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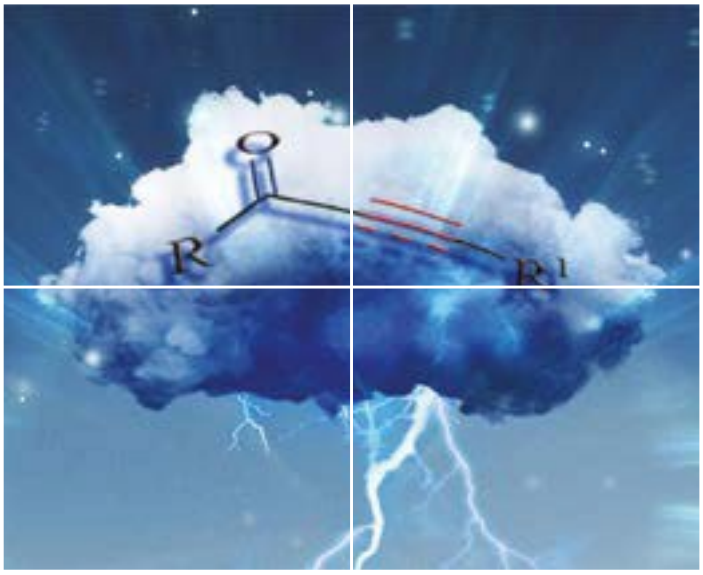

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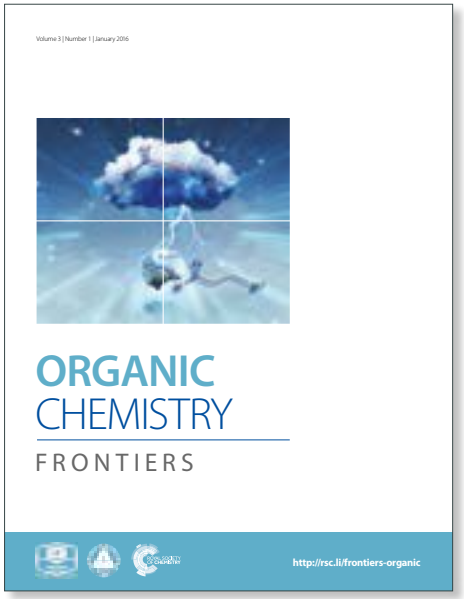

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RESEARCH ARTICLE

Enantioselective Synthesis of Trifluoromethylated Dihydroquinoxalinones *via* Palladium-catalyzed Hydrogenation

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A highly enantioselective palladium-catalyzed asymmetric hydrogenation of 3-(trifluoromethyl)quinoxalinones has been successfully developed, providing a general and facile access to chiral 3-(trifluoromethyl)-3,4-dihydroquinoxalinones with up to 99% ee. In addition, the 3-(trifluoromethyl)-3,4-dihydroquinoxalinones can be conveniently converted into 2-(trifluoromethyl)-1,2,3,4-tetrahydroquinoxalines in excellent yields without loss of optical purity.

Chiral dihydroquinoxalinones represent important structure motifs in natural products and synthetic bioactive molecules as well as pharmaceuticals.[1] As indicated in Figure 1, Kinin B1 is applied to the treatment of inflammation and pain in septicemia,[2a] and GW420867X is utilized as a non-nucleoside HIV-1 reverse transcriptase inhibitor (Fig. 1).[2b]

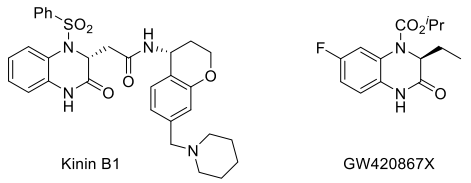
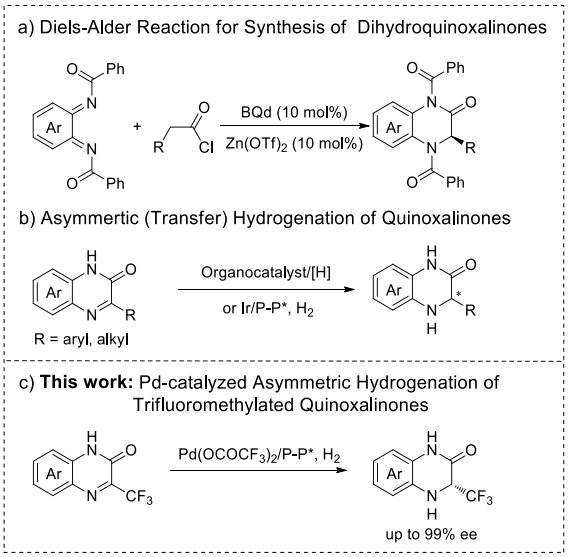


Figure 1. Selected bioactive chiral dihydroquinoxalinones

Consequently, the synthesis of chiral dihydroquinoxalinones has attracted considerable attention, and many strategies have been successfully developed. The common strategies for the synthesis of the chiral dihydroquinoxalinone were using amino acid derivatives or chiral esters as starting materials.[3-4] In 2006, an elegant Hetero-Diels-Alder reaction for asymmetric synthesis of chiral dihydroquinoxalinone derivatives was developed by Lectka' group.[5] Subsequently, the asymmetric hydrogenation,[6] transfer hydrogenation and tandem cyclization/transfer hydrogenation of quinoxalinones have been successfully achieved by Rueping, Vidal-Ferran, Shi, et al.[7] Despite their impressive significance, the synthesis of chiral trifluoromethylated dihydroquinoxalinones is still an area which has been rarely explored to date. In general, the introduction of fluorine into molecules can enhance the lipophilicity, metabolic stability, and bioavailability of the parent compounds, which has achieved extensive attention in the fields of pharmaceuticals, agrochemicals, fragrances and materials.[8] Therefore, an efficient and atom-economic approach toward the synthesis of chiral trifluoromethylated dihydroquinoxalinones from the simple and abundant starting materials is still highly desirable in organic synthesis and drug research.



Scheme 1 Asymmetric synthesis of chiral dihydroquinoxalinones

In the past decades, homogeneous palladium catalyst has been successfully applied for asymmetric hydrogenation of various aromatics[9] and imine substrates.[10] Considering the ready availability and easy preparation of trifluoromethylated quinoxalinones, we envisioned that chiral trifluoromethylated dihydroquinoxalinones could be easily synthesized through Pd-catalyzed asymmetric hydrogenation of these compounds. As we all known, the C=N of quinoxalinone was easily reduce in the presence of metal catalyst (Pd、Ir and Rh) and hydrogen source to afford the 3,4-dihydroquinoxalinone, which have been reported by Fuente[11a], Vidal-Ferran[6] and Xu's group.[11b] However, the amide of dihydroquinoxalinone is not easy reduce catalyzed by metal catalyst (Pd、Ir and Rh) with hydrogen source. Therefore, the chemoselectivity may be very good between C=N and C=O. In addition, the aromaticity of trifluoromethylated quinoxalinones which was attributed to the presence of keto and enol tautomeric forms might cause

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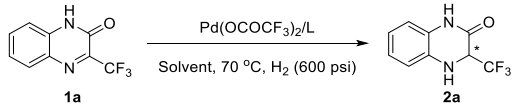
the low reactivity.[12a] Moreover, the easy cleaved of C–F bond in transition-metal-catalyzed systems could make the hydrogenation of trifluoromethylated quinoxalinones challenging.[12b] Herein, we reported a highly enantioselective palladium-catalyzed hydrogenation of trifluoromethylated quinoxalinones to trifluoromethylated dihydroquinoxalinone derivatives with up to 99% of enantioselectivity and yield.

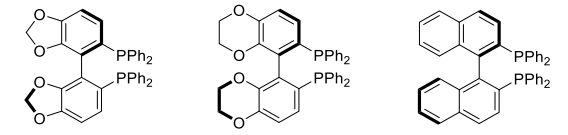
To test the viability of our proposed protocol, readily synthetic 3-(trifluoromethyl)quinoxalinone (**1a**) was chosen as the model substrate. Gratifyingly, the reaction proceeded smoothly to afford the desired product **2a** in 76% conversion and 97% ee in the presence of $Pd(OCOCF_3)_2$/(*R*)-SegPhos in 2,2,2-trifluoroethanol (TFE) at 70 °C for 48 h (Table 1, entry 1). Subsequently, various solvents including toluene, DCM and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were tested, and HFIP was proved to be the best one (entries 2-4). The fluorinated solvent HFIP not only have acidic properties, but also have H–bonding with substrate in the asymmetric hydrogenation process, which could also explain the stereochemical models in Figure 3.[9g,13] Next, we further screened several commercially available chiral bisphosphine ligands (entries 4-9), and the best result was achieved with (*R*)-SegPhos **L1** (entry 4, 96% ee).

Table 1 Optimization of the reaction conditions [a]

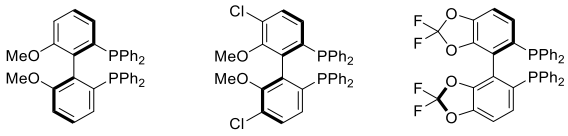


1a 2a

Entry	Solvent	L	Conv. (%)[b]	Ee (%)[c]
1	TFE	**L1**	76	97
2	Toluene	**L1**	<5	/
3	DCM	**L1**	62	22
4	HFIP	**L1**	>95	96
5	HFIP	**L2**	>95	92
6	HFIP	**L3**	>95	86
7	HFIP	**L4**	>95	93
8	HFIP	**L5**	>95	88
9	HFIP	**L6**	92	95
10[d]	HFIP	**L1**	>95	96
11[e]	HFIP	**L1**	>95	96
12[f]	HFIP	**L1**	93	95
13[g]	HFIP	**L1**	95	95



(*R*)-SegPhos **L1** (*R*)-SynPhos **L2** (*R*)-BINAP **L3**



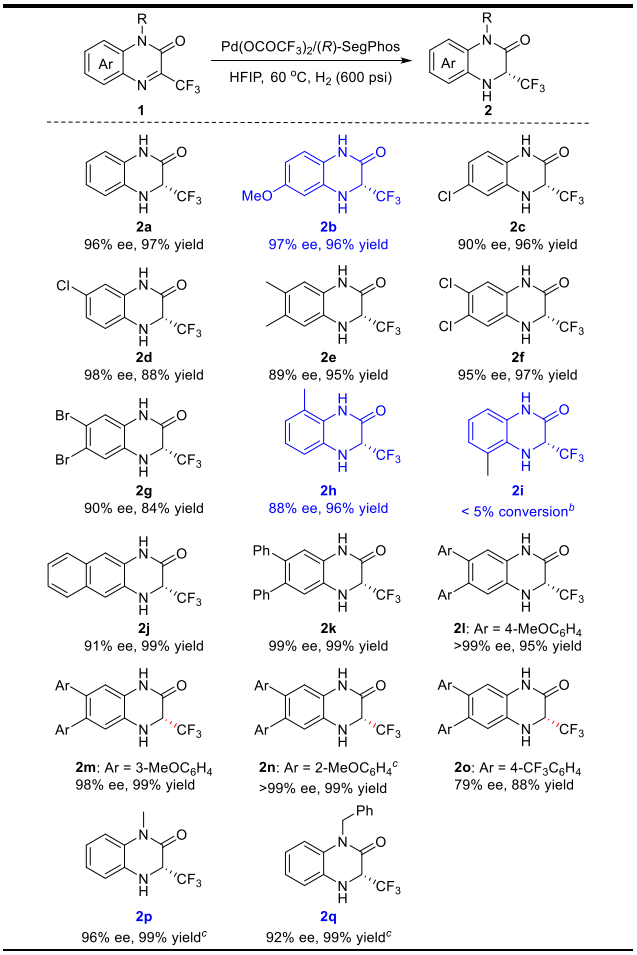
(*R*)-MeO-BiPhep **L4** (*R*)-Cl-MeO-BiPhep **L5** (*R*)-DifluorPhos **L6**

[a] Conditions: **1a** (0.125 mmol), $Pd(OCOCF_3)_2$ (4.0 mol %), ligand (4.8 mol %), H_2 (600 psi), solvent (3.0 mL), 70 °C, 48 h. [b] Determined by ^1H NMR. [c] Determined by HPLC. [d] $Pd(OCOCF_3)_2$ (3.0 mol %), ligand (3.6 mol %). [e] 60 °C. [f] 50 °C. [g] H_2 (400 psi).

The lower catalyst loading (3 mol % Pd) and temperature (60 °C) did not affect the yield and ee value of **2a** (entries 10-11). However, further decreasing the temperature and hydrogen pressure also did not affect the ee value of **2a**, but the yield was slightly decreased (entries 12-13). Thus, the optimized conditions were established as follows: $Pd(OCOCF_3)_2$/**L1**, H_2 (600 psi), HFIP and 60 °C.

With the optimized reaction conditions in hand, we next examined the substrate scope, and the results were summarized in Table 2.

Table 2 Substrate scope for synthesis of chiral 3-(trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-ones [a]

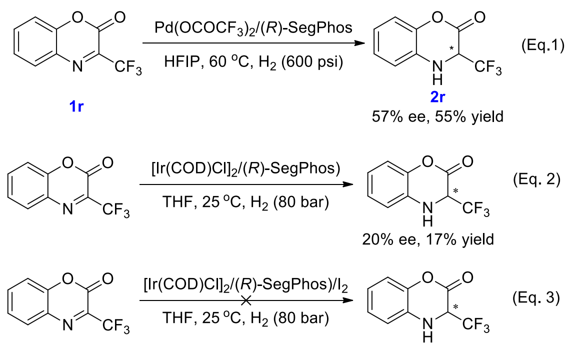


[a] Reaction conditions: **1** (0.25 mmol), $Pd(OCOCF_3)_2$ (3.0 mol %), (*R*)-SegPhos (3.6 mol %), H_2 (600 psi), HFIP (3.0 mL), 60 °C, 48 h, Isolated yields. The ee values determined by HPLC. [b] Determined by ^1H NMR. [c] $Pd(OCOCF_3)_2$ (4.0 mol %), (*R*)-SegPhos (4.8 mol %), 70 °C.

As expected, various substrates performed well under the standard reaction conditions. The electronic properties of substituent on the aromatic ring had a marginal effect on the reactivity and enantioselectivity (**2a to 2h**). However, the position of substituent on the aromatic ring is very important. For example, the substrate containg a methyl group at 8-position on the phenyl ring was suitable, affording the desirable product with 88% ee and 96% yield (**2h**). But the methyl group at 5-position on the phenyl ring of 3-(trifluoromethyl)-quinoxalinone have very low activity (**2i**, yield<5%) due to the steric effect. Furthermore, the

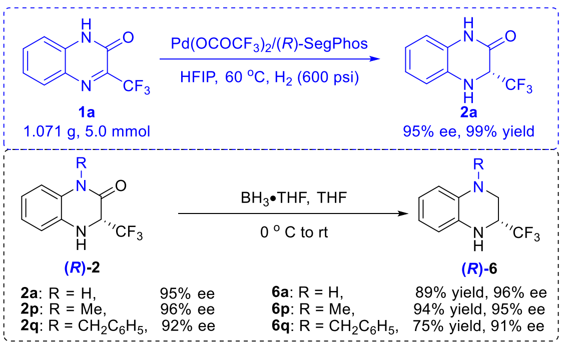
introduction of aryl at 6,7-position on the phenyl ring of 3-(trifluoromethyl)-quinoxalinone were also examined (**2j**-**2o**). The positions of substituent on the aryl ring did not inhibit the reactions, but the electronic properties of substituent on the aryl ring had a certain effect on the reaction (**2l** to **2o**). Interestingly, the methyl and benzyl substitution at the N1 position of the quinoxalinone (**1p and 1q**) was hydrogenated with 4% catalyst loading at 70 ºC, giving the desirable product with 96% and 92 ee, respectively.

In order to understand the difference between Pd and Ir complex in this catalyzed asymmetric hydrogenation,[6] 3-(Trifluoromethyl)-2*H*-benzo[*b*][1,4]oxazin-2-one (**1r**) was selected as a model, which is also suitable substrate under the standard condition, giving the product with 55% yield and 57% ee (2r, Scheme 2, Eq. 1). However, the desired product was obtained only in 17% yield with 20% ee value, when the reaction was catalyzed by $[Ir(COD)Cl]_2$/(*R*)-SegPhos/H_2 (80 bar) in tetrahydrofuran (THF) at 25 ºC (Eq. 2). In addition, we try to added 5 mol% I_2 in the $[Ir(COD)Cl]_2$/(*R*)-SegPhos, unfortunately, no desired product was obtained (Eq. 3). These results indicated that Pd catalyst have more advantage than that of Ir complex in asymmetric hydrogenation of trifluoromethyl quinoxalinone series.



Scheme 2. Synthesis of chiral 3-(trifluoromethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one

After establishing the facile approach for synthesis of chiral trifluoromethylated dihydroquinoxalinones by asymmetric hydrogenation, the product elaboration was achieved. The scale-up experiment was carried out at 5.0 mmol scale (Scheme 3). To our delight, the desired chiral 3-(trifluoromethyl)-3,4-dihydroquinoxalin-one **2a** was obtained without the loss of activity and enantioselectivit (95% ee, 99% yield).



Scheme 3. Scale-up experiment and product elaboration

Reduction of **2** using BH_3·THF at 0ºC and room temperature giving the chiral trifluoromethylated tetrahydroquinoxalines **6** without loss of optical purity (Scheme 3),[14] which is an essential scaffold in numerous important pharmaceutical compounds and bioactive natural products.[15] The absolute configuration of the product **6a** was determined based on single crystal X-ray diffraction analysis (Figure 2) (see the ESI†).

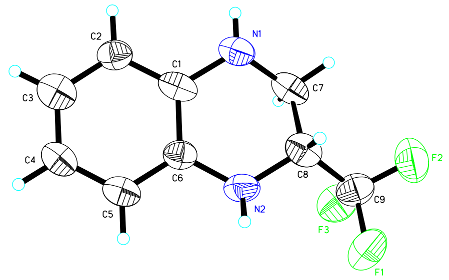


Figure 2. X-ray crystal structure of compound **6a**

Based on the above results, the stereochemistry of this reaction could be explained by the stereochemical models [9g] in Figure 3.

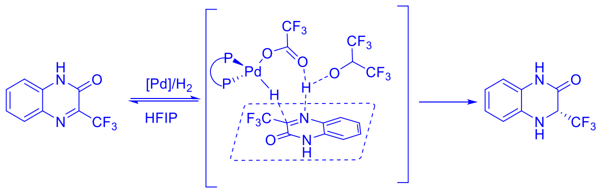


Figure 3. Stereochemical model.

Conclusion

In conclusion, we have successfully developed an efficient and direct protocol for synthesis of chiral trifluoromethylated dihydro-quinoxalinones by palladium-catalyzed hydrogenation of the corresponding trifluoromethylated quinoxalinones with up to 99% ee. Meanwhile, chiral trifluoromethylated tetrahydroquinoxalines could be efficiently prepared by reducing the chiral trifluoromethylated dihydroquinoxalinones. Further investigations on asymmetric hydrogenation of fluorinated heteroaromatics are currently on going in our laboratory.

Experimental

A typical procedure for palladium-catalyzed asymmetric hydro-genation of 3-(trifluoromethyl)quinoxalinone **1a**

Ligand (*R*)-SegPhos (5.4 mg, 0.009 mmol) and $Pd(OCOCF_3)_2$ (2.6 mg, 0.0075 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give the catalyst. This catalyst was taken into a glovebox filled with nitrogen and dissolved in dry HFIP (3 mL). To a mixture of 3-(trifluoro-methyl)quinoxalinone (0.25 mmol), the catalyst solution was

added, and then the mixture was transferred to an autoclave, which was charged with H_2 (600 psi). The autoclave was stirred under directed conditions for 48 h, then the hydrogen was carefully released, the autoclave was opened, and the reaction mixture was evaporated. Purification was performed on silica gel using *n*-hexane/ethyl acetate as the eluent to give the chiral products **2a** as a white solid (53 mg, 97% yield, 96% ee). The enantiomeric excess was determined by chiral HPLC (OD-H elute: *n*-hexane/*i*-propanol = 90/10, detector: 230 nm, flow = 1.0 mL/min^{-1}), 30 ^{o}C, t_1 = 12.6 min (maj), t_2 = 14.5 min.

Acknowledgements

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