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New Insights into the Torquoselectivity of the Staudinger Reaction

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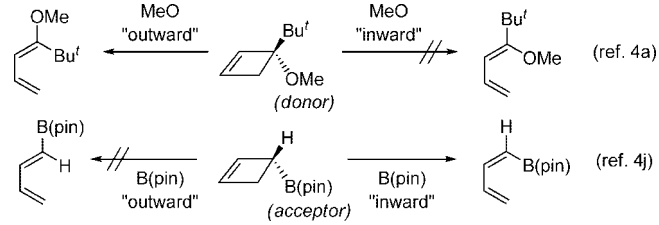
Abstract: To understand the torquoselectivity and the electronic effects of the Staudinger reaction, a study using a combination of experiments and DFT calculations has been conducted for the reactions of an unsymmetric cyclic ketene and cyclic imines with different electronic properties. The predominant formation of the donor-in β-lactams, the torquoelectronically disfavored products, was observed for the first time. The Hammett analyses reveal a close relationship between the donor-out/donor-in product ratio and the electronic nature of the imines. The kinetic competition experiments and DFT calculations indicate that the two-step Staudinger reaction shows different rate-determining steps in the donor-in and donor-out pathways. Our investigations reveal that the torquoelectronic control in the Staudinger reaction is quite different from that in the ring-opening reaction of cyclobutene derivatives. The diastereoselectivity of the Staudinger reaction involving an unsymmetric disubstituted ketene cannot be simply rationalized or predicted by the torquoelectronic model.

Introduction

Pericyclic reactions comprise a major category of reactions of theoretical and synthetic importance.[1] Key theories in organic chemistry, such as the frontier molecular orbital (FMO) theory,[2] were developed on the basis of detailed investigation into these reactions. The FMO theory can rationalize or predict the reaction mode (conrotation versus disrotation) of an electrocyclic reaction. In 1984, Kirmse, Rondan, and Houk disclosed another theory in electrocyclic reactions, which was referred to as "torquoselectivity" or "torquoelectronic effect",[3] to describe the different rotation trend of substituents (inward versus outward). It was found that, in the electrocyclic ring-opening of substituted cyclobutenes, "donor" substituents tend to undergo an outward rotation, while "acceptor" substituents tend to undergo an inward rotation (Scheme 1).[4a,j] This electrocyclic theory successfully rationalized and predicted many experimental findings and was found to be general in various electrocyclic reactions, such as thermal ring-opening of cyclobutenes, pentadienyl cation cyclization, hexatriene−cyclohexadiene interconversion, and electrocyclic ring-openings of β-lactone enolates.[3c,4,5]

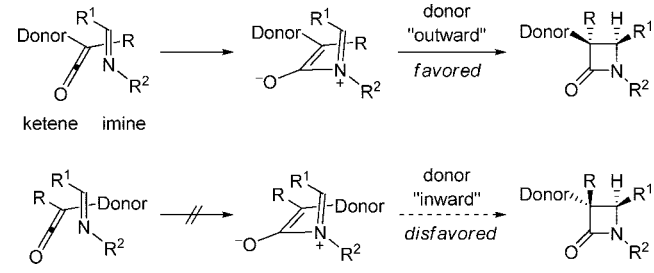
The ketene−imine [2 + 2] cycloaddition, known as the Staudinger reaction,[6] is one of the most versatile methods to synthesize β-lactam derivatives.[7] Mechanistic studies revealed that two key steps are involved in the β-lactam formation: (a) the nucleophilic attack of an imine to a ketene to generate a zwitterionic intermediate; (b) the cyclization of the zwitterionic intermediate.[7a] In addition to the reaction mechanism, the diastereoselectivity is also a crucial issue of the Staudinger reaction under intensive investigations for several decades.[8−10] Many experimental and theoretical studies disclosed that the "torquoelectronic effect" is applicable to this cycloaddition

Scheme 1. Classic Examples of Torquoselectivity in Cyclobutene Ring-Opening Reactions[a]



[a] B(pin) = 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl.

Scheme 2. Torquoselectivity in the Staudinger Reaction



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Scheme 3

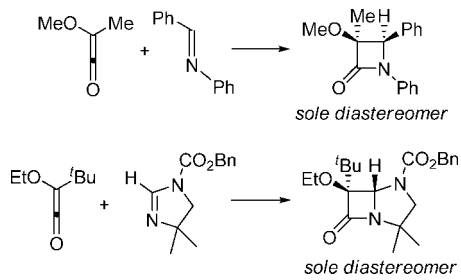
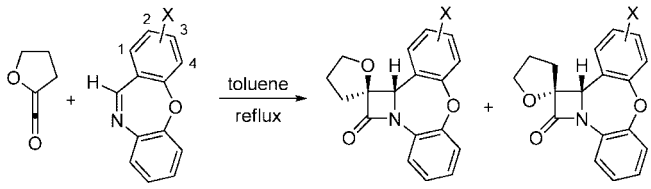


Table 1. Reactions of Cyclic Ketene **1** with Cyclic Imines **2**



entry		Imine	yield (%)[a]	**3**/**4** ratio[b]
1	**2a**	X = 3-Me	72	87:13
2	**2b**	X = 2-Me	66	84:16
3	**2c**	X = H	62	80:20
4	**2d**	X = 2-Cl	74	49:51
5	**2e**	X = 2-NO_2	80	24:76

[a] Combined yield after column chromatography. [b] Determined by integrations of ^{1}H NMR of the reaction mixture.

reaction and its diastereoselectivity is controlled by this effect, since the geometry of the transition state structures for the conrotatory ring-closure of the zwitterionic intermediates strongly resembled that for the electrocyclic ring-opening of cyclobutenes.[11] It has been found that, in the cyclization step of the Staudinger reaction, "donor" substituents tend to occupy outward position (Scheme 2), while "acceptor" substituents give an opposite result. In some cases,[11c,d] "torquoselectivity" overwhelms the steric effect if these two factors both affect the stereochemistry (Scheme 3).

However, we found that the torquoelectronic control in the Staudinger reaction is quite different from that in the ring-opening reaction of cyclobutene derivatives. In the electrocyclic reaction, there is only one step in both donor-out and donor-in pathways. Thus, the stereoselectivity is controlled by the energy difference of the donor-out and donor-in transition states, and the torquoselectivity is applicable to such reaction without any prerequisite. In contrast, in the Staudinger reaction, there are two steps, the nucleophilic attack and the ring closure, in both donor-out and donor-in pathways. Although the ring-closure step is controlled by the torquoselectivity, it may not be always the rate-determining step, especially for the disubstituted ketene participating Staudinger reaction. Thus, the application of the torquoselectivity to rationalize or predict the diastereoselectivity in the Staudinger reaction is not unconditional. With the aid of joint forces of experiments and DFT calculations, we reinvestigated the torquoelectronic effect in the Staudinger reaction of the unsymmetric disubstituted ketene. We found that the diastereoselectivity could not be simply rationalized or predicted by the torquoelectronic model, and torquoelectronically disfavored β-lactam products even predominated in some cases. The torquoelectronic effect could be used to rationalize or predict the diastereoselectivity only when the ring-closure step is rate-determining in both donor-in and donor-out pathways. Herein, we present our results to provide new insights into the torquoelectronic effect of the Staudinger reaction.

Results and Discussion

Reactions of the Unsymmetric Cyclic Ketene with Cyclic Imines. To investigate the diastereoselectivity without interference of the imine isomerization,[12,13] we chose a series of cyclic imines **2a**−**e** with different electronic substituents to react with unsymmetric disubstituted ketene **1** (Table 1). Since such cyclic imines could not isomerize in the reaction, they are supposed to produce the donor-out (trans) cycloadducts exclusively according to the torquoselectivity. Surprisingly, the reactions of cyclic ketene **1** (generated *in situ* from 2-tetrahydrofuroyl chloride in the presence of triethylamine) with imines **2a**−**e** produced unexpected results. For imines **2a**−**c**, donor-out β-lactams **3a**−**c** were the major products. However, for imines **2d**−**e** with electron-withdrawing groups, donor-in β-lactams **4d**−**e**, which are disfavored according to the torquoselectivity,

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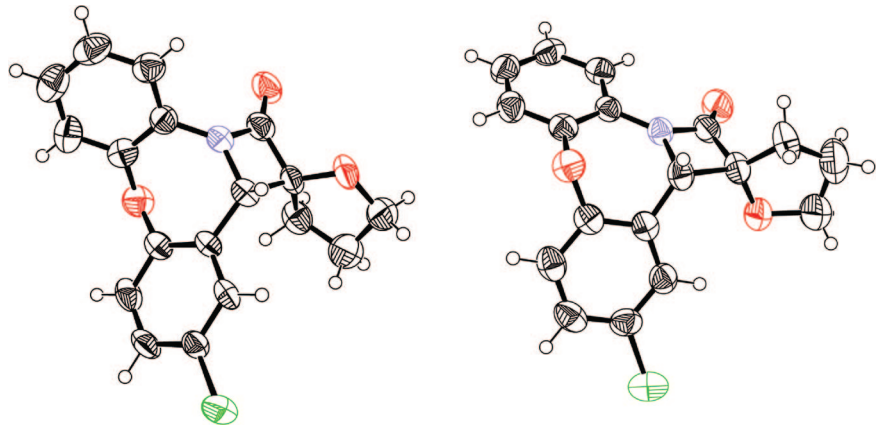

Figure 1. X-ray structures of β-lactams **3d** (left) and **4d** (right). Ellipsoids are drawn at 50% probability.

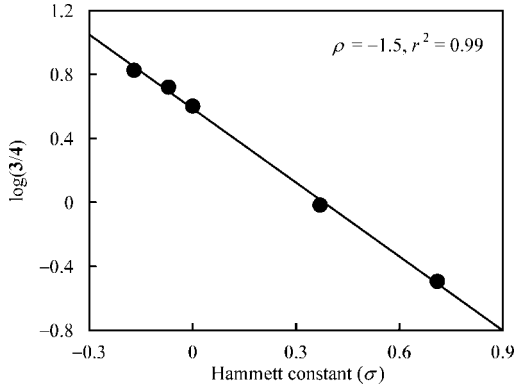

Figure 2. Hammett plot for the diastereomeric ratio versus the electronic effect of imine substituents.

became the major products. The stereostructures of β-lactams **3** and **4** were identified by the X-ray diffraction analysis (**3d** and **4d**, Figure 1) and 1D NOE experiments. More importantly, we found that the logarithm of the donor-out to donor-in product ratios (**3/4**) and Hammett constants[14] of imine substituents have a very good linear correlation ($r^2 = 0.99$) with a slope of -1.5 (Figure 2). This suggests that electronic effect plays a critical role in these reactions.

To the best of our knowledge, the linear free energy relationship (LFER) of the torquoselectivity in the Staudinger reaction has never been observed previously. To disclose the origin of this intriguing phenomenon and to better understand the torquoselectivity in the Staudinger reaction, we conducted further mechanistic investigations (kinetics and DFT calculations) into this reaction system.

Kinetic Competition Experiments. To further explore the substituent effects, we designed and conducted a series of intermolecular kinetic competition experiments (Table 2). In these experiments, a mixture of the same equivalent of imine **2c** and another substituted imine (**2a**, **2b**, **2d**, or **2e**) reacted with cyclic ketene **1**. The reaction was quenched at low conversion of imines, and the reaction mixture was directly submitted to ^{1}H NMR analysis to obtain the ratios of donor-out and donor-in products. In each set of experiments, four different β-lactam products, including **3c**, **4c**, **3x**, and **4x** (where **x** = **a**, **b**, **d**, or **e**), were generated. Experiments revealed that the donor-out product ratios (i.e., **3x/3c**) and the donor-in product ratios (i.e., **4x/4c**) varied regularly with the electronic effect of imine substituents: when the imine became more electron-deficient, the donor-out product ratio decreased, and the donor-in product ratio increased. The logarithms of both donor-out product ratios and donor-in product ratios correlate well with Hammett

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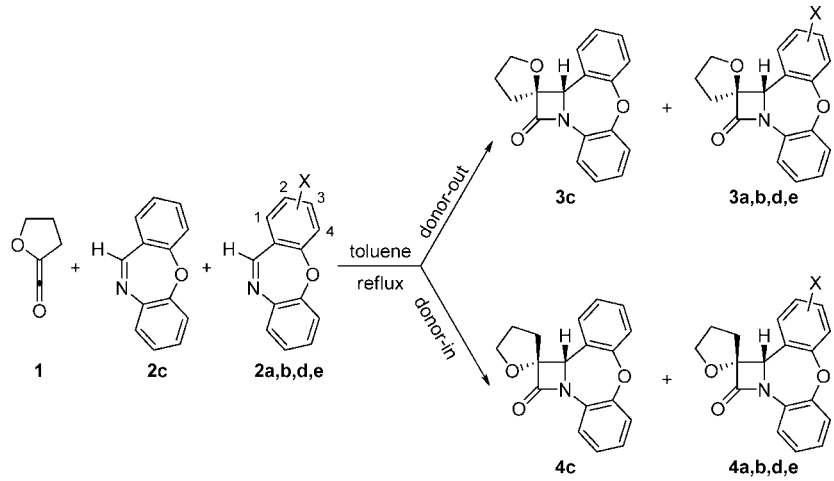
Table 2. Results of Kinetic Competition Experiments



Imine	**2a** (X = 3-Me)	**2b** (X = 2-Me)	**2d** (X = 2-Cl)	**2e** (X = 2-NO_2)
donor-out ratio	**3a**:**3c** = 57:43	**3b**:**3c** = 57:43	**3d**:**3c** = 34:66	**3e**:**3c** = 22:78
donor-in ratio	**4a**:**4c** = 44:56	**4b**:**4c** = 48:52	**4d**:**4c** = 65:35	**4e**:**4c** = 73:27

constants with calculated ρ values of -0.78 and $+0.63$, respectively (Figure 3).

It was proposed that, in the Staudinger reaction, the rate of the first step (the nucleophilic attack of an imine to a ketene) increases as the imine becomes more electron-rich ($\rho < 0$ in the Hammett plot); the rate of the second step (the ring-closure of the zwitterionic intermediate) increases as the imine becomes more electron-deficient ($\rho > 0$ in the Hammett plot).[10b] The kinetic competition experiments showed a negative slope for the donor-out pathway, suggesting that the nucleophilic attack is rate-determining in this pathway. In contrast, a positive slope for the donor-in pathway suggests that the ring closure is rate-determining. This means donor-in and donor-out pathways may have different rate-determining steps. Reviewing the intriguing stereochemical outcomes observed in the reactions of **1** with **2a**−**e** (Table 1), we hypothesized that the change of rate-determining steps in the Staudinger reaction is responsible for the observed electronic tuning of the diastereoselectivity. To confirm this hypothesis and to gain a deeper understanding of the diastereoselectivity, we conducted DFT calculations on these reactions.

DFT Calculations on the Staudinger Reactions of Ketene 1 with Imines 2a−e. The reactions of cyclic ketene **1** with imines **2a**−**e** were selected as model reactions for the density functional theory (DFT) calculations.[15] Structural optimization and single-point energy were obtained at the B3LYP/6−31G(d) level[16,17] in the gas phase. The free energies in solution (ΔG_{sol}) were computed by the CPCM method[18,19] in toluene. The potential free energy surfaces of these reactions were obtained, and a representative potential free energy surface (for the reaction of **1** with **2c**) is shown in Figure 4.[20]

The first step of the reaction is the generation of two possible zwitterionic intermedidates (**IN-in-c** and **IN-out-c**), and the second step is the ring closure to form the corresponding β-lactam products. In the first step, the imine attack from the less hindered side of the ketene (the donor-in pathway, the formation of **IN-in-c**) is favored by 1.3 kcal/mol in terms of Gibbs free energy compared with the attack at the hindered side (the donor-out pathway, the formation of **IN-out-c**). The generated zwitterionic intermediate, **IN-in-c**, is 3.2 kcal/mol more stable than **IN-out-c**. However, in the second step, the free energy of the donor-in transition state for the ring-closure step (via **TS2-in-c**) is 3.1 kcal/mol higher than that of the donor-

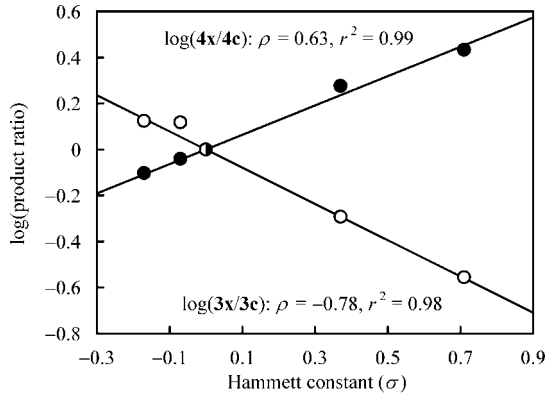


Figure 3. Hammett plot for kinetic competition experiments.

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(16) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
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(19) The gas-phase energies are given in the Supporting Information. The calculated potential erengy surfaces in the gas phase are similar to those in solution.
(20) Diffuse function is believed to be necessary for decribing reactions involving zwitterionic intermediates and transition states. Thus, we calculated the potential energy surfaces for the reaction of **1** with **2c** on the CPCM-B3LYP/6−31+G(d)//B3LYP/6−31G(d) level (see the Supporting Information for details). The calculated energy surface is very similar to that shown in Figure 4, and this calculation predicts a donor-out/donor-in ratio of 96:4, which is close to that calculated on the CPCM-B3LYP/6−31G(d) level (91:9). This indicates that the 6−31G(d) basis set is suitable for investigating the present reactions. In addition, we also calculated the energies of two rate-determining transition states, **TS1-out-c** and **TS2-in-c**, on the CPCM-B3LYP/6−31+G(d) level. The result is also very close, predicting a donor-out/donor-in ratio of 97:3.

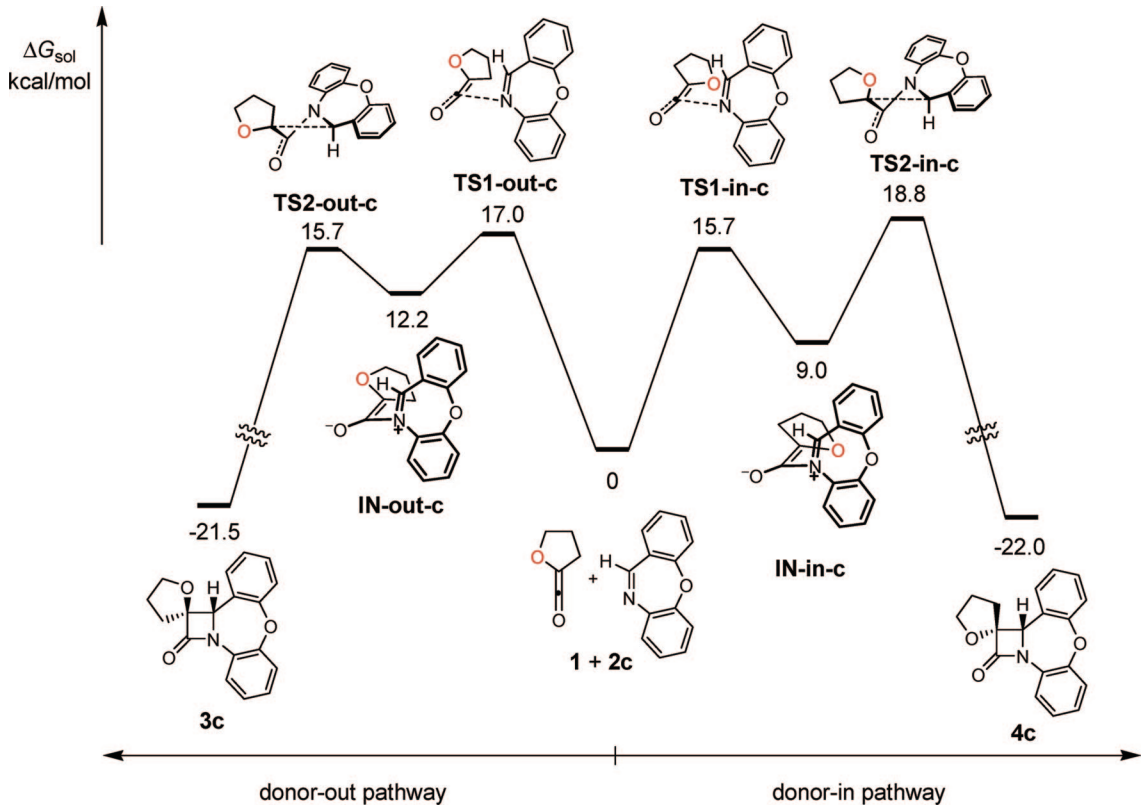


Figure 4. Calculated energy surfaces for the reaction of ketene **1** with imine **2c** at the B3LYP/6−31G(d) + ΔZPVE level of theory (toluene was used as solvent within the CPCM method). **TS2-out-c** is calculated on the B3LYP/6−31G(d)//B3LYP/6−31G level.

Table 3. Calculated Transition State Energies ($\Delta G^{\ddagger}$) for the Reactions of Ketene **1** with Imines **2a**−**e** (in kcal/mol)

Imine	$\Delta G^{\ddagger}$ (**TS1-out**)	$\Delta G^{\ddagger}$ (**TS2-in**)	$-\Delta\Delta G^{\ddagger}$(**out**−**in**)	calcd **3/4** ratio	exptl **3/4** ratio
2a	17.0	19.1	2.1	94:6	87:13
2b	17.1	19.3	2.2	95:5	84:16
2c	17.0	18.8	1.8	91:9	80:20
2d	18.1	18.5	0.4	63:37	49:51
2e	19.2	18.0	−1.2	17:83	24:76

out transition state (via **TS2-out-c**). This is in good agreement with the torquoselectivity theory. If the ring-closure steps in both pathways were the rate-determining steps, the donor-out selectivity would be very high (for a 3.1 kcal/mol free energy difference, donor-out/donor-in ratio would be >98:2 at 110 °C). In fact, in the donor-in pathway, the ring closure is the rate-determining step, while, in the donor-out pathway, the generation of the zwitterionic intermediate is the rate-determining step. Thus, it is clear that the product distribution is not simply determined by the energy difference of the two different ring-closure transition states, **TS2-in-c** and **TS2-out-c**. According to the DFT calculation results, the real energy difference between the rate-determining transition states of two pathways is 1.8 kcal/mol (18.8 vs 17.0 kcal/mol), corresponding to a donor-out/donor-in ratio of 91:9 at 110 °C, which is close to our experimental result (**3c/4c** = 80:20).[20]

For other imines we studied, the ring-closure steps are always rate-determining in the donor-in pathways. In contrast, the nucleophilic attack steps are always rate-determining in the donor-out pathways. The calculated transition state energies of these two steps are listed in Table 3. It was found that the transition state energies of **TS1-out** and **TS2-in** varied regularly according to the electronic property of imines. Thus, energy differences between the rate-determining transition states of two

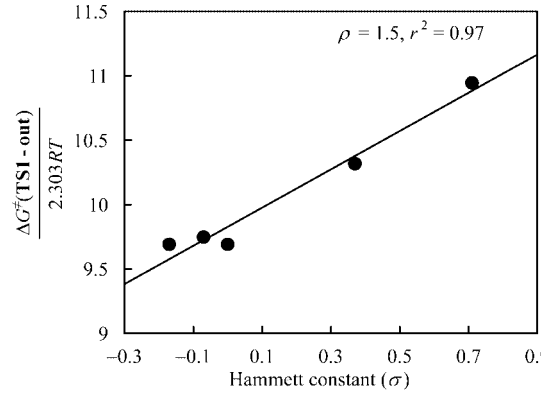


Figure 5. Hammett plot for the calculated outward nucleophilic attack transition state energies versus the electronic effect of imines **2a**−**e**.

pathways, $-\Delta\Delta G^{\ddagger}$(**out-in**), also varied regularly. According to calculated energy differences, our DFT calculations predicted a series of **3/4** ratios, which were close to the experimentally determined ones (Table 3). This encouraging agreement between experiments and calculations further confirmed that the rate-determining steps for donor-in and donor-out pathways are indeed different, and the ratio of the diastereomeric products is determined by the energy difference of the corresponding rate-determining transition states, not by the torquoelectronic effect.

Our calculations also reveal the influence of the electronic effect of imines on the two-step process of the Staudinger reaction. It is well-known that the nucleophilicity of the imine decreases when electron-withdrawing groups exist. This could account for the increase of the activation free energy of the nucleophilic attack [$\Delta G^{\ddagger}$(**TS1-out**)] when the employed imine becomes more electron-deficient (from **2a** to **2e**). The calculated

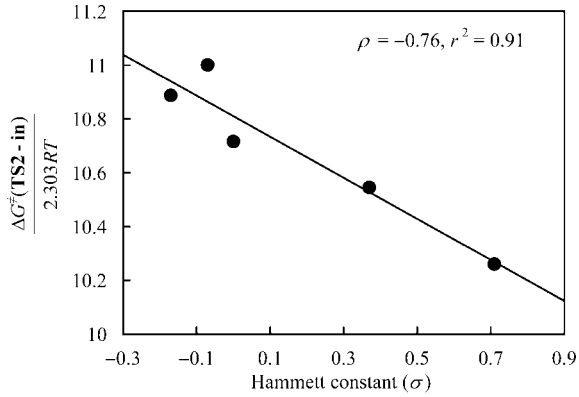


Figure 6. Hammett plot for the calculated inward ring-closure transition state energies versus the electronic effect of imines **2a**−**e**.

energies of $\Delta G^{\ddagger}$(**TS1-out**) correlate well with Hammett constants of imine substituents with a ρ value of +1.5 (Figure 5). On the other hand, the free energy of the donor-in ring-closure transition state, $\Delta G^{\ddagger}$(**TS2-in**), decreased as the corresponding imine becomes more electron-deficient (from **2a** to **2e**). The calculated energies of $\Delta G^{\ddagger}$(**TS2-in**) also correlate well with Hammett constants of imine substituents with a ρ value of −0.76 (Figure 6). This is in excellent agreement with our previous conclusion that the nucleophilic-addition-like ring-closure step could be facilitated by the electron-withdrawing groups on the imine moiety.[10b] Both $\Delta G^{\ddagger}$(**TS1-out**) and $\Delta G^{\ddagger}$(**TS2-in**) are in good correlation with the electronic nature of the employed imines. Consequently, their difference, $\Delta\Delta G^{\ddagger}$(**out-in**), correlates well with the electronic effect. Because the $\Delta\Delta G^{\ddagger}$(**out-in**) value directly relates to the donor-out/donor-in product ratio (**3/4**), this well accounts for the good correlation between log(**3/4**) and Hammett constants (Figure 2).

The above analysis shows that the torquoelectronic control in the Staudinger reaction is quite different from that in the electrocyclic reaction. In the electrocyclic ring-opening reaction of cyclobutene derivatives, both donor-in and donor-out pathways are single-step reactions, so the transition state energy difference of these two ring-opening manners will directly determine the ratio of donor-in and donor-out products. In contrast, the Staudinger reaction is a two-step reaction, which could have either the first or the second step as the rate-determining step. According to the torquoselectivity theory, in the Staudinger reaction, the donor-out ring-closure transition state is always favored over the donor-in ring-closure transition state. However, their energy difference would not always determine the ratio of donor-in and donor-out products. If the ring-closure steps are rate-limiting in both donor-in and donor-out pathways, the Staudinger reaction will be similar to the electrocyclic reaction. If the ring-closure step is not the rate-determining step, the situation becomes more complex, as demonstrated by what we have discussed before. At this stage, through a combined experimental and computational study, we provide clear guidance for the scope of the applicability of the torquoselectivity in the Staudinger reaction: the torquoelectronic effect could be used to rationalize or predict the diastereoselectivity of the reaction only when the ring-closure step is rate-determining in both donor-in and donor-out pathways.

DFT Rationalization on the Staudinger Reaction of Ketene 1 with Electron-Rich Imines. Previous reports from Hegedus' laboratory indicated that the reactions of disubstututed ketenes

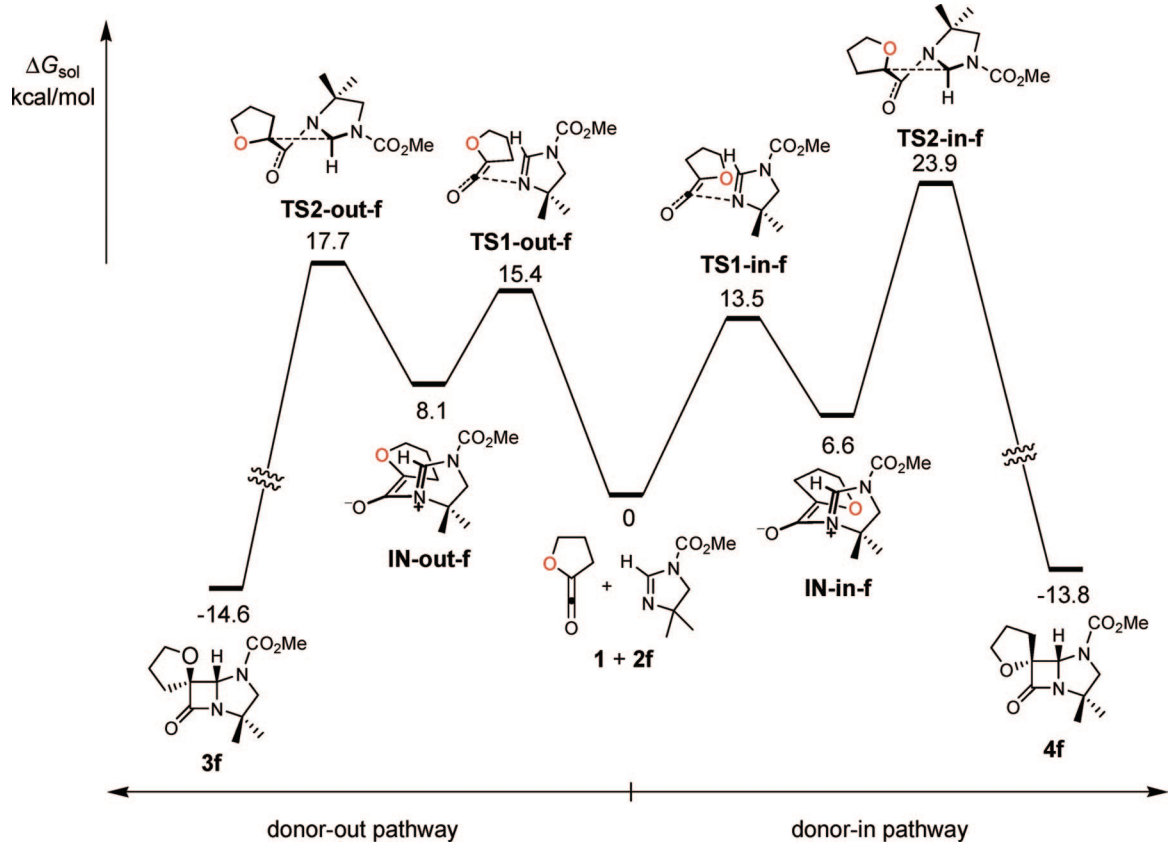


Figure 7. Calculated energy surfaces for the reaction of ketene **1** with imine **2f** at the B3LYP/6−31G(d) + ΔZPVE level of theory (acetonitrile was used as solvent within the CPCM method).

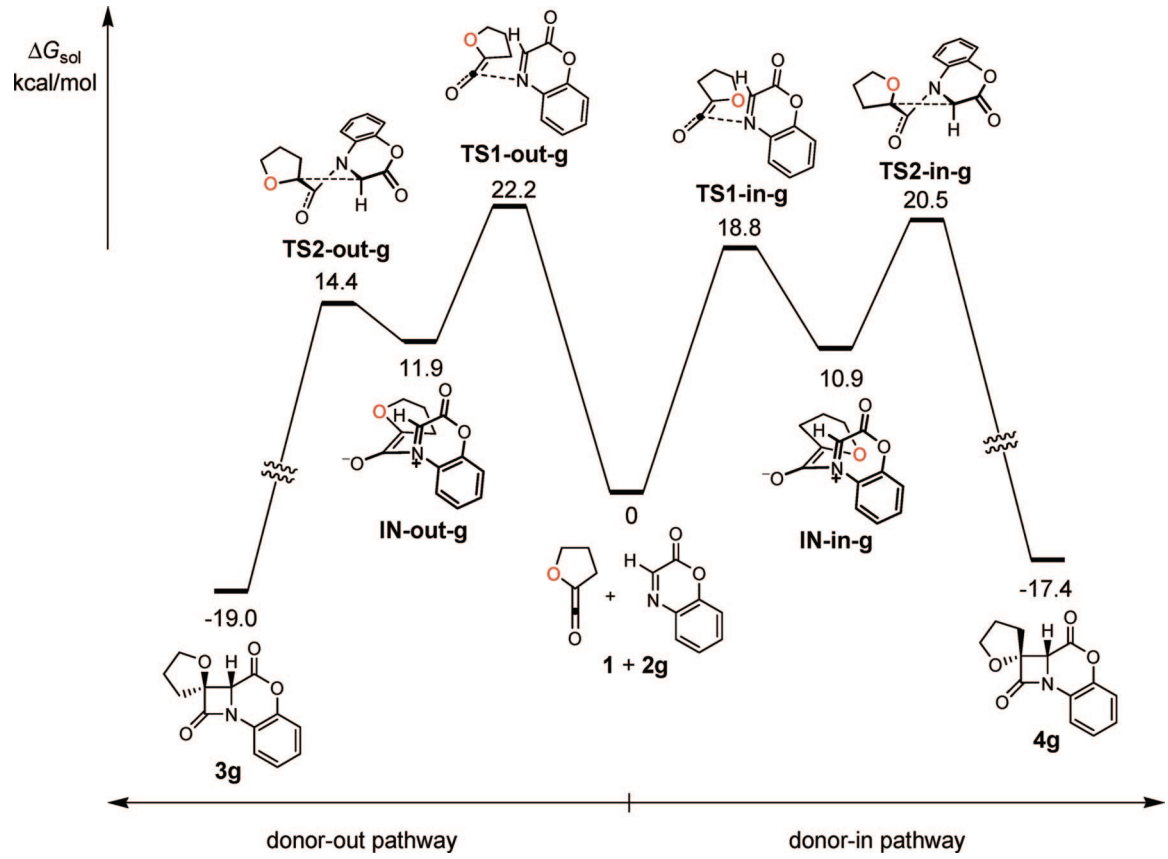
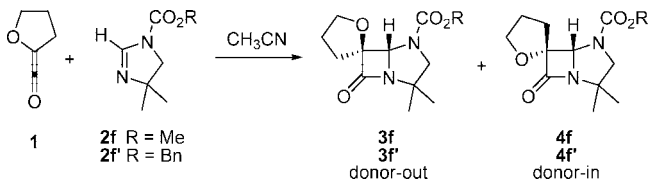
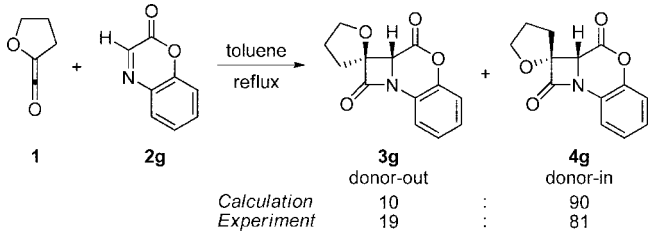


Figure 8. Calculated energy surfaces for the reaction of ketene **1** with imine **2g** at the B3LYP/6−31G(d) + ΔZPVE level of theory (toluene was used as solvent within the CPCM method).

Scheme 4



Scheme 5



and various cyclic imines perfectly followed the torquoselctivity theory and no exception was found.[11a,c,d] For example, in the reaction of ketene **1** with a cyclic imine, 5,5-dimethyl-imidazoline-3-carboxylate **2f′**, the donor-out product **3f′** was the sole product (Scheme 4), which is quite different from our experiments employing cyclic imines **2a**−**e**. To understand the origin of this difference, we conducted DFT calculations on the model reaction of **1** with **2f** (Figure 7). The computational results indicated that, in both donor-out and donor-in pathways, the activation energies for the nucleophilic attack steps decreased compared with those of the reaction of **1** with **2c** (the donor-in pathway: 13.5 kcal/mol versus 15.7 kcal/mol; the donor-out pathway: 15.4 kcal/mol versus 17.0 kcal/mol). Meanwhile, the activation energies for the ring-closure steps increased compared with those of the reaction between **1** and **2c** (the donor-in pathway: 23.9 kcal/mol versus 18.8 kcal/mol; the donor-out pathway: 17.7 kcal/mol versus 15.7 kcal/mol). Ring-closure steps both become rate-determining in these two pathways, so the torquoselectivity will completely control the product distribution. The donor-out transition state **TS2-out-f** is 6.2 kcal/mol more favored than the donor-in transition state **TS2-in-f** in acetonitrile, leading to the exclusive formation of β-lactam **3f**. This computation is in very good agreement with the previous experimental result by Hegedus et al. From a theoretical viewpoint, this is because the electron-rich nature of 5,5-dimethyl-imidazoline-3-carboxylate facilitates the nucleophilic attack of the imine to the ketene but disfavors the intramolecular ring closure, making the second steps in both donor-out and donor-in pathways rate-limiting.

After an extensive literature survey, we found that almost all previous experiments discussed to elucidate the torquoselectivity in the Staudinger reaction employed unsymmetric disubstituted ketenes and electron-rich cyclic imines, such as imidazoline, thiazoline, and oxazine derivatives.[11a,c,d] In all these cases, the ring-closure steps would be rate-determining, so torquoselectivity was observed.

DFT Prediction and Experimental Verification of the Staudinger Reaction of Ketene 1 with Another Cyclic Electron-Deficient Imine. At this stage, it is clear that electron-rich imines can help the torquoelectronic effect control the diastereoselectivity of the Staudinger reaction. In contrast, we envisioned that, if electron-deficient imines are used, the nucleophilic attack will be disfavored but the intramolecular ring-closure will be favored.

In such a case, the nucleophilic attack may become the rate-determining step, and the diastereoselectivity would be mainly controlled by the steric effect. Thus, the donor-in product, which is against the torquoselectivity but sterically favored, may predominate. To verify this hypothesis, we chose a cyclic iminoester **2g** with an electron-withdrawing carbonyl group directly attached to the imine moiety as the substrate. To our best knowledge, cyclic iminoester **2g** has never been employed in the Staudinger reaction, so we would like to calculate this reaction first. DFT calculations on this system predicted that the donor-in product would be the major product and the donor-out/donor-in ratio would be 10:90 [$\Delta G^{\ddagger}$(**TS1-out**) − $\Delta G^{\ddagger}$(**TS2-in**) = 1.7 kcal/mol, Figure 8]. Then, imine **2g** was synthesized and reacted with ketene **1** under standard conditions. Gratifyingly, the donor-in product **4g** was formed predominantly and the donor-out/donor-in ratio is 19:81, close to the computational prediction (Scheme 5).

Conclusion

By combining experiments and DFT calculations, we have investigated the influence of the electronic effect of imines on the diastereoselectivity in the Staudinger reaction involving an unsymmetric disubstituted ketene and cyclic imines with different electronic properties. The predominant formation of the donor-in β-lactams, the torquoelectronically disfavored products, was observed for the first time. The Hammett analyses reveal a close relationship between the donor-out/donor-in product ratio and the electronic nature of the imines, which was not clear until the present study. After in-depth investigations, including kinetic competition experiments and DFT calculations, the energy profiles for the model Staudinger reactions have been obtained and the influence of the electronic effect of the imine substituents on each step of the reaction has been clarified.

From the above analyses, some new insights into the torquoselectivity of the Staudinger reaction have been achieved. An important conclusion from these studies is that the torquoelectronic control in the Staudinger reaction is different from that in the electrocyclic reaction. In the electrocyclic reaction, there is only one step in both donor-out and donor-in pathways. Thus, the stereoselectivity is controlled by the energy difference of the donor-out and donor-in transition states, and the torquoselectivity is applicable to such reaction without any prerequisite. In contrast, in the Staudinger reaction, there are two steps, the nucleophilic attack and the ring closure, in both donor-out and donor-in pathways. Although the ring-closure step is controlled by the torquoselectivity, it is not always rate-determining. Thus, the application of the torquoselectivity to rationalize or predict the diastereoselectivity in the Staudinger reaction is not unconditional. Our investigations indicate that the Staudinger reaction is controlled by the torquoselectivity only when the ring-closure step is rate-limiting in both donor-in and donor-out pathways; otherwise, the diastereoselectivity is not determined by the energy difference of two ring-closure transition states, and the final stereochemical outcome may deviate from the torquoselectivity. In a word, it is the two-step nature of the Staudinger reaction that makes the torquoelectronic control in the Staudinger reaction different from that in the electrocyclic reaction. The present work also provides implications in analyzing the stereochemical problem in a reaction involving a multistep process.

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Supporting Information Available: Experimental details, copies of ^{1}H NMR spectra of the products, computational details, and complete ref 15. This material can be obtained free of charge via the Internet at http://pubs.acs.org.

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