



Selective Catalysis

Tunable Titanocene Lewis Acid Catalysts for Selective Friedel– Crafts Reaction of Indoles and *N*-Sulfonylaldimines

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Abstract: A new strategy to control the selective Friedel–Crafts reaction of indoles and imines under mild conditions was developed. Phenol derivatives were established as efficient ligands to finely tune the activity of titanocene dichloride. Cp₂TiCl₂ and phenol catalyzed the mono-Friedel–Crafts reaction of indoles and *N*-sulfonyl aldimines with good yields (91 %), whereas *o*-aminophenol significantly enhanced the activity of the titanocene catalyst and promoted the synthesis of bisindole with excellent yields (98 %). The new organometallic Lewis acid catalysts are air-tolerant, can be used with low catalyst loading

(3 mmol-%) and are compatible with $-NO_{2}$, -F, -CI, -Br, and -OMe (30 examples with yields from good to excellent). The titanocene catalysts were fully characterized by NMR and HRMS analysis. The results suggest that $Cp_2TiCl(OC_6H_5)$ (I) and $Cp_2TiCl(OC_6H_4NH_3^+CI^-)$ (II) were catalytic species for the monoand double-Friedel–Crafts reactions, respectively. Distinguished from single functional acid catalysts I, catalyst II showed a catalytic cooperative effect of two acid components, which led to a fine tuning of the reactivity as well as to the selectivity of the desired reaction pathways.

Introduction

Indolylalkane and its derivatives are a class of metabolites that are widely distributed in flowering plants and in continental or marine protozoa. Both 3-indolylmethanamine and bis(3-indolyl)methane derivatives are pivotal structural motifs of natural products, pharmaceuticals, and agrochemicals. They are also key intermediates for the synthesis of complexes of alkaloids, which can be used to build dendrimer skeletons.^[1] Friedel-Crafts reactions represent the main thoroughfare by which C-C bonds are introduced on the indole framework.^[2] Consequently, numerous catalytic systems have been developed for the mono-Friedel-Crafts reaction such as SnCl₄,^[3] InCl₃,^[4] Cu(OTf)₂,^[5] Yb(OTf)₃^[6] and bis(oxazoline)-Cu^{II}.^[7] For double-Friedel-Crafts reaction of indoles, FeCl₃,^[8] In(OTf)₃,^[9] Y(OTf)₃,^[10] $Dy(OTf)_{3_{1}}^{[11]} LiClO_{4_{1}}^{[12]}$ and $[Ir(COD)(SnCl_{3})Cl(m-Cl)]_{2_{1}}^{[13]}$ showed significant activity. However, most of these methods are limited to the catalysis of either mono- or double-Friedel-Crafts reaction because it is difficult to tune and tailor the acidity of the Lewis acid catalyst.^[14]

Jorge^[15] attempted to develop a tunable catalyst system in which the mono-Friedel–Crafts reaction of indoles and imines was catalyzed by Cu^I(OTf), whereas in the presence of Cu^{II}(OTf)₂

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201501122. the double-Friedel–Crafts reaction was achieved. This case effectively confirmed that the selectivity of the Friedel–Crafts reaction can be controlled by tuning the Lewis acidity of catalysts. Unfortunately, metal triflates are intrinsically unstable and require inert atmosphere for manipulation. Therefore, a tunable organometallic Lewis catalyst that can be adjusted by altering the ligands, and that can be used to promote the selective Friedel–Crafts reaction, is appealing.

Titanocene dichloride is of great interest as an organometallic Lewis acid precursor because of its kinetic stability, diverse range of coordination modes and electronically tunable Lewis acid centers.^[16] Moreover, the coordination of soft organometallic acceptors with hard donors of Brønsted acids might provide a new dimension for cooperative binary acid catalysis that exhibit unexpected reactivity and selectivity patterns. Varying co-ligands might change Lewis acidity of titanocene catalysts, and therefore activate organic substrates for a desirable catalytic cycle.^[17]

Herein, we reported a binary acid system featuring an airstable organometallic precursor, titanocene dichloride, combined with simple organic cooperative Brønsted acids, which catalyzed mild and highly efficient Friedel–Crafts reactions of indoles and *N*-sulfonyl-substituted aldimines. Oxygen hard donor ligands are important in the design of efficient catalysts of early transition metals.^[18] The mono-Friedel–Crafts products were selectively obtained in good yields with phenol as ligand, whereas the use of *o*-aminophenol as a co-ligand afforded bisindole with excellent yields. This mild, operationally simple, and functional group compatible method is characterized by an exquisite selectivity profile that is dictated by the mode of coordination. The mechanistic studies, including ¹H NMR titration and

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ESI(+)-MS analysis, elucidated the interaction between Cp_2TiCl_2 and co-ligands, which illuminated an unexpected chemoselectivity of the Friedel–Crafts reactions.

Results and Discussion

In light of our previous findings that salicylato-titanocene complexes function as organometallic Lewis acids,^[19] a selection of oxygen donor ligands were examined in the reaction of Nmethylindole (1a) and N-(2-chlorobenzylidene)-4-methylbenzenesulfonamide (2a). Given the synergistic effect in C-C forming reactions using binary catalysts of organometallic Lewis acid and Brønsted acids, 5-sulfosalicylic acid, phthalic acid, benzoic acid, and anthranilic acid were evaluated. None of them provide satisfactory results, which indicated that strong acids were unsuitable for the selective Friedel-Crafts reaction. We hypothesized that a higher activity of binary acid systems could be achieved by employing weak acids such as phenol and analogues (Scheme 1). Gratifyingly, phenol drastically accelerated the titanocene-catalyzed mono-Friedel-Crafts reaction and afforded 3a in 91 % yield with 95 % selectivity (3a/4a 95:5). The use of functionalized phenols gave disappointing results. Strikingly, the use of p-aminophenol as co-ligand resulted in a selectivity switch under identical reaction conditions, favoring the formation of 4a. To highlight the crucial and beneficial role played by the amino group on the selectivity of the Friedel-Crafts reaction, the amino group was masked and the catalyst showed a preference for the formation of 3a. Parallel experiments were performed to consider the effect of the steric and electronic nature of the functional groups. Reactions with substrates bearing an amino group in the meta- or para-position of phenol were not comparable with o-aminophenol in terms of reactivity or chemoselectivity because the steric hindrance had a negative effect on coordination. o-Aminophenol was found to be superior for the double-Friedel-Crafts reaction, affording 98 % yield and up to 98 % selectivity (3a/4a 2:98). Further screening involving substrates with other functional groups such as methyl-, chloro-, or nitro-groups on the oaminophenol was also conducted. Benzene-1,2-diamine, featuring two amino groups, was shown to be a valid ligand, indicating that oxygen is an integral part of complex formation through coordination with titanium. This result supports the conclusion that the coordination between phenol and [Cp₂TiCl₂] is crucial for the formation of **3a** and suppressed competitive formation of 4a under basic conditions. On the other hand, [Cp₂TiCl₂] coordinated with o-aminophenol, which successfully tuned mono-Friedel-Crafts reaction to complete double-Friedel-Crafts reaction. Control experiments carried out under the same conditions showed, not surprisingly, that [Cp₂TiCl₂] was almost inert in promoting the Friedel–Crafts reaction; only 39 % yield of 3a was isolated.

Emboldened by our initial success, a wide range of reaction parameters were examined to determine the optimized reaction conditions. As shown in Table S1 (see the Supporting Information), the screening results indicated that a higher catalyst loading (> 5 %) had a negative impact on the reaction (entries





Scheme 1. The effect of the ligand on the Ti-catalyzed selective Friedel–Crafts reaction.

4–5). Upon reducing the catalyst loading to 3 mol-%, **3a** was isolated in 70 % yield and **4a** in 90 % yield by employing different co-ligands (entry 3). The use of an increased amount of **1a** gave **3a** in excellent yield (91 %) and with a selectivity of up to 95 % (entry 6). The use of one extra equivalent of indole might make the catalytic system less acidic and prevent **3a** from being consumed to produce **4a**.^[20] The 2:1 ratio of **1a** and **2a** was also optimum for the double Friedel–Crafts reaction, producing the product in 98 % yield and with 98 % selectivity (entry 6).

With the optimal reaction conditions in hand, we set out to explore the generality of the mono-Friedel-Crafts reaction with respect to a variety of indole derivatives and N-sulfonylaldimines. As shown in Table 1, regardless of the electronic and steric nature of the substituents, [Cp2TiCl2]-catalyzed mono-Friedel-Crafts reaction provided exclusively the 3-indolylmethanamine products in moderate to good yields, depending on the employed co-ligands. Both electron-rich indole derivatives and heteroaromatic compounds proved to be very effective, affording the Friedel-Crafts addition products in good yields (78-91 %) as single regioisomers (entries 1-5). The reactions of N-methylindole and indole proceeded particularly smoothly to afford the corresponding products in 91 and 89 %, respectively (entries 1 and 2). Interestingly, the incorporation of bulky substituents at C2 of the indole did not have a detrimental effect on the reactivity (entry 3). N-(4-Methylphenyl)sulfonylarylimines with various R⁴ groups reacted smoothly to give the corresponding products in good yields. Weak electron-withdrawing groups (entries 8-10) such as F, Cl, Br at the 4-position gave higher yields than substrates with an electron-donating group



Table 1. Titanocene-catalyzed selective Friedel-Crafts reaction.[a]



	$R^{3} \xrightarrow{P} R^{4} \xrightarrow{R^{3}} Cp_{2}TiCl_{2}, R^{3} \xrightarrow{CH_{3}CN} \xrightarrow{CH_{3}CN} \xrightarrow{N} \xrightarrow{N} \xrightarrow{N} \xrightarrow{R^{1}} 25 \ ^{\circ}C \qquad 1$			$-R^{2}_{+} \underbrace{\begin{matrix} N \\ R^{4} \\ R^{4} \\ 25 \ ^{\circ}C \\ 2 \end{matrix} \overset{Ts}{\overset{(Cp_{2}\text{TiCl}_{2})}{\overset{R^{3}}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{R^{4}}{\underset{R^{5}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{R^{4}}{\underset{R^{5}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{R^{4}}{\underset{R^{5}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{\underset{R^{4}}{\overset{(Cp_{2}\text{TiCl}_{2})}{\underset{R^{4}}{R^{4$		
Entry	1			2 Yield [%] ^[b]		
	R ¹	R ²	R ³	R ⁴	3	4
1	Me	Н	Н	o-Cl	3a (91)	4a (98)
2	Н	Н	Н	o-Cl	3b (89)	4b (93)
3	Н	Me	Н	o-Cl	3c (78)	4c (90)
4	Н	Н	OPh	o-Cl	3e (79)	4e (98)
5	pyrrole			o-Cl	3f (80)	4f (84)
6	H	Н	Br	o-Cl	3d (56)	4d (80)
7	Me	Н	Н	Н	3g (84)	4g (95)
8	Me	Н	Н	p-F	3i (84)	4i (90)
9	Me	Н	Н	p-Cl	3j (89)	4j (97)
10	Me	Н	Н	<i>p</i> -Br	3k (78)	4k (90)
11	Me	Н	Н	p-NO ₂	3I (53)	4I (70)
12	Me	Н	Н	o-OMe	3m (67)	4m (85)
13	Me	Н	Н	<i>p</i> -OMe	3n (70)	4n (74)
14	Н	Н	Br	<i>p</i> -OMe	3o (62)	4o (87)
15	Н	Н	Н	Н	3h (82)	4h (90)

[[]a] Reaction conditions: indole (2.0 mmol), *N*-sulfonylaldimine (1.0 mmol), $[Cp_2TiCl_2]$ (0.03 mmol), phenol (0.06 mmol) or *o*-aminophenol (0.06 mmol), 25 °C, CH₃CN. [b] Isolated yield obtained after purification by column chromatography.

such as MeO (entries 12 and 13). Substrates with strong electron-withdrawing groups such as nitro-substituted arylimine reacted much more slowly and gave relatively low yield (entry 11).

We then examined the scope of the double-Friedel-Crafts reaction. The reactions of various indole derivatives with 2a were not significantly influenced by the electronic properties of the indole ring (Table 1, entries 1-6). For example, 1-methyl-, 2methyl-, 5-benzyloxy-indole and indole, with electron-donating groups, were all excellent substrates for the reaction, resulting in 90-98 % yield, with up to 93 % selectivity. The introduction of an electron-withdrawing group onto the indole ring led to a slight decrease in yield (entry 6). The generality of the reaction was further extended by varying the imines. Aryl imines with different electronic properties (entries 9-10, 11, and 14-15) could be readily converted into the desired adducts in 85-97 % yield with excellent selectivity. The use of a strong electronwithdrawing or an electron-donating group as R⁴ group in the para-position was detrimental to the performance of the reaction (entries 11 and 13).

To shed light on the action of titanocene Lewis acid catalysts for selective Friedel–Crafts reaction, the interaction between Cp₂TiCl₂ and co-ligands were investigated by ¹H NMR and ESI(+)-MS analysis. ¹H NMR experiments, which were conducted using Cp₂TiCl₂ and phenol in CDCl₃ (Figure 1), showed that no coordination occurred and only one Cp singlet of Cp₂TiCl₂ at δ = 6.59 ppm (purple triangles) was detected. When base aniline was added,^[21] a new titanocene complex species I was formed, which resonated at δ = 6.39 ppm (red circle). The signal of I increased whereas that of Cp₂TiCl₂ declined gradually. Finally, the mixture was composed almost completely of complex **I**. The peak area ratio of the Cp protons of the new titanocene complex species **I** to H_a of the aromatic ring at $\delta = 6.63$ ppm (red diamond) was 10:2, which presumably meant that only one molecule of phenol was in coordination. The presence of the new species was further supported by ESI(+)-MS experiments performed in the positive ion mode (Scheme S1 in the Supporting Information). The ion peak at *m*/*z* 270.9534, corresponding to [**I**-CI]⁺, was detected in the CH₃CN solution of Cp₂TiCl₂ and phenol. The cationic titanocene moiety could be considered as an evidence for the coordination between Cp₂TiCl₂ and phenol. Moreover, other groups^[22,23] have experimentally demonstrated



Figure 1. ¹H NMR spectra of a titration of a mixture of $[Cp_2TiCl_2]$ (1.0 equiv.) and phenol (2.0 equiv.) in $CDCl_3$. \blacktriangle Cp protons of $[Cp_2TiCl_2]$; \bigcirc Cp protons of $[Cp_2TiCl(OPh)]$; Spectrum **a** obtained from a mixture of Cp_2TiCl_2 and phenol; Spectrum **b** obtained by adding aniline (1.0 equiv.) to **a**.





that coordination of epoxides to Cp_2TiCl_2 is accompanied by dissociation of the chloride anion to form the true cationic active species. Therefore, it can be concluded that in the mono-Friedel–Crafts reaction, precatalyst titanocene dichloride is readily converted into one detectable titanocene species in CD_3Cl and presumably $Cp_2TiCl(OC_6H_5)$ I complex was the true catalyst.

The interaction between Cp_2TiCl_2 and o-aminophenol was further illustrated by conducting the same experiments de-

scribed above. ¹H NMR spectra were recorded using Cp₂TiCl₂ and *o*-aminophenol in [D₆]DMSO (Figure 2). Cp protons of the new titanocene complex species **II** at $\delta = 6.48$ ppm (red circle) were observed. The active hydrogen atom of **II** was observed at $\delta = 9.75$ ppm (red diamond), and this atom represented the key to changing the pathway from mono- to double-Friedel–Crafts reaction. Ion peaks at *m*/*z* 286.0693 and 322.0451, corresponding to [**II**-2Cl]²⁺ and [**II**-Cl]⁺, respectively, were detected (Scheme S2 and S3 in the Supporting Information). The cationic



Figure 2. ¹H NMR spectra of a titration of a mixture of $[Cp_2TiCl_2]$ (1.0 equiv.) and *o*-aminophenol (2.0 equiv.) in $[D_6]DMSO$. \blacktriangle Cp protons of $[Cp_2TiCl_2]$; \blacklozenge Cp protons of $[Cp_2TiCl(OPhNH_3^+Cl^-)]$; \blacklozenge active hydrogen of $[Cp_2TiCl(OPhNH_3^+Cl^-)]$; Spectrum **c** obtained from the *o*-amniophenol; Spectrum **d** obtained by adding Cp_2TiCl_2 to **c**.



Scheme 2. Proposed mechanism for titanocene-catalyzed selective Friedel-Crafts reactions.





titanocene moieties could be considered as a support for coordination of Cp₂TiCl₂ with one molecule of *o*-aminophenol. This suggested that in the double-Friedel–Crafts reaction, precatalyst titanocene dichloride was easily converted into the detectable titanocene species in [D₆]DMSO, and Cp₂TiCl(OC₆H₄NH₃⁺Cl⁻) II might be the true catalyst.

A proposed cooperative catalytic cycle is outlined in Scheme 2. Titanocene dichloride coordinates with phenol and transforms into $[Cp_2Ti(OC_6H_5)]^+$ [I-Cl]⁺ with the single functional Lewis acid site. The first step is the formation of A, which is formed by coordination of N-sulfonylaldimine with oxophic Ti^{IV} ion. N-Sulfonylaldimine is activated by I to increase the electrophilicity of the imine carbon of A. The nucleophilic carbon of indole attacks the imine carbon of **A** leading to the formation of the Friedel-Crafts product in transition state B. Once the product is released, Ti chelate ion I is regenerated. Similarly, Cp₂TiCl₂ coordinates with *o*-aminophenol to produce catalyst Cp₂TiCl(OC₆H₄NH₃⁺Cl⁻) II ion, which bears both Lewis and Brønsted acid sites. Subsequently the addition of N-sulfonylaldimine with indole leads to the formation of 3-indolylmethanamine through states C and D. The association of 3-indolylmethanamine from II triggers its reaction with another indole to form bisindole compounds^[24] (see the transition state E). Then the Ti chelate ion II is again formed.

Conclusions

We have developed a highly selective Friedel-Crafts reaction of indoles and imines catalyzed by cooperative organometallic Lewis and Brønsted acid catalysts. Based on mechanistic studies, it can be speculated that $Cp_2TiCl(OC_6H_5)$ I and $Cp_2TiCl(OC_6H_4NH_3^+Cl^-)$ II are catalytic species for mono- and double-Friedel-Crafts reactions, respectively. These results revealed an unexpected selectivity in the Friedel-Crafts reactions that was achieved by single Lewis acid and cooperative Lewis/ Brønsted acid catalysis. With their unprecedented selectivity these practical organometallic catalysts can be used to achieve both mono-Friedel–Crafts reaction of indoles and N-sulfonylaldimines catalyzed by Cp₂TiCl₂ and phenol in good yields, and oaminophenol assisted titanocene catalyst promoted the synthesis of bisindole in excellent yields. This method thus provides a direct and broadly applicable synthetic approach to 3-indolylmethanamines and bisindole compounds.

Experimental Section

Physical Measurements: ¹H and ¹³C NMR spectra were recorded with a Bruker EQUINX55 (400 MHz for ¹H; 101 MHz for ¹³C) spectrometer in CDCl₃ or $[D_6]DMSO$.

General Procedure for the Preparation of N-Sulfonyl Aldimines: *N*-Sulfonylaldimines described were prepared by condensation of the corresponding aldehydes with *p*-toluenesulfonamide according to the reported procedure with minor modifications: the aldehyde (25.0 mmol), *p*-toluenesulfonamide (25.0 mmol), and Si(OEt)₄ (27.5 mmol, 1.1 equiv.) were combined in a flask equipped with an oil–water separator and heated at 160 °C for 10 h. The produced EtOH was collected in the oil-water separator and released at regular intervals. After cooling, the residue of the reaction was recrystallized twice from EtOAc/hexanes.

General Procedure for the Catalytic Mono-Friedel–Crafts Reaction: A nitrogen-flushed 10 mL test tube, equipped with a magnetic stirrer and a septum, was charged with *N*-sulfonyl aldimines **1** (1.0 mmol) and indole **2** (2.0 mmol) in one portion. Cp₂TiCl₂ (0.03 mmol) and phenol (0.06 mmol) were added at 25 °C in CH₃CN and the mixture was stirred until the reaction was completed as indicated by TLC. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on neutral silica gel (ethyl acetate/*n*-hexane) to afford the product, which was characterized by ¹H and ¹³C NMR spectroscopy.

General Procedure for the Catalytic Double-Friedel–Crafts Reaction: A nitrogen-flushed 10 mL test tube, equipped with a magnetic stirrer and a septum, was charged with *N*-sulfonylaldimines **1** (1.0 mmol) and indole **2** (2.0 mmol) in one portion. Cp₂TiCl₂ (0.03 mmol) and *o*-aminophenol (0.06 mmol) were added at 25 °C in CH₃CN and the mixture was stirred until the reaction was completed as indicated by TLC. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on neutral silica gel (ethyl acetate/*n*-hexane) to afford the product, which was characterized by ¹H and ¹³C NMR spectroscopy.

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