of racemic secondary alcohols. Over the last decades, introduction of the fluorine into molecules has receiving increasing attention in the field of medicinal, agricultural, and material chemistry, primarily because the isosteric replacement of hydrogen by fluorine enhanced the lipophilicity, metabolic stability, and bioavailability of the parent compounds. Consequently, reliable methods toward the facile generation of optically active fluorinated pyrazolidinones would be very desirable in organic synthesis and drug research. However, the methods to chiral pyrazolidinones were still limited to transformation from chiral materials, classical chemical resolution or kinetic resolution involving pyrazolidine imides, and the synthesis of fluorinated pyrazolidinones is rarely explored. Considering the ready availability and easy preparation of fluorinated pyrazol-5-ols, asymmetric hydrogenation of these compounds would provied an atom-economical and straightforward access to optically pure pyrazolidinones (Scheme 1).

Despite much progress have been achieved in asymmetric hydrogenation of heteroaromatics including quinolines, isoquinolines, quinoxalines, pyridines, indoles, pyrroles, (benzo)furans, (benzo)thiophenes, imidazoles, indolizines, pyrimidines, and naphthyridines a great deal of problems still exist unsettled in this field. Such as, catalytic asymmetric hydrogenation of aromatic rings containing free hydroxyl, amido or other electron-enriched functional group and the heteroarenes containing two or more adjacent heteroatoms. The intrinsic problems are apparent: (i) the inherent stability resulting from aromaticity; (ii) the strong coordination effects endowed by the heteroatoms; (iii) the difficulty to control the stereoselectivity; (iv) the facile cleavage of heteroatoms bond. Therefore, the hydrogenation of this kind of electron-enriched aromatic pyrazol-5-ols with free hydroxy and two adjacent nitrogen-atoms is of great challenge and significance. Herein, we wish to report our initial findings on the development of Pd-catalyzed asymmetric hydrogenation of fluorinated pyrazol-5-ols with excellent enantioselectivities, yields, and diastereoselectivities.

**Scheme 1** Challenges in asymmetric hydrogenation of fluorinated pyrazol-5-ols.

At the outset, the readily available 1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol 1a, which can be synthesized from the easily accessible starting materials ethyl 4,4,4-trifluoro-3-oxobutanoate and phenylhydrazine, was selected as the model substrate for investigation. To our disappointment, the hydrogenation failed to proceed in the presence of common Rh, Ru, and Ir catalysts (Scheme 2). This may be ascribed to the strong coordination effects and high electron-enriched nature of fluorinated pyrazol-5-ols that impeded the hydrogenation.

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In principle, this kind of substrates exist in three tautomeric forms, i.e., the OH-
(form A), the NH- (form B) and the CH-isomer (form C) (Scheme 3). 1,4-
Hydroxy naphthalene (OH6) could promote 1,4-dihydroxynaphthalene
and form its stable tautomer tetralin6. 25 On the basis of these analyses, we envisioned that the combi-
nation of a Pd catalyst which is tolerant to acid excellently
and a Brønsted acid
could promote 1,4-dihydroxynaphthalene and accelerate iminium–amine isomerization to facilitate hydrogenation. 26

Further examinations were focused on ligand screening. From the evaluation of the various commercially available chiral axial
bisp hosphine ligands, excellent enantioselectivity was obtained with
ligand L2 (entry 6), providing the product in 96% ee and 81% isolated yield. When reaction time was prolonged to 48 hours, the yield was further improved without loss of enantioselectivity (entry 10). Therefore, the optimal condition was established as:
Pd(OCCOF3)2/L2/TFA in dichloromethane.

With the optimal conditions in hand, exploration of substrate scope was carried out, and the results were summarized in Table 2. Gratifyingly, a variety of 1-aryl substituted substrates were smoothly
converted to the corresponding pyrazolidinones with excellent enantioselectivities (82-96% ee). The electronic properties of the substituents on the phenyl ring had little effect on the activity and enantioselectivity (entry 5 vs entries 6-8). However, the hydrogenation of 2-o-tolyl-substituted pyrazol-5-ol 1b gave moderate 82% of enantioselectivity and 67% yield (entry 2). When TangPhos L5, which was developed by Zhang’s group in 2002, 28 was employed and the temperature was elevated to 100 °C, the pyrazol-5-ol substrates (1h-1j) bearing pentafluor ethyl substituent could also be hydrogenated with excellent enantioselectivities and yields (entries 9-10).

Table 1 Optimization of asymmetric hydrogenation of pyrazol-5-ol 1a. 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OCCOF3)2 + L1</td>
<td>TFA</td>
<td>54</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OCCOF3)2 + L1</td>
<td>TFA</td>
<td>52</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OCCOF3)2 + L1</td>
<td>L-CSA</td>
<td>46</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OCCOF3)2 + L1</td>
<td>D-CSA</td>
<td>39</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OCCOF3)2 + L1</td>
<td>TsOH·H2O</td>
<td>32</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OCCOF3)2 + L2</td>
<td>TFA</td>
<td>81</td>
<td>96</td>
</tr>
</tbody>
</table>

1 Reaction conditions: Pd(OCCOF3)2 (2 mol %), ligand (2.1 mol %), 1a (0.3 mmol), Additive (0.3 mmol), H2 (1200 psi), DCM (2 mL), 60 °C, 48 h. 2 Determined by HPLC. 3 Use TFE as solvent. 48 h.

For the sake of further application possibility, a range of 4-substituted-(trifluoromethyl)-1H-pyrazol-5-ols (3a-3g) was also investigated (Table 3). The substrates with alkyl-substituent at 4-position could be hydrogenated smoothly, providing the...
corresponding the 2,4,5-trisubstituted pyrazolidinone derivatives with high enantioselectivity and diastereoselectivity. The high diastereoselectivity probably ascribes to the thermodynamic stability of trans products under this harsh acidic condition. Substrates bearing long alkyl or bulky substituents at C4-position gave slightly higher enantioselectivity (entry 1 vs entries 3, 6, 7).

Table 3 Pd-catalyzed asymmetric hydrogenation of pyrazol-5-ols 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>C2H4</td>
<td>72 (4a)</td>
<td>89 (-)</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>4-MeC2H4</td>
<td>97 (4b)</td>
<td>88 (+)</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>C2H4</td>
<td>93 (4c)</td>
<td>94 (+)</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>4-MeC2H4</td>
<td>92 (4d)</td>
<td>93 (+)</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>3-MeC2H4</td>
<td>90 (4e)</td>
<td>92 (+)</td>
</tr>
<tr>
<td>6</td>
<td>&quot;Pr</td>
<td>C6H6</td>
<td>95 (4f)</td>
<td>93 (+)</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>C6H6</td>
<td>94 (4g)</td>
<td>95 (45.5R)</td>
</tr>
</tbody>
</table>

*Pd(OOCF2)2 (4 mol%), (S,S’,R,R’)-TangPhos (5.2 mol%), 3 (0.2 mmol), H2 (1200 psi), L-CSA (0.2 mmol), TFE (2 mL), 100 °C, 48 h. In all cases δr > 20.1. *Isolated yields. Determined by HPLC.

The absolute configurations of hydrogenation products 2a and 4g were determined by X-ray diffraction analysis by recrystallization from the mixture solvent dichloromethane/n-hexane. The configurations of the other chiral products are assigned by analogy.

Scheme 4 Reactions for mechanistic investigation. All reactions were carried out under the condition of Pd(OOCF2)2 (4 mol%), (S)-MeO-Biphep (5.2 mol%), substrate (0.2 mmol), H2 (1200 psi), TFA (0.2 mmol), DCM (2 mL), 60 °C, 48 h.

In order to verify our hypothesis that the hydrogenation carried out via capture of the active tautomers, we synthesized three compounds (form A type 5, form B type 6 and form C type 8) and subject them to identical hydrogenation reaction (Scheme 4). As expected, no reaction was observed for the substrate 5; for substrate 6, low 10% ee and 14% yield were obtained; the CH-form substrate 8 gave excellent 91% ee with 89% yield. Based on the experimental results and stereochemistry of the products, we proposed that the reaction experienced the process of Bronsted acid promoted tautomerization to form CH-form tautomer C, followed by Pd-catalyzed asymmetric hydrogenation of the active tautomer C to give the optically active pyrazolidinones. And this preliminary result demonstrated the practicability of our strategy that asymmetric hydrogenation of the inseparable active isomers to realize hydrogenation of the intractable isomericable substrates.

Conclusions

An efficient palladium-catalyzed asymmetric hydrogenation of fluorinated aromatic pyrazol-5-ols has been developed via capture of active tautomers. A wide variety of 2,5-disubstituted and 2,4,5-trisubstituted pyrazolidinone derivatives have been synthesized with up to 96% and 95% ee, respectively. The hydrogenation pathway includes Bronsted acid promoted tautomerization of pyrazol-5-ols and palladium-catalyzed asymmetric hydrogenation of active tautomer. This study provides some enlightenment on the application of asymmetric hydrogenation and useful information for the design of new reactions. Further study on applying this novel strategy to other aromatic compounds and exploration of the application of the chiral pyrazolidinones is in progress in our laboratory.

Acknowledgements

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Notes and references


For a report on asymmetric hydrogenation of benzosoxazoles with the cleavage of heteratoms bond, see: R. Ikeda, R. Kuwano, Molecules, 2012, 17, 6901.


