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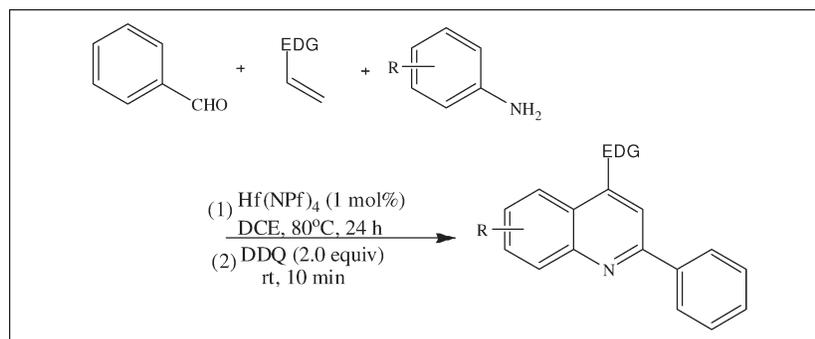
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Hafnium (IV) bis(perfluorooctanesulfonyl)amide (Hf(NPf)<sub>4</sub>) catalyzed the one-pot synthesis of substituted quinolines in fluorous media. By simple phase separation, the fluorous phase containing the catalyst can be used several times.

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## INTRODUCTION

Quinolines and their derivatives are very important synthons of many natural products and semisynthetic biologically active compounds. Many multisubstituted quinolines are important pharmaceutical compounds, and they exhibit a wide spectrum of biological activity [1]. Methods introduced by Skraup [2], Doebner and Miller [3], Conrad and Limbach [4], Combes [5], and Pfitzinger [6] are some of the classic ways to synthesize quinolines. A number of general synthetic methods have also been reported [7]. However, all of these methods have problems, including drastic reaction conditions, low yields, and severe side reactions. Therefore, development of a more practical and economical method for synthesis of quinolines is highly desirable. Recently, Shindoh *et al.* reported that triflic imide could catalyze the auto-tandem synthesis of quinolines by three-component reactions followed by oxidation reactions [8]. However, the catalyst triflic imide could not be recycled.

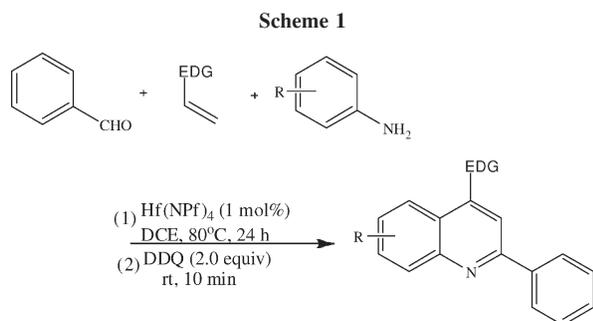
There has been rapidly increasing interest in the design and the synthesis of compounds that exhibit high affinities for “fluorous” phases since the technique of “fluorous biphasic system” (FBS) was described by Horváth and Rábai [9,10]. The technique of FBS, as a phase-separation and catalyst immobilization technique, has become one of the most important methods for facile catalyst separation from the reaction mixture and recycling of the catalyst [11]. In this catalytic system,

the metallic catalyst coordinated by perfluoroalkylated ligands can be retained in the fluorous phase after the reaction. Recently, novel Lewis acids of lanthanide tris(perfluorooctanesulfonyl)methide {Ln[C(SO<sub>2</sub>Rf<sub>8</sub>)<sub>3</sub>], Rf<sub>8</sub> = (CF<sub>2</sub>)<sub>7</sub>CF<sub>3</sub>, Ln(CPf<sub>3</sub>)<sub>3</sub>} [12], lanthanide bis(perfluorooctanesulfonyl)amide {Ln[N(SO<sub>2</sub>Rf<sub>8</sub>)<sub>2</sub>]<sub>3</sub>, Ln(NPf<sub>2</sub>)<sub>3</sub>} [13], and lanthanide perfluorooctanesulfonate [Ln(OSO<sub>2</sub>Rf<sub>8</sub>)<sub>3</sub>, Ln(OPf<sub>3</sub>)<sub>3</sub>] [14,15] received special interest because they have the characteristics of low hygroscopicity, ease of handling, robustness for the reuse, and high solubility in fluorous solvent.

During our studies to explore the utility of fluorinated Lewis acid catalysts in fluorous solvents [15], we found that the three component reaction of aldehydes, anilines, and electron-rich olefins followed by oxidation can proceed smoothly to afford quinolines in the presence of hafnium bis(perfluorooctanesulfonyl)amide [Hf(NPf)<sub>4</sub>] in a FBS system (Scheme 1). Concurrently, we also found that the catalytic system could be reused by simple phase separation.

## RESULTS AND DISCUSSION

Initially, the effect of catalyst loading and cosolvents using was examined. The results were summarized in Table 1. A mixture of benzaldehyde (1.2 equiv), aniline (1.2 equiv), and allyltriisopropylsilane (1 equiv) in the presence of Hf(NPf)<sub>4</sub> (1 mol%) in DCE (2 mL) and



perfluorodecalin ( $C_{10}F_{18}$ , *cis* and *trans*-mixture) (2 mL) was stirred at 80°C for 24 h, then the mixture was cooled to ambient temperature, followed by addition of 2,3-dichloro-5,6-dicyano-1,2-benzoquinone (DDQ, 2 equiv), and the reaction mixture was stirred in the same temperature for 10 min to afford the product in 76% yield (Table 1, entry 1). Although the catalyst loading was decreased from 1 to 0.5, and 0.25 mol %, lower product yields of 50, and 22% were obtained (Table 1, entries 2 and 3), and no reaction was observed in the absence of  $Hf(NPf_4)_4$  (Table 1, entry 4). Several other cosolvents, such as MeCN, PhMe,  $H_2O$ , and THF, were tested, and less effective and lower product yields of 10–67% were obtained (Table 1, entries 5–8). DCE proved to be the most efficient one and was selected to be the reaction cosolvent for the subsequent exploration.

With the optimum reaction conditions in hands, we next investigated the scope of the reaction using different reactants. As shown in Table 2, several different substituted anilines and two kinds of electron-rich olefins were tested. The reactions of different reactants afforded the corresponding substituted quinolines in moderate to good yields. The substituents on the aniline had no obvious effect on the conversion. The reactivity of electron-rich olefin allyltriisopropylsilane (Table 2, entries 1–5) is higher than styrene (Table 2, entries 6–10). It may be caused by the different electron effect of the two electron-rich olefins. When the reaction was finished, the reaction mixture was cooled to room temperature, and the fluorous phase with  $Hf(NPf_4)_4$  can be separated from the organic layer and return to the bottom layer. The recycle results (Table 2, entry 1) indicate that the catalyst does not lose its activity and can be reused without significant loss in activity up to four cycles. When the reaction was finished, the reaction mixture was cooled to room temperature, and the fluorous phase with  $Hf(NPf_4)_4$  can be separated from the organic layer and return to the bottom layer. Based on GC-MS and  $^{19}F$  NMR data, no distribution of  $Hf(NPf_4)_4$  was found in organic layer and only a trace amount of perfluorodecalin leached to organic phase can be detected.

According to the literatures [8],  $Hf(NPf_4)_4$  catalyzes the reaction as a mild Lewis acid. The reaction may proceed via 1,2,3,4-tetrahydroquinolines as intermediates formed by the reaction of the aldehyde, aniline, and electron-rich olefin. Subsequently, the intermediates were further oxidized by DDQ to give the product quinoline. These reactions take place as a one-pot reaction.

In conclusion,  $Hf(NPf_4)_4$  is demonstrated to be new and highly effective catalyst for one-pot synthesis of substituted quinolines in FBS. By simple phase separation of the fluorous phase containing the catalyst, the reaction can be repeated many times. Further study on the application of FBS to other reactions, which can be promoted by such Lewis acids, is under way in this laboratory.

## EXPERIMENTAL

Chemicals used were obtained from commercial suppliers and used without further purifications.  $^1H$  NMR and  $^{19}F$  NMR spectra were recorded with a Bruker Advance RX500 spectrometer. Mass spectra were recorded on a Saturn 2000GC/MS instrument. Inductively coupled plasma (ICP) spectra were measured on an Ultima2C apparatus. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

**Typical procedure for preparation of  $Hf(NPf_4)_4$ .**  $Hf(NPf_4)_4$  was prepared according to the literatures [13]. Anhydrous methanol (10 mL) was added by  $HN(SO_2C_8F_{17})_2$  (0.981 g, 1 mmol) and Hafnium (IV) chloride (0.080 g, 0.25 mmol), which was stirred continuously at 50°C for 16 h. After being cooled to room temperature, the mixture was evaporated and dried at 80°C /0.01 mmHg for 16 h to give white powders of Hafnium (IV) bis(perfluorooctanesulfonyl)amide complex in 96% yield (0.984 g). ICP: Calcd. for  $C_{64}O_{16}N_4F_{136}S_8Hf$ : Hf, 4.35%. Found: Hf, 4.33%. *Anal.* Calcd for  $Hf[N(SO_2C_8F_{17})_2]_4$ : C, 18.75. Found: C, 18.65.

**Typical procedure for the preparation of quinolines.** A mixture of benzaldehyde (0.133 g, 1.2 mmol), aniline (0.116 g,

**Table 1**  
Effect of catalyst loading and reaction solvent.<sup>a</sup>

Entry	Catalyst loading (mol %)	Cosolvent	Yield (%) <sup>b</sup>
1	1	DCE	76
2	0.5	DCE	50
3	0.25	DCE	22
4	–	DCE	–
5	1	PhMe	65
6	1	$H_2O$	10
7	1	THF	56
8	1	MeCN	67

<sup>a</sup> The reaction condition:  $Hf(NPf_4)_4$  (0.041 g, 0.01 mmol), benzaldehyde (0.133 g, 1.2 mmol), aniline (0.116 g, 1.2 mmol) and allyltriisopropylsilane (0.198 g, 1 mmol), Cosolvent (2 mL) and perfluorodecalin ( $C_{10}F_{18}$ , *cis* and *trans*-mixture, 2 mL), 80°C, 24 h; DDQ, 0.454 g, 2 mmol.

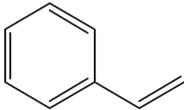
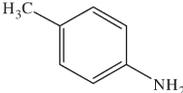
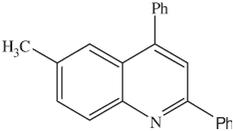
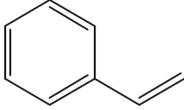
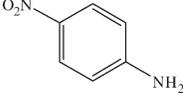
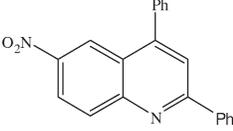
<sup>b</sup> Isolated yields.

**Table 2**  
Hf(NPf)<sub>4</sub>-catalyzed preparation of quinolines.<sup>a</sup>

Entry	Electron-rich olefins	Anilines	Product	Yield (%) <sup>b</sup>
1				76, 74, 74, 73
2				81
3				79
4				69
5				82
6				59
7				65
8				63

(Continued)

**Table 2**  
(Continued)

Entry	Electron-rich olefins	Anilines	Product	Yield (%) <sup>b</sup>
9				65
10				73

<sup>a</sup>The reaction condition: Hf(NPf)<sub>4</sub> (0.041 g, 0.01 mmol), benzaldehyde (0.133 g, 1.2 mmol), aniline (1.2 mmol) and electron-rich olefins (1 mmol), DCE (2 mL) and perfluorodecalin (C<sub>10</sub>F<sub>18</sub>, *cis* and *trans*-mixture, 2 mL), 80°C, 24 h; DDQ, 0.454 g, 2 mmol.

<sup>b</sup>Isolated yields base on the starting alcohol.

1.2 mmol), and allyltriisopropylsilane (0.198 g, 1 mmol) in the presence of Hf(NPf)<sub>4</sub> (0.041 g, 0.01 mmol) in DCE (2 mL) and perfluorodecalin (C<sub>10</sub>F<sub>18</sub>, *cis* and *trans*-mixture, 2 mL). The mixture was stirred at 80°C for 24 h, then the mixture was cooled to ambient temperature, followed by addition of DDQ (0.454 g, 2 mmol), and the reaction mixture was stirred in the same temperature for 10 min. Then, the fluororous layer on the bottom was separated for the next reaction. The reaction mixture (organic phase) was filtered through a short pad of celite. The organic layer was added saturated aqueous solution of NaHCO<sub>3</sub>, and the aqueous phase was extracted twice with CHCl<sub>3</sub>. Combined organic layers were washed with saturated aqueous solution of NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel column to afford the product (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 90/10). Selected data: 6-Trifluoromethyl-4-(triisopropylsilyl)methyl-2-phenylquinoline, colorless solid; mp 103–105°C; <sup>1</sup>H NMR(500 MHz, CDCl<sub>3</sub>) δ = 1.10 (d, *J* = 10.5 Hz, 18 H), 1.19–1.12 (m, 3H), 2.75 (s, 2H), 7.46–8.22 (m, 8H), 8.37 (s, 1H). MS (EI) *m/z* 444 (*M*<sup>+</sup>).

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