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COMMUNICATION

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Organometallic titanocene complex as highly efficient bifunctional catalyst for intramolecular Mannich reaction

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Bifunctional catalysts bearing two catalytic sites, Lewis acidic organometallic titanocene and Brønsted acidic COOH, have been assembled *in situ* from Cp_2TiCl_2 with carboxylic acid ligands, showing high catalytic activity over an intramolecular Mannich reaction towards synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones. The determination of the bifunctional catalyst $Cp_2Ti(C_8H_4NO_6)_2$ was elucidated by single X-ray HR-MS and investigation of catalytic behavior. In particular, masking the Brønsted acidic COOH catalytic site with dormant COOMe lowered the reaction yield greatly, indicating that two catalytic sites work together to maintain high catalytic efficiency.

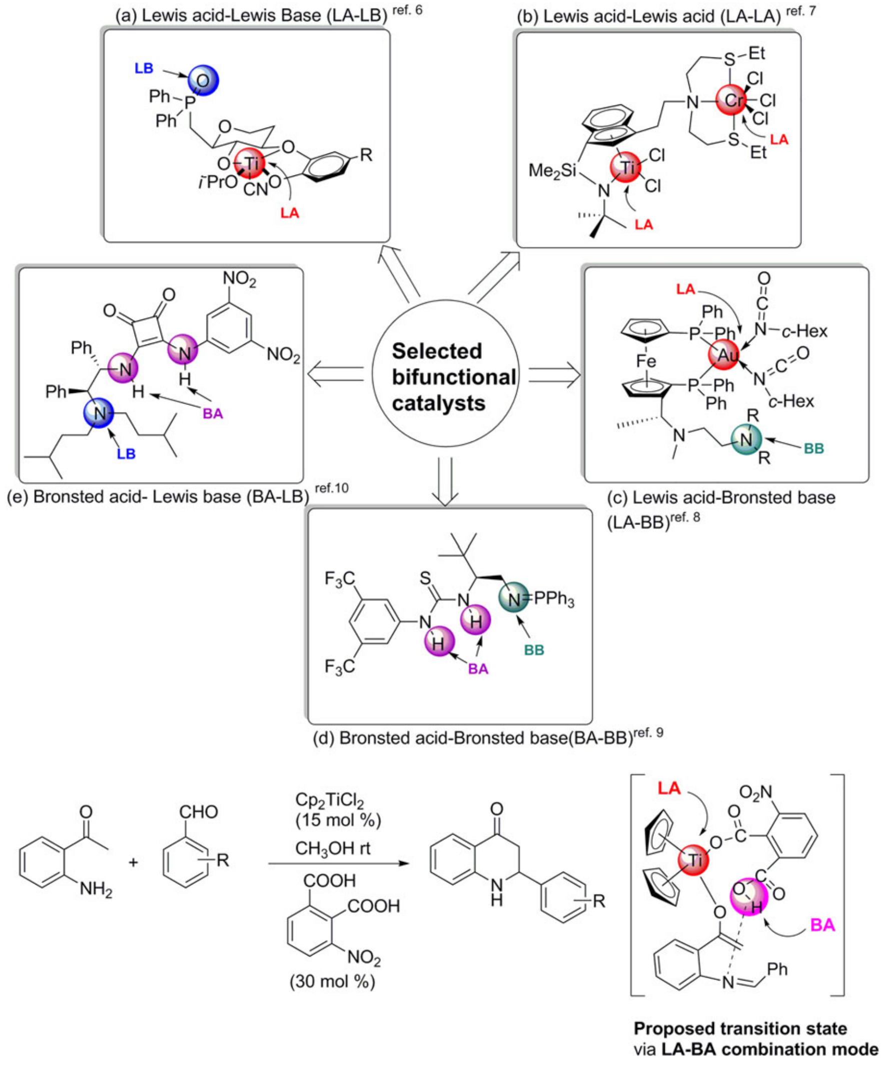
KEYWORDS

bifunctional catalysts, intramolecular Mannich reaction, Titanocene complex

1 | INTRODUCTION

Multi-catalysis, including bifunctional catalysis,[1] cascade catalysis,[2] double activation catalysis[3] and synergistic (cooperative) catalysis,[4] has become a promising and powerful strategy for many difficult or unattainable chemical transformations, owing to its multiple activation effect on substrates, compared with mono-catalysis. In particular, bifunctional catalysis, where two discrete catalytic site resides in one molecule, can not only activate both the nucleophile and electrophile simultaneously, but also bring two reactants close to each other, facilitating the creation of new bonds.[5] From the perspective of acid–base theory, reports of successful chemical transformation via the bifunctional catalysis mechanism can be classified into the following modes: Lewis acid–Lewis base (LA–LB),[6] Lewis acid–Lewis acid (LA–LA),[7] Lewis acid–Brønsted base (LA–BB),[8] Brønsted acid–Brønsted base (BA–BB)[9] and Brønsted acid–Lewis base (BA–LB) (Scheme 1).[10] However, there are rare homogeneous bifunctional catalysis reports that fall into the Lewis acid–Brønsted acid (LA–BA) combination.[11] Therefore, it is of great importance to design a novel bifunctional catalytic system via the LA–BA combination, thus consummating bifunctional catalytic combinational modes, as well as providing practicable strategies to realize challenging chemical transformations.

Ti (IV) salts have long been employed as efficient Lewis acidic catalysts in synthetic organic chemistry.[12] However, there are still great challenges in terms of their efficiency and the adaptability of their application as catalysts in industry, owing to inherent characteristic air and water sensitivity. One workable solution is to employ a readily activated chemically inert Ti (IV) precursor, and Cp_2TiCl_2 has proven be an excellent model, which can be easily activated *in situ* by ligand substitution. By using various *O*-, *N*-donor ligands, Cp_2TiCl_2 has been successfully activated and applied in many important C–C and C–N bond formations.[13] Nevertheless, the ordinary ligand activation strategy can only boost the Lewis acidity of the Ti (IV) centre, limiting catalytic capability. We hypothesize that the application of functional ligands may solve this dilemma, as the added functional group on the ligands may serve as a new catalytic site in the *in situ* assembled titanocene complex. Herein, we present our further study on activation of Cp_2TiCl_2 with a double carboxylic acid-containing ligand to generate a bifunctional catalyst in LA–BA



SCHEME 1 Various combinational modes of bifunctional catalyst

mode *in situ*, where the Ti (IV) centre functions as the Lewis acidic catalytic site and the COOH group on the ligand functions as the Brønsted acidic catalytic site (Scheme 1).

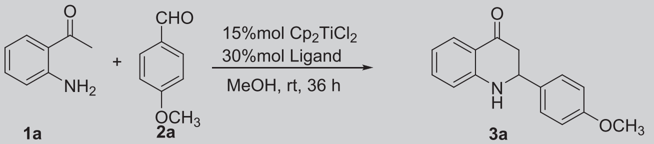
2 | RESULTS AND DISCUSSION

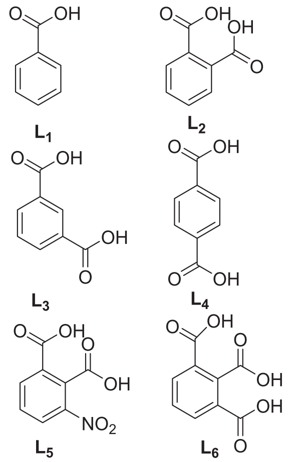
To test our model of the establishment of an LA–BA bifunctional catalyst, intramolecular Mannich reactions between *o*-amino acetophenone (**1a**) and *p*-methoxybenzaldehyde (**2a**) were chosen as the model reaction, one of the most efficient approaches to obtain an important class of bioactive dihydro-4-quinolones.[14] As shown in Table 1, the catalyst-free condition did not lead to any product being produced (entry 1). When Cp_2TiCl_2 was employed as the catalyst, 16% yield of product was detected, indicating that unmodified titanocene also is not effective (entry 2). As mentioned in the Introduction, the designed bifunctional catalyst must have two functional groups, one for coordinating with the Ti centre, the other functioning as a Brønsted acid.

Based on our previous work,[13d,15] COOH was chosen as the ligand to coordinate with Cp_2TiCl_2 to form a more active titanocene organometallic complex. Benzoic acid (**L_1**) was used as the starting point to locate the optimal bifunctional ligand, with only a slight yield improvement to 20% yield (entry 4). However, after introducing the ligand bearing an extra COOH group (**L_{2}–$_{4}$**), the yield was elevated to 45–50% (entries 5–7). Thus, further investigation was based on **L_2** owing to its higher catalytic efficiency. Introduction of an electron-withdrawing group, including NO_2 (**L_5**) and COOH (**L_6**), led to a higher reaction yield, especially for **L_5**, for which the reaction yield could reach 90%, the optimal ligand we have screened (entry 8). For the complementary comparison of mono-catalysis with multi-catalysis, **L_5** alone was used to catalyse the reaction and only 40% yield of product was obtained, showing the necessity of cooperation between Lewis acid Cp_2TiCl_2 and Brønsted acid **L_5**.

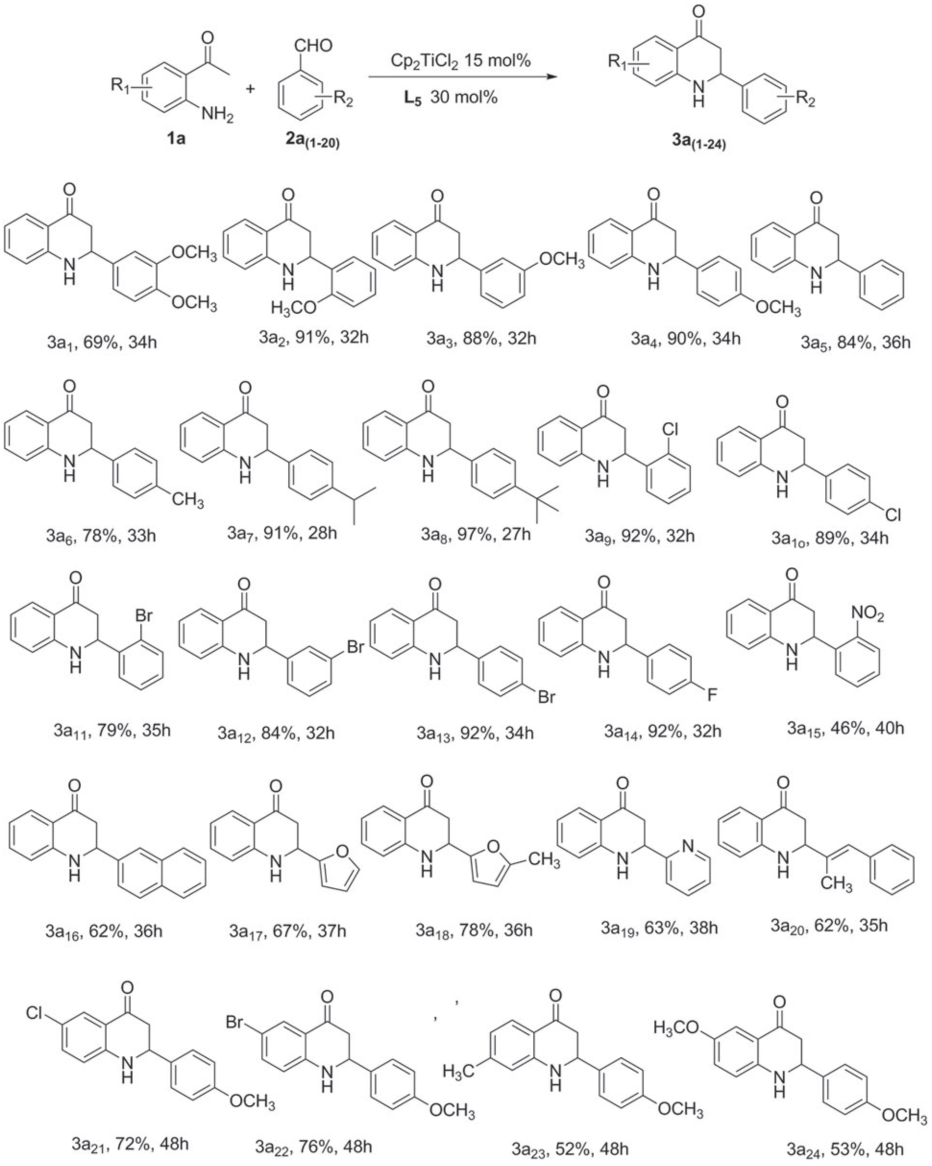
To demonstrate the utility of this method, substrate scope was explored extensively via the variation of the reactant aldehydes. As shown in Scheme 2, aromatic aldehydes bearing electron-donating groups (**$3a_1$–$3a_4$**) gave 2-aryl-2, 3-dihydroquinolin-4(1H)-ones in good to high yields. The exception was when two -OMes were carried, were the yield decreased to only 69%. This might be because of the strong electron-donating ability of atomic oxygen's lone electron pair to the –CHO group through *p*–*π* conjugation, decreasing the reaction activity of aldehyde with the amino group to form imine. The entries of those aldehydes with mild electron-withdrawing substituent groups, including Cl (**$3a_9$–$3a_{10}$**), Br (**$3a_{11}$–$3a_{13}$**) and F (**$3a_{14}$**), were proved to be well tolerated under the optimized conditions, as the reaction yield was at least 84%. The exception is when Br- was at the *o*-position to the -CHO group (**$3a_{11}$**, 79% yield). We tentatively attributed this poorer performance to steric

TABLE 1 Optimization of the reaction conditions.



Entry	Deviation from standard conditions	Yield (%)	Ligands screened
1	None	—	
2	Cp_2TiCl_2	16	
3	L_5	40	
4	$Cp_2TiCl_2 + L_1$	20	
5	$Cp_2TiCl_2 + L_2$	50	
6	$Cp_2TiCl_2 + L_3$	48	
7	$Cp_2TiCl_2 + L_4$	45	
8	$Cp_2TiCl_2 + L_5$	90	
9	$Cp_2TiCl_2 + L_6$	60	

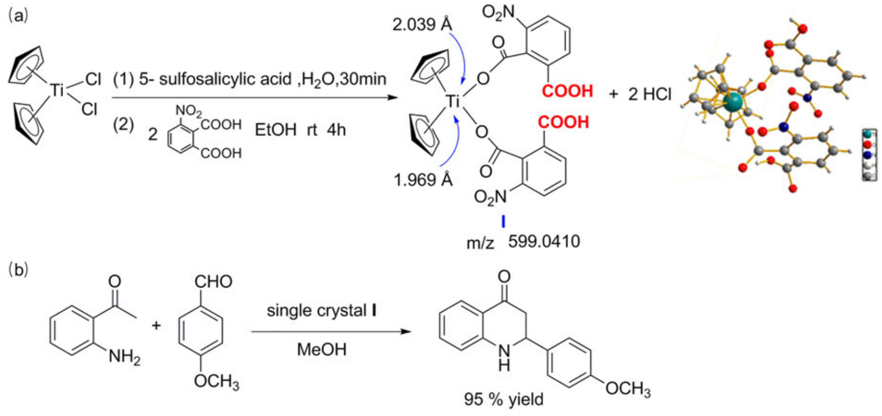
(a) All reactions were conducted on a 1 mmol scale. (b) Isolated yields.



SCHEME 2 Substrates scope for the synthesis of 2-aryl-2,3-dihydro-4-quinolones. [a] Reaction conditions: a mixture of 1a (1 mmol), 2a (1 mmol), and catalyst (15 mol% Cp2TiCl2, 30 mol% L5) in MeOH (2 mL) were stirred at r.t. for a period time needed; [b] Isolated yields

hindrance caused by bulky Br rather than Cl for imine formation. However, when strong electron-withdrawing groups were attached on the aromatic aldehydes, a relatively low yield of 46% was obtained (**3a$_{15}$**). Optimized conditions were also viable for regular heteroaromatic aldehydes, where 2-aryl-2,3-dihydro-4-quinlones could be generated in moderate yields (**3a$_{17}$–3a$_{19}$**). Substituted *o*-amino acetophenones in terms of the diversity of the electronic nature of the substituent were also examined. Our method worked well for the substrates bearing weak electrophilic-withdrawing groups, like Cl- (**3a$_{21}$**) and Br- (**3a$_{22}$**), as well as electrophilic-donating groups like Me- (**3a$_{23}$**) and MeO- (**3a$_{24}$**), where the product could be generated in 52–76% yield.

Although during the screening experiment, it has been verified that Cp_2TiCl_2 and L_5 worked in concert, catalysing the intramolecular Mannich reaction efficiently, how they cooperate during the reaction was unknown. To gain more information on the true catalytic species, single crystal analysis is most straightforward and convincing. Fortunately, the reaction of Cp_2TiCl_2 with ligand L_5 gave a crystalline complex, $Cp_2Ti(C_8H_4NO_6)_2$, **I** (CCDC1882248; Scheme 3a), which was also corroborated by ESI-MS analysis, as a signal with an *m*/*z* value at 599.0410 was detected. Analyzing the crystallographic data, it can be seen that the bond lengths of Ti–O (Ti–O002, 2.039 Å and Ti–O00a, 1.969 Å) were longer than those of any of our previous synthesized titanium complexes (specific information is available in the Supplementary Material), which is most likely linked to the enhanced Lewis acidity of the Ti (IV) centre. Exploration of the coordination between Cp_2TiCl_2 and

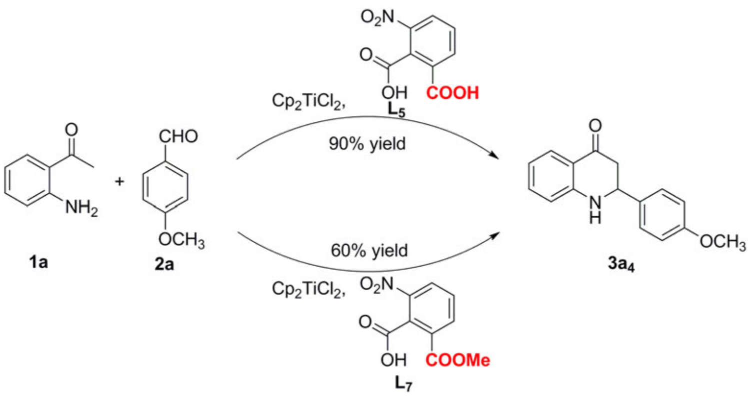


SCHEME 3 [a] Preparation and X-ray crystal structure of organometallic structure I; [b] a mixture of 1a (1 mmol), 2a (1 mmol), single crystal I in MeOH (2 mL) were stirred at r.t. for 32 h

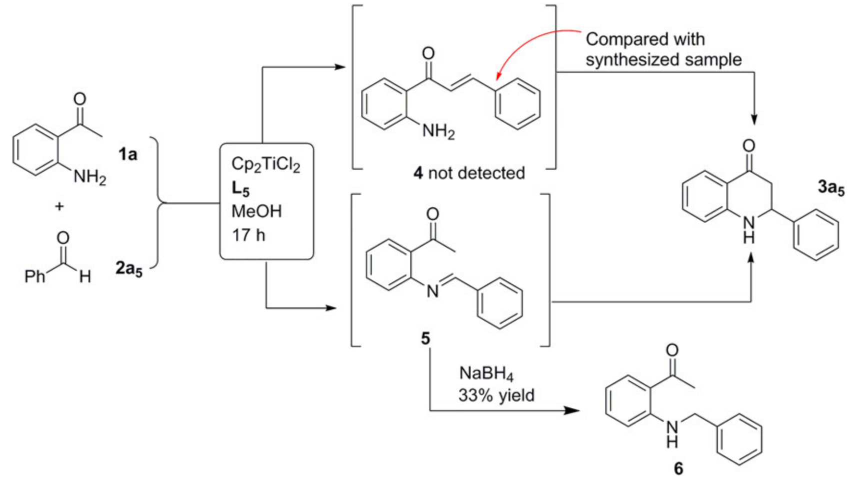
L_5 indicated that complex $Cp_2Ti(C_8H_4NO_6)_2$ was the activated version of titanocene complex, although whether it was the true catalyst for the intramolecular Mannich reaction was still ambiguous. Therefore, the model reaction was carried out in the presence of crystal $Cp_2Ti(C_8H_4NO_6)_2$, as shown in Scheme 3b. Gratifyingly, the title product **3a₄** could be produced in 93% yield. Taking the structural information and catalytic performance of single crystal **I**, it is reasonable to draw a conclusion that the true catalytic species is complex **I**.

The next task is to confirm whether the COOH on the spectator ligand functions as the Brønsted acid catalytic site. It is widely acknowledged that the confirmation of a reaction through the bifunctional mechanism is challenging, mainly owing to the difficulty of the acquisition of the co-crystal structure of the substrate catalyst. However, masking one catalytic site with an inert group is well accepted and adopted as an alternative strategy.[16] The methyl group was chosen to mask the COOH group as it not only can be restrained from showing its Brønsted acidic catalytic ability, but also does not change the electronic nature of the spectator ligand. As shown in Scheme 4, when ligand $\mathbf{L_7}$ was used replacing $\mathbf{L_5}$, the reaction yield dropped to 60%, suggesting that COOH on the spectator ligand $\mathbf{L_7}$ worked as the second catalytic site.

Given that the bifunctional catalysis species had been confirmed, we next focused on mapping the reaction route for the reaction. There are two possible reaction routes from starting materials to final product 2-aryl-2,3-dihydroquinolin-4(1H)-ones: (1) initiated by the aldol condensation between *o*-amino acetophenone **1a** with benzaldehyde to form 2′-aminochalcones **4**, followed by intramolecular aza-Michael addition; and (2) imine formed first, followed by intramolecular Michael addition. Although the imine route was proposed to be dominant during the reaction, the evidence is not solid, confined to the instability of the *in situ* formed imine intermediate.[17] As shown in Scheme **5**, there were no aldol adduct 2′-aminochalcones, **4**, whose synthesis and spectra can be found in the Supporting Information, detected during the full reaction process, monitored by comparing the ^{1}H NMR spectra of the reaction mixture with synthesized samples. As the imine adduct, **5**, is too unstable to survive flash column chromatography, its identity and determination of content were conducted by reduction of the reaction mixture to form more stable amine, **6**. When $NaBH_4$ was adopted as the reductant,



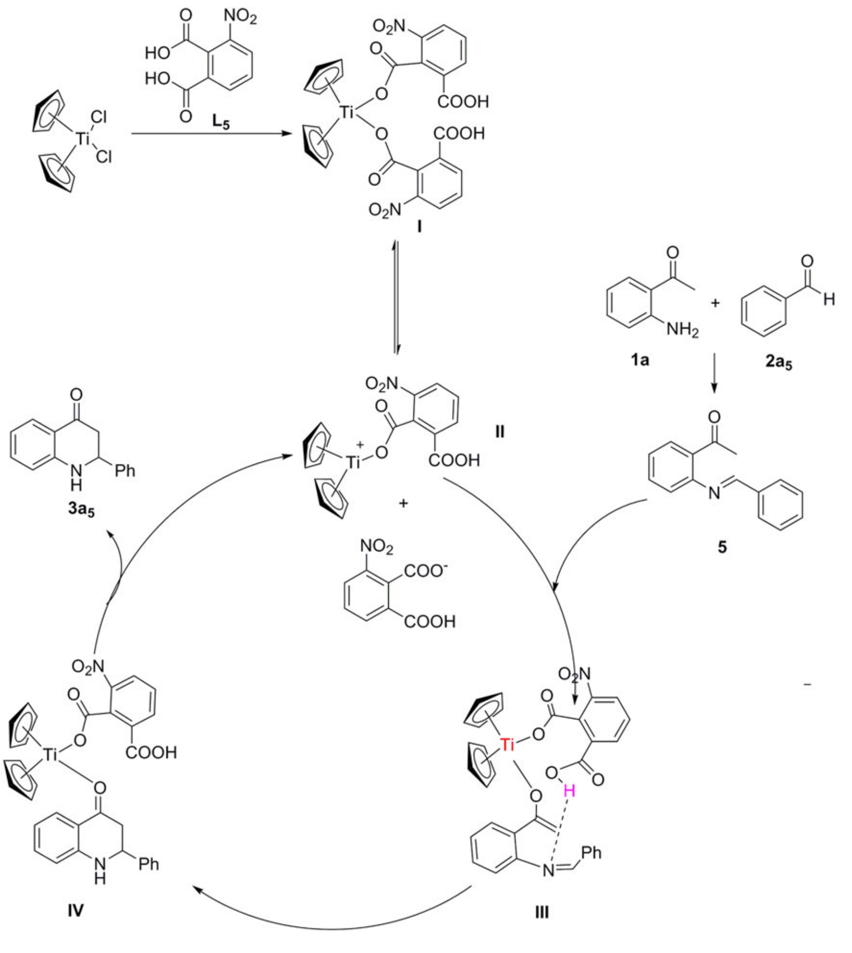
SCHEME 4 The comparison of synthesis of product 3a4 with the involvement of ligand L5 and L7 respectively, where in the bottom trial the 3-COOH on L5 was masked with Me group to be L7



SCHEME 5 Evaluation on two possible reaction routes for the intramolecular Mannich reaction

amine **6** was produced in 33% yield, indicating that the reaction was carried out through the imine route.

On the basis of these results, a plausible reaction mechanism for the intramolecular Mannich reaction is proposed in Scheme 6. Initially, inert pre-catalyst Cp_2TiCl_2 was activated with 3-nitrophthalic acid to generate active intermediate **I**, verified by single X-ray spectroscopy and ESI–MS, in which the O–Ti bonding is fully lengthened, suggesting that the Lewis acidity of Ti (IV) centre is greatly enhanced, thus facilitating the formation of Ti (IV) species (**II**) via breakage of the bonds of O–Ti for further nucleophilic attack. For the substrate side, intermediate imine **5** was produced under the catalysis of the acid catalyst. Once the imine **5** was formed, it functioned as a ligand to coordinate cation species **II** to form Ti complex **III**, the key transition state for the



SCHEME 6 Proposed mechanism for Intramolecular Mannich reaction catalysed by Titanocene-based bifunctional catalyst

reaction, in which the Ti (IV) centre as the Lewis acidic catalytic site activated the acetyl group, and the COOH on the spectator ligand played the Brønsted acidic catalytic role, activating imine **5** via the H-bonding between H atom on COOH and the N atom on imine. This was followed by the nucleophilic attack of enol to activated imine, and the product **3a$_5$** was formed as a transient ligand. Finally, **3a$_5$** dissociated from complex **III**, leading to free product and regeneration of the catalyst **II**.

3 | CONCLUSION

In conclusion, we have established a novel LA–BA bifunctional catalytic system, which could catalyse an intramolecular Mannich reaction with high efficiency, generating a series of 2-aryl-2,3-dihydroquinolin-4(1H)-ones. In addition, mechanistic study via *in situ* NMR and trapping the transient intermediate indicates that the Mannich reaction undergoes the imine route. Our work not only provides a new approach to achieve highly catalytic organometallic titanocene species, but also presents a paradigm for LA–BA bifunctional catalysis.

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SUPPORTING INFORMATION

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