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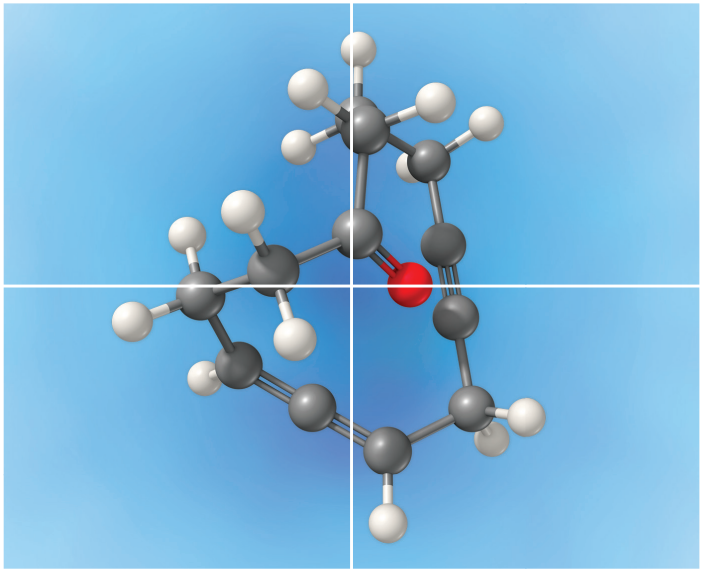

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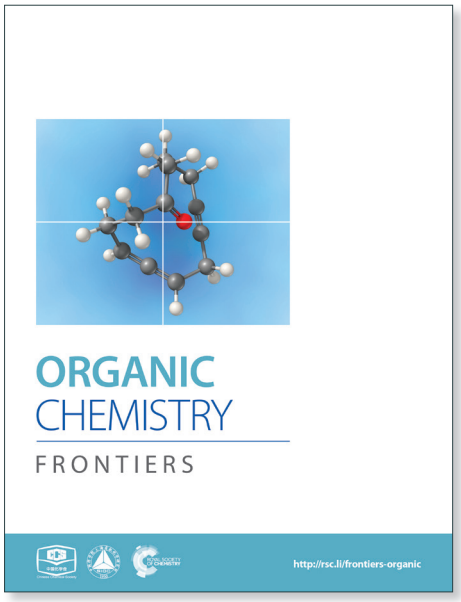

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ARTICLE TYPE

Enantioselective Synthesis of Trifluoromethyl Substituted Piperidines with Multiple Stereogenic Centers *via* Hydrogenation of Pyridinium Hydrochlorides

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An enantioselective iridium-catalyzed hydrogenation of trifluoromethyl substituted pyridinium hydrochlorides is described. Introduction of trifluoromethyl group increases the reactivity due to the electron-withdrawing effect. Three stereogenic centers could be generated in one operation. This methodology provides a convenient route to chiral polysubstituted piperidines with up to 90% ee.

Chiral piperidines are valuable and prevalent substructures in biologically active natural products, synthetic bioactive compounds and medicines.[1] Especially, the introduction of novel substituents on these frame syntheses of multiple stereocenters piperidines has been the focus of many chemists.[2] Among them, selective introduction of trifluoromethyl groups can greatly modify the biological properties of the target molecules which are broadly present in plentiful important drugs, such as JAK inhibitorn (Figure 1).[3] Although organofluorine chemists have made tireless efforts, stereoselective synthesis of trifluoromethyl piperidines with multiple stereogenic centers is still an area which has been rarely explored to date.[4]

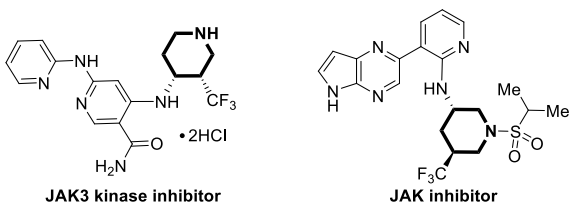
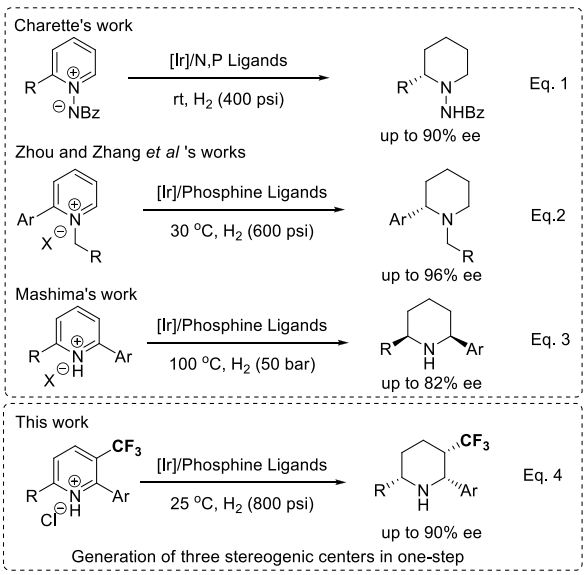


Figure 1. Selected biologically active molecules containing the trifluoromethylpiperidine motif

And the piperidines with multiple stereogenic centers are of great significance, together with our ongoing efforts in the development of asymmetric hydrogenation of *N*-heteroaromatics, we envision that asymmetric hydrogenation of such polysubstituted trifluoromethyl pyridines would provide a straightforward access to these compounds. However, due to the stabilizing aromaticity[5] and strong coordination ability of pyridines and the corresponding products, which might poison catalysts, only a few homogeneous Rh and Ir catalysts[6] and organocatalyst[7] have been applied to synthesize chiral piperidines through asymmetric hydrogenation of special pyridines bearing strong electron-withdrawing group or pyridinium salts in the past 15 years (Eq. 1 and Eq. 2). Notably, very recently, Mashima and co-workers reported an iridium-catalyzed asymmetric hydrogenation of pyridinium salts,[6i] giving the chiral piperidines with two or three stereogenic centers in 28-82% ee and moderate yields (Eq. 3). Herein, we report an efficient asymmetric hydrogenation of poly-substituted pyridinium salts with excellent enantio- and diastereo-selectivity (Eq. 4). Notably, introduction of trifluoromethyl group increases the reactivity due to the electron-withdrawing effect. Three stereogenic centers could be generated in one operation.



On the basis that the extraneous Brønsted acid could activate substrates and accelerate iminium/enamine isomerization to facilitate hydrogenation,[8] we tried asymmetric hydrogenation of pyridinium hydrochloride. To our delight, 6-methyl-2-phenyl-3-trifluoromethylpyridinium hydrochloride (**1a**•HCl) could be hydrogenated in full conversion with 67% ee and excellent diastereoselectivity (Table 1, entry 1). Subsequently, different solvents were examined (entries 2-7) and the mixture solvents of dichloromethane (DCM) and isopropanol with a ratio of 3/1 gave the best result in terms of both enantioselectivity and conversion (85% ee and >95% conversion; entry 6). Sequentially, various halogen source additives (TCCA: trichloroisocyanuric acid,

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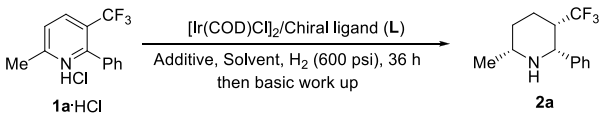
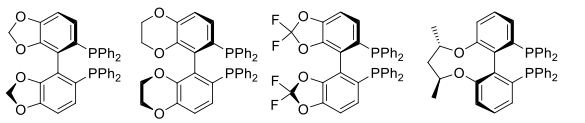
DCDMH: 1,3-dichloro-5,5-dimethylhydatoin and DBDMH: 1,3-dibromo-5,5-dimethylhydatoin) were tested, and gave similar ee values between 81-85% (entries 8-10). Some commercially available chiral bisphosphine ligands were also evaluated (entries 11-13), and the best result was achieved with (*R*)-DifluorPhos **L3** (88% ee and >95% conversion; entry 12). Finally, the 90% ee was achieved when the temperature was decreased to 25 °C, but the conversion reduced to 85%. Gratifyingly, full conversion with the identical enantioselectivity was obtained (entry 15, 90% ee) when the hydrogen pressure was raised to 800 psi with 2.5 mol% catalyst. Thus, the optimized conditions were established as: $[Ir(COD)Cl]_2$/(*R*)-DifluorPhos/TCCA/(DCM/*i*-PrOH)/H_2 (800 psi) /25 °C.

Table 1. The evaluation of reaction parameters[a]



1a·HCl 2a

Entry	Solvent	Additive	L	Conv. (%) [b]	Ee (%) [c]
1	THF	TCCA	**L1**	>95	67
2	DCM (D)	TCCA	**L1**	91	82
3	Benzene	TCCA	**L1**	89	79
4	*i*-PrOH(P)	TCCA	**L1**	97	79
5	D/P (1:1)	TCCA	**L1**	>95	82
6	D/P (3:1)	TCCA	**L1**	>95	85
7	D/P (4:1)	TCCA	**L1**	>95	83
8	D/P (3:1)	DCDMH	**L1**	>95	83
9	D/P (3:1)	DBDMH	**L1**	>95	81
10	D/P (3:1)	NCS	**L1**	>95	82
11	D/P (3:1)	TCCA	**L2**	96	78
12	D/P (3:1)	TCCA	**L3**	>95	88
13	D/P (3:1)	TCCA	**L4**	>95	79
14[d]	D/P (3:1)	TCCA	**L3**	85	90
15[e]	D/P (3:1)	TCCA	**L3**	>95	90

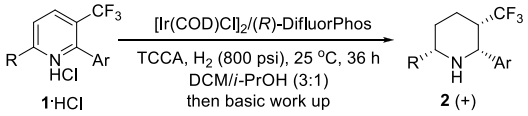


L1: (*R*)-SegPhos **L2**: (*R*)-SynPhos **L3**: (*R*)-DifluorPhos **L4**: (R_{ax},*S*,*S*)-C_3-TunePhos

[a] Reaction condition: **1a**•HCl (0.125 mmol), $[Ir(COD)Cl]_2$ (2.0 mol%), Ligand (4.4 mol%), H_2 (600 psi), solvent (3.0 mL), additive (10 mol%), 36 h, 50 °C. [b]Reaction conversion and d.r. were determined by ^{1}H NMR spectroscopy. In all cases, d.r. >20:1. [c] Determined by HPLC analysis of the corresponding *N*-benzoyl derivatives. [d] 25 °C. [e] $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-DifluorPhos (5.5 mol%), H_2 (800 psi), 25 °C.

With the optimized reaction conditions in hand, exploration of substrate scope was carried out (Table 2). As expected, various substrates performed very well under the standard reaction conditions. The electronic properties and position of substituents on the aromatic ring had marginal effect on the reactivity and enantioselectivity (entries 1-8). Subsequently, the 6-ethyl-2-phenyl-3-(trifluoromethyl)pyridinium hydrochloride (**1i**•HCl) was also tested, 87% ee and 82% yield were obtained (entry 9). The absolute configuration of hydrogenation product **2f** was assigned to be *cis*-(2*R*,3*S*,6*R*) based on single crystal X-ray diffraction analysis (Figure 2).[9]

Table 2. Asymmetric hydrogenation of 3-(trifluoromethyl) pyridinium hydrochloride (1 •HCl)[a]



1·HCl **2** (+)

Entry	R/Ar	Yield (%)[b]	Ee (%)[c]
1	Me/C_6H_5	95 (**2a**)	90
2	Me/4-MeC_6H_4	84 (**2b**)	89
3	Me/3-MeC_6H_4	84 (**2c**)	88
4	Me/4-MeOC_6H_4	94 (**2b**)	88
5	Me/2-Naphthyl	93 (**2e**)	89
6[d]	Me/4-$C_6H_5C_6H_4$	90 (**2f**)	87 (2*R*,3*S*,6*R*)
7	Me/4-$CF_3C_6H_4$	85 (**2g**)	86
8	Me/3,5-$F_2C_6H_3$	72 (**2h**)	84
9	Et/C_6H_5	82 (**2i**)	87

[a] Reaction condition: **1**•HCl (0.125 mmol), (*R*)-DifluorPhos (5.5 mol%), $[Ir(COD)Cl]_2$ (2.5 mol%), H_2 (800 psi), DCM/*i*-PrOH (3:1, 3.0 mL), TCCA (10 mol%), 36 h, 25 °C. [b] Isolated yields and in all cases d.r. >20:1. [c] Determined by HPLC analysis of the corresponding benzamide. [d] The absolute configuration was determined by single crystal X-ray diffraction analysis of **2f**.

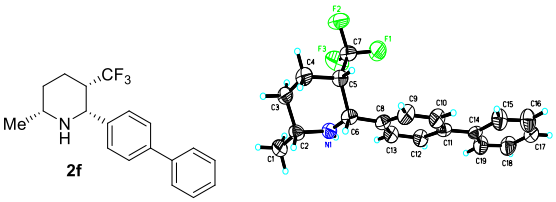


Figure 2. X-ray crystal structure of compound **2f**

In order to further estimate the application possibility, we applied this attractive protocol to the hydrogenation of the simple 2,6-disubstituent pyridinium hydrochloride. Gratifyingly, the reaction proceeded with moderate enantioselectivity and moderate to good reactivity (Scheme 1). In contrast to the asymmetric reduction of 3-(trifluoromethyl) pyridinium hydrochloride **1**, in these cases the reactions were carried out under relatively harsh conditions (1200 psi hydrogen pressure and 80 °C). The reactivity discrepancy of these two type substrates might be ascribed to the electron-withdrawing ability of trifluoromethyl group that activates pyridine to facilitate hydrogenation.

Scheme 1. Asymmetric hydrogenation of 2,6-disubstituent pyridinium hydrochloride (3•HCl)[a]

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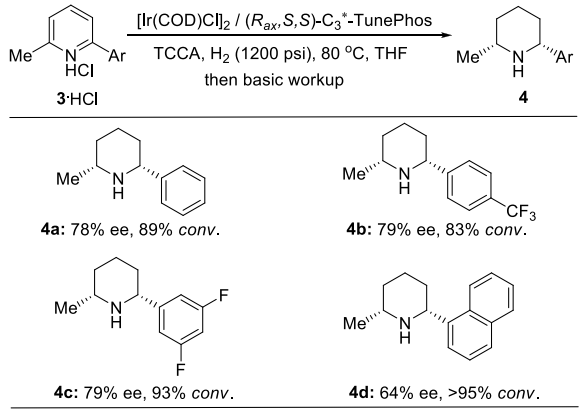

[a] Reaction condition: **3**•HCl (0.125 mmol), (R_{ax},*S*,*S*)-C_3*-TunePhos (2.2 mol%), [Ir(COD)Cl]$_2$ (1.0 mol%), H_2 (1200 psi), THF (3.0 mL), TCCA (10 mol%), 24 h, 80 °C. Reaction conversion and d.r. were determined by ^{1}H NMR spectroscopy. In all cases, d.r. >20:1.

In conclusion, an efficient and direct approach to chiral trifluoromethyl substituted piperidines with multiple stereogenic centers has been successfully developed *via* iridium-catalyzed asymmetric hydrogenation of the corresponding pyridinium hydrochlorides with up to 90% ee. Three stereogenic centers could be generated in one operation. Introduction of trifluoromethyl group increases the reactivity of pyridine hydrogenation due to strong electron-withdrawing effect. Meanwhile, this attractive protocol can also be applied to the asymmetric hydrogenation of the simple 2,6-disubstitued pyridinium hydrochlorides with moderate reactivity and enantioselectivity. Further investigations on asymmetric hydrogenation of poly-substituted heteroaromatics are currently ongoing in our laboratory.

Experimental Section

A typical procedure for asymmetric hydrogenation of 1a

In a nitrogen-filled glove box, a mixture of [Ir(cod)Cl]$_2$ (2.1 mg, 0.0031 mmol) and (*R*)-DifluorPhos (4.7 mg, 0.0069 mmol) in dichloromethane/isopropanol (3:1, 1.0 mL) was stirred at room temperature for 15-20 min, the mixture was transferred by a syringe to a stainless steel autoclave, in which substrate **1a**•HCl (34.0 mg, 0.20 mmol) and TCCA (2.9 mg, 0.0125 mmol) had been placed beforehand. Then, dichloromethane/isopropanol (3:1, 2.0 mL) was added. The hydrogenation was performed at 25 °C under 800 psi of hydrogen for 36 h. After carefully releasing the hydrogen, triethylamine (56 μL, 0.40 mmol) was added and the mixture was stirred for 30 min. The organic layer was separated and extracted with dichloromethane twice, and the combined organic extracts were dried over sodium sulfate and concentrated in *vacuo*. The resulting residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate to give the desired product **2a** as pale oil (29 mg, 95% yield). Enantiomeric excess was determined by HPLC for the corresponding benzamide (OJ-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 220 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 10.6 min (maj), t_2 = 15.3 min (90% ee).

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9 CCDC 1009006 contains the supplementary crystallographic data for this paper. These can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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