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Tunable regiodivergent phosphine-catalyzed [3 + 2] cycloaddition of alkynones and trifluoroacetyl phenylamides†

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Alkynones can be activated by phosphine as a nucleophilic catalyst, and then trapped by a series of trifluoroacetyl phenylamides to afford cycloaddition products. Through subtly adjusting the substituent of trifluoroacetyl phenylamides, the addition of water and changing the reaction temperature, two kinds of highly regioselective cycloaddition products were obtained in moderate to excellent yields. Plausible mechanisms were proposed and supported by the deuterium-labeling experiments and DFT calculations. DFT calculations demonstrate that the currently accepted intramolecular proton transfer processes involved in these reactions are impossible, and these proton transfer processes can proceed with the assistance of substrates containing an acidic moiety or by the addition of water. Our mechanistic studies provide reasonable explanations for the regioselectivity affected by the protic additive H_2O, and the reaction temperature.

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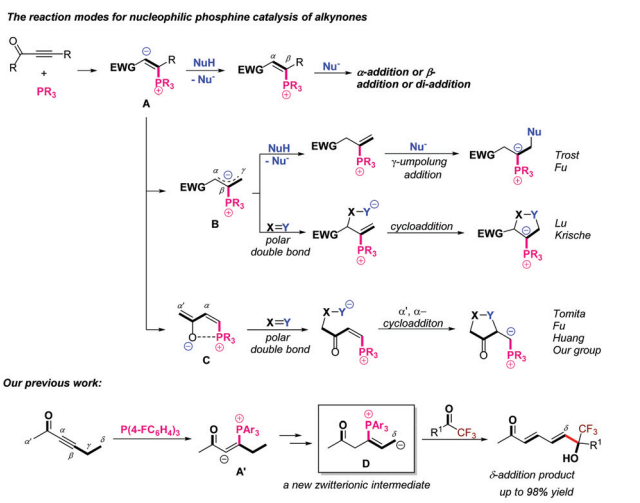
Introduction

In recent years, the nucleophilic phosphine-catalyzed reactions[1] have been recognized as reliable methods which could combine olefins,[2] allenes,[3] alkynes,[4] or Morita–Baylis–Hillman adducts (MBHADs)[5] with other electrophilic or nucleophilic blocks to afford highly functionalized products; the related isomerization, addition and cycloaddition reactions have been explored, expanded and applied. Alkynones as activated π system substrates have been frequently utilized in a large number of nucleophilic phosphine-catalyzed reactions, such as addition,[6] umpolung addition,[4b,7] and cycloaddition[4a,8a,b] reactions. Based on the commonly accepted mechanisms for the nucleophilic phosphine-catalyzed reactions of electrophilic π systems,[9] the first step is nucleophilic addition of phosphine to electrophilic π systems. In this case, zwitterionic intermediate **A** is first formed by the nucleophilic addition of tertiary phosphine to the alkynones, which subsequently undergo α-addition,[10] β-addition[11] or di-addition[12] with a variety of nucleophiles to afford highly functionalized products (Scheme 1). On the other hand, the zwitterionic intermediate **A** can be transformed to a zwitterionic intermediate **B** *via* a 1,3-proton shift (γ–α shift), which subsequently undergoes γ-umpolung addition[4b,13] with nucleophiles or cycloaddition reactions with electrophilic π systems (Scheme 1).[14] Alternatively, the zwitterionic intermediate **A** can be transformed to another zwitterionic intermediate **C** *via* 1,3-proton shift (α′–α shift), which can conduct α′,α-cycloadditions with a



Scheme 1 The reaction modes of phosphine-catalyzed reactions of alkynones with other substrates.

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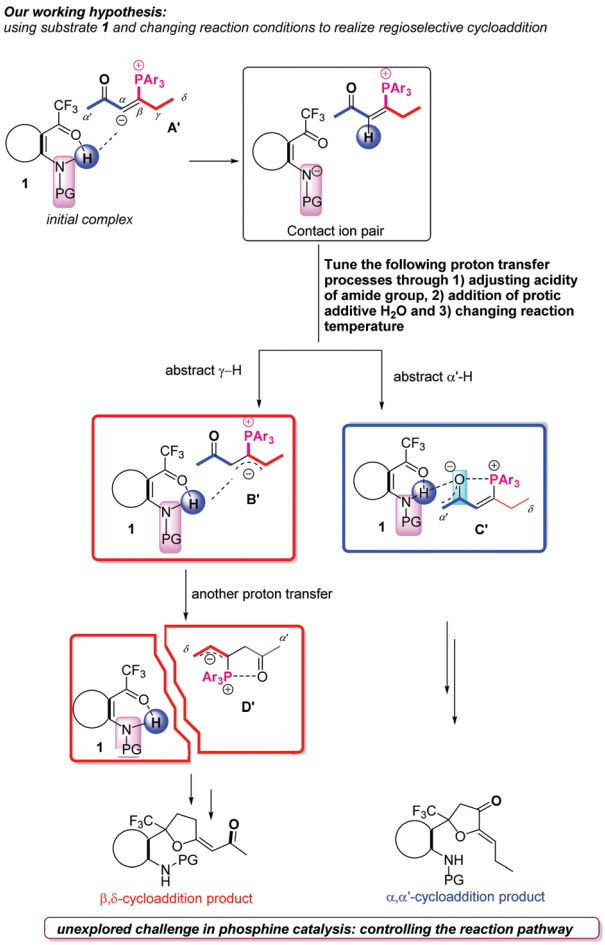
range of electrophilic π systems (Scheme 1).[15] Very recently, we first reported the phosphine-catalyzed δ-carbon addition of alkynones with electron-deficient carbonyl groups to generate 1,3-diene derivatives (Scheme 1);[16] a novel zwitterionic intermediate **D**, which was probably converted from zwitterionic intermediate **A′** *via* two proton shift processes, was identified as the key intermediate and reacted with trifluoroacetyl compounds to afford δ-addition products. On the basis of previous reports, the related four zwitterionic intermediates **A**, **B**, **C** and **D** were critical to direct the subsequent transformations. These zwitterionic intermediates **A**, **B**, **C** and **D** can be converted reversibly, and their versatile reactivities can be tuned by adjusting substituents in the substrates.[17] However, there are challenges to deliberately control their conversions, and further achieve highly regioselective phosphine-catalyzed reactions of alkynones with other substrates.[18]

On the basis of previous reports by our group and others, we realized that these zwitterionic intermediates **A–D** shown in Scheme 1 are critical intermediates to direct the following transformations and envisaged that adjusting the substituents in the substrates or changing the reaction conditions can further achieve highly regioselective phosphine-catalyzed reactions of alkynones with a range of electrophilic π systems. Considering the amide group,[19] widely utilized as an important moiety in organocatalysts,[20] bifunctional catalysts,[1j] ligands[21] and directing groups[22] in substrates to direct transformations, we designed substrate **1** having an amide group, and hypothesized that it could assist the proton transfer processes[23] due to the acidity of the NHAc moiety, which makes the zwitterionic intermediate **A′** be transformed into zwitterionic intermediates **B′**, **C′** or **D′** (Scheme 2). In addition, the addition of a protic additive, such as H_2O, and changing the reaction temperature may tune these proton transfer processes to afford different regioselective cycloaddition products (Scheme 2). Based on the working hypothesis, we systematically investigated the phosphine-catalyzed cycloaddition reactions of alkynones with a range of trifluoroacetyl phenylamides, producing cycloadducts containing a CF_3 group, which may have further synthetic applications since in a variety of pharmaceutical compounds the incorporation of a CF_3 group is often found to give special chemical properties, metabolic stability, lipophilicity and solubility.[24] Herein, we would like to report the regiodivergent[25] phosphine-catalyzed [3 + 2] cycloaddition of alkynones with a series of trifluoroacetyl phenylamides, affording two kinds of cycloaddition products in moderate to excellent yields; we also conducted mechanistic studies to reveal the detailed mechanisms through deuterium-labeling experiments and DFT calculations.



Scheme 2 Tunable regioselective cycloaddition.

Results and discussion

Experimental investigations

We initially tested the reaction outcomes in the presence of $P(4\text{-}FC_6H_4)_3$ and optimized the reaction conditions employing 2-(2,2,2-trifluoroacetyl)phenylamide **1a** and alkynone **2a** as substrates. The results are shown in Table 1. It was found that α′,α-cycloaddition product **4a** was obtained in 74% yield with 3.0 equiv. of **2a** in toluene at room temperature for 72 h (entry 1). The solvent effect was next investigated, and it was identified that toluene was still better than other solvents, such as THF, dioxane, and DCM (entries 2–4). Decreasing the reaction temperature to 10 °C improved the yield to 88% (entry 5). However, the reaction did not take place when a 4 Å molecular sieve was added as an additive (entry 6), suggesting that a trace of water might be a co-catalyst in this cycloaddition reaction at low temperature. Interestingly, the β,δ-cycloaddition product **3a** was mainly accessed at 65 °C with the same substrates **1a** and **2a** in 67% yield and hydration product **3a′** was obtained in 11% yield as a by-product (entry 7). Enhancing the concentration of the reaction mixture, the yield of β,δ-cycloaddition product **3a** decreased to 52%; however, the yield of hydration product **3a′** simultaneously increased to 24% (entry 8). Adding a 4 Å molecular sieve into the reaction system did not influence the reaction proceeding (entry 9), but the addition of phenol would impede the reaction proceeding, only affording the desired β,δ-cycloaddition product **3a** in 23% yield (entry 10).

Having established the optimal reaction conditions, we next surveyed the substrate scope of the reaction by using a

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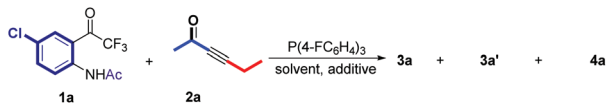
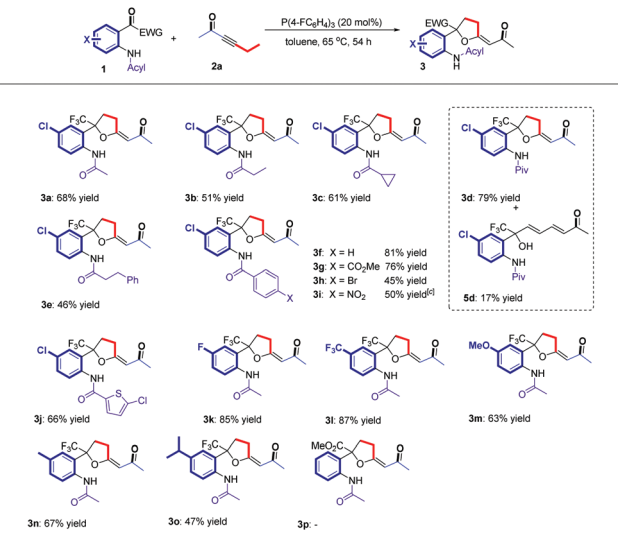
Table 1 Optimization of the reaction conditions for regiodivergent [3 + 2] cycloaddition of 2-(2,2,2-trifluoroacetyl)phenylamide **1a** with alkynone **2a**[a,b]



Entry[a]	Additive (mg)	Solvent	Temp (°C)	Time (h)	Yield (%)[b] 3a	3a′	4a
1	—	Toluene	r.t	72	—	—	74
2	—	THF	r.t	72	—	—	13
3	—	Dioxane	r.t	72	—	—	36
4	—	DCM	r.t	54	—	—	73
5	—	***Toluene***	***10***	***54***	—	—	***88***
6	4Å MS (100)	toluene	10	54	—	—	—
7	—	***Toluene***	***65***	***72***	***67***	***11***	—
8	—	Toluene (0.5 mL)	65	48	52	24	—
9	4Å MS (100)	Toluene	65	48	57	12	—
10	PhOH	Toluene	65	48	23	17	—

[a] The reaction was carried out using **1a** (0.2 mmol), **2a** (3.0 equiv.), cat. (0.04 mmol), in the indicated solvent (1.0 mL) in a Schlenk tube at the indicated temperature. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture by using 4-Bromobenzotrifluoride as the internal standard.

Table 2 Substrate scope for the reaction at 65 °C[a,b]

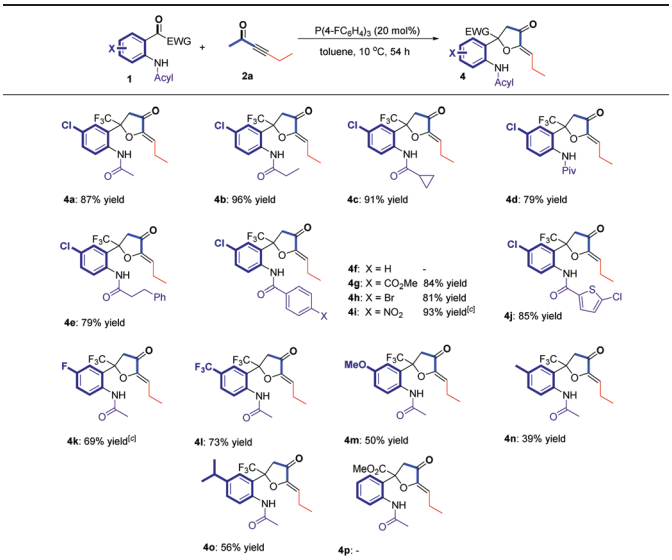


[a] The reaction was carried out using **1** (0.2 mmol), **2a** (0.6 mmol) and P(4-FC_6H_4)$_3$ (0.04 mmol), in toluene (1.0 mL) in a Schlenk tube at 65 °C. [b] Isolated yield. [c] DCM (1 mL) was used as solvent.

range of 2-(2,2,2-trifluoroacetyl)phenylamides **1** with different substituents (Table 2). First, we tested 2-(2,2,2-trifluoroacetyl) phenylamides **1** with different *N*-acyl groups. It was found that acetyl, propionyl, cyclopropanecarbonyl, pivaloyl and 3-phenylpropanoyl substituted 2-(2,2,2-trifluoroacetyl)phenylamides all afforded the desired β,δ-cycloaddition products **3a–3e** in 46–79% yields. We isolated diene product **5d** in 17% yield, which indicated that increasing the steric hindrance of the amide group would impede the cycloaddition process. Using the benzoyl substituted 2-(2,2,2-trifluoroacetyl)phenylamide **1f** as the substrate also gave the corresponding product **3f** in 81% yield. Changing the substituents (CO_2Me, Br, NO_2) on the benzene ring afforded the corresponding products **3g–3i** in yields ranging from 45% to 76%, but the NO_2 substituted product **3i** was a mixture of *cis*- and *trans*-isomers ($Z:E$ = 1 : 1). Substrate **1j** bearing the 5-chlorothiophene-2-carbonyl group was also tolerated, affording the corresponding product **3j** in 66% yield. Next, the substituents on the aniline ring were examined with substrates **1k–1o**. Substrates **1k** and **1l**, containing electron-withdrawing group (F, CF_3), afforded the corresponding products in higher yields (85% yield and 87% yield) than those of substrates **1m–1o**, containing electron-donating groups such as OMe, Me and i-Pr (67% yield to 47% yield). These results indicate that an electron-withdrawing group on the aniline ring probably facilitates the addition of zwitterionic intermediate **D′** to the substrate **1**. However, using substrate **1p** having a CO_2Me moiety instead of the CF_3 moiety failed to give the desired product **3p**; probably, **1p** was unstable at high temperature and the reaction only give a complex mixture.

Subsequently, we examined the phosphine-catalyzed cycloadditions of substrates **1a–1p** at 10 °C. As shown in Table 3, changing the acyl group on the aniline with propionyl and cyclopropanecarbonyl groups could improve the product yields, giving the desired products **4b** in 96% yield and **4c** in 91% yield, respectively. Increasing the steric hindrance of the

Table 3 Substrate scope for the reaction at 10 °C[a,b]



[a] The reaction was carried out using **1a** (0.2 mmol), **4** (0.6 mmol), P(4-FC_6H_4)$_3$ (0.04 mmol) in toluene (1 mL) in a Schlenk tube at 10 °C. [b] Isolated yield. [c] DCM (1 mL) was used as solvent.

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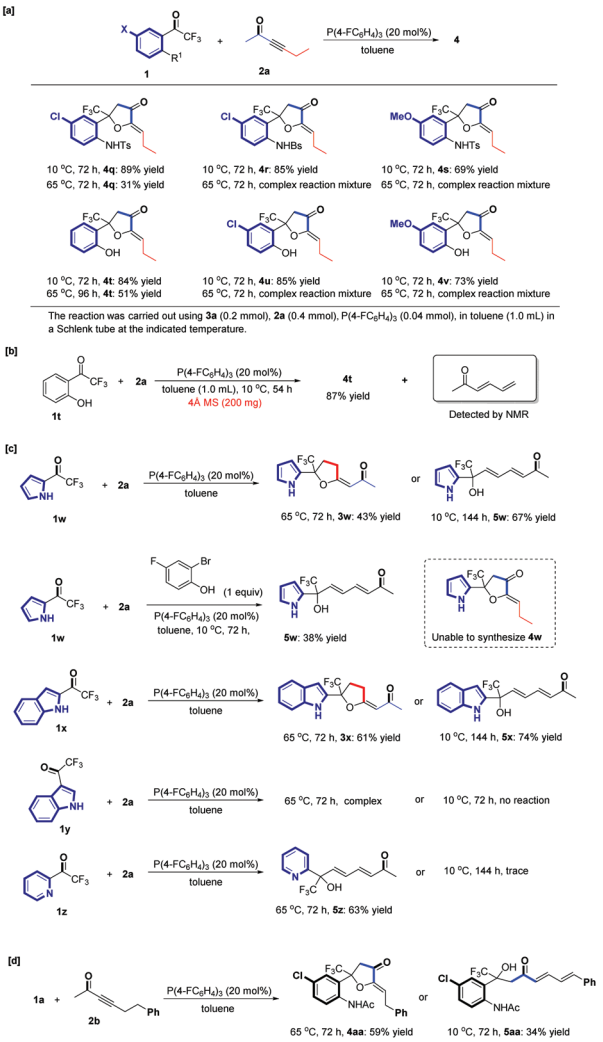
carbonyl group or extending the carbon chain of the *N*-protecting group gave the desired products **4d** and **4e** in moderate yields. Unlike the reactions carried out at high temperature, the replacement of the aliphatic carbonyl group with a benzoyl group on substrate **1** did not give the corresponding product **4f**; however, introducing substituents such as CO_2Me, Br, or NO_2 on the benzoyl group could afford the corresponding products **4g–4i** in good to excellent yields ranging from 81% to 93%, presumably due to the influence of the electronic properties of the benzoyl group. Substrate **1j** bearing the 5-chlorothiophene-2-carbonyl group afforded the corresponding product **4j** in 85% yield. Furthermore, the substituents on the aniline ring were also examined at 10 °C. Substrates **1k** and **1l**, containing an electron-withdrawing group, such as F and CF_3, gave the corresponding products **4k** and **4l** in moderate yields (69% yield and 73% yield); and substrates containing electron-donating groups, such as OMe, Me or i-Pr, impeded the reaction proceeding, producing the desired products **4m–4o** in low yields. Similarly, using substrate **1p** having a CO_2Me moiety instead of a CF_3 moiety could not give the desired product **4p**; most of **1p** was recovered, indicating the low reactivity of a substrate having an ester substituted carbonyl group.

The examination of substrate scope indicated that the amide group at the *ortho* position of the trifluoroacetyl group played a decisive role to affect the product selectivity. We hypothesized that varying the acidity of the NHAcyl moiety of substrate **1** probably affected the product regioselectivity. Thus, we synthesized a series of substrates **1q–1s** containing different *N*-sulfonyl groups, which are more acidic than those substrates containing the *N*-acyl group,[26] which were tested in these phosphine-catalyzed cycloaddition reactions. In addition, substrates **1t–1v** containing the phenolic hydroxyl group were also investigated. We found that the α′,α-cycloaddition product **4q** was the only isolated product in 89% yield at 10 °C or in 31% yield at 65 °C. Products **4r** and **4s** were obtained at 10 °C in 85% yield and 69% yield, respectively. Similarly, **4t** was the only isolated product at 10 °C in 84% yield or at 65 °C in 51% yield, as in a preliminary exploration in our previous work.[16] Products **4u** and **4v** were obtained at 10 °C in 85% yield and 73% yield, respectively. When the amide group was replaced by *N*-sulfonyl groups or the hydroxyl group, the obtained products could not be switched to β,δ-cycloaddition products **3** by increasing the reaction temperature and only complex reaction mixtures were obtained at 65 °C (Scheme 3a).

It was interesting that the reaction of **1t** containing an OH moiety with **2a** proceeded smoothly under the standard reaction conditions with a 4 Å molecular sieve to remove water, affording the α′,α-cycloaddition product **4t** at 10 °C, which is contrary to earlier results that a trace of water is an indispensable co-catalyst for the reaction of **1a** having an NHAc moiety (Scheme 3b); the preliminary calculation results show that the abstraction of α′-H is more favored over the abstraction of γ-H, which leads to the α′,α-cycloaddition product and may account for the experimental observation (for details, see ESI†). In addition, (*E*)-hexa-3,5-dien-2-one was detected as a byproduct simultaneously (Scheme 3b). These observations showed that varying the acidity of the NHAcyl moiety indeed affected the product regioselectivity, exclusively giving the corresponding α′,α-cycloaddition product without the assistance of water. Reducing the pK_a of substrate **1** *via* varying the NHAcyl moiety probably makes the α′,α-H shift process more favorable, leading to an α′,α-cycloaddition product without the assistance of water. On the other hand, substrates having a pyrrole or indole moiety, which are less acidic than those substrates containing an *N*-acyl group, were also tested. The β,δ-cycloaddition products **3w** and **3x** were obtained at 65 °C in 43% yield and 61% yield, respectively. When the reaction was carried out at 10 °C, only the δ-addition products **5w** and **5x** were isolated in 67% yield and 74% yield, respectively. The addition of 2-bromo-4-fluorophenol as an additive could not switch the product's regioselectivity, only generating the δ-addition products **5w** in a 38% yield (Scheme 3c). Upon moving the trifluoroacetyl group from the C2 position of indole to the C3 position, the reaction only gave a complex mixture at 65 °C.



Scheme 3 Substrate containing substituents with different acidities.

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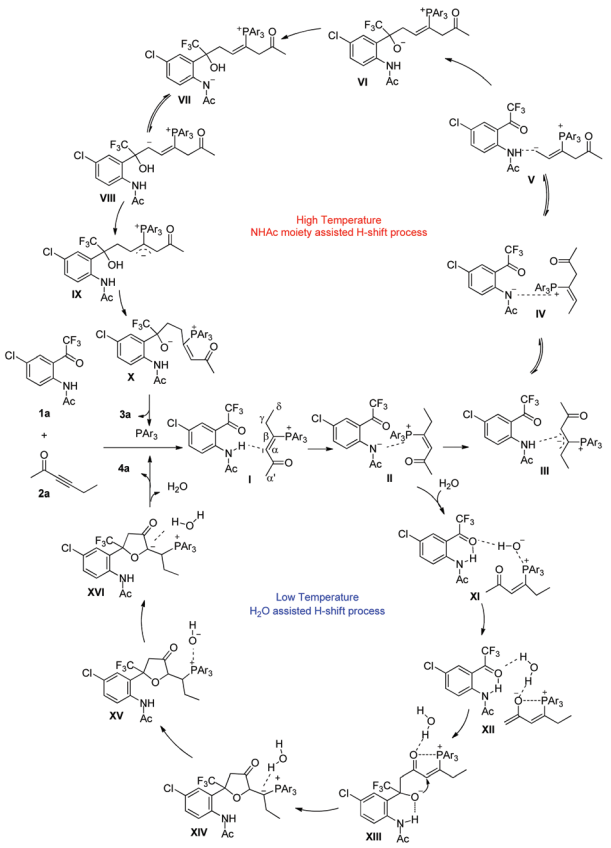
Substrate **1z** without the *N*-acyl group could not afford the cycloaddition product at 10 °C or at 65 °C, and only the δ addition product **5z** was detected in 63% yield, as in our previous report. When 6-phenylhex-3-yn-2-one **2b** was replaced to hex-3-yn-2-one **2a**, steric hindrance probably influenced the reaction pathway, leading to the α′,α-cycloaddition product **4aa**, obtained at 65 °C in 59% yield, and the α′ addition product **5aa** accessed at 10 °C in 34% yield (Scheme 3d). A phenyl group substituted in the δ position prevented the δ addition occurring and benefited the addition at the α′ position.

Mechanistic studies

Proposed reaction pathways. We proposed the following mechanism depicted in Scheme 4 to account for the reaction outcomes. The reaction starts with the addition of tertiary phosphine to the alkynone **2a** to afford a zwitterionic intermediate which is associated with substrate **1a** to form complex **I**. Probably due to the acidity of the NHAc moiety in substrate **1a**, the proton is transferred to the carbanion to form a contact ion pair **II**. Subsequently, the nitrogen anion moiety in **II** abstracts one γ-H to give intermediate **III**. Then, the proton is transferred to the carbanion to generate another contact ion pair **IV**. Again, the nitrogen anion moiety abstracts δ-H to furnish an intermediate **V**, which undergoes an addition to generate an intermediate **VI**. Probably due to the basicity of the alkoxide anion moiety, it first abstracts the hydrogen from the NH moiety in **VI**, giving an intermediate **VII**. Subsequently, the nitrogen anion moiety of intermediate **VII** abstracts δ-H to furnish intermediate **VIII**, which undergoes another proton transfer process to give intermediate **X**. Finally, intermediate **X** undergoes cyclization to afford the β,δ-cycloaddition product **3** and releases the tertiary phosphine.

If the protic additive H_2O is added to the reaction system, the nitrogen anion moiety in **II** probably first abstracts proton from H_2O to give intermediate **XI**. Subsequently, the OH moiety in **XI** abstracts one α′-H to give a stable complex **XII** through hydrogen-bonding interaction. A subsequent addition takes place to give intermediate **XIII**, which undergoes cyclization to form intermediate **XIV**. With the assistance of water, 1,2-H shift processes proceed *via* intermediate **XV** to afford **XVI**, which is similar to Yu's studies on Lu's [3 + 2] cycloaddition reaction.[27] Elimination of water and the tertiary phosphine generates the α′,α-cycloaddition product **4**. Our proposed mechanism involves a series of H-shift processes, and thus deuterium-labeling experiments have been undertaken to understand and give evidences to the suggested reaction mechanism. DFT calculations were also carried out to rationalize the regioselectivity affected by the substrates, the additives and the reaction temperatures, and to understand the detailed reaction mechanism.



Scheme 4 A plausible reaction mechanism.

Deuterium-labeling experimental investigations

For the optimal conditions, trace water in the solvent was an indispensable co-catalyst to afford α′,α-cycloaddition products at 10 °C; in contrast, water was no longer necessary during the β,δ-cycloaddition process (Table 1). To gain some insights into the reaction mechanism, several deuterium-labeling experiments were performed at different temperatures. The reaction of **1a** with **2a** was first carried out in the presence of D_2O (20 equiv.) at 65 °C under the standard reaction conditions. The reaction proceeded smoothly to give the corresponding partially deuterated addition product [D]-**3a** in 58% yield along with the deuterium incorporation at the C1–C6 positions (Scheme 5a). The addition of D_2O did not improve the product yield significantly, indicating that water did not play a significant role in the reaction at high temperature; however, the reaction involving several H-shift processes led to the deuterium incorporation at D^1–D^6 positions. Under the standard reaction conditions with the addition of a 4 Å molecular sieve, using 80% N–H deuterated [D]-**1a** as the substrate produced the corresponding deuterated product [D]-**3a′** in 61% yield with 18% and 20% D contents incorporated at the D^1 and D^5 positions, respectively (Scheme 5b). The deuterium incorporated at the D^5 position was probably due to the deuterium being transferred from the NDAc moiety to the β-carbon, as in the suggested process from **I** to **II** shown in Scheme 4. The deuterium incorporated at the D^1 position was in a *syn* position with respect to the CF_3 substituent. This unexpected and stereospecific deuterium incorporation revealed that intramolecular proton exchange processes probably existed, as illustrated in Scheme 5c. The oxygen anion moiety of intermediate

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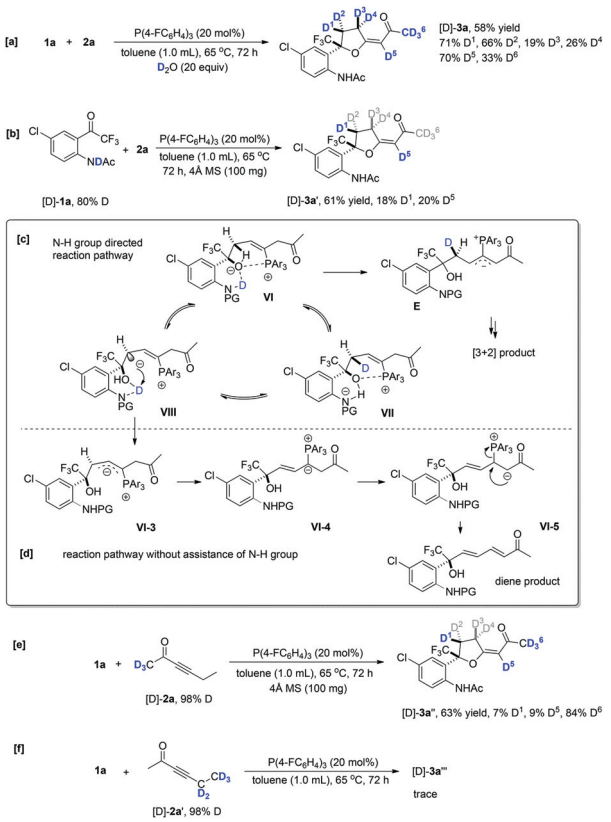
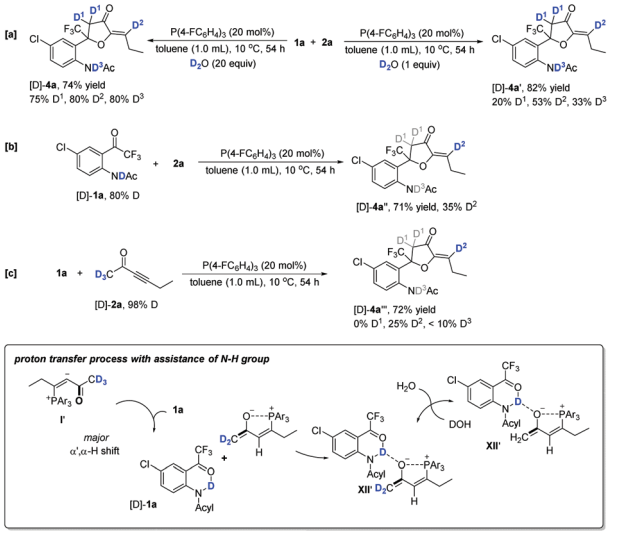


Scheme 5 Deuterium-labeling experiment at 65 °C and result discussion.

VI can abstract the proton in the D^1 position to afford intermediate **VIII**, and then the deuterium of N–D is transferred to C1, generating intermediate **VII**; the nitrogen anion moiety can abstract the proton of the hydroxy group to give intermediate **VI** again (Scheme 5c). During the proton exchange cycle, the electrostatic interaction between phosphonium and the oxygen anion maintained the configuration, leading to stereospecific deuterium incorporation. Moreover, the acetyl group made the proton exchange reversible and stabilized the oxygen anion, which benefited the next cycloaddition step. Without the assistance of the acetyl group, zwitterion **VI-3** probably prefers to undergo isomerization to give another intermediate **VI-4**, which subsequently produces zwitterion **VI-5** through a classic proton transfer, finally affording the diene product **3′** (Scheme 5d). Using deuterated hex-3-yn-2-one [D]-**2a** with a 98% D content as the substrate produced the corresponding deuterated product [D]-**3a″** in 63% yield, along with very low deuterium content at the D^1 and D^5 positions, suggesting that the hydrogen atoms at the α′ position of **2a** did not involve several proton transfer processes in the reaction at 65 °C (Scheme 5e). Using deuterated hex-3-yn-2-one [D]-**2a′** with a 98% D content as the substrate, the reaction did not take place efficiently, and only gave trace amounts of the desired product (Scheme 5f).

Next, the reaction of **1a** with **2a** was investigated in the presence of D_2O (20 equiv.) at 10 °C under the standard reaction conditions, giving the corresponding partially deuterated addition product [D]-**4a** in 74% yield along with the deuterium incorporation only at the D^1–D^3 positions (Scheme 6a). The use of 1.0 equiv. of D_2O significantly decreased the deuterium incorporation ratio at the D^1–D^3 positions (Scheme 6a). This result suggested that water assisted the proton transfer processes shown in Scheme 4 and the hydrogen atoms at the γ-position and δ-position of **2a** did not involve the proton transfer processes. Under the standard reaction conditions, using 80% N–H deuterated [D]-**1a** as the substrate produced the corresponding deuterated product [D]-**4a″** in 71% yield, in which the deuterium was only transferred from the N atom to the D^2 position with a 35% D content (Scheme 6b). As proposed in Scheme 4, the deuterium is transferred from the NDAc moiety to the β-carbon and then, through a water-assisted 1,2-H shift, arrives at the D^2 position; the deuterium content is lost, probably due to the water involved in these proton transfer processes. Under the standard reaction conditions, using deuterated hex-3-yn-2-one [D]-**2a** with a 98% D content as the substrate produced the corresponding deuterated product [D]-**4a‴** in 72% yield, in which the deuterium incorporation at C1 totally decreased, probably due to the exchange of H_2O with the zwitterionic intermediates in solvent (Scheme 6c).

As aforementioned, the reaction of **1t** containing an OH moiety with **2a** conducted smoothly without a trace of water. Thus, the deuterium-labeling experiments of **1t** with **2a** were also carried out in the absence of water. Under the standard reaction conditions, using deuterated hex-3-yn-2-one [D]-**2a** (2.0 equiv.) with a 98% D content as the substrate produced the corresponding deuterated product [D]-**4t** in 89% yield, in which the deuterium incorporation at D^1 was totally lost (Scheme 7a). However, reducing the amount of [D]-**2a** to 1.0 equiv. provided [D]-**4t′** in 78% yield with a 30% D content at



Scheme 6 Deuterium-labeling experiment at 10 °C and result discussion.

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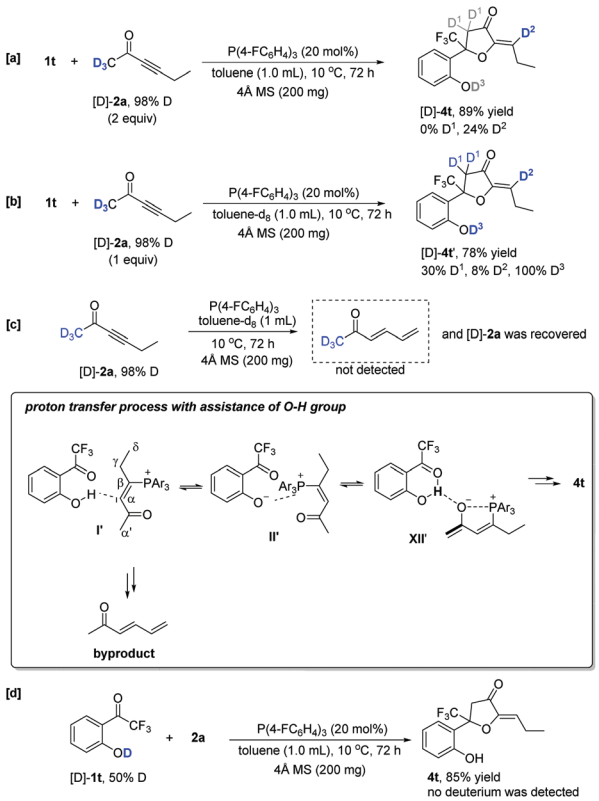

Scheme 7 Deuterium-labeling experiment using **1t** at 10 °C and result discussion.

D^1 (Scheme 7b). Considering the obtained byproduct (*E*)-hexa-3,5-dien-2-one, shown in Scheme 3b, we deduced that the deuterium at D^1 probably exchanged with the hydrogen atoms in other zwitterionic intermediates if the concentration of **2a** was high. Without substrate **1t**, the [D]-**2a** itself could not afford the (*E*)-hexa-3,5-dien-2-one under the standard conditions, indicating that the substrate **1t** assisted the generation of (*E*)-hexa-3,5-dien-2-one (Scheme 7c). Based on crude ^{31}P NMR spectrum analysis (see ESI† for the details) and the proposed mechanism, we considered that the OH group of substrate **1t** also assists the α′,α-H shift process *via* intermediates **II′** and **XII′** to afford product **4t**; however, these steps, involving proton transfer processes, are reversible, which allows intermediate **I′** to be converted into byproduct (*E*)-hexa-3,5-dien-2-one. Interestingly, using 50% O–H deuterated [D]-**1t** as the substrate, the product was obtained without any deuterium incorporation. The deuterium of the OH group was probably easy to lose under this reaction condition, which failed to transfer to the product (Scheme 7d).

Rationalization of regioselectivity. In order to understand the regioselectivity affected by the reaction temperature, we performed DFT calculations on the suggested reaction pathways shown in Scheme 4. We first investigated the proposed reaction pathway for the PPh_3 catalyzed reaction of **1a** and **2a** to produce **3a**, and the solvation Gibbs free energy profiles in toluene are shown in Scheme 8. As shown in Scheme 8a, the addition of catalyst PPh_3 to alkynone **2a** leads to the formation of zwitterionic intermediate **INT1** *via* the transition state **TS0**, which is endergonic by 24.9 kcal mol^{-1}. The intermediate **INT1** associates with substrate **1a** to generate complex **INT2**. The proton transferred from the NHAc moiety to the α-carbon to generate a contact ion pair **INT3** *via* **TS1**, which is located 4.3 kcal mol^{-1} above intermediate **INT2**; converting **INT2** into **INT3** is exergonic by 4.9 kcal mol^{-1}, indicating this step is thermodynamically favorable. This result agrees with the finding in the deuterium-labeling experiments in which the deuterium incorporation can be found at the D^5 position using 80% N–H deuterated [D]-**1a** as the substrate (see Scheme 5b). Subsequently, the nitrogen anion in **INT3** can either abstract γ-H to give intermediate **INT4** or abstract α′-H to give intermediate **INT4-1**. The calculation results show that intermediate **INT4** is more stable than intermediate **INT4-1** by 6.3 kcal mol^{-1}, and the corresponding transition state **TS2** is more stable than the transition state **TS2-1** by 2.2 kcal mol^{-1}. Thus, the abstraction of γ-H is more favorable, indicating that the NH-assisted γ,α-H shift is preferred without any additive. For comparison, we also investigated the intramolecular γ,α-H shift and α′,α-H shift processes, since they were frequently proposed in previous literature;[1d,10b,14a,15f,27b] however, they have not been proven experimentally or theoretically. Our calculations show that these intramolecular proton transfer processes have extremely high energy barriers, and thus we rule out these pathways (for details, see ESI†). As shown in Scheme 8b, the proton of the NHAc moiety is transferred again *via* transition state **TS3** to give another contact ion pair **INT5**, which undergoes another proton transfer *via* transition state **TS4** to form complex **INT6**. Passing through transition state **TS5** with an activation free energy of 2.6 kcal mol^{-1}, **INT6** undergoes addition to furnish the intermediate **INT7**, which is exergonic by 17.2 kcal mol^{-1}. Due to the basicity of the alkoxide anion moiety in **INT7**, it abstracts the hydrogen atom of the NHAc moiety *via* transition state **TS6** with a small energy barrier to generate intermediate **INT8**. Passing through transition state **TS7** with an activation free energy of 33.2 kcal mol^{-1}, the nitrogen anion moiety of intermediate **INT8** abstracts δ-H to furnish intermediate **INT9**. Subsequently, an intramolecular 1,4-H shift takes place *via* transition state **TS8** with an activation free energy of 31.0 kcal mol^{-1}, giving rise to intermediate **INT10**. This 1,4-H shift may explain why the deuterium incorporation can be found at the D^1 position the in deuterium-labeling experiment results (see Scheme 5b) and provides theoretical evidence for the proposed process shown in Scheme 5c. Next, intermediate **INT10** undergoes another proton transfer *via* transition state **TS9** to afford **INT11**. The cyclization occurs *via* transition state **TS10** gives the product complex **INT12**. Cleavage of this complex to yield the separate components **3a** and PPh_3 is exothermic by 10.0 kcal mol^{-1}. The calculation results show that several proton transfer processes are involved in this reaction, which may account for why the addition of D_2O leads to deuterium incorporation at the D^1–D^6 positions (see Scheme 5a). For some proton transfer processes, the activation free energies are 30 kcal mol^{-1} or so,

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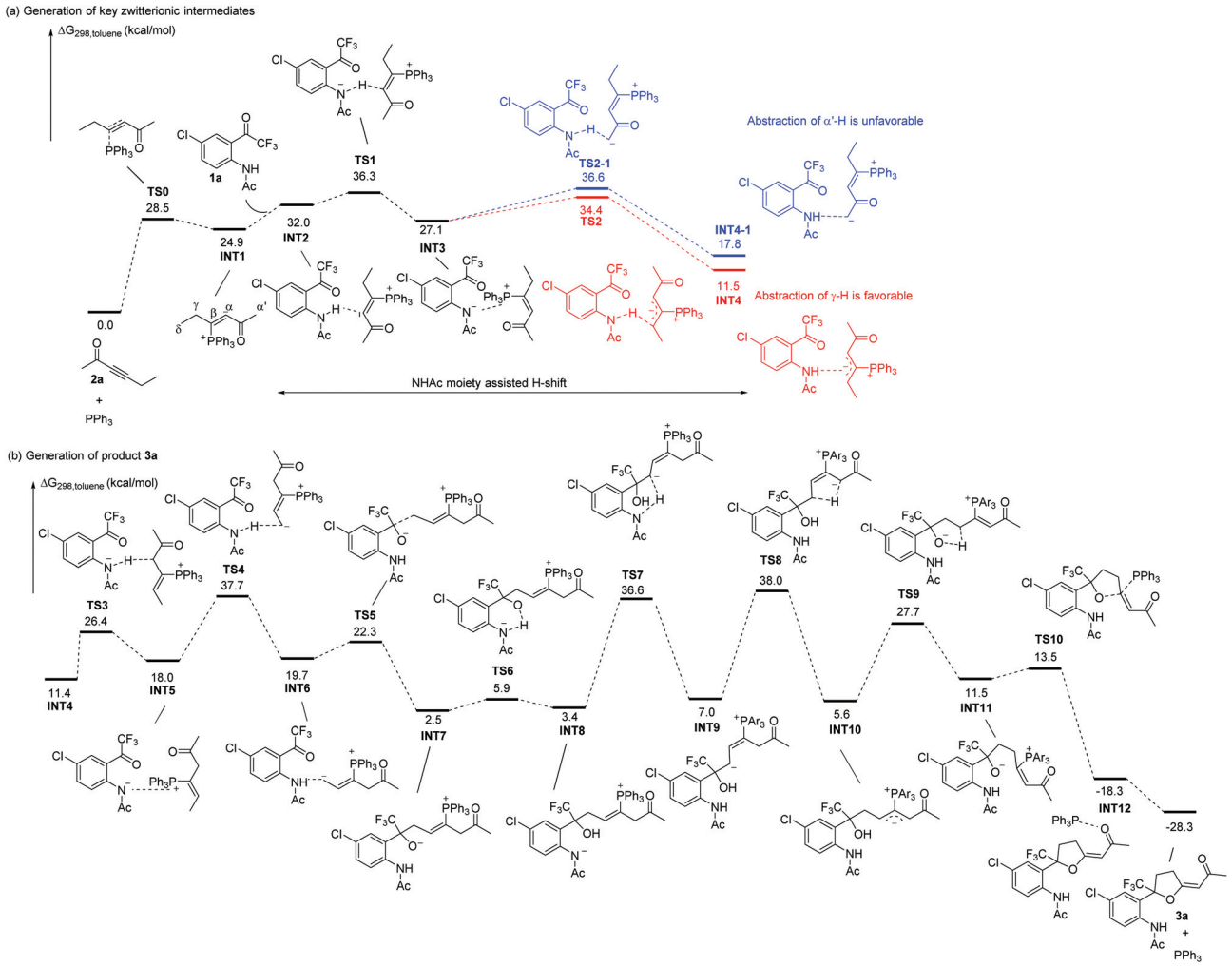

Scheme 8 Solvation Gibbs free energy profiles for the generation of key zwitterionic intermediates and the formation of product **3a**.

and therefore the reaction is difficult to proceed at 10 °C, so a high reaction temperature is necessary.

We next investigated the suggested reaction pathway for the PPh_3 catalyzed reaction of **1a** and **2a** to produce **4a**, and the solvation Gibbs free energy profiles in toluene are shown in Scheme 9. Since a trace amount of H_2O was necessary for the reaction at 10 °C, we speculated that the H_2O plays a role in assisting the H-shift processes. A similar H_2O assisted [1,2] proton shift process in Lu's [3 + 2] cycloaddition reaction has been investigated theoretically by Yu's group.[27a] In this case, a contact ion pair **INT3** is also generated at the initial stage; however, the nitrogen anion in **INT3** does not directly abstract γ-H or abstract α′-H in the presence of water. The addition of H_2O leads to the formation of a stable complex **INT13**. Subsequently, the nitrogen anion moiety in **INT13** abstracts a proton from H_2O to give complex **INT14** *via* transition state **TS11**, which only requires 3.3 kcal mol^{-1}. The hydroxyl anion in **INT14** is highly attracted by the PPh_3 moiety, which can abstract α′-H to give complex **INT15** or γ-H abstract to give complex **INT15-1**. In this case, the abstraction of α′-H by the hydroxyl anion with an activation free energy of 17.3 kcal mol^{-1} *via* transition state **TS12** gives complex **INT15**; however, it requires 28.0 kcal mol^{-1} to overcome transition state **TS12-1** to form complex **INT15-1**. Thus, the abstraction of α′-H is more favorable, indicating that the H_2O assisted α′,α-H shift process is preferred in the presence of water, which is probably due to the stronger basicity of the hydroxyl anion than the nitrogen anion. In addition, complex **INT15** is probably stabilized by hydrogen bonding between water, substrate **1a** and the zwitterion, which probably makes the following addition step proceed easily. Passing through transition state **TS13** with an activation free energy of 9.1 kcal mol^{-1}, **INT15** is converted into **INT16**, which is exergonic by 10.7 kcal mol^{-1}. Undergoing cyclization, the intermediate **INT17** is generated *via* transition state **TS14** with an energy barrier of 6.7 kcal mol^{-1}. The [1,2] proton transfer from **INT17** to **INT19** also requires water's assistance; the energy barrier without water's assistance is 47.6 kcal mol^{-1} (for the whole reaction pathway without water, see ESI†). The proton transfer from water to the carbon atom connected with the phosphorus atom *via* transition state **TS15**

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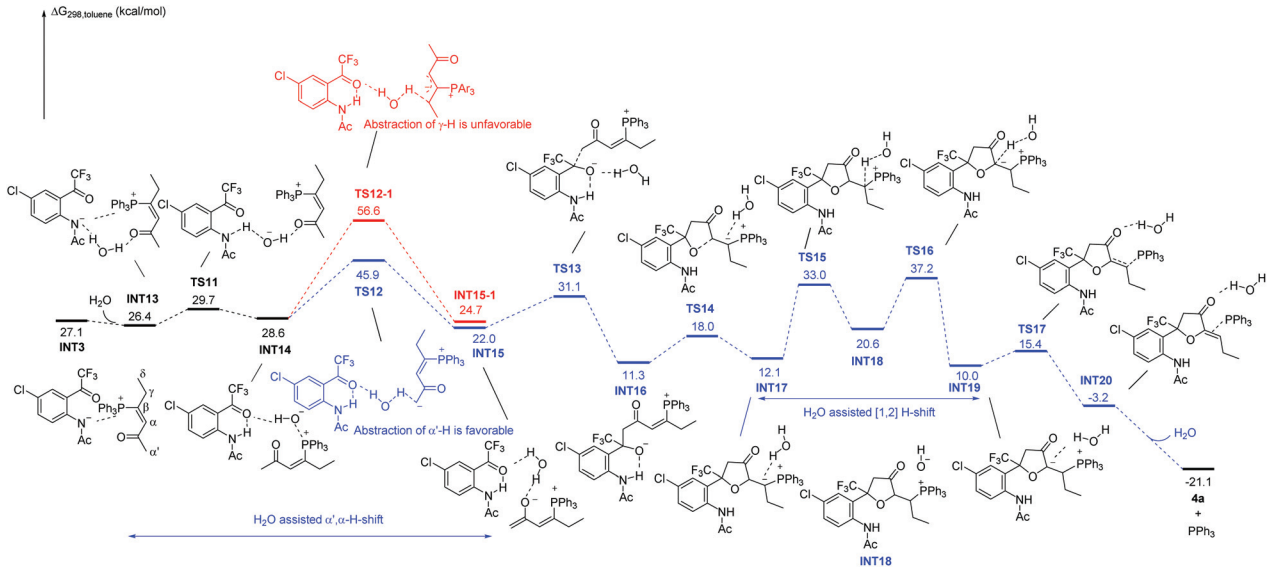

Scheme 9 Solvation Gibbs free energy profiles for the generation of key zwitterionic intermediates and the formation of product **4a**.

requires an activation free energy of 20.9 kcal mol^{-1}, generating intermediate **INT18**. Similarly, the abstraction of a proton by the hydroxyl anion with an activation free energy of 16.6 kcal mol^{-1} *via* transition state **TS16** gives rise to another complex, **INT19**. Passing through transition state **TS17**, the elimination of PPh_3 produces the product complex **INT20**. Cleavage of complex **INT20** to yield the separate components **4a**, H_2O and PPh_3 is exothermic by 17.9 kcal mol^{-1}. In this case, the highest activation free energy is only 20 kcal mol^{-1} or so, and the reaction can proceed at low reaction temperature. Our calculation results agree with the results in deuterium-labeling experiments, which found deuterium incorporation ratios at D^1–D^3 position (see Scheme 6a). However, the thermodynamically controlled β,δ-cycloaddition product is still preferred at higher temperatures under the water-assisted pathway. Thus, with or without water-assistance, the β,δ-cycloaddition product is always obtained at a higher temperature, which agrees with the experimental results.

Conclusions

We have disclosed the regiodivergent phosphine-catalyzed [3 + 2] cycloaddition of 2-(2,2,2-trifluoroacetyl)phenylamides and alkynones, affording a series of β,δ-cycloaddition products **3** or α′,α-cycloaddition products **4** in moderate to good yields. The experimental results demonstrated that product regioselectivity could be switched through adjusting the acidities of substrates *via* varying the NHAcyl moiety in substrate **1**, changing the reaction temperature and the addition of the protic additive H_2O. Based on deuterium labeling experiments and systematic theoretical studies, we have disclosed a detailed reaction mechanism for the phosphine-catalyzed cycloaddition reactions of alkynones with trifluoroacetyl phenylamides. The calculation results ruled out the intramolecular proton transfer processes frequently proposed in previous reports; our theoretical studies also provide reasonable explanations for why the regioselectivities of products can be controlled by the protic additive H_2O and the reaction temperature. In the absence of water, the NHAc moiety of substrate **1** plays an important role in assisting the proton transfer process, leading to the key zwitterionic intermediate which directly forms the β,δ-cycloaddition products **3**; the high reaction temperature is required to overcome the high activation energy barriers for some proton transfer processes. For the addition of protic additive H_2O, the important proton transfer processes are assisted by H_2O, affording the key zwitterionic intermediate which directly generates α′,α-cycloaddition products **4**; in this case, the high reaction temperature is not necessary. Further applications of the phosphine-catalyzed cycloaddition reactions are underway in our lab.

Computational methods

All DFT calculations were performed with the Gaussian 09 program.[28] The geometries of all the minima and transition states have been optimized at the M06-2X/6-31G(d) level of theory.[29] The subsequent frequency calculations on the stationary points were carried out at the same level of theory to ascertain the nature of the stationary points as minima or first-order saddle points on the respective potential energy surfaces. All the transition states were characterized by one and only one imaginary frequency pertaining to the desired reaction coordinate. The intrinsic reaction coordinate (IRC) calculations were carried out at the same level of theory to further authenticate the transition states. The conformational space of the flexible systems was first searched manually. Thermochemical corrections to 298.15 K were calculated for all minima from unscaled vibrational frequencies obtained at this

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same level. The solvent effect was estimated by the IEFPCM method with radii and nonelectrostatic terms for the SMD solvation model[30] in toluene (ε = 2.3741). Solution-phase single point energy calculations were performed at the M06-2X/6-311+G(d,p) level based on the gas phase optimized structures.

Conflicts of interest

There are no conflicts of interest to declare.

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