

Strong Lewis acid air-stable cationic titanocene perfluoroalkyl(aryl)sulfonate complexes as highly efficient and recyclable catalysts for C–C bond forming reactions†

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A series of strong Lewis acid air-stable titanocene perfluoroalkyl(aryl)sulfonate complexes $\text{Cp}_2\text{Ti}(\text{OH}_2)_2(\text{OSO}_2\text{X})_2\cdot\text{THF}$ ($\text{X} = \text{C}_8\text{F}_{17}$, **1**·THF; $\text{X} = \text{C}_4\text{F}_9$, **2**·H₂O·THF; $\text{X} = \text{C}_6\text{F}_5$, **3**) were successfully synthesized by the treatment of Cp_2TiCl_2 with $\text{C}_8\text{F}_{17}\text{SO}_3\text{Ag}$, $\text{C}_4\text{F}_9\text{SO}_3\text{Ag}$ and $\text{C}_6\text{F}_5\text{SO}_3\text{Ag}$, respectively. In contrast to well-known titanocene bis(triflate), these complexes showed no change in open air over three months. TG-DSC analysis showed that **1**·THF, **2**·H₂O·THF and **3** were thermally stable at 230 °C, 220 °C and 280 °C, respectively. Conductivity measurements showed that these complexes underwent ionic dissociation in CH₃CN solution. X-ray analysis results confirmed that **2**·H₂O·THF and **3** were cationic. ESR spectra showed that the Lewis acidity of **1**·THF (1.06 eV) was higher than that of Sc^{3+} (1.00 eV) and Y^{3+} (0.85 eV). UV/Vis spectra showed a significant red shift due to the strong complex formation between 10-methylacridone and **2**·H₂O·THF. Fluorescence spectra showed that the Lewis acidity of **2** ($\lambda_{\text{em}} = 477$ nm) was higher than that of Sc^{3+} ($\lambda_{\text{em}} = 474$ nm). These complexes showed high catalytic ability in various carbon–carbon bond forming reactions. Moreover, they show good reusability. Compared with **1**·THF, **2**·H₂O·THF and **3** exhibit higher solubility and better catalytic activity, and will find broad applications in organic synthesis.

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Introduction

Since the discovery of the Zeigler–Natta catalyst, titanium(IV) compounds, derived from halide, alkoxide, phenolate, or triflate ligands, have attracted much interest in the past few decades due to their extensive application in organic synthesis.¹ Among them, the titanocene complexes have attracted much attention because of their high potential in catalysis.² Recently, many research groups have made great contributions to the development of highly efficient catalytic systems based on titanocene complexes.³ For example, Ashfeld developed a

bifunctional titanocene-catalyzed ($\text{Cp}_2\text{TiCl}_2/\text{Zn}/\text{Ac}_2\text{O}/\text{R}_3\text{P}$; $\text{R} = t\text{-Bu}$, 4-OMeC₆H₄) multicomponent coupling based on the redox- and Lewis acid-relay catalysis, resulting in a convergent assembly of 1,4-dienes, 1,5-enynes, unsymmetrical diaryl-ethynyl methanes, and β -alkynyl ketones.⁴ Kambe *et al.* found that the $\text{Cp}_2\text{TiCl}_2/n\text{-BuMgCl}$ catalytic system shows high efficiency and regioselectivity in C–Si⁵ and C–C bond-forming reactions.⁶ Huang *et al.* reported titanocene-catalyzed dehydroxylative radical coupling of hemiaminal with active alkenes.⁷ Roy *et al.* demonstrated a titanocene(III) chloride (Cp_2TiCl) mediated radical induced Wagner–Meerwein-type rearrangement, for the preparation of homoallyl amines and substituted alkenes stereoselectively.⁸ Among these catalytic systems, most of them^{4–8} focus on the Ti^{IV}–Ti^{III} multivalent ability. However, their potential as air-stable Lewis acid catalysts for organic synthesis has rarely been studied, which may be owing to the lower Lewis acidity of Cp_2TiCl_2 and its derivatives.⁹

To increase the Lewis acidity of the titanocene complexes, one method is to attach electron-withdrawing group(s) on titanium. For example, titanocene bis(triflate) $\text{Cp}_2\text{Ti}(\text{OSO}_2\text{CF}_3)_2$ was successfully synthesized by Thewalt and Klein,¹⁰ and was employed by the groups of Bosnich and Collins for the formation of C–C bonds.¹¹ However, the anhydrous titanocene bis(triflate) was hygroscopic^{11a} and easily formed the aquo

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† Electronic supplementary information (ESI) available: CIF files of **2**·H₂O·THF and **3**, ¹H and ¹³C NMR spectra, MS spectral characterization data for compounds in application reaction; the copies of all compounds' spectra including the ¹H NMR, ¹³C NMR spectra and the ¹H NMR and ¹⁹F NMR spectra of complexes **1**·THF, **2**·H₂O·THF and **3**. CCDC 894849 and 938518. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4dt00549j

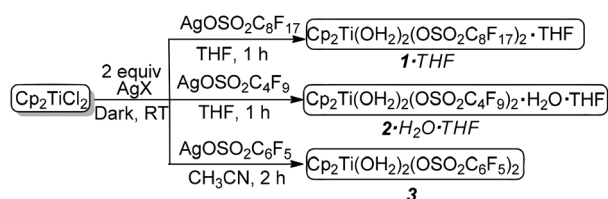
complexes $\text{Cp}_2\text{Ti}(\text{OH}_2)_2(\text{OSO}_2\text{CF}_3)_2 \cdot \text{THF}$ ($4 \cdot \text{THF}$),^{11d} which were also active as Brønsted and/or Lewis acid catalysts;^{11a-c} Brønsted acidity was disadvantageous for applications involving asymmetric catalysis.^{11f} Recently, Otera and co-workers found that the longer perfluorooctanesulfonate groups could be used as effective counter anions to provide air-stable and water-tolerant organometallic species in sharp contrast to the corresponding hygroscopic organometallic triflates.¹² Based on this idea and as part of our ongoing efforts devoted to metallocene complexes, herein we put forth a full account of synthesis and characterization of a series of air-stable titanocene perfluoroalkyl(aryl)sulfonate complexes $\text{Cp}_2\text{Ti}(\text{OH}_2)_2(\text{OSO}_2\text{X}) \cdot \text{THF}$ ($\text{X} = \text{C}_8\text{F}_{17}$, $1 \cdot \text{THF}$; $\text{X} = \text{C}_4\text{F}_9$, $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$; $\text{X} = \text{C}_6\text{F}_5$, 3). Furthermore, their catalytic activities are assessed in various C–C bond-forming reactions, including the Strecker reaction, the Mannich-type reaction, allylation of aldehydes, the Mukaiyama aldol reaction, the Friedel–Crafts acylation and the aza-Friedel–Crafts reactions.

Results and discussion

Shown in Scheme 1 is the synthetic route to the titanocene perfluoroalkyl(aryl)sulfonate complexes **1–3** by treatment of Cp_2TiCl_2 with silver perfluoroalkyl(aryl)sulfonate (AgX , for **1**, $\text{X} = \text{OSO}_2\text{C}_8\text{F}_{17}$; for **2**, $\text{X} = \text{OSO}_2\text{C}_4\text{F}_9$; for **3**, $\text{X} = \text{OSO}_2\text{C}_6\text{F}_5$) (2 equiv.) in THF or CH_3CN , respectively.

^1H NMR and elemental analysis results show that the freshly prepared samples after recrystallization from THF–hexane contained 2 or 3 water molecules along with solvating THF for **1** and **2**, and contain only two H_2O molecules for **3**. Many attempts to prepare the complexes without hydrates failed. Since the preparation was not done in the glove box, the solvent transformation may cause some air moisture to enter into the reaction mixture. Upon keeping the freshly prepared complexes **1** and **2** in open air for 2 days, the desolvation of the THF was observed and the water molecule number increased to 4. It should be noted that after keeping in open air over three months, the solid samples remained as dry crystals or powder and exhibited no sign of skeleton change upon ^1H NMR spectroscopy analysis. Therefore, the titanocene perfluoroalkyl(aryl)sulfonate complexes are storable in open air, showing a great advantage over titanocene bis(triflate) from an operational point of view.^{11a}

The cationic structures of $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ and **3** in the solid state were confirmed by X-ray analysis. The crystals suitable for the X-ray diffraction analysis were obtained by diffusion of



Scheme 1 Synthesis of **1**·THF, **2**·H₂O·THF and **3**.

hexane into a saturated solution of complexes in THF. An ORTEP representation of $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ and **3** and selected bond lengths and angles are shown in Fig. 1 and 2. It is clear that the titanocene component in $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ and **3** is cationic, while the $\text{Cp}_2\text{Ti}(\text{OSO}_2\text{CF}_3)_2$ possesses a covalent structure.¹⁰ The anhydrous titanocene bis(triflate) [$\text{Cp}_2\text{Ti}(\text{OSO}_2\text{CF}_3)_2$] readily formed aquo complexes [$\text{Cp}_2\text{Ti}(\text{OH}_2)_2(\text{OSO}_2\text{CF}_3)_2$], which are cationic complexes.^{11d} The titanium atom in the cationic ion is coordinated by two water molecules, which lie on the plane that bisects the angle between the Cp ring planes. The $\text{C}_4\text{F}_9\text{SO}_3^-/\text{C}_6\text{F}_5\text{SO}_3^-$ ions, the dissociated H_2O molecules, and the solvating ligand THF are packed around the complex cationic ion in such a way that their oxygen atoms point towards the H_2O ligands. The $\text{C}_4\text{F}_9/\text{C}_6\text{F}_5$ side chains of the anions, on

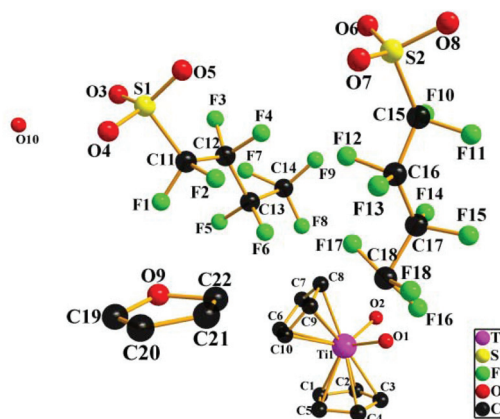


Fig. 1 ORTEP view of the crystal structure of $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$. Selected bond lengths (Å) and angles ($^\circ$): Ti1–O1, 2.026(3); Ti1–O2, 2.006(2); Ti1–C1, 2.343(4); Ti1–C2, 2.337(4); Ti1–C3, 2.336(3); Ti1–C4, 2.356(3); Ti1–C5, 2.355(3); Ti1–C6, 2.358(3); Ti1–C7, 2.363(3); Ti1–C8, 2.341(3); Ti1–C9, 2.353(3); Ti1–C10, 2.327(4); O2–Ti1–O1, 90.75(10). The torsion angle between the two Cp ring planes is 46.9 degrees. The proton is omitted for clarity.

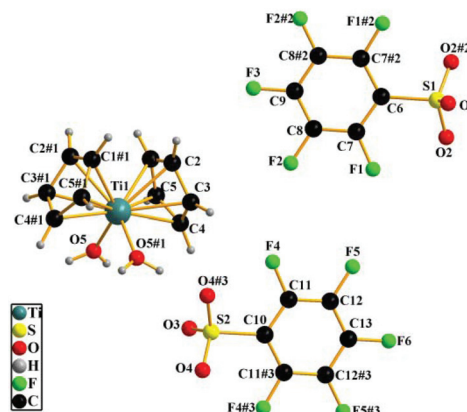


Fig. 2 ORTEP view of the crystal structure of **3**. Selected bond lengths (Å) and angles ($^\circ$): Ti1–O5, 2.0226(17); Ti1–O5#, 2.0226(17); Ti1–C1, 2.351(2); Ti1–C2, 2.354(2); Ti1–C3, 2.374(2); Ti1–C4, 2.357(2); Ti1–C5, 2.364(2); Ti1–C1#, 2.351(2); Ti1–C2#, 2.354(2); Ti1–C3#, 2.374(2); Ti1–C4#, 2.357(2); Ti1–C5#, 2.364(2); O5–Ti1–O5A, 92.75(11). The torsion angle between the two Cp ring planes is 47.00 degrees.

the other hand, are clustered together to produce hydrophobic domains. Unfortunately, in spite of many attempts, we were unable to obtain suitable crystals of **1**·THF for X-ray analysis. However, due to the similar chemical structure, we deduced that **1**·THF could also be cationic organometallic species, which was confirmed by conductivity measurements.

Conductivity measurements were applied to investigate their ionic dissociation behaviour in CH₃CN. The large molar conductivity values (**1**·THF: $\Lambda = 117 \mu\text{S cm}^{-1}$; **2**·H₂O·THF: $\Lambda = 165 \mu\text{S cm}^{-1}$; **3**: $\Lambda = 143 \mu\text{S cm}^{-1}$ in CH₃CN (1.0 mmol L⁻¹) at 15 °C) are consistent with the complete ionization into a 1 : 2 electrolyte,¹⁴ implying that these complexes are cationic in the solid state and in solution.

The thermal behaviour of three complexes **1**·THF, **2**·H₂O·THF and **3** was investigated by TG-DSC under a N₂ atmosphere (Fig. 3). The TG-DSC curves showed three stages of weight loss. The endothermic step below 100 °C can be assigned to the removal of water molecules corresponding to obvious endothermic peaks. Complexes **1**, **2** and **3** are thermally stable and could remain stable up to about 230 °C, 220 °C and 280 °C, respectively. Obviously, the complex **3** shows better thermal stability, which may be owing to the perfluorophenyl anions. Then two weight losses of exothermic nature appear, plausibly due to the oxidation of organic entities with a large quantity of heat to release. We observed the removal of perfluoro(alkyl)phenylsulfuryl ligands at 300 °C, leaving titanium fluoride behind. We also employed ¹H and ¹⁹F NMR techniques to analyze the **2**·H₂O·THF samples, which underwent thermal treatment at 180 °C for two days, and no change was observed.

Another notable feature is the unusual solubility of **1**·THF, **2**·H₂O·THF and **3** in acetone, THF, CH₃CN, EtOAc and MeOH (Table 1). One can see that **2**·H₂O·THF and **3** show higher solubility in common polar organic solvents compared with the solubility of **1**·THF. It is deduced that such a difference may be owing to the strongly lipophobic property of the perfluorooctyl group.¹³ Another quite surprising behaviour is that these complexes is insoluble in CH₂Cl₂, because CH₂Cl₂ is usually the best solvent for similar titanocene bis(triflate).^{11d} Consistently, they are not soluble in much less polar toluene and nonpolar

Table 1 The solubility of titanocene perfluoro(octane, butane, phenyl) sulfonates in organic solvents at 25 °C^a

Solvent	1 ·THF ^b	2 ·H ₂ O·THF ^b	3 ^b
Acetone	284	1541	968
MeOH	136	746	534
THF	130	827	638
EtOAc	26	395	278
CH ₃ CN	510	1027	742
Et ₂ O	13	116	87
CH ₂ Cl ₂	0	0	0
Toluene	0	0	0
<i>n</i> -Hexane	0	0	0

^a All samples are freshly prepared and recrystallized. ^b Solubility g L⁻¹.

n-hexane. Furthermore, as they are apparently insoluble in water, these complexes are hydrophobic, which could be attributed to the fluoroalkyl(aryl) chain in the sulfonate ligand.

Then, we decided to estimate their Lewis acidity by different ways, since the titanocene Lewis acid is desired to be as strongly acidic as possible to acquire higher catalytic activity. First, to estimate the Lewis acidity of **1** exactly, we measured the ESR spectra of the O₂^{·-}·**1** complex to determine its ΔE value,¹⁵ which is the binding energy of Lewis acid metal ions with O₂^{·-}.

As shown in Fig. 3 (top), the ΔE value of the titanium complex (O₂^{·-}·**1**) is significantly larger (Ti⁴⁺: $g_{zz} = 2.0289$, $\Delta E = 1.06$ eV) than that of Sc(OTf)₃ ($g_{zz} = 2.0304$, $\Delta E = 1.00$ eV) and it is the largest among the ΔE values ever reported by the Fukuzumi group.^{15b} Since the Lewis acids with a ΔE value larger than 0.88 eV were presumed to be capable of inducing C–C bond-forming reactions,^{12a} thus, it is reasonable to expect that the Lewis acidity of **1** is higher enough to trigger synthetically useful reactions. We also applied UV/Vis spectra (Fig. 4, middle) to qualitatively determine the Lewis acidity of **2**, and observed a significant red shift due to the strong complex formation between 10-methylacridone and **2**, illustrating a larger Lewis acidity of **2**. Meanwhile, we estimated the Lewis acidity of **2** by the red shift (λ_{em}) of Lewis acid metal ions (Ti⁴⁺) with 10-methylacridone on the basis of fluorescence spectra. The fluorescence maximum (λ_{em}) of **2** is at 477 nm (Fig. 4, bottom), which is slightly larger than that for Sc³⁺ (474 nm).¹⁶ In addition, we also employed the Hammett indicator method to determine the acidity of **1**·THF, **2**·H₂O·THF and **3**, and found that all of them have relatively strong acidity showing the acid strength $0.8 < \text{Ho} \leq 3.3$ (Ho being the Hammett acidity function).¹⁷ The characteristics of these complexes encouraged us to evaluate their performance as Lewis acid catalysts for carbon–carbon bond-forming reactions, such as the Strecker reaction, the Mannich-type reaction, the Mukaiyama aldol reaction, allylation of aldehydes, the Friedel–Crafts acylation and the aza-Friedel–Crafts reactions.

The Strecker reaction is one of the most efficient and straightforward methods for the synthesis of α -aminonitriles,¹⁸ which are very important intermediates for the synthesis of α -amino acids and various nitrogen-containing heterocycles.¹⁹ In recent years, in the search for novel and efficient protocols for the synthesis of α -aminonitriles, a broad range of metal

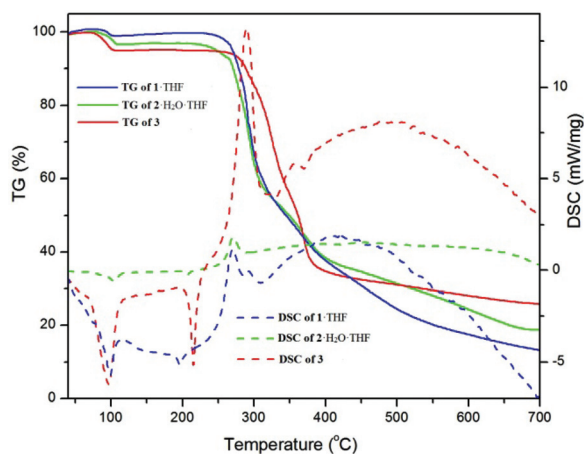


Fig. 3 TG-DSC curves of complexes **1**·THF, **2**·H₂O·THF and **3**.

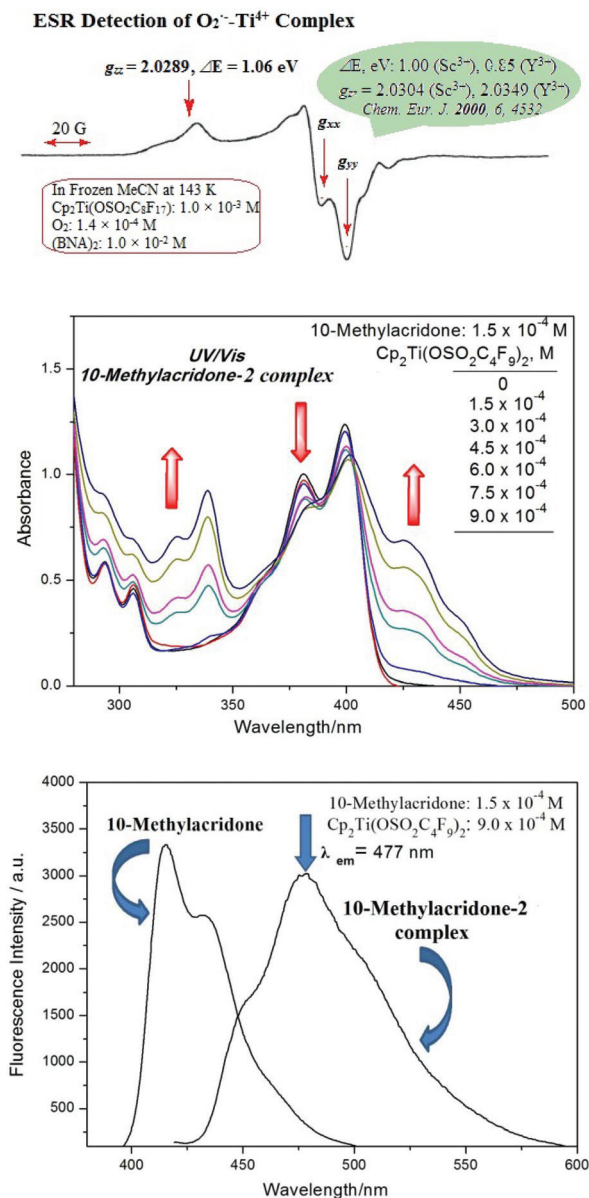
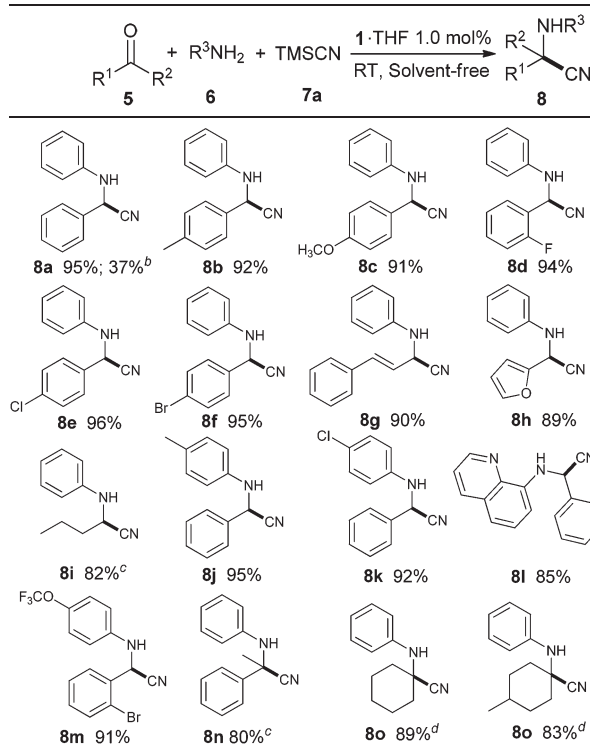


Fig. 4 Top: ESR spectra of O₂^{•-}-Ti⁴⁺ (1); middle: UV/Vis spectral changes of complex formation between 10-methylacridone and 2; bottom: fluorescence spectral changes of complex formation between 10-methylacridone and 2.

complexes, Lewis acids, solid acids and organic catalysts have been developed to promote this reaction.²⁰ However, some of these methods have one or more disadvantage(s) such as low reactivity, poor selectivity, the use of organic solvents and/or the need for strictly anhydrous reaction conditions. It is highly desirable to develop catalytic systems that can affect the Strecker reaction under solvent-free conditions with excellent efficiency and stereoselectivity. We hence assessed the catalytic efficiency with 1·THF in one-pot Strecker reaction under solvent-free conditions, and high efficiency and chemoselectivity were obtained (Table 2).

In order to demonstrate the excellent catalytic efficiency of 1·THF, we examined the Strecker reaction of different

Table 2 The Strecker reaction of aldehydes/ketones with amines and trimethylsilylcyanide catalyzed by 1·THF^a



^a Catalyst 1·THF (0.01 mmol); R¹C(O)R² (5; 1.0 mmol); R²NH₂ (6; 1.0 mmol); TMSCN (7a; 1.2 mmol); solvent-free conditions; temp: RT; **8a–8h**, **8j–8m**: 30 min; isolated yield. ^b Cp₂TiCl₂ (0.01 mmol). ^c **8i**: 1 h, isolated yield. ^d **8n–8p**: 2 h, isolated yield.

aldehydes/ketones with aniline and trimethylsilyl cyanide in the presence of 1.0 mol% of catalyst 1·THF. Aromatic aldehydes with electron-donating and electron-withdrawing groups were employed. Despite variation of the reaction rate, the yields are high. However, the yield of **9a** is only 37% in the presence of Cp₂TiCl₂. The aromatic aldehydes with electron-withdrawing groups (e.g., F, Cl, and Br) exhibit higher reactivity in the Strecker reaction than that with electron-donating groups on the *para*-position of the phenyl plane (e.g., methyl and methoxyl) (Table 2, **8a–8f**, 91–96%). Gratifyingly, cinnamaldehyde and furfural are also tolerated in this process, and show high reactivity with 90% and 89% yields, respectively (**8g**, **8h**). In addition, the alkyl aldehydes also show good reactivity with 82% yield (**8i**) in the presence of 1·THF. Substituted phenylamine and 8-aminoquinoline also exhibit high reactivity in this catalytic system with benzaldehyde and trimethylsilylcyanide and the yields are 95%, 92% and 85%, respectively (**8j**, **8k**, **8l**). 2-Bromobenzaldehyde was reacted with trifluoromethoxyaniline to obtain compound **8m** in the yield of 91%. Acetophenone, cyclohexanone and 4-methylcyclohexanone were reacted with aniline and trimethylsilylcyanide, giving **8n**, **8o**, and **8p** in 80%, 89% and 83% yield, respectively. Thus, efficient protocols for the synthesis of α-aminonitriles have been developed.

The Mannich-type reaction is a powerful tool for the preparation of synthetically useful β-amino carbonyl compounds,

which are extremely important compounds as biologically active molecules.²¹ A proper control of the three components (enol silyl ether donor, amine, aldehyde acceptor) of the Mannich-type reaction is challenging, since the side reactions such as the aldol reaction may lower the product yield. Impressive achievements have been made in the Mannich-type reactions over various Lewis acid catalysts.²² However, the methods involving the aldol addition side products, longer reaction time, and the use of imine are “environmentally unfriendly” and not “atom economical”. Recently, synthetic methods involving the rare-earth and lanthanide triflates as catalysts for the Mannich-type reactions have been reported.²³ Lanthanide triflates as attractive catalysts have high catalytic activity, low toxicity, and air stability, but they are not recyclable. Another disadvantage is that most of these catalysts require organic solvents as media. Thus, we assessed **3** as a catalyst (1.0 mol%) in one-pot Mannich-type reaction at room temperature under solvent-free conditions, and good-to-excellent yields were obtained (Table 3).

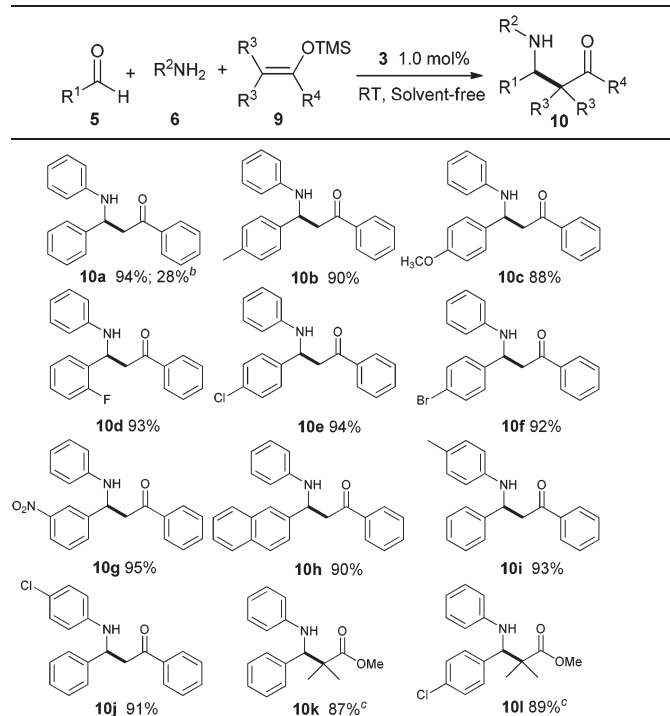
As shown in Table 3, the reactions of a variety of aromatic aldehydes with aniline and trimethyl(1-phenyl-vinyloxy)silane (Table 3) were assessed, and the yields of **10a–10g** are 88–95%. However, the yield of **10a** was only 28% using Cp_2TiCl_2 as the catalyst. The aromatic aldehydes with electron-withdrawing groups (*e.g.*, F, Cl, Br, and NO_2) exhibited higher reactivity in

the Mannich-type reaction than that with electron-donating groups (*e.g.*, methyl and methoxy) (Table 3, **10b–10g**). 2-Naphthaldehyde was also tolerated in this process, providing compound **10h** in 90% yield (Table 3, **10h**). Substituted anilines were also examined with benzaldehyde and trimethyl(1-phenyl-vinyloxy)silane, while the electron-donating groups (CH_3) and electron-withdrawing groups (Cl) can proceed smoothly to afford their corresponding products in high yields (Table 3, **10i**, **10j**). In addition, ketene silyl acetals also have good reactivity in the current catalytic system with benzaldehyde (4-chlorobenzaldehyde) and aniline in the yield of 87% and 89%, respectively (Table 3, **10k**, **10l**).

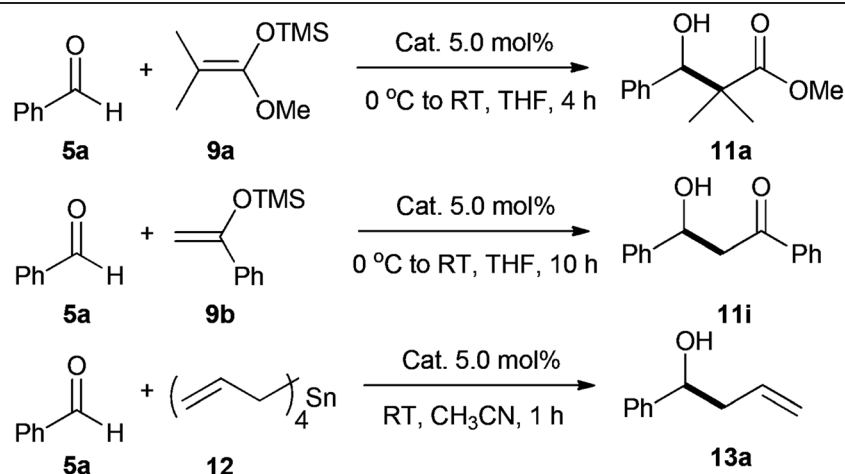
Due to the fact that the above two kinds of reactions only need a weak Lewis acid catalyst, we investigated other C–C bond-forming reactions requiring highly acidic Lewis acid catalysts. The allylation of aldehydes and the Mukaiyama-aldol reaction mediated by a Lewis acid are the most convenient processes for the construction of carbon–carbon bonds in organic synthesis. This route provides a rapid access to synthesis of β -hydroxy ester/ketones and homoallylic alcohol derivatives; these motifs often exist in natural products and bioactive molecules.²⁴ Several efficient Lewis acid catalysts based on titanium, zirconium, copper and Brønsted acids have been developed.²⁵ But in most cases, the temperature of $-20\text{ }^\circ\text{C}$ to $-80\text{ }^\circ\text{C}$ and strictly anhydrous conditions are required. Recently, the highly efficient system of silica-Sc-IL/[DBIm]SbF₆ developed by Kobayashi proved to be the most promising method, which required ionic liquids as co-catalysts.²⁶ Therefore, a highly efficient method for these reactions is still desired.

The catalytic activities of Cp_2TiCl_2 , **1**·THF, **2**·H₂O·THF, and **3** together with **4**·THF were assessed for various carbon–carbon bond-forming reactions. First, reactions of benzaldehyde with nucleophiles, such as ketene silyl acetals, enol silyl ethers and tetraallyltin, were scrutinized (scheme in Table 4). All reactions were carried out in the presence of above catalysts, and the yields of the respective products are compiled in Table 4. High yields were attained over **2**·H₂O·THF/**3**, while the other catalysts showed much lower yields, plausibly due to their lower Lewis acidity or moisture-sensitive features. Notably, the solvents in these reactions, such as THF and CH_3CN , were used as received owing to the water-tolerance ability of the titanocene perfluoroalkyl(aryl)sulfonate complexes, in sharp contrast to titanocene of **4**·THF. To our surprise, titanocene perfluorooctanesulfonate (**1**·THF) only shows moderate catalytic efficiency in the above carbon–carbon bond-forming reactions compared with **2**·H₂O·THF/**3**. We speculated that the relatively lower catalytic efficiency of **1**·THF may be owing to the strongly lipophobic property of the perfluorooctyl group because the perfluoro anions well wrapping the cationic metal center make the lipophilic substrates hard to approach the center metal atom for activating. Besides, due to the strongly lipophobic property of the perfluorooctyl group, the complex usually exhibited moderate solubility in common organic solvents, which may be another reason for the decline of catalytic efficiency. Thus, **2**·H₂O·THF and **3** as Lewis acid catalysts are better than **1**·THF for

Table 3 The Mannich-type reaction of aldehydes, amines and enol silyl ethers/ketene silyl acetals catalyzed by **3**^a



^a Catalyst **3** (0.01 mmol); R^1CHO (**5**; 1.0 mmol); R^2NH_2 (**6**; 1.0 mmol); enol silyl ethers (**9**; 1.2 mmol); solvent-free conditions; temp: RT, **10a–10j**; 20 min, isolated yield. ^b Cp_2TiCl_2 (0.01 mmol). ^c **10k**, **10l**: 1.5 h, isolated yield.

Table 4 Yield [%] in reactions of benzaldehyde with silyl and stannyl nucleophiles catalyzed by Cp_2TiCl_2 , titanocene perfluoroalkyl(aryl)sulfonate complexes and titanocene bis(triflate)s (4·THF)

Entry	Nu	Product	Catalyst				
			Cp_2TiCl_2	1·THF	2·H ₂ O·THF	3	4·THF
1 ^a	9a	11a	26	79	94	89	81
2 ^b	9b	11i	19	72	90	85	76
3 ^c	12	13a	12	80	95	90	84

^a Catalyst (0.05 mol); 5a (1.0 mmol); 9a (1.2 mmol); THF (3 mL); temp: 0 °C to RT; 4 h; isolated yield. ^b Catalyst (0.05 mol); 5a (1.0 mmol); 9b (1.2 mmol); THF (3 mL); temp: 0 °C to RT; 10 h; isolated yield. ^c Catalyst (0.05 mol); 5a (1.0 mmol); 12 (0.3 mmol); CH₃CN (3 mL); temp: RT; 1 h; isolated yield.

carbon–carbon bond-forming reactions. In addition, perfluoro-octanesulfonate compounds (PFOS) have been found to be potentially toxic to animals and human beings^{27a} and will result in environmental pollution.^{27b} However, perfluorobutanesulfonate and perfluorophenylsulfonate compounds exhibited lower toxicity to humans and animals than PFOS,²⁸ which fulfills the requirement of green chemistry.

Next, we mainly assessed the catalytic activities of 2·H₂O·THF and 3. The reactions of different aldehydes and benzaldehyde dimethyl acetal with nucleophiles, such as ketene silyl acetals, enol silyl ethers and tetraallyltin, were examined over 2·H₂O·THF/3 (Table 5).

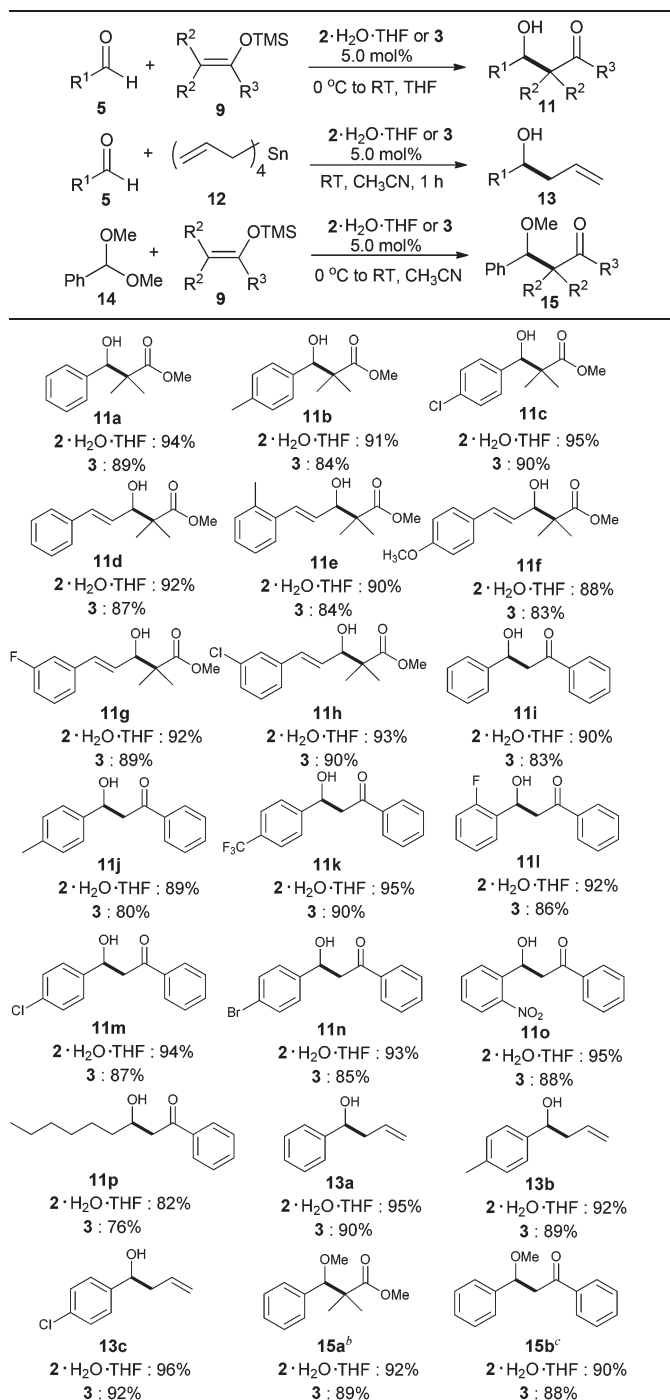
As expected, the β-hydroxy ester/ketone derivatives and homoallylic alcohols can be obtained in high yields in THF or CH₃CN (Table 5). For the Mukaiyama-aldol reaction, aldehydes with electron-withdrawing groups (*e.g.*, CF₃, Cl, Br, and NO₂) in the phenyl plane exhibit higher reaction activity than the aldehydes with electron-donating groups (*e.g.*, methyl) (Table 5, 11b, 11c, 11j–11o). The cinnamaldehyde derivatives with a double bond are also tolerated in this catalytic system, and they successfully react with ketene silyl acetals to form 1,2-addition adducts in high yields (Table 5, 11d–11h). The alkyl aldehyde also shows good reactivity with 82% yield (Table 5, 11p), while the yield of 11p with the complex 1·THF under current conditions is only 58%. For the allylation of aldehydes, different aromatic aldehydes also show high reactivity with tetraallyltin (Table 5, 13–13c). In addition, benzaldehyde dimethyl acetal, as a substitution of benzaldehyde, can react

with different enol silyl ethers to give the desired products in high yields (Table 5, 15a, 15b). It is worth noting that 3 also showed relatively high catalytic efficiency towards the Mukaiyama-aldol reaction and allylation of aldehydes (Table 5).

Later we moved to the Lewis acid-catalyzed Friedel–Crafts acylation of aromatic compounds, which is another important C–C bond forming reaction in organic chemistry.²⁹ Some traditional Lewis acids (such as ZnCl₂, AlCl₃, FeCl₃, SnCl₄, and TiCl₄) or strong protic acids (like HF, CF₃SO₃H or H₂SO₄) were utilized to catalyze the electrophilic acylation reaction.³⁰ However, more than stoichiometric amounts of catalysts are needed owing to the formation of a strong complex from the interaction between the catalyst itself and the ketone product.³¹ Whereas the compound Sc(OTf)₃ was applied in this reaction and a good result can be achieved,³² the high price of Sc(OTf)₃ limits its application. Furthermore, many catalysts, such as NbCl₅/AgClO₄ and Hf(OTf)₄/AgClO₄, were reported as Friedel–Crafts acylation catalysts, while larger equivalents of potentially explosive perchlorate salts have to be used as co-catalysts.³³

Thus, we assessed 2·H₂O·THF as a catalyst for the Friedel–Crafts acylation of structurally diverse anisoles with 2.0 equiv. of acetic(propionic) anhydride at room temperature under solvent-free conditions and good yields were obtained (Table 6, 18a–18i, 76–92%). Differently substituted benzene (*e.g.* methoxy, ethoxyl, and butoxy) has high reactivity in the current catalytic system with acetic anhydride and the yield is high from 84% to 87% (Table 6, 18a–18c). The electron-

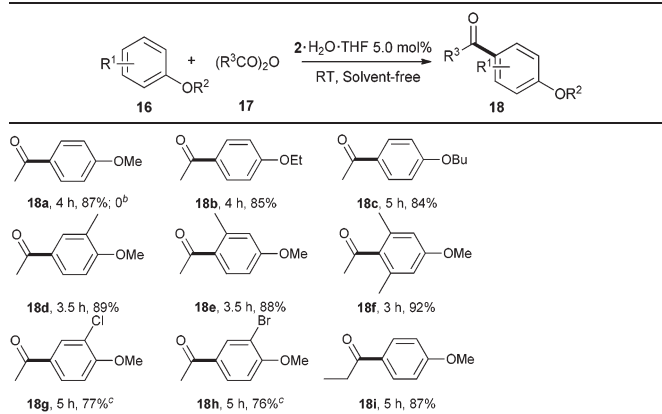
Table 5 The Mukaiyama-aldol reaction of aldehydes with ketene silyl acetals/enol silyl ethers and allylation of aldehydes catalyzed by $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ or **3**^a



^a Catalyst $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ or **3** (0.05 mmol); R^1CHO (**5**; 1.0 mmol) or $\text{Ph}(\text{OMe})_2$ (**14**; 1.0 mmol); ketene silyl acetals/enol silyl ethers (**9**; 1.2 mmol) or tetraallyl tin (**12**; 0.3 mmol); THF- CH_3CN (3 mL); temp: RT; **11a–11h**: 4 h; **11i–11o**: 10 h; **11p**: 12 h; **13a–13c**: 1 h, isolated yield. ^b **15a**: 5 h, isolated yield. ^c **15b**: 12 h, isolated yield.

donating groups attached to the aromatic ring enhance the reaction activity (Table 6, **18d–18f**), but the anisole with 2-Cl and 3-Br groups keeps remains intact at room temperature,

Table 6 Friedel–Crafts acylation of alkyl aryl ethers with anhydrides catalyzed by $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ ^a



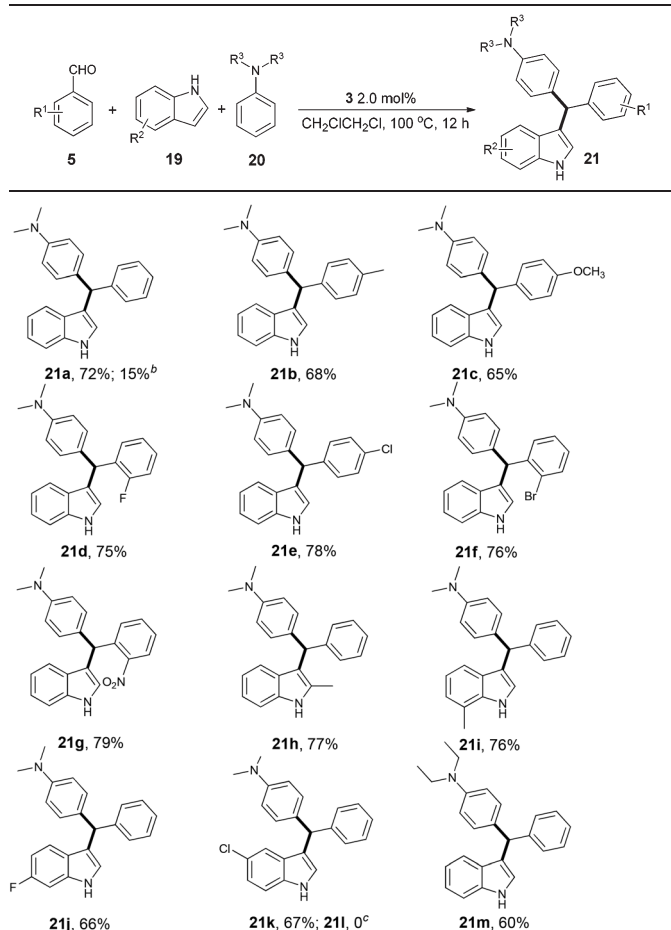
^a Catalyst $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ (0.05 mmol); **16** (1.0 mmol); **17** (2.0 mmol); solvent-free conditions; temp: rt., 4 h, isolated yield. ^b No catalyst or the catalyst was Cp_2TiCl_2 (0.05 mmol), 12 h. ^c At 50 °C.

giving their corresponding products in lower yields even at 50 °C (Table 6, **18g**, **18h**). Meanwhile, propionic anhydride also exhibits good reactivity with 80% yield (Table 6, **18i**). Furthermore, the reaction shows high regioselectivity (*para*-regioisomer > 99%). Controlled experiments were performed in the absence of $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ or in the presence of Cp_2TiCl_2 , no products are obtained. Therefore, in contrast to Cp_2TiCl_2 , the complex $2 \cdot \text{H}_2\text{O} \cdot \text{THF}$ can be considered to be an excellent catalyst in view of catalytic efficiency and *para*-regioselectivity in the Friedel–Crafts acylation.

Indoles are an important class of heterocycles that exist in many natural products.³⁴ Many natural and synthetic indoles exhibit a broad range of biological activities, including anticancer,^{35a} antiangiogenic,^{35b} antiparasitodal^{35c} and antitumor activities.^{35d} Among indole derivatives, bis-indolyl alkanes, 3-alkyl indoles, and 3-diarylmethyl indoles are important class of bioactive metabolites, which can be synthesized with Lewis acids (e.g. InCl_3 ($\text{In}(\text{OTf})_3$),^{36a} $\text{Sc}(\text{OTf})_3$,^{36b} FeCl_3 ,^{36c} CeCl_3 ,^{36d} or $\text{Al}(\text{OTf})_3$ ^{36e}) or protic acids (e.g. HCl , HClO_4 , and H_2SO_4). Although the synthesis of 3-alkyl indoles has been extensively studied, the synthesis of other unsymmetrical indole derivatives is still highly desirable in synthetic community since it needs more practical procedures and mild reaction conditions.³⁷

Herein we report the complex **3**-catalyzed one-pot three-component aza-Friedel–Crafts reactions of indoles, aldehydes, and tertiary aromatic amines. The reactions generated the corresponding 3-diarylmethyl indole derivatives in good yields under mild reaction conditions (Table 7). In order to demonstrate the good catalytic efficiency of **3**, the scope of indoles and benzaldehydes for the three-component aza-Friedel–Crafts reactions using **3** as a catalyst was evaluated. One can see that benzaldehydes bearing electron-withdrawing groups (F, Cl, Br, and NO_2) give the corresponding products in higher yields than those with electron-donating groups (CH_3 and OCH_3) (Table 7, **21b–21g**). In contrast, indoles bearing electron-donating groups (methyl) show slightly higher reactivity than those

Table 7 The aza-Friedel–Crafts reactions of indoles, aldehydes and *N,N*-dialkylaniline catalyzed by **3**^a



^a Catalyst **3** (0.02 mmol); R^1CHO (**5**; 1.0 mmol); indoles (**19**; 1.0 mmol); *N,N*-dialkylaniline (**20**; 1.1 mmol); solvent: $\text{CH}_2\text{ClCH}_2\text{Cl}$ (3 mL); temp: $100\text{ }^\circ\text{C}$; isolated yield. ^b Cp_2TiCl_2 (0.02 mmol). ^c PhCHO (1.0 mmol); 5-nitroindole (1.0 mmol); *N,N*-dimethylaniline (**20a**; 1.1 mmol).

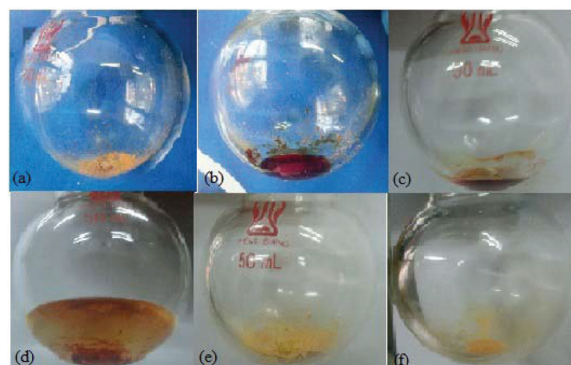


Fig. 5 (a) Catalyst 2- H_2O -THF (0.05 mmol, 45 mg); (b) adding starting materials [PhOMe (1.0 mmol, 108 mg) + Ac_2O (2.0 mmol, 204 mg)]; (c) the reaction was complete as indicated by TLC; (d) adding 10 mL *n*-hexane; (e) removing the liquid reaction mixture with a syringe (or filtration) and washing the residue with hexane (three times); (f) scraping the catalyst on the flask wall (43 mg).

with electron-withdrawing groups, like F and Cl (Table 7, **21h–21k**). However, the yield of **21a** was only 15% using Cp_2TiCl_2 as a catalyst. Meanwhile, *N,N*-diethylaniline can also react with benzaldehyde and indole to give 60% yield (Table 7, **21m**). It is worth noting that no reaction was observed when 5-nitroindole (bearing the strong electron-withdrawing group) was employed as the substrate (Table 7, **21l**).

To test the reusability of the catalyst and the reproducibility of the catalytic performance, 1-THF or 2- H_2O -THF/**3** was subjected to recycling experiments of above reactions (eqn (1): **5a** + **6a** + **7a** → **8a**; eqn (2): **5a** + **6a** + **9b** → **10a**; eqn (3): **5a** + **9a** → **11a**; eqn (4): **16a** + **17a** → **18a**). We took the Friedel–Crafts acylation (**16a** + **17a** → **18a**) as an example for the catalyst recovery process. As shown in Fig. 5, the catalyst can be easily recycled by adding the solvent *n*-hexane (three times). Moreover, the final recovered catalyst was analyzed by ^1H NMR. It is clear that ^1H NMR spectra of the recovered catalyst are the same as that of the catalyst 2- H_2O -THF (Fig. 6), implying that the

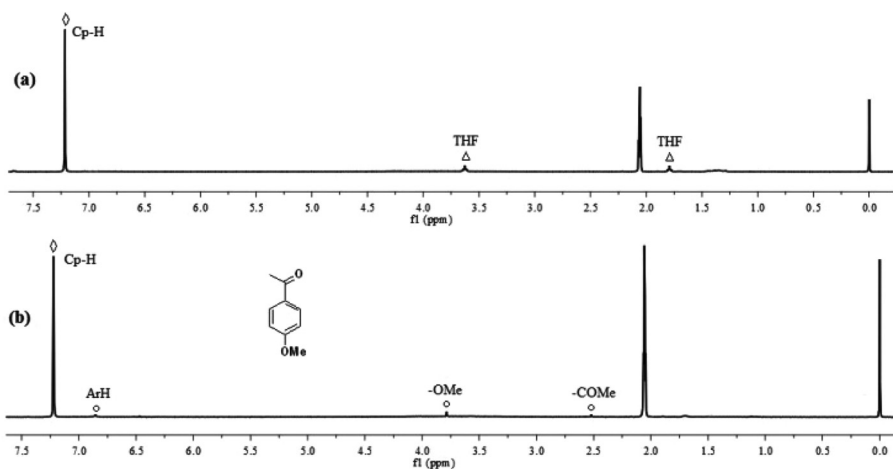
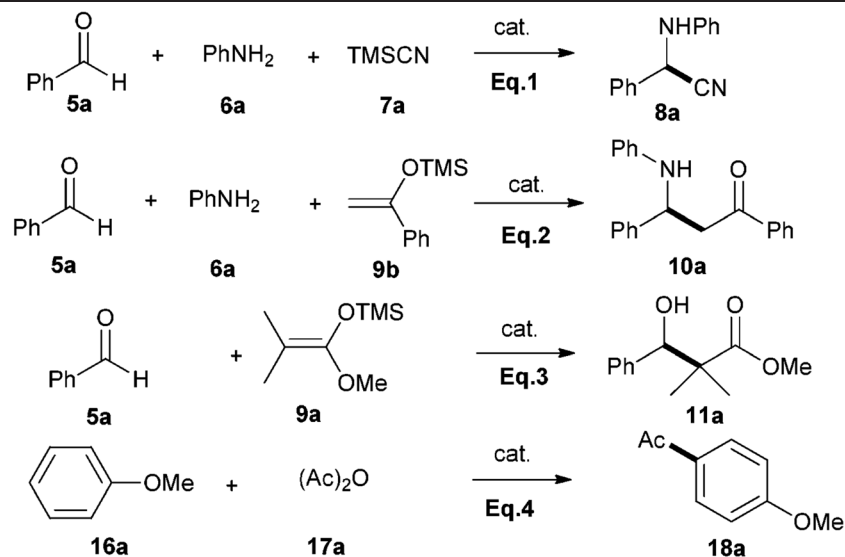


Fig. 6 The ^1H NMR spectral comparison of the recovered catalyst **1** in the Friedel–Crafts acylation as shown in the scheme in Table 1 (\diamond = catalyst peak (Cp-H); \triangle = THF peak; \circ = recycled catalyst contains some impurities which are products and starting materials).

Table 8 Yields of the Strecker reaction (eqn (1)); Mannich-type reaction (eqn (2)); Mukaiyama aldol reaction (eqn (3)) and Friedel–Crafts acylation (eqn (4)) by recovered catalyst^a

Cycle	Yield ^e (%) eqn (1) ^a	Cat. ^f (%)	Yield ^e (%) eqn (2) ^b	Cat. ^f (%)	Yield ^e (%) eqn (3) ^c	Cat. ^c (%)	Yield ^e (%) eqn (4) ^d	Cat. ^f (%)
1	95	96	94	96	94	96	87	89
2	96	97	95	97	95	97	88	90
3	95	97	94	96	96	98	86	88
4	95	96	94	96	94	96	87	88
5	96	97	93	95	94	97	88	91

^a 5a (1.0 mmol); 6a (1.0 mmol); 7a (1.2 mmol); 1-THF (0.01 mmol); rt. ^b 5a (1.0 mmol); 6a (1.0 mmol); 9b (1.2 mmol); 3 (0.01 mmol); RT. ^c 5a (1.0 mmol); 9a (1.2 mmol); cat. 2-H₂O·THF/3 (0.05 mmol); RT. ^d 16a (1.0 mmol); 17a (2.0 mmol); 2-H₂O·THF (0.05 mmol); RT. ^e The isolated yield of the desired product. ^f The isolated yield of the recovered catalyst.

catalyst is stable and suitable for reuse. According to this procedure, the above reactions were carried out and the results are shown in Table 8. The change in product yield was negligible in a trial of five recycling experiments.

Conclusion

We have synthesized and characterized a series of mono-nuclear titanocene perfluoroalkyl(aryl)sulfonate complexes. These complexes are strongly acidic and air-stable, and show high catalytic activity in the Strecker reaction, the Mannich-type reaction, allylation of aldehydes, the Mukaiyama aldol reaction, the Friedel–Crafts acylation and the aza-Friedel–Crafts reactions. Moreover, these complexes show good reusability. Compared with 1-THF, 2-H₂O·THF and 3 exhibit higher solubility and better catalytic activity. Due to their high catalytic efficiency, stability, storability, low toxicity and reusability, they will find broad applications in organic synthesis.

Experimental section

General

All chemicals were purchased from Aldrich. Co. Ltd as well as other chemical providers and used as received unless other-

wise indicated. The preparation of the catalyst was carried out under a nitrogen atmosphere with freshly distilled solvents. THF and hexane were distilled from sodium/benzophenone. Acetonitrile was distilled from CaH₂. The NMR spectra were recorded at 25 °C on an INOVA-400M (USA) calibrated with tetramethylsilane (TMS) as an internal reference. Elemental analyses were performed using a VARIO EL III. TG-DSC analysis was performed on a HCT-1 (HENVEN, Beijing, China) instrument. The conductivity was measured on a REX conductivity meter DDS-307. IR spectra were recorded on a NICOLET 6700 FTR spectrophotometer (Thermo Electron Corporation). X-ray single crystal diffraction analysis was performed with SMART-APEX and RASA-7A by Shanghai Institute Organic Chemistry, China Academy of Science. The Lewis acidity estimation was performed by means of ESR in Osaka University. UV/Vis (SHIMADZU UV-1601) and fluorescence spectroscopy (HITACHI F-4600) were performed in the State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University (China). The acidity was measured by the Hammett indicator method as described previously. Acid strength was expressed in terms of Hammett acidity function (H₀) as scaled by a pK_a value of the indicators.

Preparation of 1-THF. To a solution of Cp₂TiCl₂ (0.249 g, 1.0 mmol) in 20 mL THF was added a solution of AgOSO₂C₈F₁₇ (1.24 g, 2.05 mmol) in 10 mL THF. After the mixture was stirred

at 25 °C for 1 hour in the absence of light, it was filtered. The filtrate was placed in a small jar, which was put into a larger jar containing dry hexane (40 mL). The larger jar was sealed and refrigerated for 24 h. The yellow crystals were obtained (744 mg, 58%). $^1\text{H NMR}$ (400 MHz, acetone- d_6): δ 7.22 (s, 10H, Cp), 3.64 to 3.61 (m, THF), 1.82 to 1.76 (m, THF); $^{19}\text{F NMR}$ (376 MHz, acetone- d_6): δ -81.67 (t, $J = 19.9$ Hz, 3F, CF_3^-), -115.03 (s, 2F, $-\text{CF}_2^-$), -121.06 to 121.12 (m, 2F, $-\text{CF}_2^-$), -122.14 to -122.51 (m, 6F, $-\text{CF}_2^-$), -123.26 to -123.33 (m, 2F, $-\text{CF}_2^-$). -126.73 to -126.80 (m, 2F, $-\text{CF}_2^-$); IR(KBr): $\nu = 3512, 3427, 3117, 2903, 1629, 1442, 1364, 1253, 1148, 1065, 826, 737, 641$ cm^{-1} ; elemental analysis calculated (%) for $\text{Cp}_2\text{Ti}(\text{OSO}_2\text{C}_8\text{F}_{17})_2$ after pumping for a week: $\text{C}_{26}\text{H}_{10}\text{F}_{34}\text{O}_6\text{S}_2\text{Ti}$: C, 26.55; H, 0.86; found: C, 26.62; H, 0.87.

Preparation of 2-H₂O·THF. To a solution of Cp_2TiCl_2 (0.249 g, 1.0 mmol) in 20 mL THF was added a solution of $\text{AgOSO}_2\text{C}_4\text{F}_9$ (0.832 g, 2.05 mmol) in 10 mL THF. After the mixture was stirred at 25 °C for 1 hour in the absence of light, it was filtered. The filtrate was placed in a small jar, which was put into a larger jar containing dry hexane (40 mL). The larger jar was sealed and refrigerated for 24 h. The yellow crystals were obtained (631 mg, 70%). $^1\text{H NMR}$ (400 MHz, acetone- d_6): δ 7.22 (s, 10H, Cp), 3.64 to 3.61 (m, THF), 1.82 to 1.76 (m, THF); $^{19}\text{F NMR}$ (376 MHz, acetone- d_6): δ -81.81 (t, $J = 20.3$ Hz, 3F, CF_3^-), -115.03 (s, 2F, $-\text{CF}_2^-$), -122.04 to 122.10 (m, 2F, $-\text{CF}_2^-$), -126.57 to -126.68 (m, 2F, $-\text{CF}_2^-$); IR(KBr): $\nu = 3439, 3104, 2874, 1635, 1441, 1358, 1262, 1217, 1134, 1063, 1022, 815, 744, 703, 661$ cm^{-1} ; elemental analysis calculated (%) for $\text{Cp}_2\text{Ti}(\text{OSO}_2\text{C}_4\text{F}_9)_2$ after pumping for a week: $\text{C}_{18}\text{H}_{10}\text{F}_{18}\text{O}_6\text{S}_2\text{Ti}$: C, 27.85; H, 1.30; found: C, 27.82; H, 1.35.

Crystal data for 2-H₂O·THF: $\text{C}_{22}\text{H}_{24}\text{F}_{18}\text{O}_{10}\text{S}_2\text{Ti}$; $M_r = 898.40$, monoclinic, space group $P2_1/c$, $a = 16.1896(17)$ Å, $b = 12.8505(13)$ Å, $c = 19.6306(15)$ Å; $V = 3538.8(6)$ Å³; $T = 293(2)$ K; $Z = 4$; reflections collected/unique, 23 243/6888, $R_{\text{int}} = 0.0175$, final R indices [$I > 2\sigma(I)$] $R_1 = 0.0536$, $wR_2 = 0.1465$; R indices (all data), $R_1 = 0.0597$, $wR_2 = 0.1484$. GOF = 1.089; CCDC no. 894849.

Preparation of 3. To a solution of Cp_2TiCl_2 (0.249 g, 1.0 mmol) in 20 mL CH_3CN was added a solution of $\text{AgOSO}_2\text{C}_6\text{F}_5$ (0.791 g, 2.05 mmol) in 10 mL CH_3CN . After the mixture was stirred in the absence of light at room temperature for 2 hours, it was filtered and evaporated in a vacuum and the resulting residue was diluted with 10 mL THF followed by five drops of dry hexane and then was kept in the refrigerator for 24 hours, the yellow crystal was obtained (517 mg, 73%). Recrystallization of this complex in THF-hexane produced good crystals suitable for X-ray analysis. Mp: 214–216 °C; $^1\text{H NMR}$ (400 MHz, acetone- d_6): δ 7.13 (s, 10H, Cp), $^{19}\text{F NMR}$ (376 MHz, acetone- d_6): δ -139.33 (s, 2F, C_6F_5^-), -152.20 (s, 1F, C_6F_5^-), -163.00 (s, 2F, C_6F_5^-); IR(KBr): $\nu = 3411, 1632, 1518, 1313, 1253, 1124, 1031, 965, 823, 725$ cm^{-1} ; elemental analysis calculated (%) for $\text{C}_{22}\text{H}_{14}\text{F}_{10}\text{O}_8\text{S}_2\text{Ti}$ (as two hydrates): C, 37.30; H, 1.99; found: C 37.28; H, 2.01.

Crystal data for 3: $\text{C}_{22}\text{H}_{14}\text{F}_{10}\text{O}_8\text{S}_2\text{Ti}$; $M_r = 708.35$, monoclinic, space group $C2/m$, $a = 14.3586(13)$ Å, $b = 15.8694(16)$ Å, $c = 12.0211(11)$ Å; $V = 2593.8(4)$ Å³; $T = 100(2)$ K; $Z = 4$; reflections collected/unique, 9551/2501, $R_{\text{int}} = 0.0257$, final R indices

[$I > 2\sigma(I)$] $R_1 = 0.0294$, $wR_2 = 0.0771$; R indices (all data), $R_1 = 0.0337$, $wR_2 = 0.0795$. GOF = 1.146; CCDC no. 938518.

Typical procedure for the solubility of 1·THF, 2·H₂O·THF and 3. Acetone (0.5 mL) was placed in a test tube; the complex 1·THF was added gradually at room temperature. When the amount of added 1·THF exceeded 142 mg, insoluble 1·THF appeared. Based on these data, the solubility of 1·THF was determined to be 284 g L⁻¹. According to the same procedure, the solubilities of complexes 2·H₂O·THF and 3 were determined.

Typical procedure for conductivity measurements. Acetonitrile (10 mL) was placed in a beaker; the complex 2·H₂O·THF (4.5 mg, 0.005 mmol) was added at room temperature. The probe was placed in the solution for the measurement of relative conductivity. According to the same procedure, the conductivities of 1·THF and 3 were measured.

ESR detection of the O₂^{·-}/1 complex. A quartz ESR tube (4.5 mm i.d.) containing an oxygen-saturated solution of dimeric 1-benzyl-1,4 dihydronicotinamide (BNA)₂ (1.0×10^{-2} M) and 1·THF (1.0×10^{-3} M) in MeCN was irradiated in the cavity of the ESR spectrometer with the focused light of a 1000 W high-pressure Hg lamp through an aqueous filter. Dimeric (BNA)₂, which was used as an electron donor to reduce oxygen, was prepared according to the literature. The ESR spectra of the O₂^{·-}/1 complex in frozen MeCN were measured at 143 K with JEOL X-band apparatus under nonsaturating microwave power conditions. The g values were calibrated precisely with a Mn^{2+} marker, which was used as a reference.

UV/Vis spectral detection of the 10-methylacridone/2·H₂O·THF. The formation of metal ion complexes with 10-methylacridone was examined from the change in the UV/Vis spectra in the presence of various concentrations of metal ions (M^{n+}) using a Hewlett-Packard 8452 A diode array spectrophotometer. The formation constants were determined from linear plots of $(A - A_0)^{-1}$ versus $[\text{M}^{n+}]^{-1}$, in which A and A_0 are the absorbance at λ_{max} in the presence of the metal ion and the absorbance at the same wavelength in the absence of the metal ion, respectively.

Typical procedure for fluorescence spectral detection of 2·H₂O·THF. The fluorescence measurement of 10-methylacridone/2·H₂O·THF was performed on a spectrofluorophotometer. The excitation wavelength of 10-methylacridone/2·H₂O·THF was 413 nm in MeCN. The MeCN solutions were deaerated by argon purging for 7 min prior to the measurements.

Crystal data refinement details

Refinement of F^2 against all reflections. The weighted R -factor wR and the goodness of fit S are based on F^2 , conventional R -factors R are based on F , and F is set to zero for negative F^2 . The threshold expression of $F^2 > 2$ sigma (F^2) is used only for calculating R -factors (gt), etc. and is not relevant to the choice of reflections for refinement. R -Factors based on F^2 are statistically about twice as large as those based on F , and R -factors based on ALL data will be even larger. Data collection: Bruker SMART; cell refinement: Bruker SAINT; data reduction: Bruker

SHELXTL; program(s) used to solve structures: SHELXS97 (Sheldrick, 1990); program(s) used to refine structures: SHELXL97 (Sheldrick, 1997); molecular graphics: Bruker SHELXTL; software used to prepare material for publication: Bruker SHELXTL. CCDC-894849 and CCDC-938518 contain the supplementary crystallographic data for this paper.

Typical procedure for the Strecker reaction of benzaldehyde (5a) with aniline (6a) and trimethylsilyl cyanide (7a) catalyzed by 1·THF. A mixture of PhCHO (106 mg, 1 mmol), PhNH₂ (93 mg, 1 mmol), trimethylsilylcyanide (119 mg, 1.2 mmol) and catalyst 1·THF (9 mg, 0.01 mol) was stirred at room temperature until the reaction was complete. It was subjected to evaporation in a vacuum at room temperature, the residue was dissolved in CH₂Cl₂ (10 mL × 3) and the catalyst was collected by means of filtration for the next cycle of reaction. To the filtrate, after evaporation of the solvent a pale yellow solid mixture was obtained. The products **8a** were isolated by silica gel column chromatography on silica gel (petroleum ether–EtOAc = 8 : 1) with a yield of 95% (198 mg) as a pale yellow solid. Aldehydes/ketones (**5**) and amines (**6**) and nucleophiles trimethylsilyl cyanide (**7a**) are commercially available.

Typical procedure for the Mannich-type reaction of benzaldehyde (5a) with aniline (6a) and trimethyl(1-phenyl-vinyl)silane (9b) catalyzed by 3. The complex **3** (7 mg, 0.01 mmol), PhCHO (106 mg, 1.0 mmol), PhNH₂ (93 mg, 1.0 mmol) and trimethyl(1-phenyl-vinyl)silane (230 mg, 1.2 mmol) were placed in a 50 mL round-bottomed flask. Then the mixture was stirred at room temperature until the reaction was complete as indicated by TLC. Then the solvents of the resulting mixture were removed by evaporation under vacuum, the residue was dissolved in CH₂Cl₂ (10 mL × 3) and the catalyst was collected by means of filtration for the next cycle of reaction. The filtrate was subjected to volatilization and pale yellow solids were obtained, the products **10a** were isolated by silica gel column chromatography on silica gel (petroleum ether–EtOAc = 5 : 1) in yield 94% (283 mg) as a white solid. Aldehydes (**5**) and amines (**6**) and nucleophiles ketene silyl acetals (**9a**) and enol silyl ethers (**9b**) are commercially available.

Typical procedure for the Mukaiyama-aldol reaction of benzaldehyde (5a) with ketene silyl acetals (9a) catalyzed by 2·H₂O·THF. The complex 2·H₂O·THF (45 mg, 0.05 mmol) and ketene silyl acetal (**9a**) (209 mg, 1.2 mmol) were added to a solution of PhCHO (**5a**) (106 mg, 1.0 mmol) in THF (3.0 mL) at 0 °C. Then the temperature was raised to room temperature slowly. After the mixture was stirred at room temperature for 5 h and monitored by TLC, it was subjected to evaporation under vacuum at room temperature, the residue was dissolved in *n*-hexane (10 mL × 3) and the catalyst was collected by means of filtration for the next cycle of reaction. To the combined hexane solution, MeOH and HCl (aq.) were added and the mixture was stirred for 15 minutes. NaHCO₃ (aq.) was added for neutralization. The mixture was subjected to evaporation, and the solids thus obtained were dissolved in AcOEt and water. After extraction with AcOEt (three times), the organic layer was washed with NaCl (aq.) and dried over

MgSO₄. After evaporation, the residue was subjected to silica gel column chromatography (petroleum ether–ethyl acetate = 10 : 1), and colourless crystals of (**11a**) were obtained (196 mg, isolated yield 95%). Aldehydes (**5**) and nucleophiles ketene silyl acetals (**9a**) and enol silyl ethers (**9b**) are commercially available.

Typical procedure for allylation of benzaldehyde (5a) with tetraallyltin (12) catalyzed by 2·H₂O·THF. The complex 2·H₂O·THF (45 mg, 0.05 mmol) was added to a solution of benzaldehyde (106 mg, 1.0 mmol) in CH₃CN (3.0 mL). Tetraallyltin (**12**; 0.3 mmol) was then added to the mixture at room temperature. After the mixture was stirred at room temperature for an hour and monitored by TLC, it was evaporated in a vacuum at room temperature. *n*-Hexane (10 mL × 3) was added to the residue; the catalyst was precipitated and was recovered by filtration for the next reaction cycle. The combined *n*-hexane solution was concentrated, and then MeOH and HCl (aq.) were added and stirred for 15 min. NaHCO₃ (aq.) was added for neutralization. After the mixture was subjected to evaporation, the as-obtained solids were dissolved in AcOEt and water. After extraction with AcOEt (three times), the organic layer was washed with NaCl (aq.) and dried over MgSO₄. After evaporation, the GLC yield was measured. Alternatively, the residue was subjected to silica gel column chromatography (petroleum ether–ethyl acetate = 8 : 1) and **13a** was obtained as a colorless oil (139 mg, isolated yield 95%). Aldehydes (**5**) and tetraallyltin (**12**) are commercially available.

Typical procedure for the Mukaiyama-aldol reaction of benzaldehyde dimethyl acetal (14) with ketene silyl acetals or enol silyl ethers (9) catalyzed by 2·H₂O·THF. The operation method is similar to Mukaiyama-aldol reaction of benzaldehyde(**5a**) with ketene silyl acetals (**9a**). The solvent was replaced with CH₃CN. Benzaldehyde dimethyl acetal (**14**) and nucleophiles ketene silyl acetals (**9a**) and enol silyl ethers (**9b**) are commercially available.

Typical procedure for Friedel–Crafts acylation of anisole (16a) with acetic anhydride (17a) catalyzed by 2·H₂O·THF. To a 50 mL round-bottom flask were added anisole (**16a**) (108 mg, 1.0 mmol), acetic anhydride (**17a**) (204 mg, 2.0 mmol) and the catalyst 2·H₂O·THF (45 mg, 0.05 mmol). Then the mixture was stirred at room temperature until complete consumption of the starting material as monitored by TLC or GC-MS analysis. After that, the residue was dissolved in *n*-hexane (10 mL × 3) and the catalyst was collected by means of filtration for the next cycle of reaction. The solvent was removed by evaporation in a vacuum and was then subjected to silica gel column chromatography; the Friedel–Crafts acylation product (**18a**) was obtained: 131 mg, isolated yield 87%. Alkyl aryl ethers (**16**) and anhydrides (**17**) are commercially available.

Typical procedure for the aza-Friedel–Crafts reaction of benzaldehyde (5a) with indole (19a) and *N,N*-dimethylaniline (20a) catalyzed by the complex 3. To a 50 mL round-bottom flask were added benzaldehyde (106 mg, 1.0 mmol), indole (117 mg, 1.0 mmol), *N,N*-dimethylaniline (133 mg, 1.1 mmol), CH₂ClCH₂Cl (3 mL) and catalyst **3** (14 mg, 2 mol%). Then the mixture was stirred at 100 °C until complete consumption of

the starting material as monitored by TLC. Then the reaction mixture was evaporated in a vacuum, CH₂Cl₂ (10 mL × 3) was added to the reaction mixture and the catalyst was filtered for the next cycle of reaction. The combined CH₂Cl₂ solution was removed by evaporation in a vacuum and was then subjected to silica gel column chromatography; the one-pot three-component aza-Friedel–Crafts product (**21a**) was obtained, white solid, 235 mg, isolated yield 72%. Aldehydes (**5**) and indoles (**19**) and the nucleophile *N,N*-dialkylaniline (**20**) are commercially available.

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