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## Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub>-catalyzed Friedel–Crafts acylation in a fluorous biphase system

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Abstract—In a fluorous biphase system,  $Hf[N(SO_2C_8F_{17})_2]_4$  complex (1 mol%) catalyzes Friedel–Crafts acylation of aromatic compounds such as anisole, toluene and chlorobenzene, and the corresponding aromatic ketones are obtained in satisfactory to high yields. The catalyst is selectively soluble in lower fluorous phase and can be easily recovered by simple phase separation. Furthermore, the catalyst can be reused without decrease of activity in most cases. © 2005 Elsevier Ltd. All rights reserved.

Friedel–Crafts acylation is one of the most common and useful synthetic routes for introducing functional substituents to aromatic rings, and industrially important as well.<sup>1</sup> The reaction is generally performed by using aluminum trichloride (AlCl<sub>3</sub>) as a Lewis acid. A common problem, particularly in an industrial process, is that at least stoichiometric quantities of the Lewis acid are required and are destroyed upon work-up leading to serious environment concerns with strongly acidic waste streams. The development for truly catalytic Friedel–Crafts acylation with recoverable and recyclable catalysts is strongly in demand.

In an effort to procure an effective catalyst for Friedel– Crafts acylation, much research has been performed.<sup>2</sup> Kobayashi's group has reported the catalytic use of metal trifluoromethanesulfonates (e.g.,  $Hf(OSO_2CF_3)_4$ and  $Sc(OSO_2CF_3)_3$ ) for excellent Friedel–Crafts acylation and has shown that the catalyst may be recycled in selected instances.<sup>3</sup> In most cases, however, high catalyst loadings and/or extended reaction time were required for satisfactory yields. Thus, the search for milder and more environmentally benign conditions is still in demand especially for industrial applications.

On the other hand, a fluorous biphase system (FBS) brings about potential advantages over classical homo-

geneous catalysis and can be shown to be one of environmentally benign techniques for phase separation and catalyst immobilization.<sup>4</sup> Our recent works in FBS have found that metal (e.g., Hf, Sc and Yb) complexes with bis(perfluorooctanesulfonyl)amide ligands are excellent active and recyclable catalysts in the fluorous immobilized phase for Baeyer–Villiger oxidation,<sup>5</sup> Diels–Alder reaction<sup>6</sup> and esterification,<sup>7</sup> far superior to the corresponding metal trifluoromethanesulfonates. In this letter a mild and effective method for fluorous biphase Friedel–Crafts acylation was performed by Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub>. It was found that under mild conditions the catalyst can function efficiently at low catalytic loadings (1 mol%) and can be easily recovered and reused.

Friedel–Crafts acylation of anisole with acetic anhydride was carried out in FBS to investigate the potential of Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub> at low catalytic loading (1 mol%) under mild conditions. As shown in Table 1, with respect to Hf<sup>IV</sup>-based catalysts (entries 1 and 2), Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub> showed significantly higher activity than Hf(OSO<sub>2</sub>CF<sub>3</sub>)<sub>4</sub>, even though the latter gave a relatively higher activity than the other listed metal trifluoromethanesulfonates. This result can be attributed to the presence of the powerfully electron-withdrawing  $-N(SO_2C_8F_{17})_2$  ligand bearing the higher fluorine load.<sup>8</sup> As for M(OSO<sub>2</sub>CF<sub>3</sub>)<sub>n</sub> (*n* = 3,4) catalysts, yield (from moderate to low) followed the order of Hf<sup>IV</sup> > Sc<sup>III</sup> > Ga<sup>III</sup> > Bi<sup>III</sup>  $\gg$  Yb<sup>III</sup> > Al<sup>III</sup> (entries 2–7), and there was no significant difference in the regioselectivity (*p*-regioisomer > 97%) except for Ga<sup>III</sup> catalyst (*o*/*p* = 19/81).

*Keywords*: Lewis acid catalyst; Fluorous biphase system; Perfluorinated ligand; Friedel–Crafts acylation; Regioselectivity.

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## **Table 1.** Effect of catalysts<sup>a</sup>

	OMe + Ac <sub>2</sub> O 1.0 mmol 2.0 mmol	Cat. (1 mol%) chlorobenzene 1.5 mL SV 135 1.5 mL 100 °C, 1 h	
Entry	Catalyst	Yield <sup>b,c</sup> (%)	Isomer distribution/a:b <sup>d</sup>
1	$Hf[N(SO_2C_8F_{17})_2]_4$	80	0:100
		92 <sup>e</sup>	<1:99 <sup>e</sup>
2	Hf(OSO <sub>2</sub> CF <sub>3</sub> ) <sub>4</sub>	49	3:97
3	$Sc(OSO_2CF_3)_3$	45	2:98
4	$Ga(OSO_2CF_3)_3$	42	19:81
5	$Bi(OSO_2CF_3)_3$	39	2:98
6	$Yb(OSO_2CF_3)_3$	16	3:97
7	$Al(OSO_2CF_3)_3$	8	3:97
8 <sup>f</sup>	AlCl <sub>3</sub>	2	0:100
9	None	0	_

<sup>a</sup> Reaction conditions: see typical procedure.<sup>†</sup>

<sup>b</sup> Acylation products: *o*-(**1a**), *p*-methoxyacetophenone (**1b**).

<sup>c</sup> Isolated yield after chromatography, with respect to anisole.

<sup>d</sup> Determined by GC–MS and NMR analysis.

<sup>e</sup> 3 mol% of Hf[N(SO<sub>2</sub>C<sub>8</sub> $F_{17}$ )<sub>2</sub>]<sub>4</sub> was used.

<sup>f</sup> 10 mol% of AlCl<sub>3</sub> was used.

In addition, the activity of AlCl<sub>3</sub> (entry 8), a wellknown industrially used catalyst for Friedel–Crafts acylation, was significantly low under the present mild reaction conditions. No product was obtained in the absence of the catalyst (entry 9). Accordingly, Hf[N(SO<sub>2</sub>- $C_8F_{17})_2$ ]<sub>4</sub> was considered to be an excellent catalyst in terms of good yield of 80% and *p*-regioselectivity of 100%.<sup>†,‡</sup>

Several aromatic compounds were subjected to the  $Hf[N(SO_2C_8F_{17})_2]_4$ -catalyzed Friedel–Crafts acylation

using acetic, n-butyric and benzoic anhydride, or n-butyryl and benzoyl chloride as an acylating agent. The results summarized in Table 2. In all are cases. Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub> showed a relatively higher activity than Hf(OSO<sub>2</sub>CF<sub>3</sub>)<sub>4</sub>. As expected, acylation of more electron rich aromatic compounds (o-, m-dimethoxybenzene of entries 6–15, mesitylene of entry 16) proceeded more smoothly than anisole (entries 1-5), and produced a single regioisomer in excellent yields. On the other hand, less electron rich toluene (entry 17) underwent acylation more slowly than anisole. These conditions allowed the acylation of anisole, o-, m-dimethoxybenzene with anhydrides, similarly to acid chlorides, even though they were less regioselective in a few cases (entries 3 and 5).

Furthermore, the recycling performance<sup>9</sup> of  $Hf[N(SO_2C_8F_{17})_2]_4$  for all of the reactions in Table 2 except benzoylation of toluene (entry 17) was also investigated. The operation (see footnote †) was quite similar to that we have reported for Baeyer–Villiger oxidation,<sup>5</sup> that is, the lower fluorous catalytic phase was directly reused in the next reaction by combining with another mixture of reactants more than three times without decrease in catalytic activity. Typical results are shown in Scheme 1.

The benzoylation of less reactive substrates such as xylene, toluene and chlorobenzene catalyzed by 1 mol% Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub> were examined with excess of substrates. The results are summarized in Table 3. Although the benzolyation of chlorobenzene (entry 5) was slow, the elongation of reaction time led to the middle yield of 45% as well. The benzoylation of *o*-, *m*- and *p*-xylene (entries 2–4) proceeded fast to afford the corresponding 3,4-, 2,4- and 2,5-dimethylbenzophenone in 92%, 96% and 98% yields, respectively. With respect to toluene (entry 1), it reacted also smoothly to produce methylbenzophenone (*o*/*m*/*p* = 10/2/88) in 96% yield.

<sup>&</sup>lt;sup>†</sup>*Typical procedure* (Table 1, entry 1): to a mixture of GALDEN<sup>®</sup> SV 135 (1.5 mL; a suitable fluorous solvent for FBS<sup>5c</sup>) and chlorobenzene (1.5 mL) were added Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub> (41 mg, 0.01 mmol), anisole (108 mg, 1.0 mmol) and acetic anhydride (204 mg, 2.0 mmol). The reaction mixture was stirred continuously at 100 °C for 1 h. Once the stirring was stopped, the reaction mixture settled down at room temperature and turned into two liquid phases within 5 min, that is, an upper toluene and a lower SV 135 phase. Pure p-methoxyacetophenone product was obtained from the upper phase after silica gel chromatography and reduced pressure evaporation (120 mg, 80%) isolated yield). The lower fluorous phase containing the catalyst was reused in the subsequent recycling reactions, to which chlorobenzene (1.5 mL), anisole (108 mg, 1.0 mmol) and acetic anhydride (204 mg, 2.0 mmol) were added, respectively. The other operations and procedure (e.g., stirring at 100 °C for 1 h, product separation) were the same as described above for the first cycle. Such a procedure was repeated a further two times. Substantially, the yields of *p*-methoxyacetophenone were 81% and 79% in the succeeding two times, respectively.

<sup>&</sup>lt;sup>‡</sup> Synthesis of  $Hf[N(SO_2C_8F_{17})_2]_4$  complex: to anhydrous methanol (10.0 mL) were added HN(SO\_2C\_8F\_{17})\_2 (5.89 g, 6.0 mmol) and HfCl<sub>4</sub> (0.48 g, 1.5 mmol), which was stirred continuously at 50 °C for 15 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 97% yield (5.96 g). Hf[N(SO\_2C\_8F\_{17})\_2]\_4 elemental analysis: calcd C, 18.75; Hf, 4.35. Found: C, 18.65; Hf, 4.33. <sup>19</sup>F NMR  $\delta$  –126.2, –121.1, –114.2, –81.5.

**Table 2.** Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub>-catalyzed Friedel–Crafts acylation reactions

		ΔrH +	ArH + Acylating Agent $(1 \text{ mol}\%)^2$			
		1.0 mmol	chlo 2.0 mmol	robenzene 1.5 mL 135 1.5 mL	Aloon	
Entry	ArH	Acylating agent	Conditions (°C	C, h) Product	a Yield <sup>b,c</sup> (%)	Isomer distribution/a:b <sup>c,d</sup>
1	Anisole	Ac <sub>2</sub> O	100, 1	1b	80 (49)	0:100 (3:97)
2		n-C <sub>3</sub> H <sub>7</sub> COCl	90, 4	2a,b	90 (46)	4:96 (13:87)
3		$(n-C_3H_7CO)_2O$	90, 1	2a,b	88 (57)	18:82 (23:77)
4		PhCOCl	120, 2	3a,b	89 (43)	0:100 (11:89)
5		(PhCO) <sub>2</sub> O	120, 2	3a,b	90 (35)	3:97 (14:86)
6	o-Dimethoxybenzene	Ac <sub>2</sub> O	90, 1	4	91 (39)	
7		n-C <sub>3</sub> H <sub>7</sub> COCl	110, 1	5	94 (70)	
8		$(n-C_3H_7CO)_2O$	90, 1	5	97 (66)	
9		PhCOCl	110, 1	6	92 (67)	
10		(PhCO) <sub>2</sub> O	110, 2	6	94 (56)	
11	m-Dimethoxybenzene	Ac <sub>2</sub> O	70, 1	7	93 (35)	
12		n-C <sub>3</sub> H <sub>7</sub> COCl	70, 2	8	94	
13		$(n-C_3H_7CO)_2O$	70, 2	8	96	
14		PhCOCl	90, 4	9	90	
15		(PhCO) <sub>2</sub> O	90, 4	9	92	
16	Mesitylene	PhCOCl	110, 3	10	96	
17	Toluene	PhCOCl	110, 5	11c	35	

<sup>a</sup> Acylation products: *o*-(2a), *p*-methoxybutyrophenone (2b); *o*-(3a), *p*-methoxybenzophenone (3b); 3,4-dimethoxyacetophenone (4); 3,4-dimethoxybutyrophenone (5); 3,4-dimethoxybenzophenone (6); 2,4-dimethoxyacetophenone (7); 2,4-dimethoxybutyrophenone (8); 2,4-dimethoxybenzophenone (9); 2,4,6-trimethylbenzophenone (10); *o*-(11a), *m*-(11b), *p*-methylbenzophenone (11c).

<sup>b</sup> Isolated yield after chromatography, with respect to aromatic compound.

<sup>c</sup> Figures in parentheses refer to results using 1 mol% Hf(OSO<sub>2</sub>CF<sub>3</sub>)<sub>4</sub>.

<sup>d</sup> Determined by GC-MS and NMR analysis.



Scheme 1. Recycles of  $Hf[N(SO_2C_8F_{17})_2]_4$  catalyst under the conditions in Table 2.

In conclusion,  $Hf[N(SO_2C_8F_{17})_2]_4$  in FBS has proved to be a favorable catalyst for Friedel–Crafts acylation. We believe that the following results endow the catalytic approach with great potential for industrial appli-

Table 3. Hf[N(SO<sub>2</sub>C<sub>8</sub> $F_{17}$ )<sub>2</sub>]<sub>4</sub>-catalyzed benzoylation of aromatic compounds with benzoyl chloride

ArH	+ PhCO	Hf[N(S) (1	Hf[N(SO <sub>2</sub> C <sub>8</sub> F <sub>17</sub> ) <sub>2</sub> ]₄ (1 mol%) ArCOPh		
SV 135 1.5 mL 0.5 mL 2.0 mmol					
Entry ArH		Conditions	Product <sup>a</sup>	Yield <sup>b</sup> (%)	
		(°C, h)		(isomer distri-	
				bution/a:b:c) <sup>e</sup>	
1 Tolu	ene	110, 8	11a,b and c	96 (10:2:88)	
2 <i>o</i> -Xy	lene	120, 3	12a	92	
3 <i>m</i> -Xy	ylene	120, 3	12b	96	
4 <i>p</i> -Xy	lene	120, 3	12c	98	
5 Chlo	robenzene	130, 16	13	45	

<sup>a</sup> Acylation products: 3,4-(**12a**), 2,4-(**12b**), 2,5-dimethylbenzophenone (**12c**); *p*-chlorobenzophenone (**13**).

<sup>b</sup> Isolated yield after chromatography, with respect to PhCOCl.

<sup>c</sup> Determined by GC-MS and NMR analysis.

cation. (1) The catalyst has an excellent accelerating effect superior to the well-known trifluoromethanesulfonates; (2) high yields and regioselectivity of the desired aromatic ketones can be obtained at low catalytic loadings (1 mol%); (3) the catalyst, completely immobilized in the fluorous phase, can be recovered and reused. Further experiments are still under progress.

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- Typical recovery result: the complex Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub> was recovered from the fluorous phase without apparent weight loss, that is, 40 mg modified catalyst was recovered after the original 41 mg was recycled for 4 times. The recovered Hf[N(SO<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>2</sub>]<sub>4</sub> catalyst was characterized by elemental analysis: calcd C, 18.75; Hf, 4.35. Found: C, 18.72; Hf, 4.33.