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Air-stable μ -oxo-bridged binuclear titanium(IV) salophen perfluorooctanesulfonate as a highly efficient and recyclable catalyst for the synthesis of bis(indolyl) methane derivatives

Jie Qiao^{a,b}, Shan Gao^a, Lingxiao Wang^b, Jiancong Wei^{b,*}, Ningbo Li^{a,b,*} and Xinhua Xu^c

^a Department of Biochemistry and Molecular Biology, Basic Medical College, Shanxi Medical University, Taiyuan 030001, China

^b Department of Chemistry, Basic Medical College, Shanxi Medical University, Taiyuan 030001, China

^c College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

Abstract

An air-stable μ -oxo-bridged binuclear Lewis acid of titanium(IV) salophen perfluorooctanesulfonate [$\{\text{Ti}(\text{salophen})\text{H}_2\text{O}\}_2\text{O}\][\text{OSO}_2\text{C}_8\text{F}_{17}]_2$ (**1**) was successfully synthesized by the reaction of $\text{Ti}^{\text{IV}}(\text{salophen})\text{Cl}_2$ with $\text{AgOSO}_2\text{C}_8\text{F}_{17}$ and characterized by different techniques such as IR, NMR and HRMS. TG-DSC analysis showed that this complex was thermally stable at 220 °C. Meanwhile, it exhibited good solubility in polar organic solvents and good ionic dissociation in CH_3CN solution. Fluorescence spectra and Hammett indicator results indicated that the complex had relatively strong acidity. And it showed high catalytic efficiency for the synthesis of bis(indolyl) methane derivatives through Friedel-Crafts reaction of aldehyde/ketone with indoles. Moreover, it can be reused five times with minimal changes in catalytic efficiency.

Keywords: $\text{Ti}^{\text{IV}}(\text{salophen})$ complex; Perfluorooctanesulfonate; Friedel-Crafts reaction; Bis(indolyl) methanes; Recyclability.

* Corresponding author.

E-mail address: jiancongwei@sxmu.edu.cn

* Corresponding author.

E-mail address: ningboli@sxmu.edu.cn; Tel./Fax: (+ 86) 351 3985152

1. Introduction

Bis(indolyl)methane derivatives have been often encountered as an important framework and intermediate in pharmaceuticals and agrochemicals, organic synthesis and materials science [1]. Various drugs and biological molecules such as anticancer agent, arsindoline A and anti-infective agent contain bis(indolyl)methane in their backbone [2,3] (Fig. 1). Based on their wide applications, novel strategies for the synthesis of bis(indolyl)methane derivatives are vital important to be developed.

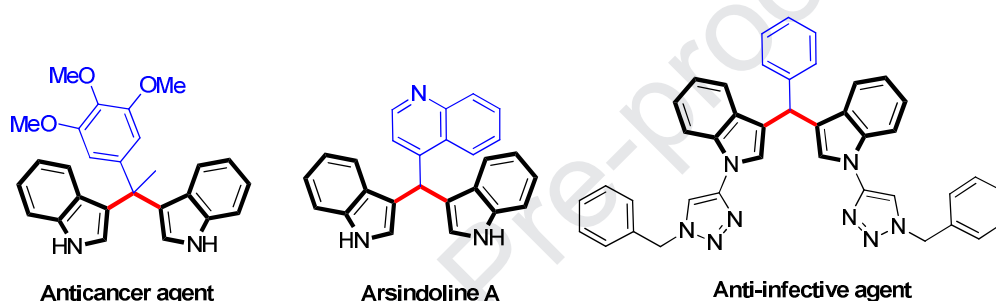


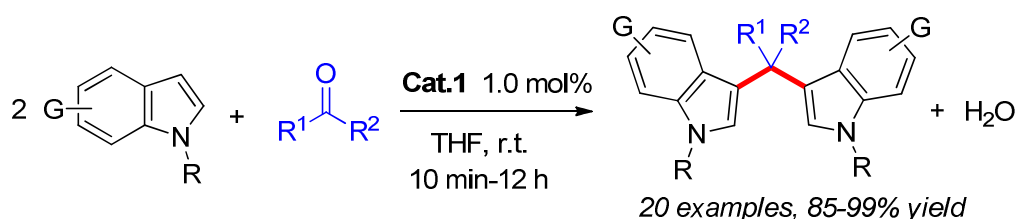
Fig. 1 Biological molecules containing bis(indolyl)methanes.

At present, one of the most convenient routes for the synthesis of bis(indolyl)methanes is through the Friedel-Crafts alkylation of aldehyde/ketone with indoles in the presence of either protic acid or Lewis acid. Those reported catalysts including $\text{H}_3\text{PW}_{12}\text{O}_{40}$ [4], silica supported sulfuric acid [5], itaconic acid [6], InCl_3 [7], FeCl_3 [8], LiClO_4 [9], SbCl_3 [10], ZrOCl_2 [11], $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ [12], CAN [13], $\text{Dy}(\text{OTf})_3$ [14], $\text{Ln}(\text{OTf})_3$ [15], $\text{Yb}(\text{OTf})_3/\text{SDS}$ [16], $\text{Zr}(\text{Salophen})\text{Cl}_2$ [17], I_2 [18], Br_2 [19], ionic liquid [20], *et.al.* Nonetheless, above reported methods for bis(indolyl)methanes synthesis suffer from certain drawbacks, e.g., the use of air or moisture-sensitive catalysts, requiring strict anhydrous conditions, the need for large catalytic dose, low yield, functional group intolerance, poor reusability. Although rare-earth metal triflates can effectively catalyze the reaction, their high prices limit the further utilization. Therefore, the

development of an air-stable and highly efficient and recyclable catalyst for the synthesis of bis(indolyl) methanes is still worthwhile.

Organometallic Lewis acids-catalyzed carbonyl group transformation is of great significance in organometallic chemistry and catalysis [21,22]. Among them, group 4 metal compounds drawn considerable attention owing to their highly catalytic activity and facile availability [23-25]. For example, titanium Schiff base complexes have been used as catalysts for olefin polymerization [26], ring-opening of epoxides [27], trimethylsilylcyanation or acetylation of alcohols and phenols [28,29]. However, titanium Schiff base complexes have rarely been reported as Lewis acid catalyst. The reason may be that the ligand containing N and O atoms reduces the Lewis acidity of titanium compounds. In order to increase the Lewis acidity of the titanium schiff base complexes, the direct method is to introduce electron-withdrawing group(s) into titanium [30]. In recent years, our group has reported a series of air-stable metallocene and organoantimony perfluoroalkyl(aryl)sulfonate complexes, which showed strong Lewis acidity and high catalytic activity in many organic reactions [31-37]. The above results indicate that perfluoroalkyl(aryl)sulfonate groups can be used as effective counter anions to increase the acidity as well as the water tolerance [38,39]. With this in mind, we envisioned that a perfluorooctanesulfonate group introduced into the titanium salophen compound by the replacement of a chlorine atom might enhance the acidity of the complex. In this study, an air-stable μ -oxo-bridged binuclear titanium(IV) salophen perfluorooctanesulfonate $[\{\text{Ti}(\text{salophen})\text{H}_2\text{O}\}_2\text{O}][\text{OSO}_2\text{C}_8\text{F}_{17}]_2$ (**1**) was successfully synthesized and characterized. Furthermore, we report a mild and efficient protocol for synthesis of bis(indolyl) methanes

through the Friedel-Crafts alkylation of aldehyde/ketone with indoles catalyzed by complex **1** at room temperature (Scheme 1).



Scheme 1 The synthesis of bis(indolyl) methanes

2. Experimental

All chemicals were purchased from Aladdin reagent Co. and used as received unless otherwise indicated. IR spectra were recorded on a NICOLET 6700 FTR spectrophotometer (Thermo Electron Corporation). NMR spectra were recorded at 25 °C on a INOVA-400M calibrated with tetramethylsilane (TMS) as the internal reference (USA). High resolution mass spectra were recorded using a Thermo Scientific Q Exactive in Shanxi University. TG-DSC analysis was performed using a HCT-1 (HENVEN, Beijing, China) instrument. Conductivity was measured on a REX conductivity meter DDS-307. Fluorescence spectroscopy was tested on a HITACHI F-4600 instrument in Hunan University. The acidity was measured by the Hammett indicator method as described previously. Acid strength was expressed in terms of Hammett acidity function (H_0) as scaled by the pK_a value of the indicators. The starting material $Ti^{IV}(\text{salophen})Cl_2$ was prepared according to the literature [40].

2.1 Preparation of $[Ti(\text{salophen})H_2O]_2[OSO_2C_8F_{17}]_2$ (**1**)

A THF solution (10 mL) of $AgOSO_2C_8F_{17}$ (1.21 g, 2 mmol) was added to a solution of $Ti^{IV}(\text{salophen})Cl_2$ (0.432 g, 1 mmol) in THF (10 mL). After the mixture was stirred at room temperature for 2 h in the absence of light. A brown precipitate was produced. The $AgCl$ that formed was filtered off through a fine fritted funnel. The filtrate was placed in a small jar, which was put into a larger jar containing dry hexane (20 mL). The larger jar was sealed and refrigerated for 24 h. Red solid of complex **1** were obtained (1.383 g, 78% yield of the isolated product).

1H NMR (400 MHz, $[D_6]$ acetone) δ : 9.13 (s, 4H, H-C=N), 7.84-7.82 (m, 4H, Ar), 7.76 (d, 4H, J = 7.2 Hz, Ar), 7.53 (t, 4H, J = 6.8 Hz, Ar), 7.37-7.35 (m, 4H, Ar), 7.00 (t, 4H, J = 7.2 Hz, Ar),

6.56 (d, 4H, $J = 8.0$ Hz, Ar), 3.71 (s, 4H; H₂O); ¹⁹F NMR (376 MHz, [D₆]acetone): δ : -126.66 to -126.74 (m, 2F; -CF₂-), -123.24 (s, 2F; -CF₂-), -122.09 to -122.40 (d, 6F; -(CF₂)₃-), -121.02 (s, 2F; -CF₂-), -115.11 to -115.19 (m, 2F; -CF₂-), -81.62 to -81.67 ppm (m, 3F; CF₃-); IR(KBr): $\nu = 3469$, 2923, 2856, 1605, 1554, 1254, 1148, 1052, 820, 752, 703, 647 cm⁻¹; ESI-HRMS calcd for C₅₇H₃₇F₃₄N₄O₁₄S₂Ti₂ [**1** + CH₃OH + H]⁺: 1807.0158; Found: 1807.1079.

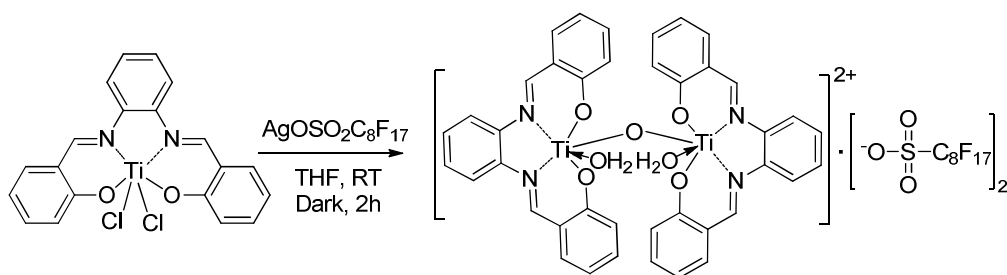
2.2 General Procedure for Synthesis of bis(indolyl) methanes:

A mixture of carbonyl compound (1 mmol), indole (0.234 g, 2 mmol) and **1** (17.7 mg, 1 mmol%) in THF (0.5 mL) was stirred at room temperature for the appropriate reaction time under the TLC analysis until indole was consumed completely. Then the solvents of the resulted mixture were removed by evaporation in vacuum, and the residue was dissolved in diethyl ether (30 mL) followed by filtration. After the catalyst was washed three times with diethyl ether (10 × 3 mL), and the catalyst was used for catalyzing the next cycle of reaction (the recovered catalyst should be dried in a vacuum oven at 60 °C for 2 hours). To the filtrate, after evaporation of the solvent a dark grayish solid mixture was obtained. Purification of the product was performed by a short column chromatography eluted with ethyl acetate/petroleum ether (1:3) to give the desired product.

3. Results and discussion

3.1 Preparation, characterization and physiochemical property of complex **1**

The synthesis of the titanium salophen compound [$\{Ti(\text{salophen})H_2O\}_2O\][OSO₂C₈F₁₇]₂ (**1**) is straightforward by treating Ti^{IV}(salophen)Cl₂ with AgOSO₂C₈F₁₇ in THF in the absence of light for 2 h, and the yield was 78%. Although we tried many ways to obtain single crystals of complex **1**, we failed to generate suitable crystals of **1**, possibly because of the randomness of the long-chain perfluorooctanesulfonate group. However, all results of IR, ¹HNMR, ¹⁹FNMR and HRMS studies indicate that complex **1** is μ -oxo-bridged binuclear structure and contains two coordinated water molecules (see ESI), which is different with the complex Ti^{IV}(salophen)(OTf)₂ reported by Moghadam *et.al.* [30]. This binuclear structure is similar to our reported organoantimony complex [34]. We found that complex **1** had excellent air-stability and could be stored open to air for one year.$



Scheme 2 The synthetic route of complex **1**

The thermal behavior of complex **1** was investigated by TG-DSC in air and in N₂ atmosphere (Fig. 2). The TG-DSC curves showed three stages of weight loss. The endothermic step below 100 °C was assigned to the removal of water molecules. Complex **1** was thermally stable up to approximately 220 °C. Further increasing temperature caused an exothermic weight loss, likely because of oxidation of organic entities together with the release of heat. At 400 °C, we observed the removal of perfluorooctanesulfonyl group, leaving titanium fluoride behind.

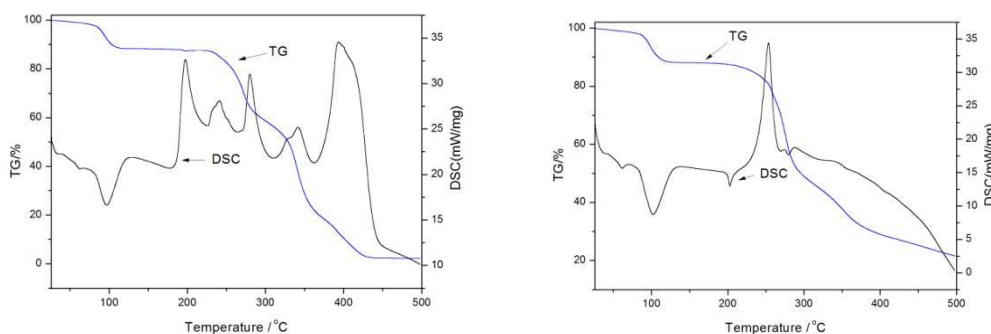


Fig. 2 The TG-DSC curves of complex **1** in performed in air (left) and N₂ (right).

Meanwhile, we estimated the Lewis acidity of complex **1** by the red shift (λ_{em}) of Lewis acid metal ions (Ti²⁺) with 10-methylacridone based on fluorescence spectra [41], which showed that the fluorescence maximum (λ_{max}) of complex was 504 nm (Fig. 3), indicating it was relatively strongly acidic [35]. In addition, the acidity measurement by the Hammett indicator method showed the acid strength to be $0.8 < H_0 \leq 3.3$ (H_0 being the Hammett acidity function) [42]. We also investigated its conductivity, and the molar conductivity (L) of **1** was $136 \mu\text{Scm}^{-1}$ in CH₃CN (1.0 mmol L⁻¹) at 25 °C, implying that it is cationic in solution. Subsequently, the solubility of **1** was evaluated. The results showed complex **1** had good solubility in acetone, THF, MeOH, CH₃CN. But it is not soluble in Et₂O, CH₂Cl₂ and toluene. On the basis of above characteristics,

we used it as a Lewis catalyst for the synthesis of bis(indolyl) methanes via the Friedel-Crafts alkylation of aldehyde/ketone with indoles.

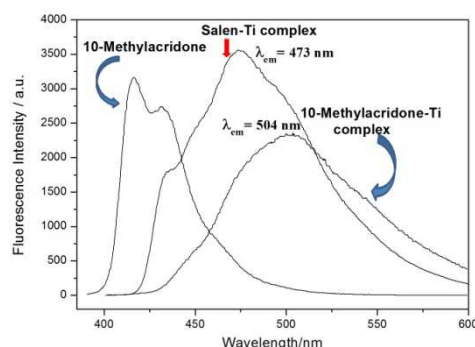
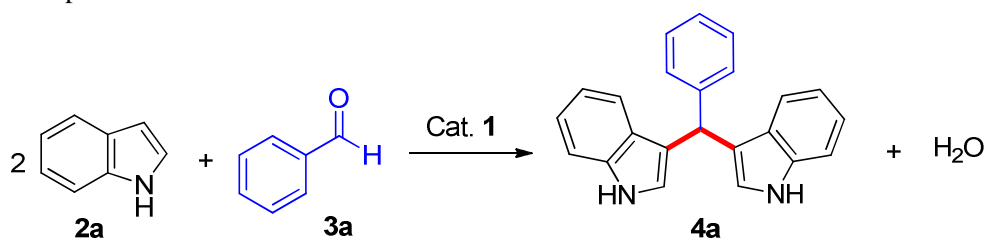


Fig. 3 The fluorescence spectrum between 10-methylacridone and complex **1**

3.2. Screening optimal conditions

Initial efforts were focused on the optimization of conditions through variation of reaction parameters using the reaction of indole with benzaldehyde as the model reaction (Table 1). Controlled experiments showed that no target product was obtained in the absence of complex **1** (entry 1). We investigated the loadings of complex **1** and found that the optimal dosage of complex **1** was only 1 mol% using THF as solvent for 10 min, and the yield was up to 97% (entries 2–5). When other solvents, such as CH₃OH, CH₃CN, Et₂O, CH₂Cl₂, H₂O, *n*-hexane and toluene were used instead of THF, the reaction gave moderate or low yields (entries 6–12). The reaction was also performed under solvent-free conditions; however, a moderate yield was obtained (entry 13). Thus, the best yield was obtained in the presence of complex **1** (1 mol%) affording the desired **4a** in THF after 10 min at room temperature.

Table 1. Optimization of reaction conditions ^a



Entry	Solvent	Catalyst (mol%)	Time (min/h)	Yield (%) ^b
1	THF	-	12 h	0
2	THF	0.5	1 h	72
3	THF	1	10 min	97

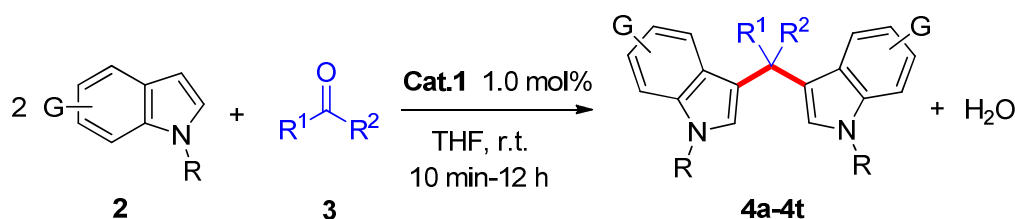
4	THF	1	20 min	97
5	THF	2	10 min	96
6	CH ₂ OH	1	1 h	80
7	CH ₃ CN	1	1 h	83
8	Et ₂ O	1	1 h	60
9	CH ₂ Cl ₂	1	3 h	56
10	H ₂ O	1	3 h	43
11	n-hexane	1	3 h	59
12	toluene	1	3 h	53
13	neat	1	20 min	82

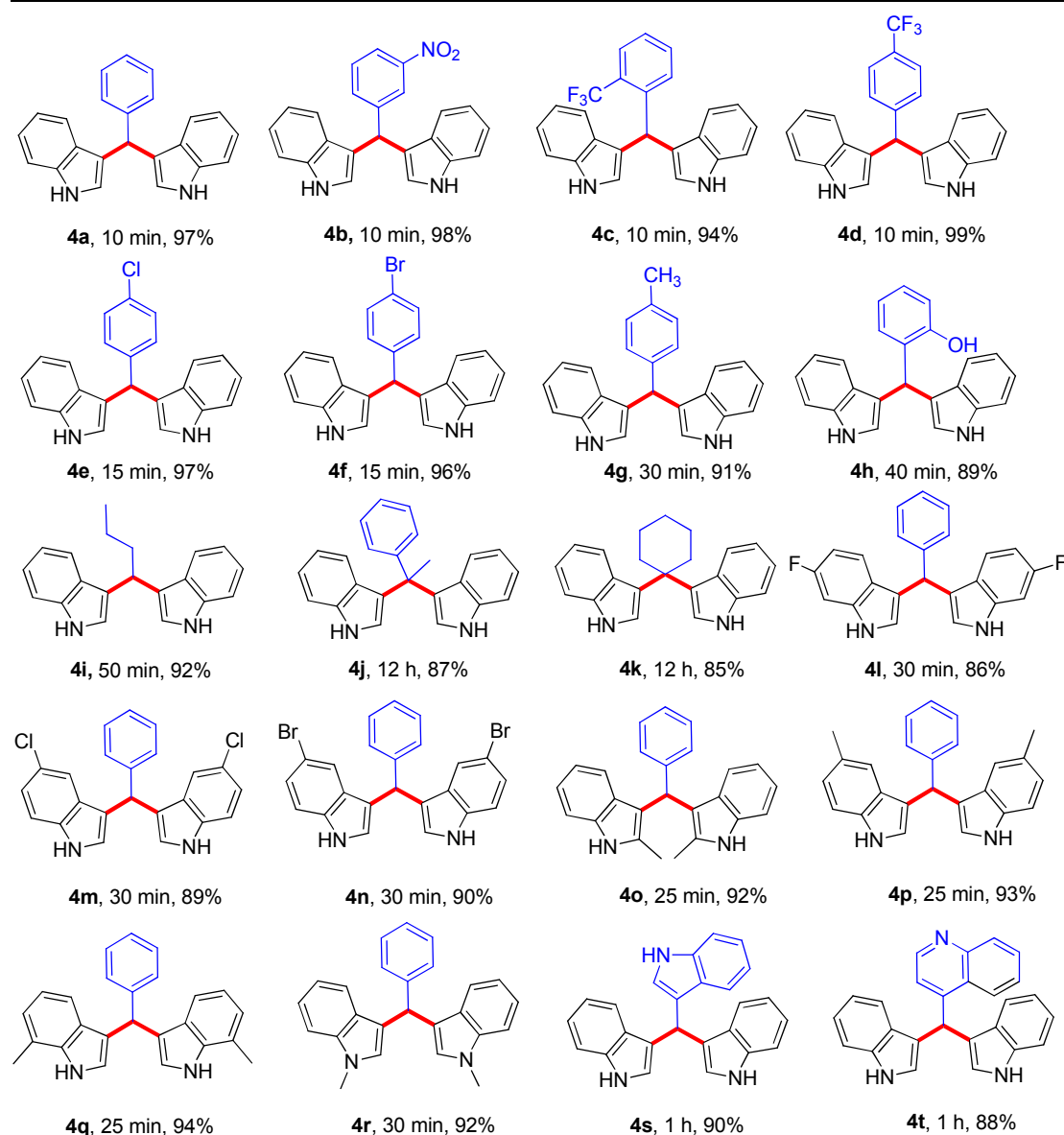
^a PhCHO: 0.5 mmol; indole: 1.0 mmol; THF: 0.5 mL; r.t.; ^b isolate yield.

3.3 The scope of Friedel-Crafts alkylation catalyzed by complex 1

To demonstrate the efficiency of the Friedel-Crafts alkylation, we explored the generality of our method by extending the optimal conditions to various substituted indoles and aldehydes/ketones, and the results were summarized in Table 2. A variety of aromatic aldehydes could efficiently undergo Friedel-Crafts alkylation to afford the corresponding products in good to excellent yields (**4a-4h**, 89-99%). Electron-donating groups (eg. Me, OH) or electron-withdrawing groups (eg. CF₃, Br, Cl and NO₂) in the benzene ring affected the reaction slightly. As for aliphatic aldehyde, a 92% yield of product was obtained (**4i**). The ketones such as acetophenone and cyclohexanone also showed good reactive activity in this catalytic system (**4j**, **4k**). Meanwhile, we also investigated different substituent indoles. The results indicated that indoles with electron-donating groups (CH₃) exhibited slightly higher reactivity than that with electron-withdrawing groups (F, Cl, Br) in the indole ring (**4l-4q**). Surprisingly, 1-methylindole also reacted with benzaldehyde in high yields (**4r**). Moreover, we synthesized two bioactive indole derivatives by the reaction of indole-3-carbaldehyde and 4-quinolinecarboxaldehyde with indole, and satisfactory yields were obtained (**4s**, **4t**).

Table 2. Friedel-Crafts alkylation of indoles with aldehydes/ketones catalyzed by complex **1**^{a,b}





^a aldehydes/ketones: 0.5 mmol; indoles: 1.0 mmol; **1**: 0.01mmol; THF: 0.5 mL; r.t.; ^b isolate yield.

3.4 Comparison of complex **1** with other catalytic systems

In addition, the merits of complex **1** were compared with other titanium compounds and those of reported catalytic systems for synthesis of bis(indolyl) methanes. Firstly, the activities of titanium compounds, such as $\text{Ti}^{\text{IV}}(\text{salophen})\text{Cl}_2$, Cp_2TiCl_2 , $\text{Ti}^{\text{IV}}(\text{salophen})(\text{OTf})_2$ together with complex **1** were estimated by the reaction of indole and benzaldehyde in THF at the temperature (Table 3). Higher yield was obtained over complex **1**, while catalysts such as titanium salophen dichloride and Cp_2TiCl_2 showed much lower yields, plausibly due to their lower Lewis acidity or moisture-sensitive properties. Although titanium salophen triflates showed good catalytic activity, the catalytic efficiency of complex **1** was better, because of the synergetic effect of bimetallic

complex **1**. Compared to other catalytic systems [9, 11, 14, 16, 17, 19, 20, 43], these results implied the advantages of this protocol are: a) low catalyst loading, b) short reaction time c) mild reaction conditions d) and high efficiency. Although the catalyst such as $\text{Zr}(\text{salophen})\text{Cl}_2$ also showed some advantages, it can't be recycled [17].

Table 3. Catalyst comparison of titanocene compounds and other catalytic systems for synthesis of bis(indolyl) methanes^a

Entry	Catalyst (mol%)	Conditions	Time(h)	Yield / (%) ^b	Ref.
1	$\text{Ti}^{\text{IV}}(\text{salophen})\text{Cl}_2$ (1 mol%)	THF, r.t.	10 min	10	-
2	Cp_2TiCl_2 (1 mol%)	THF, r.t.	10 min	69	-
3	$\text{Ti}^{\text{IV}}(\text{salophen})(\text{OTf})_2$ (1 mol%)	THF, r.t.	10 min	89	-
4	$[\{\text{Ti}(\text{salophen})\text{H}_2\text{O}\}_2\text{O}][\text{OSO}_2\text{C}_8\text{F}_{17}]_2$ (1 mol%)	THF, r.t.	10 min	97	-
5	$\text{H}_3\text{PW}_{12}\text{O}_{40}$ (12 mol%)	Neat, r.t.	2 h	84	-
6	LiClO_4 (10 mol%)	CH_3CN , r.t.	5 h	90	[9]
7	$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (10 mol%)	CH_3CN , r.t.	35 min	88	[11]
8	$\text{Dy}(\text{OTf})_3$ (10 mol%)	EtOH , r.t.	12 h	90	[14]
9	$\text{Yb}(\text{OTf})_3$ (5 mol%)/SDS (15 mol%)	H_2O , r.t.	1 h	95	[16]
10	$\text{Zr}(\text{Salophen})\text{Cl}_2$ (1 mol%)	EtOH , r.t.	10 min	95	[17]
11	Br_2 (2 mol%)	CH_3CN , 50 °C	1 min	98	[19]
12	TMG IL (3 mol%)	Neat, r.t.	40 min	96	[20]
13	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (15 mol%)	Et_2O , r.t.	2 h	90	[43]

^a PhCHO: 0.5 mmol; indole: 1.0 mmol; ^b isolate yield.

3.5 Catalyst recovery investigation

The reusability of complex **1** was also examined when indole was reacted with benzaldehyde. After the reaction finished and solvent evaporation, the residue was dissolved in diethyl ether, and the catalyst could be separated by using simple filtration, diethyl ether washing, and vacuum drying. Over the course of five trials, the yield only slightly decreased, which demonstrated that complex **1** had good recyclability (Fig. 4).

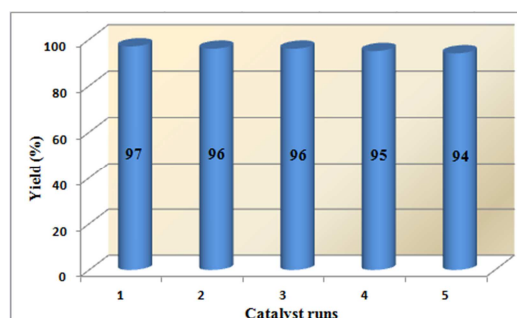
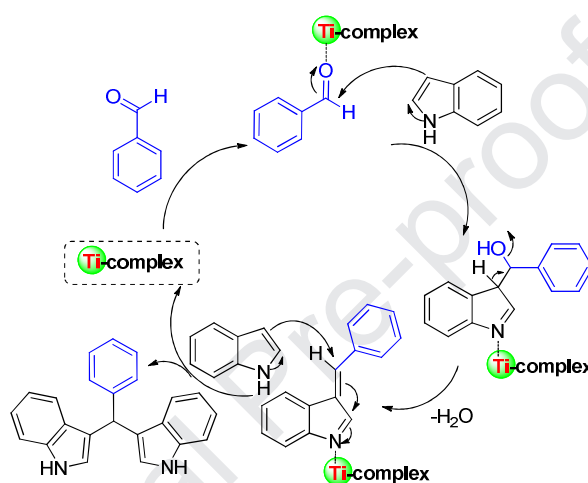


Fig. 4 Recycling test for complex **1**

3.6 Proposed mechanism

According to previous reported [17], a plausible mechanism for synthesis of bis(indolyl)methane catalyzed by complex **1** was proposed in Scheme 3. Firstly, the carbonyl group of benzaldehyde is activated by titanium salophen complex **1**. Then C3 atom of indole attacks to the activated carbonyl group to form an intermediate, which subsequently dehydrates to form the other intermediate with a double bond. Finally, a second molecule of indole attacks double bond of this intermediate to produce bis(indolyl)methane.



Scheme 3 Proposed mechanism for the synthesis of bis(indolyl) methane

4. Conclusion

In summary, we have successfully synthesized an μ -oxo-bridged binuclear Lewis acid of titanium(IV) salophen perfluorooctanesulfonate. This complex showed good air-stability, high thermostability and highly catalytic efficiency in Friedel-Crafts reaction of aldehyde/ketone with indoles. Furthermore, it can be reused five times. Compared to reported methods, this protocol showed considerable advantages such as low catalyst loadings, mild reaction conditions, short reaction time, general applicability, high efficiency and good reusability.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.inoche.2018.XXX>. These data include copies of IR, ^1H NMR, ^{19}F NMR, and HRMS spectra of catalyst and ^1H NMR, ^{13}C NMR spectra of all bis(indolyl)methanes derivatives.

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Highlights

- ▶ A general and mild protocol for the synthesis of bis(indolyl) methane derivatives
- ▶ Complex [$\{\text{Ti}(\text{salophen})\text{H}_2\text{O}\}_2\text{O}\][\text{OSO}_2\text{C}_8\text{F}_{17}]_2$ exhibited high catalytic activity.
- ▶ Only 1 mol% catalytic amount of catalyst was used.
- ▶ The catalyst can be reused five times.
- ▶ A plausible mechanistic approach has also been proposed.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

We declare that we have no conflict of interest, and have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ningbo Li
Basic Medical college
Shanxi Medical University
ningboli@sxmu.edu.cn