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Palladium-catalyzed asymmetric hydrogenation of fluorinated quinazolinones

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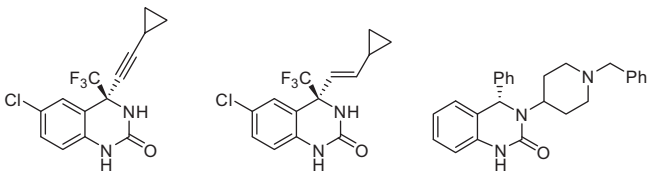
ABSTRACT

A series of fluorinated quinazolinones were hydrogenated using the chiral Pd/bisphosphine complex as the catalyst, giving the corresponding fluorinated dihydroquinazolinones with up to 98% enantioselectivity.

Quinazolinones are identified as a significant class of heterocyclic compounds and useful building blocks in the pharmaceutics because of their broad spectrum of intriguing biological activities. It is well known that the fluorinated motifs in a molecule play a pivotal role in enhancing the activity ascribed to the promoted lipophilic nature.[1] In addition, the chiral fluorinated compounds, especially the dihydroquinazolinones bearing fluorinated groups, play a vital role in fighting AIDS. As illustrated in Scheme 1, the second generation HIV nonnucleoside reverse transcriptase inhibitors (NNRTIs) DPC 961 and DPC 963, as well as Ca^{2+}/Na^{+} ion exchanger inhibitor SM-15811 with potential activity for the treatment of ischemic heart disease,[2] share the skeleton of dihydroquinazolinone in common. Therefore, the development of methods to synthesize these compounds with chiral fluorinated motifs at dihydroquinazolinones subset is still highly desirable, though there have been several reports about the enantioselective transformations of this subset.[3]

In the search for an effective way to the asymmetric hydrogenation of imines, chiral Ru, Rh, and Ir catalysts have made a great achievement.[4] Besides, over the past decade, much progress has been made in Pd-catalyzed asymmetric hydrogenation,[5] including functional olefins,[6] ketones,[7] imines,[8] enamines[9] as well as aromatic compounds.[10] In addition, Pd-catalyst system has shown its powerful ability in the hydrogenation of α-fluorinated imines with high yields and ee values.[11] However, these reports rarely involved the cyclic α-fluorinated imines, such as fluorinated quinazolinones, whose modified skeleton was a symbol of potential pharmaceutic candidates. As our ongoing program on the development of efficient method for the synthesis of chiral fluorinated compounds,[11b,12] we developed herein a Pd-catalyzed asymmetric hydrogenation to synthesize the chiral fluorinated dihydroquinazolinones.

Our study began with asymmetric hydrogenation of fluorinated quinazolinone **1a** at 50 °C using 4 mol % Ir/bisphosphine based catalyst, but only 25% ee was obtained (Table 1, entry 1). Fortunately, when Pd-catalyst was applied in this reaction, **2a** was obtained with 93% ee (Table 1, entry 2), and a small amount of sideproduct **3** was also isolated (Eq. 1). Succeeding experiments of decreasing the catalyst to 2 mol % or lowering the temperature to room temperature gave dropping yields because of the increasing of **3**.



Scheme 1. Structures of anti-HIV drug candidates DPC 961 and DPC 083, and Ca^{2+}/Na^{+} ion exchanger inhibitor SM-15811.

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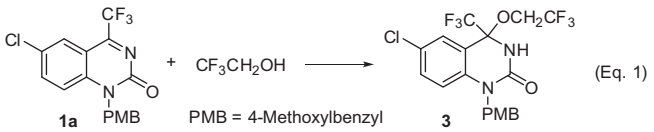
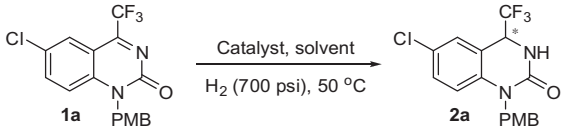
Therefore, 4 mol % catalyst loading and 50 °C were a better choice for the following optimization.



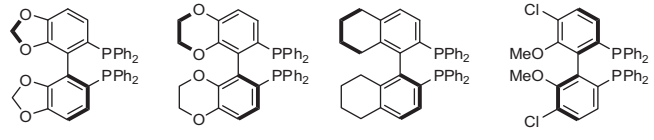
Further test of ligands showed that (*S*)-SynPhos was the best option (Table 1, entries 3–5). In order to guarantee the repeatability and the simple operation, Pd-catalyst complex Pd[(*S*)-SynPhos](OCOCF$_3$)$_2$ was synthesized other than prepared *in situ* before being applied to the hydrogenation.[13] The comparison of Pd-catalyst prepared and generated in situ was conducted and the results indicated that the prepared Pd-catalyst proceeded with a better performance in enantioselectivity (Table 1, entry 3 *vs* entry 6). The following screening of solvents showed that TFE (trifluoroethanol) was the active one (Table 1, entries 7–10). In addition, when the reaction was performed at 25 °C, the elevated enantioselectivity was neutralized by lower yield (Table 1, entry 11). Therefore, the optimized conditions were established as follows: Pd[(*S*)-SynPhos](OCOCF$_3$)$_2$/H$_2$ (700 psi)/TFE/50 °C.

With optimized conditions in hand, the reaction scope was then examined, and the results are summarized in Table 2. Excellent yields and enantioselectivities were obtained with quinazolinones bearing various substituted patterns. Electron-withdrawing, electron-donating, electron-neutral groups as well as substrates substituted at different positions on aromatic rings were all good partners for the hydrogenation, and the corresponding products **2a**–**j** were obtained with 95–98% ee and 89–98% yields. In general,

Table 1
Optimization of the asymmetric hydrogenation of quinazolinone **1a**

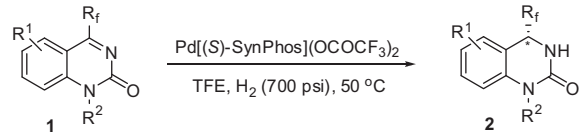


Entry[a]	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	[Ir(COD)Cl]$_2$+**L1**	Toluene	95	25
2	Pd(OCOCF$_3$)$_2$+**L1**	TFE	85	93
3	Pd(OCOCF$_3$)$_2$+**L2**	TFE	98	94
4	Pd(OCOCF$_3$)$_2$+**L3**	TFE	98	84
5	Pd(OCOCF$_3$)$_2$+**L4**	TFE	89	−89
6	Pd(**L2**)(OCOCF$_3$)$_2$	TFE	96	96
7	Pd(**L2**)(OCOCF$_3$)$_2$	Toluene	—	—
8	Pd(**L2**)(OCOCF$_3$)$_2$	THF	—	—
9	Pd(**L2**)(OCOCF$_3$)$_2$	CH_2Cl_2	—	—
10	Pd(**L2**)(OCOCF$_3$)$_2$	MeOH	—[d]	—
11[e]	Pd(**L2**)(OCOCF$_3$)$_2$	TFE	89	97



[a] Reaction conditions: Pd(OCOCF$_3$)$_2$/[Ir(COD)Cl]$_2$ (4 mol %) and ligand (4.8 mol %) or Pd(**L2**)(OCOCF$_3$)$_2$ (4 mol %), **1a** (0.125 mmol), H$_2$ (700 psi), solvent (3 mL), 50 °C, 24 h.
[b] Isolated yields.
[c] Determined by HPLC with chiral column.
[d] Nucelophilic addition sideproduct with MeOH was isolated.
[e] 25 °C.

Table 2
Pd-catalyzed asymmetric hydrogenation of quinazolinones **1**[14,15]



Entry[a]	**1** (R^1/R^2/R_f)	Yield[b] (%)	ee[c] (%)
1	6-Cl/PMB/CF$_3$	96 (**2a**)	96
2	6-Br/PMB/CF$_3$	96 (**2b**)	96
3	6-F/PMB/CF$_3$	89 (**2c**)	96
4	6-CF$_3$/PMB/CF$_3$	96 (**2d**)	96
5	6-MeO/PMB/CF$_3$	98 (**2e**)	97 (*R*)
6	6-*i*-Pr/PMB/CF$_3$	96 (**2f**)	97
7	6-Me/PMB/CF$_3$	95 (**2g**)	97
8	6-H/PMB/CF$_3$	98 (**2h**)	97
9	5,6-F$_2$/PMB/CF$_3$	89 (**2i**)	95
10	6-Cl/H/CF$_3$	94 (**2j**)	98
11	6-Cl/PMB/CF$_2$H	94 (**2k**)	94

[a] Reaction conditions: Pd[(*S*)-SynPhos](OCOCF$_3$)$_2$ (4 mol %), **1** (0.125 mmol), H$_2$ (700 psi), TFE (3 mL), 50 °C, 24 h.
[b] Isolated yield.
[c] Determined by HPLC with chiral column.

substrates bearing electron-donating and electron-neutral groups exhibited little better enantioselectivities than those bearing electron-withdrawing groups (Table 2, entries 1–4 *vs* entries 5–8). With 5,6-difluoro substituent, **2i** could also give high yield and excellent ee value (Table 2, entry 9). It is worthwhile to note that the quinazolinone **2j** without a protecting group on the nitrogen atom could also perform hydrogenation smoothly with 98% ee (Table 2, entry 10). In addition, difluoromethyl substituted quinazolinone **1k** was also attempted, and full conversion along with 94% ee was obtained (Table 2, entry 11). Although this is a little lower ee value than the substrates bearing the trifluoromethyl group, it is the best result of the asymmetric hydrogenation of difluoromethyl imine concerned with the known manuscript of Uneyama and coworkers[11a] (30% ee and 75% yield) and our previous work[11b] (69% ee and 88% yield).

After simple recrystallization from CH_2Cl_2/hexane, enantiomerically pure product **2e** (>99.9% ee) was obtained. The absolute configuration of **2e** was determined to be (*R*) by single X-ray crystallographic analysis (Fig. 1).

In conclusion, an efficient and facile method was successfully developed for asymmetric hydrogenation of fluorinated quinazolinones with the chiral Pd catalyst, providing the corresponding chiral fluorinated dihydroquinazolinones with up to 98% ee. This method provides an efficient route to enantioriched products with potential biological activity. Studies on expanding the scope to other fluorinated substrates are currently underway in our laboratory.

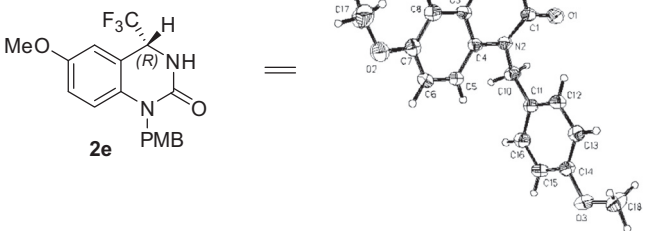


Figure 1. Absolute configuration of asymmetric hydrogenation product **2e**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.078.

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14. *General procedure for the Pd-catalyzed asymmetric hydrogenation of fluorinated quinazolinones* (Table 2, entry 1): In a glovebox, TFE (3 mL) was added to the mixture of Pd[(*S*)-SynPhos](OCOCF$_3$)$_2$ (5.3 mg, 0.005 mmol) and substrate **1** (0.125 mmol) without stirring before charged with hydrogen gas. The hydrogenation was performed at 50 °C under H_2 (700 psi) in a stainless steel autoclave for 24 h. After carefully releasing the hydrogen, the resulting mixture was concentrated under vacuum and purified by silica gel chromatography using petroleum ether/EtOAc (5/1–2/1) as eluent, the enantiomeric excess of the products were determined by HPLC with chiral columns (OD-H or AD-H).
15. *Selected physical and spectral data for* ***2a****:* Colorless oil: 44 mg, 96% yield, 96% ee, $[\alpha]_D^{20}$ +7.5 (*c* 0.76, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.10 (m, 5H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.17 (d, *J* = 16.5 Hz, 1H), 5.00 (d, *J* = 16.5 Hz, 1H), 4.85–4.68 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 154.2, 137.5, 130.6, 128.5, 128.4, 128.0, 127.9, 124.2 (d, J_{C-F} = 285.2 Hz), 116.5, 115.4, 114.6, 110.3, 55.6, 55.41 (q, J_{C-F} = 32.8 Hz). 45.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.2 (s, CF_3); HPLC (OD-H, elute: hexanes/*i*-PrOH = 80/20, detector: 254 nm, flow rate: 0.8 mL/min), t_1 = 10.0 min, t_2 = 11.1 min (maj.); HRMS (ESI-TOF) Calcd for $C_{17}H_{15}ClF_3N_2O_2$ [M+H]$^+$ 371.0769, found 371.0768.