Enantioselective Synthesis of Chiral Amides by Phosphoric Acid-Catalyzed Asymmetric Wolff Rearrangement

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SUMMARY: The enantioselective addition of potent nucleophilic reagents to ketene compounds poses challenges due to the presence of significant background reactions, along with simultaneous stereoselectivity and enantioselectivity issues in the reaction process. We present a method for enantioselective amination of ketenes employing α-aryl-α-diazoketones as ketene precursors and phosphoric acids as catalysts. Upon exposure to visible light, diazoketones undergo Wolff rearrangement to gradually generate ketenes. Subsequently, the phosphoric acid not only accelerates capture of ketenes by amines, forming a singular configuration of aminoenol intermediates, but also promotes the enantioselective proton transfer of the intermediates to yield product. Mechanism studies elucidate the reaction pathways and explain how the catalysts expedite this transformation and control enantioselectivity.

INTRODUCTION

Wolff rearrangement, involving a conversion of α-diazoketones to ketenes, offers a practical approach for synthesizing carboxylic acid derivatives when conducted in the presence of nucleophiles such as water, alcohols, or amines. Chiral amides are ubiquitously found in natural products and pharmaceutical molecules (Figure 1), underlining the significance of developing innovative methods for achieving catalytic asymmetric transformation of α-diazoketones with amines to produce chiral amides. Advancements in this area could contribute to the discovery of novel bioactive compounds or drug candidates with enhanced properties, thereby benefiting both scientific research and practical applications.

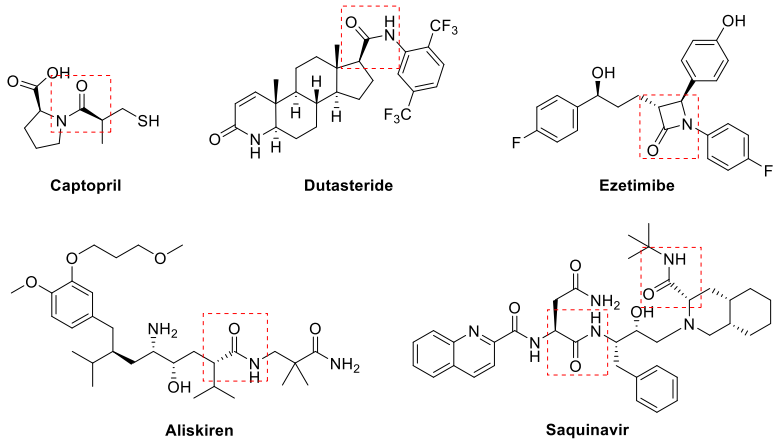


Figure 1. Bioactive compounds containing chiral amide moiety.

Ketenes are a highly electrophilic species and their direct asymmetric addition reactions with nucleophiles have been extensively studied[1,2,3,4,5,6,7,8,9]. However, the successful examples mainly

focus on oxygen-based nucleophilic reagents. For nitrogen-based nucleophilic reagents, only two examples of weak nucleophiles, 2-cyanopyrrole and hydrazoic acid, have been reported (Figure 2)[10,11,12]. No other amines have been applied to the asymmetric addition to ketenes, possibly due to their strong nucleophilic property. Recently, as a part of our study of the N−H bond insertion reactions[13,14,15,16], we investigated the reaction of α-diazoketones with amines. When we irradiated the mixture of α-diazoketone and aniline in the presence of chiral phosphoric acid we were surprise to obtain enantioenriched chiral amide, the Wolff rearrangement product. Here, we report our detailed investigations on the asymmetric Wolff rearrangement catalyzed by phosphoric acids. The reaction provides a highly efficient method for the synthesis of chiral amides.

In the synthesis of chiral amides via asymmetric Wolff rearrangement, employing α-diazoketone as a precursor for in situ generating ketene is crucial. This approach can decrease the addition rate of strong nucleophilic reagents like amine, thus providing favorable conditions for enantiocontrol[17]. During the reaction, α-diazoketone released nitrogen and is rearranged under irradiation to ketene, which is rapidly captured by the amine to form an amide through an aminoenol intermediate. However, the aminoenol intermediate has two configurations, *Z* and *E*. In order to achieve asymmetric Wolff rearrangement, the chiral catalyst must be able to regulate the *Z*/*E* configuration of the aminoenol intermediate and control the enantioselectivity of the next proton transfer step, which is obviously a big challenge. After comparing various chiral proton transfer catalysts, we are delighted to find that chiral spiro phosphoric acids[18] are efficient catalysts for this reaction (Figure 2).

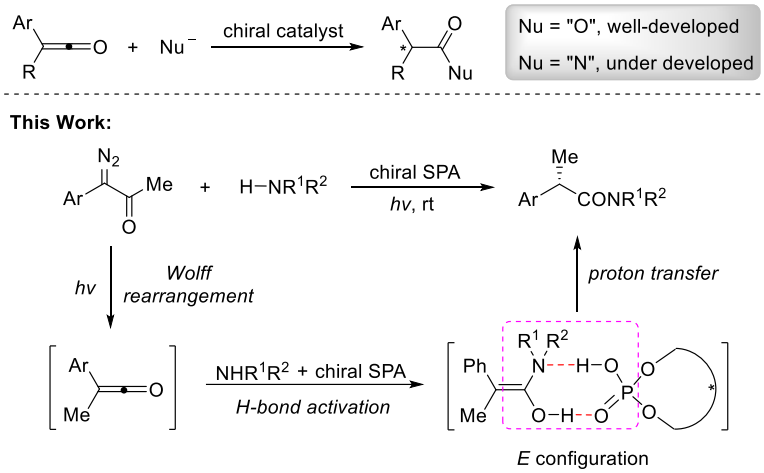


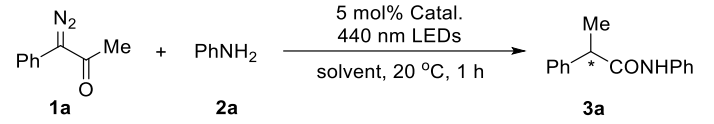
Figure 2. Synthesis of chiral amides by asymmetric Wolff rearrangement.

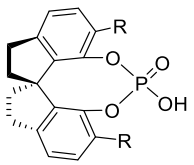
RESULTS AND DISCUSSION

Initially, we evaluated the reaction conditions by using diazoketone **1a** and aniline **2a** as standard substrates (Table 1). Stirring at 20 °C in dichloromethane (DCM) under 440 nm light irradiation for one hour led to complete conversion of **1a**, affording the amide product **3a** in 88% yield. We screened a variety of chiral proton transfer catalysts[14,15,16,18, 19] (see Supporting Information for details) and found that spiro phosphoric acid catalyst **C1** afforded chiral amide **3a** in 90% yield with 24% ee (entry 1). Subsequently, we investigated spiro phosphoric acid catalysts bearing different substituents, revealing that increasing steric hindrance on the rigid spirocyclic framework enhanced the enantioselectivity of the reaction (entries 2–8). The catalyst **C8** having bulky 2,4,6-tri(cyclohexyl)phenyls provided 75% ee of enantioselectivity (entry 8). Phosphoric acid

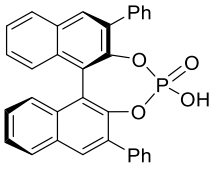
catalyst **C9** derived from the BINOL skeleton exhibited very low enantioselectivity (entry 9). Solvent screening identified toluene as optimal (entries 10–12), and increasing the solvent volume further improved the enantioselectivity of the reaction, yielding the amide product in 94% yield with 91% ee (entry 13). Reducing catalyst loading from 5 mol% to 2 mol% slightly decreased the enantioselectivity of reaction (entry 14). Detailed studies showed that irradiation wavelength and reaction temperature have no significant impact on the reaction (see Supporting Information, Table S1 to S6). Considering all factors, we chose entry 13 as the optimal reaction condition.

Table 1. Optimization of Reaction Conditions for Wolff Rearrangement[a]





(*R*)-**C1**, R = Ph
(*R*)-**C2**, R = 3,5-$(Me)_2C_6H_3$
(*R*)-**C3**, R = 3,5-$(Ph)_2C_6H_3$
(*R*)-**C4**, R = 4-PhC_6H_4
(*R*)-**C5**, R = 2-Nap
(*R*)-**C6**, R = 2,4,6-$(Me)_3C_6H_2$
(*R*)-**C7**, R = 2,4,6-$(^i Pr)_3C_6H_2$
(*R*)-**C8**, R = 2,4,6-$(Cy)_3C_6H_2$



(*R*)-**C9**

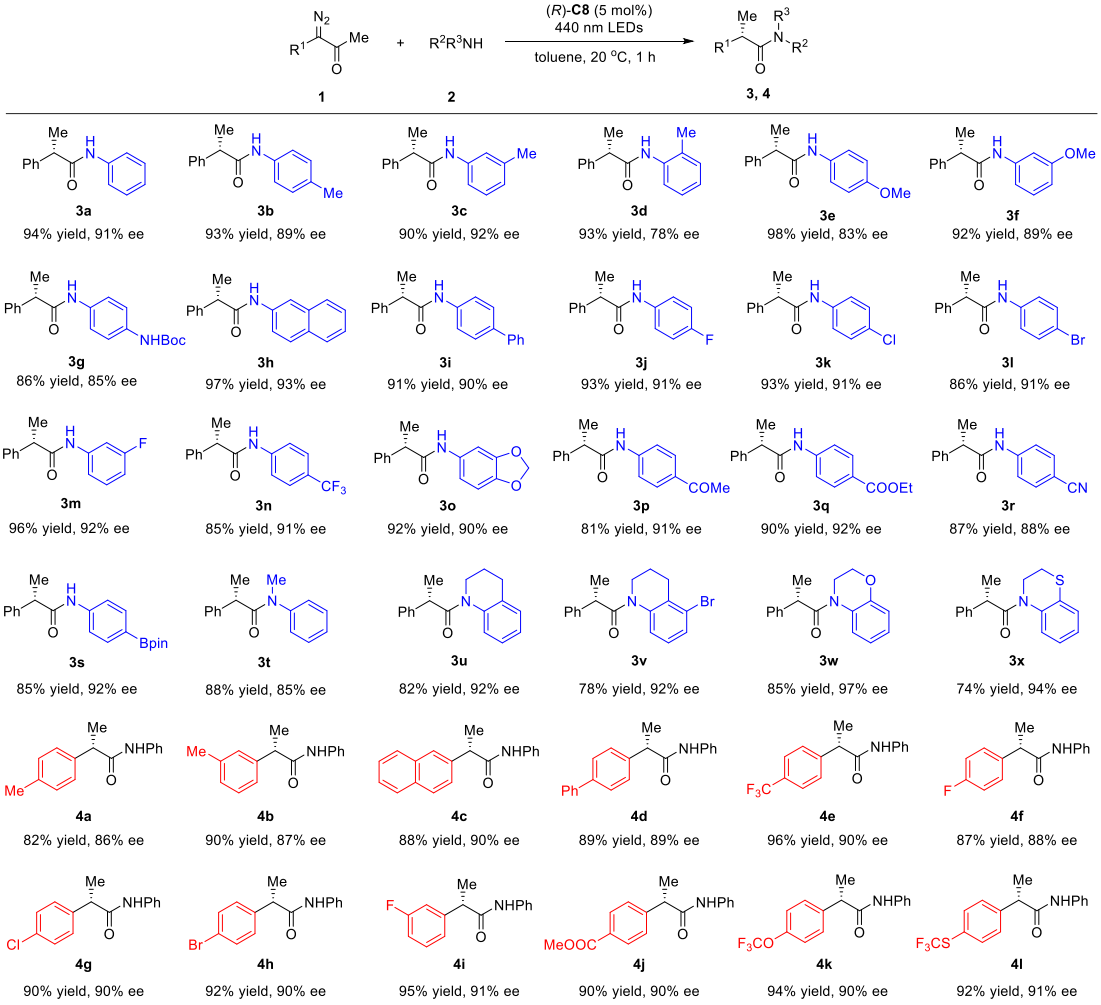
entry	catal.	solv.	yield (%)[b]	ee (%)[c]
1	(*R*)-**C1**	DCM	90	24
2	(*R*)-**C2**	DCM	93	49
3	(*R*)-**C3**	DCM	92	15
4	(*R*)-**C4**	DCM	94	39
5	(*R*)-**C5**	DCM	91	39
6	(*R*)-**C6**	DCM	93	47
7	(*R*)-**C7**	DCM	89	56
8	(*R*)-**C8**	DCM	92	75
9	(*R*)-**C9**	DCM	89	4
10	(*R*)-**C8**	MTBE	83	80
11	(*R*)-**C8**	Toluene	94	89
12	(*R*)-**C8**	CF_3Ph	87	80
13[d]	(*R*)-**C8**	Toluene	94	91
14[e]	(*R*)-**C8**	Toluene	96	88

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), Catal. (5 mol%), solv. (1 mL), 20 °C, 440 nm LEDs, 1 h. [b] Isolated yields were given. [c] The ee values were determined by chiral HPLC. [d] 2 mL toluene was used. [e] 2 mol% (*R*)-**C8** was used.

With the optimized conditions established, we explored the substrate scope of anilines in the reaction with diazoketone **1a** (Scheme 1). The electron-donating groups at the *para* position of the aniline (**3b**, **3e**, **3g**) led to a slight decrease in enantioselectivity (83–89% ee) while maintaining high yields. Electron-donating groups at the *meta* position of the aniline (**3c** and **3f**) has a relatively minor impact on the reaction. 2-Naphthylamine also afforded the desired product **3h** in high yield (97%) with excellent enantioselectivity (93% ee). Notably, 2-methylaniline (**3d**) afforded a lower enantioselectivity (78% ee), which may be attributed to increased steric hindrance. The anilines having electron-withdrawing substituents, such as halogen (**3j**–**3m**), phenyl (**3i**), trifluoromethyl (**3n**), 3,4-(methylenedioxy) (**3o**), ketone (**3p**), ester (**3q**), nitrile (**3r**) and boron ester (**3s**) all gave high enantioselectivity (88–92% ee) and yield (81–96%). It is worth mentioning that the secondary amine substrates such as *N*-methylaniline (**3t**), tetrahydroquinoline (**3u**, **3v**) and benzoxazine (**3w**) and benzothiazine (**3x**) can also undergo the reaction, displaying high enantioselectivities.

We next investigated the scope of α-diazoketones. The results showed that the substituents at the aromatic ring of 1-diazo-1-arylpropan-2-one have little effect on the reaction and chiral amides (**4a**–**4l**) can be obtained with high enantioselectivities (86–91% ee) and yields (82–96%) (Scheme 1).

Scheme 1. Substrate Scope of the Reaction of α-Aryl-α-diazoketones and Amines[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), (*R*)-**C8** (5 mol%), toluene (2 mL), 20 °C, 440 nm LEDs, 1 h. Isolated yields. The ee values were determined by chiral HPLC.

MECHANISTIC STUDIES

To understand the reaction mechanism, we studied the necessity of employing α-diazoketone as precursor of ketene (Figure 3A). Visible light irradiation of α-diazoketone alone resulted in complete conversion to phenyl methyl ketene **I**, which was confirmed by infrared spectroscopy analysis (see Supporting Information, Figure S3). A one-pot adding aniline to the solution of prepared ketene **I** at room temperature in the presence of catalyst (*R*)-**C8** yielded the racemic product **3a** in 93% yield (Figure 3A, procedure i). We also attempted to add aniline to the ketene **I** solution at −78 °C and obtained product **3a** in 91% yield with 6% ee (Figure 3A, procedure ii). At −78 °C, using equimolar (*R*)-**C8** improved the ee value of product **3a** to 86% (Figure 3A, procedure iii), approximating the result of standard catalytic reaction. These results suggest that the reaction proceeds through ketene **I**; However, no enantioselectivity with prepared ketene implies the

presence of a non-catalytic background reaction, which confirms the necessity of using α-diazoketone as the starting material of reaction.

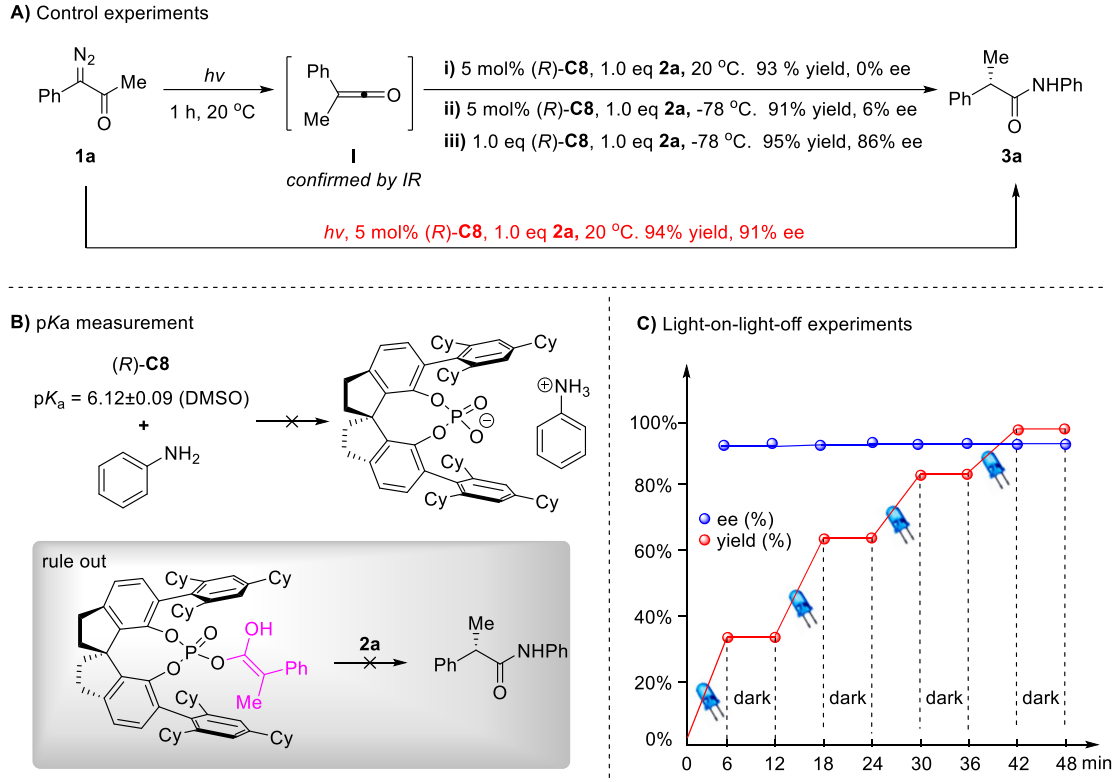


Figure 3. Control experiments.

Given the presence of both aniline and spiro phosphoric acid catalyst (*R*)-**C8** in the reaction, it is necessary to determine the true nucleophilic species. The pK_a of (*R*)-**C8** was measured to be 6.12 ±0.09 in DMSO (see Supporting Information, Figures S1 and S2) by using overlapping indicator method[20]. In contrast, the pK_a value of aniline upon protonation is 3.60 in DMSO[21]. The pK_a difference between those two species suggests that aniline is unlikely to be protonated by the spiro phosphoric acid and aniline is the nucleophilic reagent in the reaction, eliminating the possibility of catalyst anion acting as a nucleophile (Figure 3B). Additionally, the light-on/light-off experiments indicated that product **3a** was formed only under blue light irradiation and notably, the ee value of **3a** remained consistent throughout the reaction (Figure 3C). This observation suggests that the blue light is solely responsible for the diazoketone decomposition, and the reaction path should be singular.

We subsequently employed in situ infrared spectroscopy to investigate the reaction kinetics (see Supporting Information, Figures S4 to S7). The reaction rate displayed zero-order dependence on diazoketone concentration and first-order dependence on both aniline and catalyst concentration[22] (Figure 4A). Based on these kinetic experiments and the observations in Figure 3, we propose that the rate-determining step involves the nucleophilic attack of amines on the ketene species derived from diazoketone, with the catalyst participating in this process. To gain further insight into the reaction mechanism, we computed and compared the energies of aminoenol intermediates using density functional theory (see Supporting Information, Figure S8). The nucleophilic addition of amine to ketene was more likely to generate *E*-enol intermediate in the

absence of catalyst, as its energy is 2.0 kcal/mol lower than that of the *Z*-enol. Intriguingly, the presence of catalyst further enhances the stability of the *E*-enol intermediate and widens the energy gap between *Z*- and *E*-enol intermediates (Figure 4B). These findings suggest that the catalyst not only accelerates the nucleophilic addition of amine to ketene, but also promotes the preferentially formation of the *E*-enol intermediate.

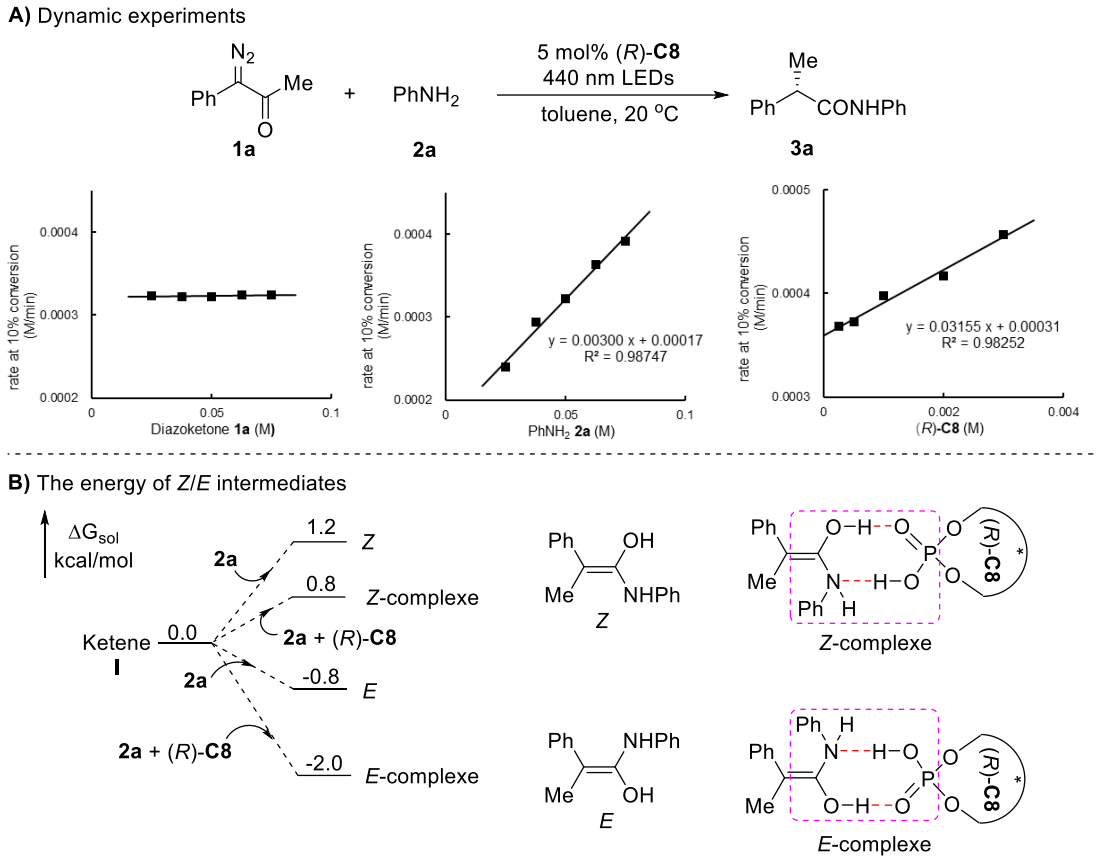


Figure 4. Mechanistic studies. **A**) Dynamic experiments. **B**) The energy of *Z*/*E* intermediates

In order to understand the origin of the enantioselectivity of the reaction, we calculated the proton transfer step by density functional theory (see Supporting Information, Figure S9). The lowest energy transition state structures of the major and minor enantiomers of product in the proton transfer step, **TS-ES-I** and **TS-ER-I** are presented in Figure 5, respectively. The calculated energy for **TS-ES-I** is 3.7 kcal/mol lower than that of **TS-ER-I**, resulting in (*S*)-product, which is consistent with the experimental observations. Both transition states show a network of hydrogen bonding interactions between the chiral catalyst and the *E*-enol. Besides, the analysis of the week interactions in the transition states by means of the independent gradient model based on Hirschfeld partition (IGMH)[23,24,25,26] shows that the weak hydrogen bonds, including C−H···O and C−H···π interactions between the *E*-enol and catalyst, present in both transition states. However, the weak interactions in the transition state **TS-ES-I** is significantly more than that in the transition state **TS-ER-I**, suggesting that the weak interactions are the key determinants of enantioselectivity.

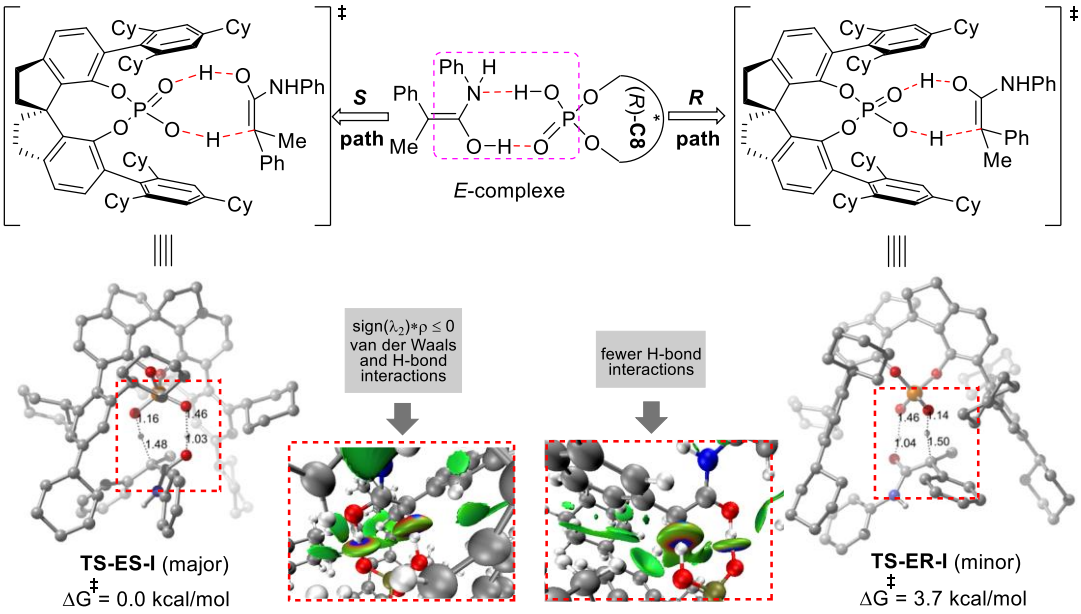


Figure 5 Lowest-energy transition state structures for *R* and *S* products optimized by DFT calculations performed at the M062X-D3/def2tzvpp (SMD-toluene)//M062X-D3/def2svp (gas) level.

CONCLUSION

In summary, we have developed a novel method for the synthesis of chiral amides by asymmetric Wolff rearrangement. This study not only addresses the asymmetric amination reactions between potent nitrogen-based nucleophilic reagents and ketene species but also offers a fresh mechanism reference for analogous reactions. The success of this transformation depends on the in situ formation of ketenes from α-diazoketone precursors. We foresee that this method, integrating visible-light photoactivation and Brønsted acid-catalyzed enantioselective proton transfer, will have more applications in the asymmetric reactions involving diazo compounds.

ACKNOWLEDGMENTS

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