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A density functional study of chiral phosphoric acid-catalyzed direct arylation of trifluoromethyl ketone and diarylation of methyl ketone: reaction mechanism and the important role of the CF_3 group†

Aiping Fu,*[a] Wei Meng,[b] Hongliang Li,[a] Jing Nie[b] and Jun-An Ma*[b]

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The detailed mechanism of the chiral phosphoric acid-catalyzed diarylation reaction between acetophenone and indole has been investigated by DFT methods and compared with that of the reaction between 2,2,2-trifluoroacetophenone and indole. The calculated results confirm our previous hypothesis that the CF_3 group in the ketone plays a perfect double role in activating the substrate and stabilizing the single arylation product of tertiary alcohol. It is also demonstrated that the different ratio of the F-substitution in the CH_3 group of methyl ketone ($CH_{3-n}F_n$, n = 0, 1, 2, 3) affects the activation energy of the key dehydration step for the proposed diarylation process differently, and determines whether the subsequent re-arylation proceeds or is being suppressed. The computational prediction that the prohibitive barriers for CF_3 and CHF_2 ketones in the rate-determining dehydration step for the diarylation process could be overcome at higher reaction temperature has been validated by our additional experiments at 80 °C. Furthermore, the origin of the high enantioselectivity of the chiral phosphoric acid-catalyzed single arylation of trifluoromethyl ketone has been studied with the two-layer ONIOM method. The experimentally observed enantiomeric excess can be successfully rationalized.

1. Introduction

The asymmetric Friedel–Crafts (FC) reaction represents one of the most powerful methods for the synthesis of versatile building blocks of biologically active aromatic compounds.[1] Recently, chiral phosphoric acid derivatives have emerged as powerful organocatalysts for the asymmetric Friedel–Crafts-type reactions of indoles with various electrophilic partners, such as imine,[2] enamide,[3] α,β-unsaturated carbonyls,[4] and nitroolefins.[5] In most of the reported reactions, the chiral phosphoric acids have been found to exhibit high degrees of reactivity and enantioselectivity.[1–5] Despite the impressive progress with chiral phosphoric acids, the direct catalytic asymmetric arylation reactions between simple ketones and indole for the synthesis of valuable chiral tertiary alcohols remain a great challenge owing to the easy diarylation of the ketones.[1] Very recently, we have reported the first highly enantioselective chiral phosphoric acid-catalyzed direct arylation of trifluoromethyl ketones.[6] In these novel reactions, chiral phosphoric acid **1** can catalyze the arylation reactions of indole **2** with the prochiral 2,2,2-trifluoroacetophenone **3a**, affording the desired α-trifluoromethyl tertiary alcohols **4a** in high yields (99%) with excellent enantioselectivities (92% ee) (eqn (1)). Moreover, diarylation was not observed under the given reaction conditions.

It is noteworthy that this direct arylation reaction can also be extended to CHF_2 and C_2F_5-ketones. As shown in eqn (2), the desired products were also achieved in high yields and excellent enantioselectivities. In sharp contrast, under the same reaction conditions, when 2-fluoroacetophenone and non-fluorinated acetophenone were used as the substrates, only the diarylated products were observed (shown in eqn (3) and (4)).

Therefore, our chiral phosphoric acid-promoted arylation reactions for CF_3- and CHF_2-ketone have overcome the main drawbacks of the formation of the bisindole products, and can be a powerful strategy to construct the optically active trifluoromethyl or difluoromethyl-substituted tertiary alcohols, which are valuable pharmaceutical intermediates and chiral building blocks. Furthermore, the interesting result that the number of the F atoms in the $CH_{3-n}F_n$ (n = 0, 1, 2, 3) group of the substrate ketones determines the final products was found in the

[a]*Institute for Computational Science and Engineering, Laboratory of New Fiber Materials and Modern Textile, the Growing Base for State Key Laboratory, Qingdao University, Qingdao 266071, China. E-mail: faplhl@eyou.com, apfu@qdu.edu.cn; Fax: +86-532-85950768; Tel: +86-532-85950767*

[b]*Department of Chemistry, Key Laboratory of Systems Bioengineering (the Ministry of Education), State Synergetic Innovation Center of Chemical Science and Engineering, Tianjin University, Tianjin 300072, China. E-mail: majun_an68@tju.edu.cn*

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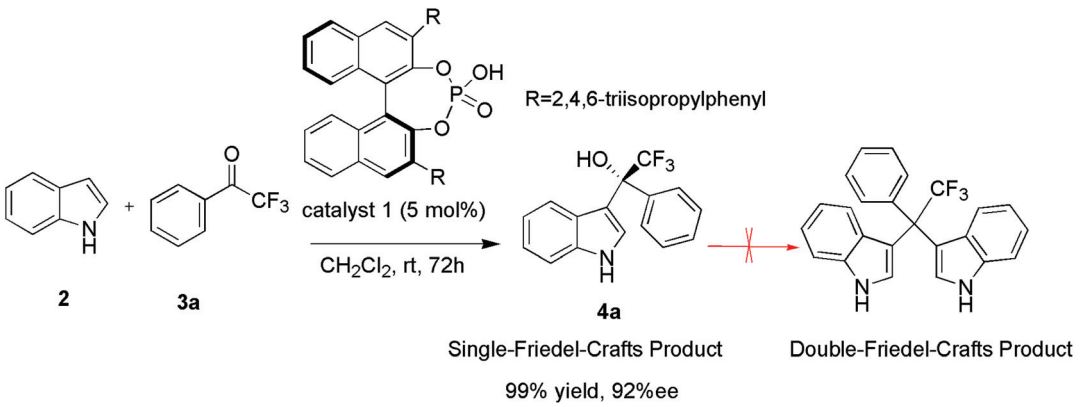

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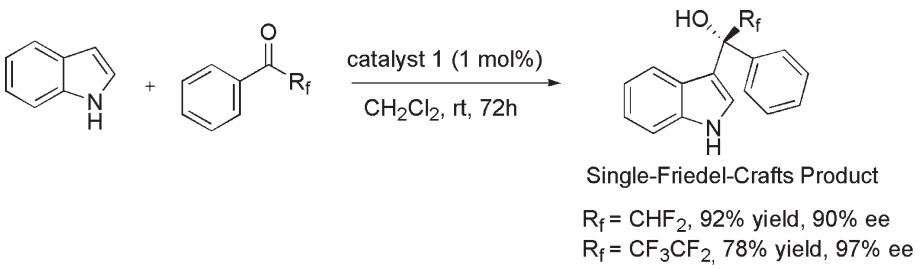

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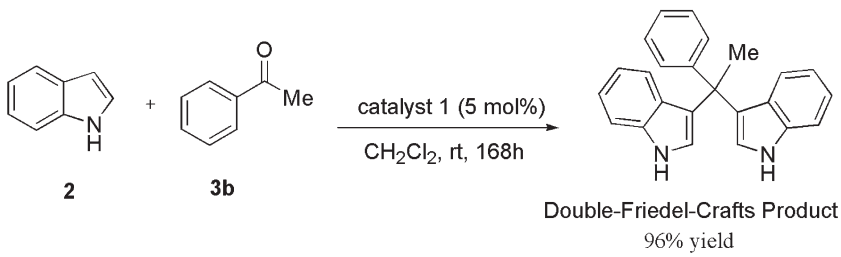

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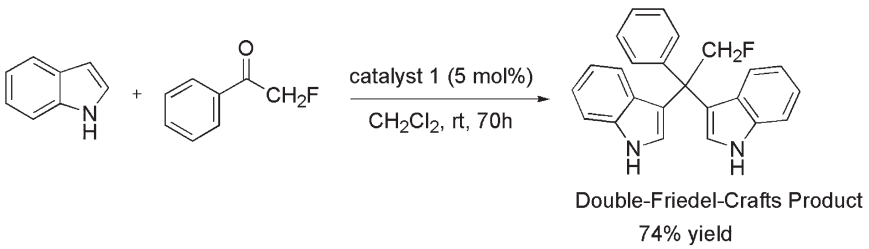


(4)

present reactions. This intriguing fluorine-substitution effect of the substrates on the reaction outcome and the important role of the chiral phosphoric acid catalyst in the reaction between carbonyl compounds and indole motivated us to study the reaction mechanism of the above mentioned arylation or diarylation process in detail. Actually, a number of chiral phosphoric acid-catalyzed asymmetric Mannich,[7] transfer hydrogenation,[8] Strecker,[9] and Friedel–Crafts reactions[10] have been studied by density functional theory methods. These pioneering theoretical and experimental studies[1–13] have established that the chiral phosphoric acids are bifunctional catalysts bearing both Lewis-basic site and Brønsted-acidic site which activate both the electrophile and nucleophile simultaneously, and this type of catalytic model was successfully used by Akiyama and Yamanaka, Goodman and Simón, and Himo *et al.* in their computational insight into the origin of the enantioselectivity of various chiral BINOL-phosphoric acid derivatives-catalyzed asymmetric reactions.[7–13] However, all these pioneering computational studies mainly focused on the reactions involving imine as the electrophile, and the reactions employing other electrophiles *e.g.* carbonyl compounds have been rarely seen.[12,13] In fact,

our chiral phosphoric acid-catalyzed arylation or diarylation reactions[6] represent one type of Friedel–Crafts reactions employing different aromatic ketones as the electrophiles. As one of the most important carbon–carbon bond forming reactions, theoretical investigation into the detailed mechanism of those kinds of reactions is crucial for further development of the bifunctional chiral Brønsted acid catalyst and for substrate scope widening. Furthermore, the insight into the remarkable product dependence on the F-substitution in the substrates for the chiral phosphoric acid-promoted process has not been explored so far. Hence, to extend the general understanding of the mechanism and stereoselectivity of the chiral phosphoric acid-catalyzed organic reactions, the present theoretical study was performed to address the following questions: (a) what is the mechanism of the chiral phosphoric acid-catalyzed arylation or diarylation processes of different ketones? (b) What is the intriguing role of the CF_3 group and how does the different ratio of the F-substitution in methyl ketone determine the final products? (c) What is the origin of enantioselectivity for the single arylation of trifluoromethyl ketones?

2. Computational details

To reduce the computational cost, for the study of the full reaction mechanisms of *catalyst 1*-mediated diarylation processes for acetophenone and 2,2,2-trifluoroacetophenone, the simplified model *e.g.* buta-1,3-diene-1,4-diol-phosphoric acid was initially used instead of the real catalyst system employed in the reaction. All ground state and transition state (TS) geometries were located using full DFT calculations at the BH and HLYP/6-31G (d) level of theory.[14] To check the validity of the results at the above computational level, we have reoptimized several important key steps employing the 6-31+G (d, p) basis set and other popular functionals, such as PBE1PBE, M06-2X and B3LYP.[14] Calculations on the real catalysts system were performed using the two-layer ONIOM method,[15] in which the higher-level layer was treated using the BH and HLYP/6-31G(d) level of theory (or the PBE1PBE/6-31G(d) and M06-2X/6-31G(d) level for comparison purposes), while the HF/3-21G was chosen for the lower-level region. Frequency calculations were also carried out at the same level of theory. Bulk effects of the solvent CH_2Cl_2 have been taken into account by means of a dielectric continuum represented by the conductor polarizable continuum model (CPCM),[16] with united-atom Kohn–Sham (UAKS) radii. The single-point calculations were done upon the optimized gas phase geometries with a dielectric constant ε = 8.93 for CH_2Cl_2. The natural population analysis was performed at the BH and HLYP/6-31G (d) level. Most of the calculations were carried out using the Gaussian 03 program,[17] and M06-2X computations were performed using Gaussian09.[17]

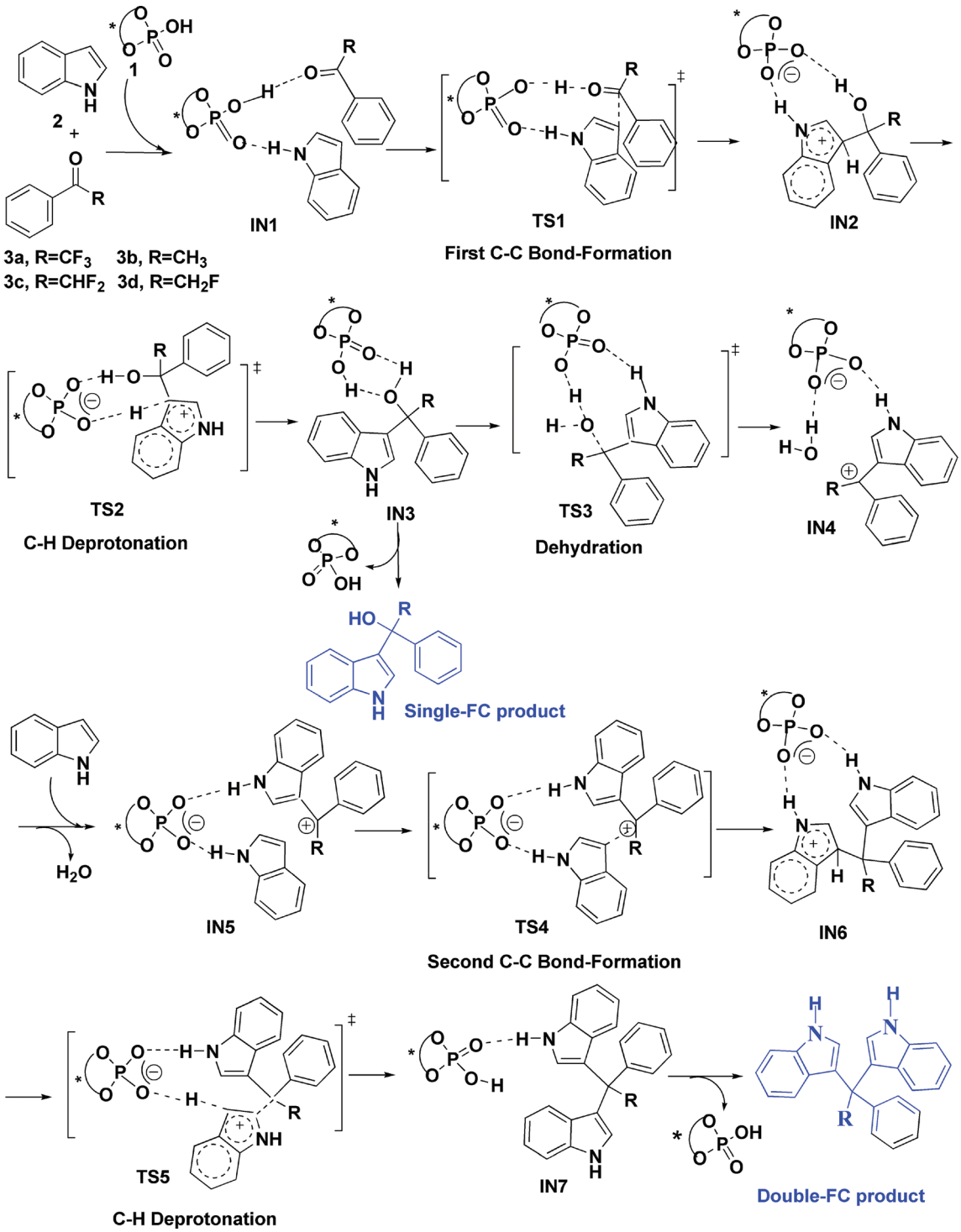
3. Results and discussion

In this section, we will first discuss the full mechanism of the Brønsted acid-catalyzed diarylation of methyl ketone and trifluoromethyl ketone. Then the important role of the CF_3 group of the substrate involved in the Friedel–Crafts reaction and the different ratio of the F-substitution effect on the final product of the fluorinated methyl ketones including monofluoro, difluoro, and trifluoro groups are investigated, and further experimental verification of our computational prediction is reported. Finally, we will explore the origin of high enantioselectivity in the chiral phosphoric acid-catalyzed single arylation between trifluoromethyl aromatic ketone and indole.

3.1 Full reaction mechanism using the simplified catalyst model

On the basis of our experimental results[6] and the relative studies of others,[7–13,18–19] the reaction mechanism of the chiral phosphoric acid-catalyzed diarylation reaction between indole and methyl ketone is proposed and illustrated in Scheme 1. Although the diarylation product for the CF_3 ketone was not observed experimentally, we also tried this process for comparison purposes. As shown in Scheme 1, the reaction started with a condensation of the ketone and indole in the presence of Brønsted acid, to give a hydrogen bond complex **IN1**. Then **IN1** underwent the enantioselective first C–C bond forming reaction through **TS1** to yield zwitterion intermediate **IN2** with the chiral phosphoric acid catalyst activating both the ketone and the indole simultaneously. The subsequent C–H deprotonation *via* **TS2** recovered the aromaticity of the indole ring and generated the hydrogen bond complex **IN3**, and then the single Friedel–Crafts product and catalyst could be released. As our experimental results reported, the arylation reaction of CF_3 ketone ceased here, while for the methyl ketone, the following chiral phosphoric acid catalyzed-dehydration process continued through **TS3** to yield the carbocation **IN4**. After removing the water and adding another indole molecule, the second Friedel–Crafts reaction started *via* **TS4** to generate **IN6**. Similarly, the subsequent C–H deprotonation yielded the catalyst and the double Friedel–Crafts product. Then the diarylation reaction was completed. According to this full mechanism, the whole diarylation reactions proceeded through three major stages: the first Friedel–Crafts, dehydration and the second Friedel–Crafts reactions. Based on our experimental observations and the envisaged mechanism, we can assume that the first Friedel–Crafts reaction controls the stereochemistry of the single arylation product and the dehydration process determines the re-arylation to proceed or not. These two steps would be the key steps for us to investigate. Next, we have performed the DFT calculations to confirm our hypothesis.

To reduce the computational cost, we carried out the study of the possible reaction mechanism with a simplified catalyst model, buta-1,3-diene-1,4-diol-phosphoric acid, which has been successfully used by Simón and Goodman in their theoretical investigations of the chiral BINOL-phosphoric acid-catalyzed reactions.[8a,9,10a,13a,b] Because there may exist several competing reaction channels due to the different approaching modes of the two reaction partners of indole and ketone, we have performed a preliminary investigation of the first C–C bond formation process of indole with **3a** and **3b** since it is



Scheme 1 Plausible reaction mechanism of the diarylation reactions for acetophenone and trifluoroacetophenone catalyzed by chiral phosphoric acid.

considered to be the stereochemistry-determining step for the chiral-phosphoric acid catalyzed Friedel–Crafts reaction and is crucial for the structure of the final product. Meanwhile, for comparison purposes, we have also considered the corresponding uncatalyzed process for 2,2,2-trifluoro acetophenone (**3a**) and acetophenone (**3b**) in an attempt to obtain insight into the role of the Brønsted acid in the reaction of aromatic C–H bonds with carbonyl compounds. The detailed discussion is presented in the ESI.† Based on the preliminary exploration of the major channel in the first C–C bond forming process (Fig. S1 and the related discussion in the ESI†), the intermediates and the transition states for the whole mechanism of the

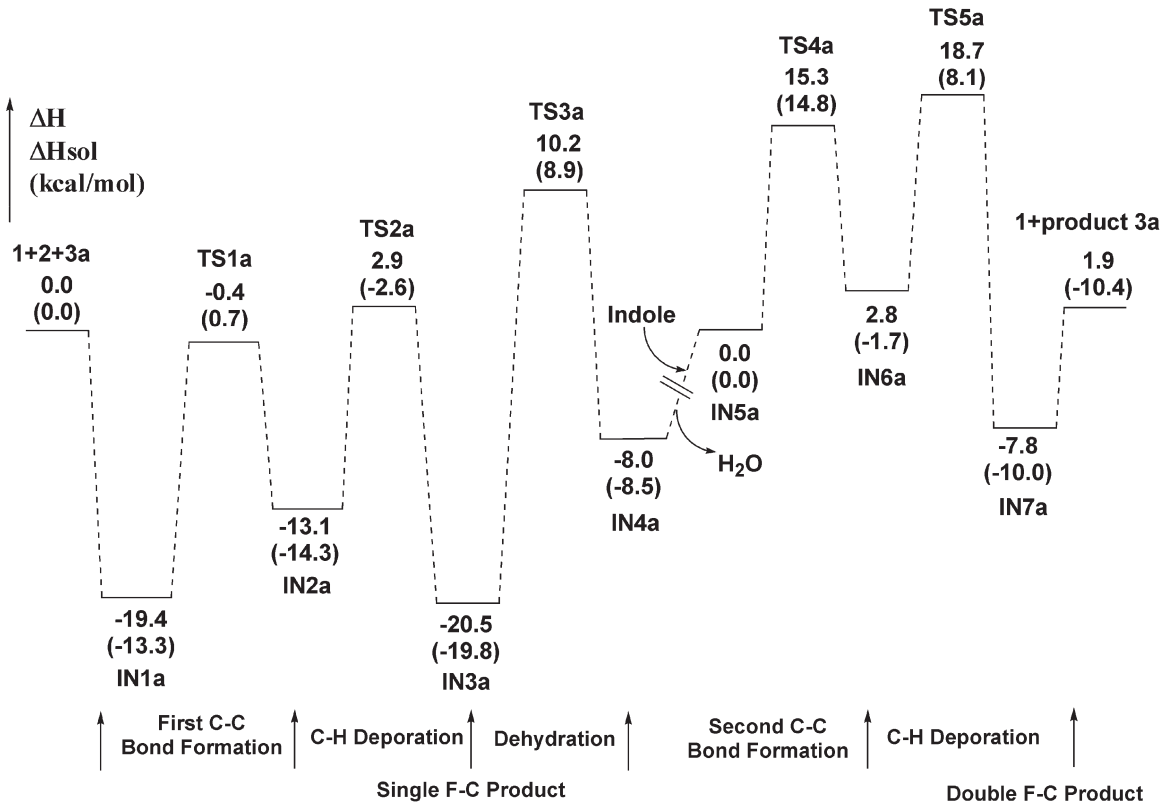


Fig. 1 BH and HLYP/6-31G (d) computed energy profiles for the simplified model of the chiral phosphoric acid-catalyzed diarylation reaction between indole and 2,2,2-trifluoroacetophenone. The values in parentheses correspond to the single point CPCM calculation in CH_2Cl_2.

diarylation process were optimized at the BH and HLYP/6-31G(d) level. The important structures and key geometric parameters for the reactions involving **3a** and **3b** are presented in Fig. S2 and S3,† respectively. The computed energy profiles of the subject reactions are illustrated in Fig. 1 and 2.

As has been proposed, in the initial step of the Friedel–Crafts reaction, the Brønsted acid, ketone, and indole first form a termolecular complex **IN1**, which is stabilized by the favorable hydrogen bond interactions of 19.4 kcal mol^{-1} for **IN1a** and 21.5 kcal mol^{-1} for **IN1b**. Calculations indicate that phosphoric acid tends to donate the acidic proton to the carbonyl oxygen of ketone with the O···H distance of 1.76 Å in **IN1a** and 1.66 Å in **IN1b**. Simultaneously, the basic site of phosphoryl oxygen can accept a hydrogen from the NH moiety of indole with the O···H distance of 1.88 Å in **IN1a** and 1.90 Å in **IN1b**. These strong hydrogen-bonding interactions can result in an increase of the electrophilic character of the carbonyl compound and the nucleophilicity of indole. Furthermore, both the H···O distances and the stabilization energies demonstrate that the hydrogen-bond interaction between the catalyst and the non-fluorinated methyl ketone **3b** is stronger than that of the CF_3 ketone **3a**. This can be attributed to the strong electron-withdrawing nature of the CF_3 group, which lowers the electron density of the oxygen in the carbonyl group (−0.60 in **IN1a** *vs.* −0.65 in **IN1b**) and makes it a weaker hydrogen bond acceptor than methyl ketone. Then the pre-activated complex **IN1** enters the following Friedel–Crafts reaction, which proceeds *via* C–C bond formation followed by deprotonation. It is generally accepted that in the Friedel–Crafts reactions, the first nucleophilic attack of the aromatic ring to the electrophilic partner is the rate-determining step and the subsequent proton transfer is a fast process. As confirmed by the potential energy surfaces for the phosphoric acid-catalyzed diarylation processes of two ketones illustrated in Fig. 1 and 2, the activation barrier for the nucleophilic attack is much higher than that of the following deprotonation process whether for the CF_3 or CH_3 ketone (19.0 *vs.*16.0 kcal mol^{-1} for CF_3 ketone, 22.7 *vs.* 15.5 kcal mol^{-1} for CH_3 ketone). Furthermore, in the key C–C bond forming step, the barrier for **TS1** involving CF_3 ketone is much lower than that involving non-fluorinated CH_3 ketone (19.0 *vs.* 22.7 kcal mol^{-1}), and the larger positive reaction enthalpy also suggests that the reaction involving methyl ketone is more endothermic than that involving CF_3 ketone. Hence, the calculated data confirm the important role of the electron-withdrawing CF_3 group in activating the substrate in the Friedel–Crafts reaction, which corresponds well with the initial FMO analysis (ESI†) and the experimental observation of the higher reactivity of CF_3 ketone. Then after the fast proton transfer process through **TS2**, the phosphoric acid bonded single arylation product **IN3** is generated. Fig. 1 and 2 clearly show that the single FC product **IN3a** is 8.2 kcal mol^{-1} more stable than that of its counterpart **IN3b**. Hence, in accord with the experimental observations, the presence of the trifluoromethyl group in the

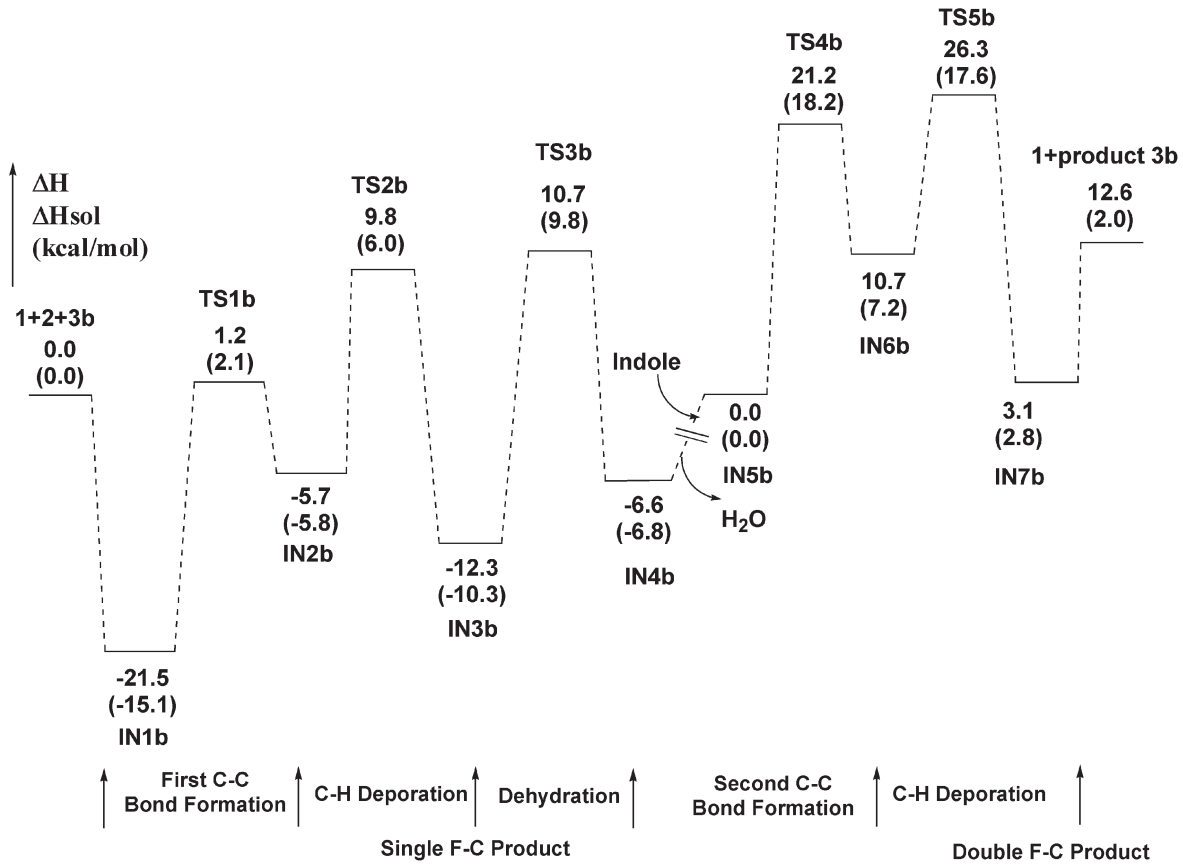


Fig. 2 BH and HLYP/6-31G (d) computed energy profiles for the simplified model of the chiral phosphoric acid-catalyzed diarylation reaction between indole and acetophenone. The values in parentheses correspond to the single point CPCM calculation in CH_2Cl_2.

substrate has resulted in a reduction of the activation barrier and an enhancement of the product stability in the single arylation process, and enables the FC reaction involving **3a** to be more favorable than its **3b** counterpart.

Following the first Friedel–Crafts reaction, in most cases, the resulting product of tertiary alcohol **IN3** would undergo a dehydration process because of the good leaving-group character of the hydroxyl moiety under the employed acidic conditions.[1] In fact, this is the main drawback of many analogous reactions between carbonyl compounds and indole promoted by Brønsted acid, in which the indolemethanol derivatives formed in the first stage are apt to dehydrate and undergo further indole addition with the formation of bisindole products. More intriguingly, our experiments have demonstrated that the incorporation of the CF_3 group into the substrate can substantially change this inclination of dehydration and makes the reaction cease at the single F–C stage. Then theoretical insight into the product switch arising from the trifluoromethyl group is continually presented in the following.

As shown in Fig. 1 and 2, the dehydration of **IN3** through **TS3** to form the carbocation **IN4** with the cleavage of the C–O bond also takes place with the assistance of the phosphoric acid catalyst which donates the proton to the single arylation product of tertiary alcohol. Although **TS3a** and **TS3b** feature nearly the same C–O bond lengths (1.88 Å), the predicted activation barrier for **3a** (30.7 kcal mol^{-1}) is substantially higher than its **3b** counterpart (23.0 kcal mol^{-1}) by 7.7 kcal mol^{-1}. Furthermore, the formation of the carbocation for **3a** is much more endergonic than **3b** (12.5 *vs.* 5.6 kcal mol^{-1}). In fact, the difficulty in formation of the carbocation for **3a** is consistent with our chemical intuition: (a) the apparent shortening of the C–O bond when comparing **IN3a** to its non-fluorinated analogue **IN3b** (1.41 *vs.* 1.42 Å) indicates that cleavage of the C–O bond is difficult for the trifluoromethyl-substituted tertiary alcohol; (b) compared with the CH_3 group, the strong electron-withdrawing nature of the CF_3 moiety could highly destabilize the positive charge in carbocation **IN4a**. Hence, compared with that of **3b** substrate, all the above discussions suggest that the dehydration process for **3a** can be effectively prohibited at room temperature, and the reaction will stop at the single Friedel–Crafts reaction stage.

Afterwards, removal of the water molecule and addition of another indole molecule triggered the second Friedel–Crafts process. Considering the overall mechanism of the diarylation process shown in Fig. 1 and 2, as we have proposed, the first C–C bond formation and the dehydration process would be the most important steps which determine the enantioselectivity and the final product, respectively. Therefore, to verify our results at the BH and HLYP/6-31G(d) level, the intermediates and the transition states for these two key steps have

Table 1 Computed activation enthalpies (kcal mol^{-1}) of the first C–C bond forming and dehydration steps for the simplified model of chiral phosphoric acid-catalyzed diarylation process between acetophenone and indole or different ratio of F-substituted acetophenone and indole at various levels of theory

	First C–C bond formation				Dehydration			
Method and basis sets	CF_3	CHF_2	CH_2F	CH_3	CF_3	CHF_2	CH_2F	CH_3
BHandHLYP/6-31G(d)	19.0	19.1	19.8	22.7	30.7	30.3	24.4	23.0
BHandHLYP/6-31+G(d, p)	19.6	19.6	20.7	23.3	30.0	26.2	21.6	20.7
PBE1PBE/6-31G(d)	10.9	11.3	11.3	15.9	27.2	26.3	20.9	20.3
PBE1PBE/6-31+G(d, p)	10.4	9.5	12.3	15.9	27.2	23.3	18.3	18.0
M06-2X/6-31+G(d, p)	11.6	12.6	13.1	16.4	28.7	26.7	21.5	20.8
B3LYP/6-31+G(d, p)	16.9	15.7	18.0	21.2	21.0	17.7	15.1	14.8

been reoptimized employing three other popular DFT methods such as PBE1PBE, M06-2X, and B3LYP at the 6-31+G-(d,p) basis set level. The calculated activation barriers for CF_3 and CH_3 ketone have been presented in Table 1.

From the table we can see that all the DFT methods exhibit a similar trend of a lower activation barrier in the first C–C bond-forming step and a much higher barrier in the dehydration process for CF_3 ketone **3a** in comparison with the non-fluorinated ketone **3b**. In the reaction pathway of **3b**, the relative energies of the two transition states for the nucleophilic attack and the dehydration step are comparative and the rate-determining step depends on the basis sets and methods. However, all the methods give a relatively low barrier which can be easily overcome at room temperature, then the experimentally observed diarylation can proceed smoothly. Instead, for the reaction pathway of CF_3 ketone **3a**, the dehydration step obviously became rate-determining with the significant barrier that could not be surmounted at the room temperature. It is worth noting that except the B3LYP method which predicts the much lower activation barrier for the dehydration step, the other three DFT methods could satisfactorily reproduce the perfect double role of the CF_3 group in activating substrates and stabilizing single arylation adduct of tertiary alcohol. In summary, given that the reactions were performed at room temperature and the dehydration barrier was enlarged to a great extent, the diarylation process is unlikely to proceed for CF_3 ketone, which is consistent with the experimental observation that indole and **3a** only yield the single Friedel–Crafts product at room temperature, while indole and CH_3 ketone afford the diarylated product under the same conditions.

Moreover, we have also considered the two key steps of diarylation for ketones involving CHF_2 and CH_2F moieties. The activation enthalpies for those two substrates at different levels are also shown in Table 1. Combined with their CF_3 and CH_3 counterparts, the remarkable fluorine effect on the final product control is also identified by the calculated barriers. As expected, the different ratios of F-substitution in CH_3 of methyl ketone can activate the carbonyl group in the C–C bond forming step, and stabilize the FC product of tertiary alcohol to a different extent. The analysis of the relationship between the LUMO energies of the electrophiles and the activation energies in the C–C bond formation steps for the set of CF_3, CHF_2, CH_2F, and CH_3 ketones has also been carried out by the semiempirical FMO theory developed by Yu *et al.*[20] and the details have been shown in Table S1.† Considering the reaction occurring at room temperature, the predicted values can also satisfactorily explain why CHF_2 only affords the single F–C product while CH_2F yields the double F–C product.

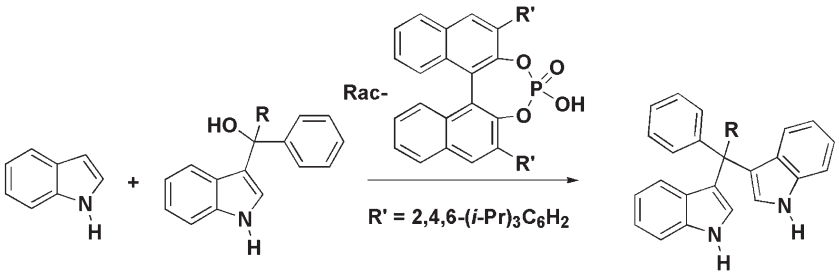
It is also worth noting that although the higher energetic barriers of the rate-determining dehydration process for CF_3 and CHF_2 methyl ketones suggest that the formation of the diarylation product is prohibited, the predicted barriers for them are in the range of 24 kcal mol^{-1} to 31 kcal mol^{-1}, which is not indeed too high to be overcome. Considering that our reported reactions took place at room temperature, we can expect that raising the reaction temperature could facilitate the rate-determining dehydration process for the subsequent re-arylation reactions. Therefore, further experimental investigation was carried out to verify the prediction based on the above discussions.

3.2 Experimental validation

To extend the hypothesis that the higher temperature could effectively activate the CF_3 and CHF_2 stabilized arylation product of tertiary alcohol, we next tried the reaction of indole with the single arylation product of trifluoromethyl ketone *e.g.* 2,2,2-trifluoro-1-(1*H*-indole-3-yl)-1-phenylethanol (product **4a** in the previous reactions) in the presence of racemic phosphoric acid **1** at the reaction conditions with higher temperature.

To our delight, the desired double arylation product was obtained in 79% yield at 40 °C (Table 2, entry 2) while the control experiment demonstrated that a higher temperature was indispensable for the success of the target reaction (Table 2, entry 2). Different polar aprotic solvents were also screened (Table 2, entries 3–5), and sharp slide of yields were observed when THF and CH_3CN were employed. In contrast, an apolar solvent toluene gave a good yield in 60 h. After performing the reaction at a higher temperature of 80 °C, a quantitative conversion of the re-arylation product was observed in 24 h (Table 2, entry 7). Otherwise, a blank experiment was conducted, showing that a phosphoric acid was vital to this transformation even at a higher temperature (Table 2, entry 10). Not surprisingly, the single Friedel–Crafts product of CHF_2 ketone (2,2-difluoro-1-(1*H*-indole-3-yl)-1-phenylethanol) also has a strong tendency to generate the re-arylation product at the

Table 2 The Brønsted acid-catalyzed rearylation reaction of 2,2,2-trifluoro-1-(1*H*-indole-3-yl)-1-phenylethanol and 2,2-difluoro-1-(1*H*-indole-3-yl)-1-phenylethanol



Entry	R	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)
1	CF_3	5	CH_2Cl_2	25	72	—
2	CF_3	5	CH_2Cl_2	40	60	79
3	CF_3	5	$CHCl_3$	40	60	75
4	CF_3	5	THF	40	60	23
5	CF_3	5	CH_3CN	40	60	40
6	CF_3	5	Toluene	40	60	82
7	CF_3	5	Toluene	80	24	98
8	CF_3	1	Toluene	80	120	73
9	CF_3	10	Toluene	80	16	91
10	CF_3	—	Toluene	80	120	—
11	CHF_2	5	Toluene	80	12	95

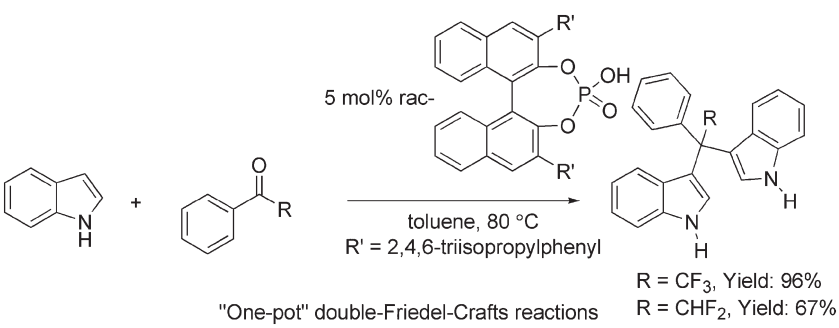
[a] Isolated yield.

raising temperature, and the bisindole product was obtained in 95% yield at 80 °C (Table 2, entry 11). Meanwhile, some "one-pot" double-Friedel–Crafts reactions were carried out smoothly under the optimal reaction conditions (eqn (5)). And it gave 96% (CF_3 ketone) and 67% (CHF_2 ketone) yield, respectively. Those additional experimental results are in good accord with our computational predictions. The experimental details are provided in the ESI.†

In conclusion, both theoretical and experimental studies demonstrate that it is possible to tune the single arylation and diarylation process by introducing the CF_3 (CHF_2) group into the substrate and altering the reaction temperatures.

3.3 Enantioselectivity using the real catalyst model

Our experiments[6] for the reaction of indole with the aromatic methyl ketones promoted by chiral phosphoric acid have shown that trifluoromethyl ketone can afford the resulting trifluoromethyl-substituted tertiary alcohol in high yield and excellent enantiomeric excess (eqn (1)). Based on the above study of the full mechanism involving a simplified model of phosphoric acid, in the following we will focus on the origin of enantioselectivity for the chiral phosphoric acid-catalyzed Friedel–Crafts reaction involving CF_3 ketone. As has been discussed, the Friedel–Crafts reaction proceeds *via* two steps *e.g.* the C–C bond formation and the subsequent C–H deprotonation process. Since the deprotonation step is neither a rate-determining nor a stereochemistry-determining one, in this section we have only focused on the enantioselective C–C bond forming process *e.g.* the aromatic indole addition to the ketone. Combined with the preliminary study using the simplified model (Fig. SI† and the related discussion), four reactive channels corresponding to two stereoisomers have been considered. These include two possible diastereomeric transition states of indole attacking the *re* and *si* faces of CF_3 ketone, and two possible relative orientations of the unsymmetrical indole to the electrophile ketone. Simón and Goodman have



(5)

suggested that the ONIOM method[8a,9,10a,13a] could be successfully used to treat large catalyst systems like BINOL-based phosphoric acid in the investigation of the reasonable mechanism and the explanation of enantioselectivity in various asymmetric reactions. Inspired by these successes, we have performed the DFT calculation of the four required TSs by a complete model for the phosphoric acid catalyst using the ONIOM method, in which all atoms in the catalyst were included in the lower-level layer except the phosphoric acid moiety, which was included in the higher-level layer, together with the ketone and indole involved in the reaction. The DFT functional of BH and HLYP combined with the 6-31G (d) basis set was used in the higher-level layer, and the HF/3-21G was used in the lower-level layer. Because the different conformation of the steric 2,4,6-triisopropylphenyl substituents on the catalyst can directly affect the stability of the different TSs and subsequently the enantioselectivity, we have carried out the conformational analysis of the catalyst and the related TSs first and the details are presented in the ESI (Fig. S5 and S6†). The most stable conformers of the TSs in the four reaction channels have been used in the following discussion of the reaction enantioselectivity.

For the purpose of clarifying the steric effect of the substituent at the 3,3′-position in the chiral phosphoric acid catalyst, we have also considered four similar TSs involving the simplified model (buta-1,3-diene-1,4-diol-phosphoric acid and biphenyl-phosphoric acid), and the optimized geometrical structures and the relative enthalpies are illustrated in Fig. S4.† The TS structures and relative enthalpies involving the complete real catalyst are shown in Fig. 3. As depicted in these figures, different orientations of the indole ring affect the energies of the resulting transition structures greatly. "TS1-endos" with the two simplified catalyst models are about 5–7 kcal mol^{-1} higher than their "*exo*" counterparts, while for the real catalyst with the bulky substituent groups at 3,3′-position, the energy difference increases to about 7–10 kcal mol^{-1}. Therefore, in the following, we only focus on the two transition states of "*exo*" orientation, *e.g.* the indole aromatic ring is in the same direction with the phenyl group of ketone. It is observed that the energy difference between the transition states involving *re*- and *si*-facial attacking of indole to ketone adopting the "*exo*" arrangement is nearly negligible since the simplified model of the catalyst lacks the bulky groups. When the full structure of the catalyst is included, as shown in Fig. 3, the most stable transition structure corresponds to the one in which indole attacks on the *re* face of the ketone, lying 2.5 kcal mol^{-1} lower in enthalpy than the *si*-facial attack. When the solvent effect is taken into account, the energy difference changes to 1.8 kcal mol^{-1}. Furthermore, the combination of PBE1PBE/6-31G (d) or M06-2X/6-31G (d) with HF/3-21G methods has also been used to reoptimize the four TSs of the complete catalyst model and the differences in enthalpy are also shown in Fig. 3. All the methods reproduce the experimentally observed configuration of the major product and the enantioselectivity (92% ee) satisfactorily. Inspection of the geometric parameters for the two lower-energy TSs with "*exo*" orientation suggests that the following two factors might be responsible for the observed enantioselectivity. First, TS1-*re-exo* has the shortest hydrogen-bond distances between the phosphoric acid catalyst and the two reaction partners (TS1-*re-exo*: 1.78 and 1.33 Å, TS1-*si-exo*: 2.07 and 1.39 Å). Secondly, TS1-*re-exo* experiences less steric repulsion when the reaction partners enter into the binding pocket of the catalyst, while in TS1-*si-exo*, the aromatic ring of indole is close to the bulky 2,4,6-triisopropylphenyl group of the catalyst and suffer from more steric hindrance. As suggested in Fig. S6,† this unfavorable interaction can be reflected by the large deviation from the eclipsing conformation of the isopropyl Hs at 4-positions on the 2,4,6-triisopropylphenyl substituents to the phenyl double bond which is required to diminish the steric repulsion between the catalyst and the substrates when the catalyst tries to accommodate the substrates into its chiral pockets. Thus, the above two factors direct the incoming indole approaching the *re*-face of ketone and, as expected, the presence of the large substituent at the 3,3′-positions is a crucial element to induce asymmetry in the chiral phosphoric acid catalyzed reactions.

4. Conclusions

In this work, the chiral phosphoric acid-catalyzed arylation and diarylation reactions between indole and $CH_{3-n}F_n$-ketones (n = 0, 1, 2, 3) have been investigated by DFT methods. The full mechanism of the diarylation process for 2,2,2-trifluoromethyl ketone and methyl ketone has been considered employing the simplified catalyst model *e.g.* buta-1,3-diene-1,4-diol-phosphoric acid using BH and the HLYP/6-31G(d) method. The two crucial steps, including the first C–C bond formation and the dehydration during the diarylation process, have been discussed employing different DFT methods. All the calculations confirmed that the dehydration process required a lower activation barrier in the case of the methyl ketone or CH_2F ketone, and the diarylation process can proceed smoothly. Moreover, the perfect double role of the CF_3 (CHF_2) group in activating the substrate for the first C–C bond forming reaction and stabilizing the single Friedel–Crafts product was identified satisfactorily. In addition, the predicted activation barriers in the dehydration process for CF_3 (CHF_2) ketone range from 24 to 31 kcal mol^{-1}, which suggests that the generation of the diarylation product is not really prevented at the higher temperature. The additional experiments at 80 °C sufficiently validated this theoretical prediction. Hence, our theoretical and experimental results suggest that the arylation and the diarylation products can be switched by tuning the temperature and the F-substituent ratio. Finally, the issues of the *re*-facial selectivity in the BINOL-phosphoric acid catalyzed arylation reaction of CF_3 ketone are also addressed. The ONIOM calculations (BH and HLYP/6-31G (d): HF/3-21G) on the transition states of the stereochemistry-determining C–C bond forming step showed that the ketone and indole were both activated by the bifunctional chiral phosphoric acid through the formation of

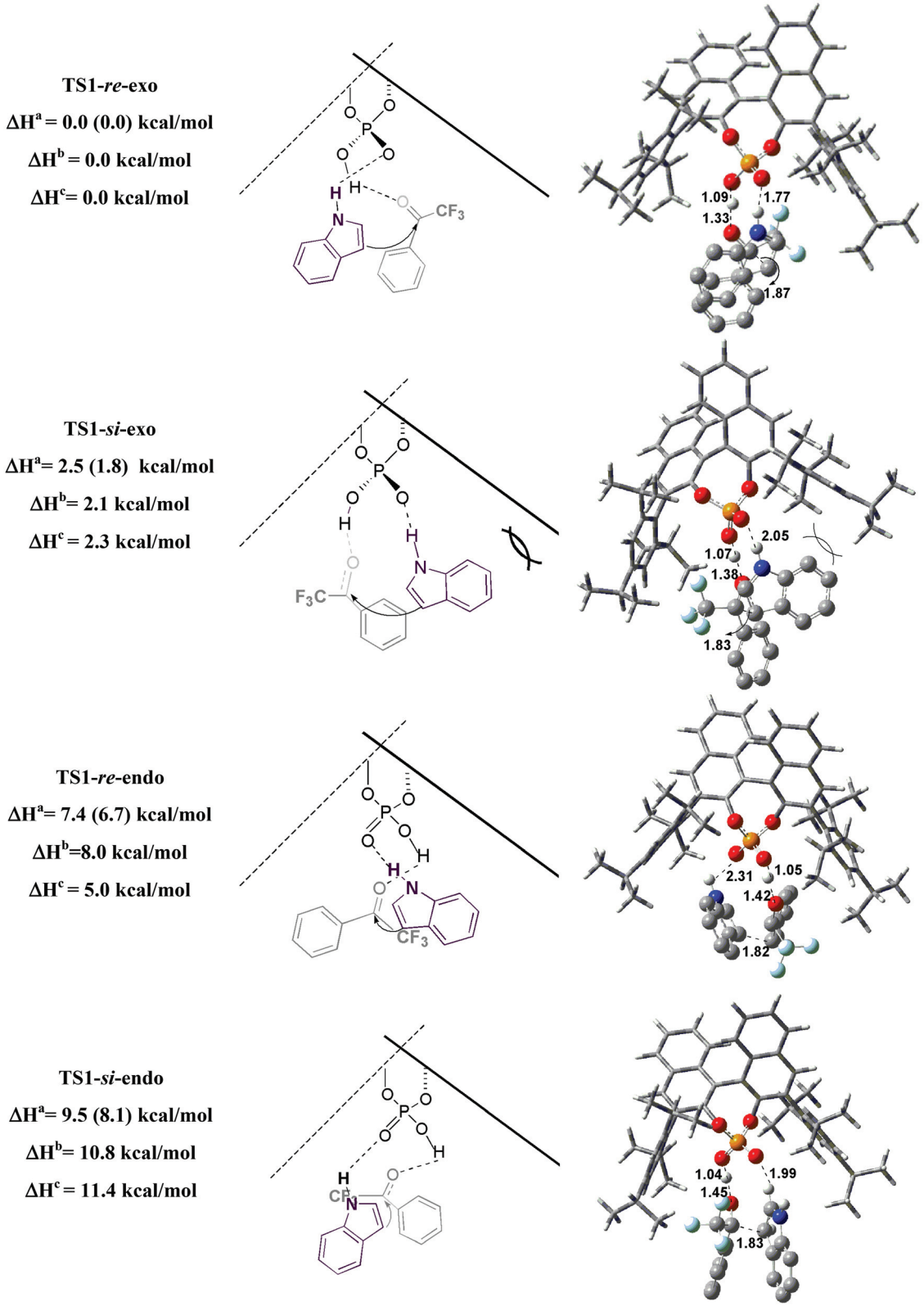


Fig. 3 DFT computed transition states and relative enthalpies for the C–C bond formation step of the chiral phosphoric acid-catalyzed Friedel–Crafts reaction (real system) between indole and 2,2,2-trifluoroacetophenone. CPCM values in CH_2Cl_2 are shown in parentheses. Atoms treated with the high level of theory are shown as a ball and stick model, while atoms in the low-level layer are shown as a tube model. (a) ONIOM (BH and HLYP/6-31G(d):HF/3-21G); (b) ONIOM (PBE1PBE//6-31G(d):HF/3-21G); (c) ONIOM (M062X//6-31G(d):HF/3-21G).

hydrogen bonds. The stronger hydrogen-bond interaction and the less steric repulsion between the bulky group at the 3,3′-position of the catalyst and the substrates existing in the *re*-facial attacking TS cause the (*R*)-enantiomer to be preferentially produced. Our calculations also successfully reproduce the observed enantioselectivity.

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References

1 For reviews, see: (*a*) S.-L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190–2201; (*b*) A. Zamfir, S. Schenker, M. Freund and S. Tsogoeva, *Org. Biomol. Chem.*, 2010, **8**, 5262–5276; (*c*) V. Terrasson, R. M. de Figueiredo and J. M. Campagne, *Eur. J. Org. Chem.*, 2010, 2635–2655; (*d*) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539–4549.

2 (*a*) Q. Kang, Z.-A. Zhao and S.-L. You, *J. Am. Chem. Soc.*, 2007, **129**, 1484–1485; (*b*) M. Terada, S. Yokoyama, K. Sorimachi and D. Uraguchi, *Adv. Synth. Catal.*, 2007, **349**, 1863–1867; (*c*) G.-W. Zhang, L. Wang, J. Nie and J.-A. Ma, *Adv. Synth. Catal.*, 2008, **350**, 1457–1463.

3 (*a*) M. Terada and K. Sorimachi, *J. Am. Chem. Soc.*, 2007, **129**, 292–293; (*b*) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2007, **46**, 5565–5567.

4 Q. Cai, Z.-A. Zhao and S.-L. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 7428–7431.

5 J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4016–4018.

6 J. Nie, G.-W. Zhang, L. Wang, A. P. Fu, Y. Zheng and J.-A. Ma, *Chem. Commun.*, 2009, 2356–2358.

7 M. Yamanaka, J. Itoh, K. Fuchibe and T. Akiyama, *J. Am. Chem. Soc.*, 2007, **129**, 6756–6764.

8 (*a*) L. Simón and J. M. Goodman, *J. Am. Chem. Soc.*, 2008, **130**, 8741–8747; (*b*) T. Marcelli, P. Hammar and F. Himo, *Chem.–Eur. J.*, 2008, **14**, 8562–8571; (*c*) T. Marcelli, P. Hammar and F. Himo, *Adv. Synth. Catal.*, 2009, **351**, 525–529; (*d*) Y. Shibata and M. Yamanaka, *J. Org. Chem.*, 2013, **78**, 3731–3736.

9 L. Simón and J. M. Goodman, *J. Am. Chem. Soc.*, 2009, **131**, 4070–4077.

10 (*a*) L. Simón and J. M. Goodman, *J. Org. Chem.*, 2010, **75**, 589–597; (*b*) C. Zheng, Y.-F. Sheng, Y.-X. Li and S.-L. You, *Tetrahedron*, 2010, **66**, 2875–2880; (*c*) T. Hirata and M. Yamanaka, *Chem.–Asian J.*, 2011, **6**, 510–516; (*d*) L. Simón and J. M. Goodman, *J. Org. Chem.*, 2011, **76**, 1775–1778.

11 (*a*) M. Yamanaka and T. Hirata, *J. Org. Chem.*, 2009, **74**, 3266–3271; (*b*) T. Akiyama, H. Morita, P. Bachu, K. Mori, M. Yamanaka and T. Hirata, *Tetrahedron*, 2009, **65**, 4950–4956; (*c*) F.-Q. Shi and B.-A. Song, *Org. Biomol. Chem.*, 2009, **7**, 1292–1298.

12 (*a*) N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 15301–15310; (*b*) S. Xu, Z. Wang, Y. Li, X. Zhang, H. Wang and K. Ding, *Chem.–Eur. J.*, 2010, **16**, 3021–3035; (*c*) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2010, **122**, 8848–8851.

13 (*a*) M. N. Grayson, S. C. Pellegrinet and J. M. Goodman, *J. Am. Chem. Soc.*, 2012, **134**, 2716–2722; (*b*) M. N. Grayson and J. M. Goodman, *J. Am. Chem. Soc.*, 2013, **135**, 6142–6148; (*c*) H. Wang, P. Jain, J. C. Antilla and K. N. Houk, *J. Org. Chem.*, 2013, **78**, 1208–1215.

14 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 1372–1377; (*b*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652; (*c*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter*, 1988, **37**, 785–789. For M06-2X, see: (*d*) Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215–241.

15 (*a*) M. Svensson, S. Humbel and K. Morokuma, *J. Chem. Phys.*, 1996, **105**, 3654–3661; (*b*) T. Vreven and K. Morokuma, *J. Comput. Chem.*, 2000, **21**, 1419–1432; (*c*) S. Dapprich, I. Komaromi, K. S. Byun, K. Morokuma and M. J. Frisch, *THEOCHEM*, 1999, 461–462.

16 (*a*) V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995–2001; (*b*) B. Barone, M. Cossi and J. Tomasi, *J. Comput. Chem.*, 1998, **19**, 404–417.

17 (*a*) M. J. Frisch,*et al.*, *GAUSSIAN03 (Revision D.01)*, Gaussian, Inc., Wallingford, CT, 2004; (*b*) M. J. Frisch, *et al.*, *GAUSSIAN 09 (Revision C.01)*, Gaussian, Inc., Wallingford, CT, 2010.

18 A. S. Cothelf, T. Hansen and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1*, 2001, 854–860.

19 (*a*) F.-L. Sun, M. Zeng, Q. Gu and S.-L. You, *Chem.–Eur. J.*, 2009, **15**, 8709–8712; (*b*) S.-G. Wang, L. Han, M. Zeng, F.-L. Sun, W. Zhang and S.-L. You, *Org. Biomol. Chem.*, 2012, **10**, 3202–3209.

20 L.-G. Zhuo, W. Liao and Z.-X. Yu, *Asian J. Org. Chem.*, 2012, **1**, 336–345.

