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Pd-catalyzed asymmetric hydrogenation of fluorinated aromatic pyrazol-5-ols *via* capture of active tautomers†

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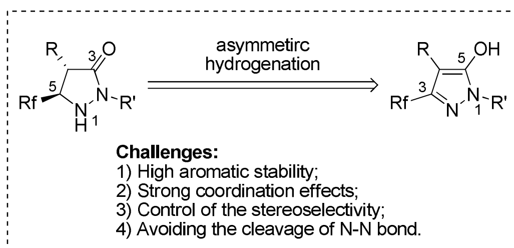
Zhang-Pei Chen,[a] Mu-Wang Chen,[a] Lei Shi,[a] Chang-Bin Yu,[a] and Yong-Gui Zhou[a,b]

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 pyrazolidinones have been synthesized with up to 96% and 95% ee, respectively. The hydrogenation pathway includes Brønsted acid promoted tautomerization of pyrazol-5-ols and Pd-catalyzed asymmetric hydrogenation of the active tautomer.

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 agrochemically active compounds.[1] Particularly, apart from drug development, optically pure pyrazolidinones have also shown great advantages in synthetic methodology.[2] For example, the chiral pyrazolidinones could act as efficient catalyst to promote Diels-Alder reactions, and catalyze kinetic resolution of racemic secondary alcohols.[3] 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.[4] Consequently, reliable methods toward the facile generation of optically active fluorinated pyrazolidinoes would be very desirable in organic synthesis and drug research. However, the methods to chiral pyrazolidinones were still limited to transformation from chiral materials,[5] classical chemical resolution[3a] or kinetic resolution involving pyrazolidinone imides,[6] 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 provid an atom-economical and straitforward access to optically pure pyrazolidiones (Scheme 1).

Despite much progress have been achieved in asymmetric hydrogenation of heteroaromatics[7] including quinolines,[8] iso-quinolines,[9] quinoxalines,[10] pyridines,[11] indoles,[12] pyrroles,[13] (benzo)furans,[14] (benzo)thiophenes,[15] imidazoles,[16] indolizines,[17] pyrimidines,[18] and naphthyridines[19] a great deal of problems still stay 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 dificulty to control the stereoselectivity; (iv) the facilely cleavage of heteroatoms bond.[20] Therefore, the hydrogenation of this kind of electron-enriched aromatic pyrazol-5-ols with free hydroxyl 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)-1*H*-pyrazol-5-ol **1a**, which can be synthesized from the easily accessible starting materials ethyl 4,4,4-trifluoro-3-oxobutanoate and phenylhydrazine,[21] 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.

[a] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China. E-mail: ygzhou@dicp.ac.cn
[b] Collaborative Innovation Centre of Chemical Science and Engineering (Tianjin), Tianjin 300071, P. R. China

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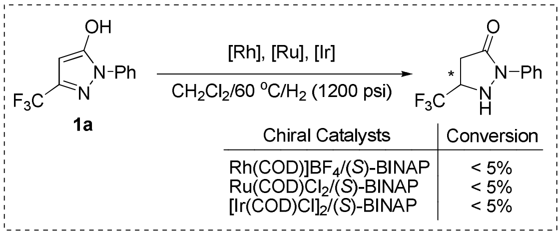
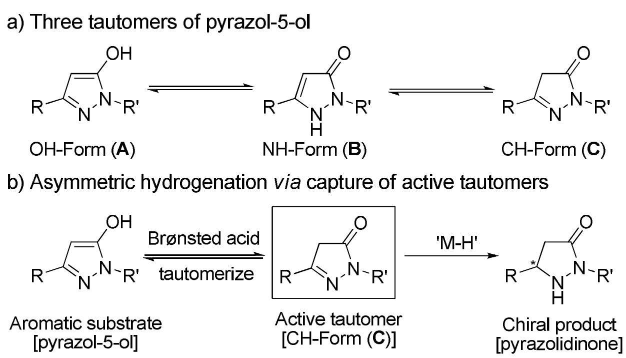


Scheme 2 Asymmetric hydrogenation of fluorinated pyrazol-5-ol **1a**

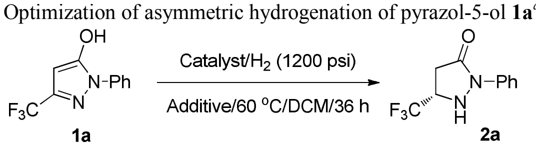
In principle, this kind of substrates exist in three tautomeric forms, i.e. the OH- (form **A**), the NH- (form **B**) and the CH-isomer (form **C**) (Scheme 3).[1e,22] Documents investigation[23] and experiment data including X-ray crystal structure[24] analysis demonstrated that form **A** is the most stable and dominant form. In view of the fact that the alkylation of pyrazol-5-ols would selectively lead to akylation products *O*-alkyl derivatives and *N*-alkyl derivatives under specifical requirements, we supposed that appropriate conditions will promote the high aromatic tautomer **A** to tautomerize to the more active tautomer **C**. The previous results have demonstrated that trifluoroacetic acid (TFA) could promote 1,4-dihydroxynaphthalene to form its stable tautomer tetralin-1,4-dione,[25] and accelerate iminium–enamine isomerization to facilitate hydrogenation.[26] On the basis of these analyses, we envisioned that the combination of a Pd catalyst which is tolerant to acid excellently[27] and a Brønsted acid could be suitable for asymmetric hydrogenation of fluorinated pyrazol-5-ols.



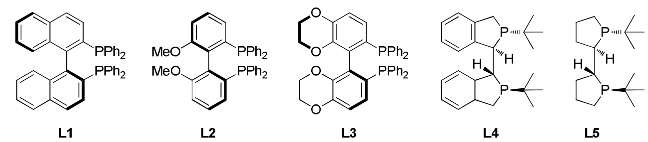
Scheme 3 The tautomeric forms of pyrazol-5-ols and hydrogenation strategy.

To our delight, the exposure of **1a** with TFA in dichloromethane furnished the desirable pyrazolidinone **2a** with 91% ee and 54% conversion using $Pd(OCOCF_3)_2$/(*S*)-BINAP as catalyst (Table 1, entry 1). When the reaction carried out in 2,2,2-trifluoroethanol (TFE), the reactivity and enantioselectivity dropped slightly (entry 2). Subsequently, the effect of other acids were investigated, and TFA was the most suitable choice in view of the reactivity and enantioselectivity.

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



Entry	Catalyst	Additive	Yield (%)[b]	Ee (%)[c]
1	$Pd(OCOCF_3)_2$ + **L1**	TFA	54	91
2[d]	$Pd(OCOCF_3)_2$ + **L1**	TFA	52	90
3	$Pd(OCOCF_3)_2$ + **L1**	*L*-CSA	46	90
4	$Pd(OCOCF_3)_2$ + **L1**	*D*-CSA	39	90
5	$Pd(OCOCF_3)_2$ + **L1**	TsOH·H_2O	32	90
6	$Pd(OCOCF_3)_2$ + **L2**	TFA	81	96
7	$Pd(OCOCF_3)_2$ + **L3**	TFA	46	93
8	$Pd(OCOCF_3)_2$ + **L4**	TFA	29	90
9	$Pd(OCOCF_3)_2$ + **L5**	TFA	20	97
10[e]	$Pd(OCOCF_3)_2$ + **L2**	TFA	94	96

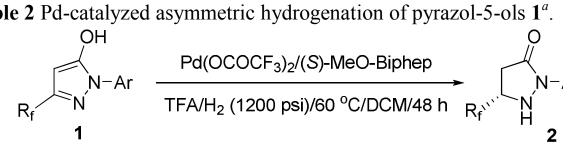


[a] Reaction conditions: $Pd(OCOCF_3)_2$ (2 mol %), ligand (2.1 mol %), **1a** (0.3 mmol), Additive (0.3 mmol), H_2 (1200 psi), DCM (2 mL), 60 °C, 36 h. [b] Isolated yields. [c] Determined by HPLC. [d] Use TFE as solvent. [e] 48 h.

Further examinations were focused on ligand screening. From the evaluation of the various commercially available chiral axial bisphosphine 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: $Pd(OCOCF_3)_2$/**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 (**1i-1j**) bearing pentafluoroethyl substituent could also be hydrogenated with excellent enantioselectivities and yields (entries 9-10).

Table 2 Pd-catalyzed asymmetric hydrogenation of pyrazol-5-ols **1**[a].

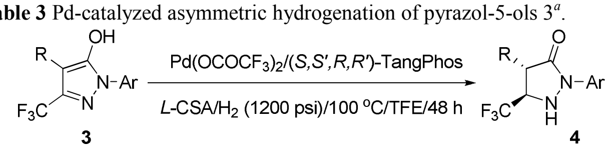


Entry	R_F	Ar	Yield (%)[b]	Ee (%)[c]
1	CF_3	C_6H_5	94 (**2a**)	96 (*S*)
2[d]	CF_3	2-MeC_6H_4	67 (**2b**)	82 (+)
3	CF_3	3-MeC_6H_4	93 (**2c**)	95 (+)
4	CF_3	4-MeC_6H_4	93 (**2d**)	96 (+)
5	CF_3	4-$MeOC_6H_4$	94 (**2e**)	95 (+)
6	CF_3	3-ClC_6H_4	89 (**2f**)	95 (+)
7	CF_3	3,4-$Cl_2C_6H_3$	90 (**2g**)	93 (+)
8	CF_3	4-FC_6H_4	93 (**2h**)	94 (+)
9[e]	C_2F_5	C_6H_5	95 (**2i**)	94 (-)
10[e]	C_2F_5	4-MeC_6H_4	92 (**2j**)	95 (-)

[a] $Pd(OCOCF_3)_2$ (2 mol%), (*S*)-MeO-Biphep (2.1 mol%), **1** (0.3 mmol), H_2 (1200 psi), TFA (0.3 mmol), DCM (2 mL), 60 °C, 48 h. [b] Isolated yields. [c] Determined by HPLC. [d] $Pd(OCOCF_3)_2$ (4 mol%), (*S*)-MeO-Biphep (4.2 mol%), 1b (0.2 mmol), H_2 (1200 psi), TFA (0.2 mmol), DCM (2 mL), 60 °C, 48 h. [e] $Pd(OCOCF_3)_2$ (4 mol%), (*S,S',R,R'*)-TangPhos (5.2 mol%), 1 (0.2 mmol), H_2 (1200 psi), *L*-CSA (0.2 mmol), TFE (2 mL), 100 °C, 48 h.

For the sake of further estimate the application possibility, a range of 4-substitued-3-(trifluoromethyl)-1*H*-pyrazol-5-ols (**3a**-3**g**) 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).

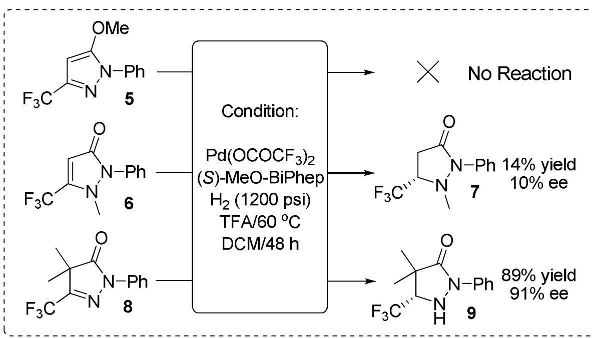
Table 3 Pd-catalyzed asymmetric hydrogenation of pyrazol-5-ols 3[a].



Entry	R	Ar	Yield (%)[b]	Ee (%)[c]
1	Me	C_6H_5	92 (**4a**)	89 (-)
2	Me	4-MeC_6H_4	97 (**4b**)	88 (+)
3	Et	C_6H_5	93 (**4c**)	94 (+)
4	Et	4-MeC_6H_4	92 (**4d**)	93 (+)
5	Et	3-MeC_6H_4	90 (**4e**)	92 (+)
6	^{n}Pr	C_6H_5	95 (**4f**)	93 (+)
7	Bn	C_6H_5	94 (**4g**)	95 (4*S*,5*R*)

[a] Pd(OCOCF$_3$)$_2$ (4 mol%), (*S,S',R,R'*)-TangPhos (5.2 mol%), **3** (0.2 mmol), H_2 (1200 psi), *L*-CSA (0.2 mmol), TFE (2 mL), 100 °C, 48 h. In all cases dr > 20:1. [b] Isolated yields. [c] 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.[29] 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(OCOCF$_3$)$_2$ (4 mol%), (*S*)-MeO-Biphep (5.2 mol%), substrate (0.2 mmol), H_2 (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 tautomer, 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 Brønsted 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 Brønsted 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.

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