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PAPER

Stereoselective control in the Staudinger reactions involving monosubstituted ketenes with electron acceptor substituents: experimental investigation and theoretical rationalization†

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The stereoselectivity of the Staudinger reactions involving monosubstituted ketenes with electron acceptor substituents was investigated experimentally by determination of the product stereochemistry and theoretically *via* DFT calculations. The results indicate that imines preferentially attack the less sterically hindered *exo*-side of the ketenes to generate zwitterionic intermediates. Subsequently, for cyclic imines, the intermediates undergo a conrotatory ring closure directly to produce β-lactams, while for linear imines, the imine moiety of the intermediates isomerizes to more stable intermediates, which further undergo a conrotatory ring closure to afford *trans*-β-lactams. The steric hindrance and the isomerization, rather than the torquoelectronic effect, play crucial roles in controlling the stereoselectivity in the practical Staudinger reactions involving monosubstituted ketenes with electron acceptor substituents, although the unaccessible borylketene with a powerful electron acceptor group controls the stereoselectivity torquoelectronically, in theory.

Introduction

The torquoselectivity, also called the torquoelectronic effect, is an important theory to rationalize the stereoselectivity in pericyclic reactions since the Woodward–Hoffmann's rule, has been widely used.[1] It was first proposed by Houk and coworkers to account for the stereoselectivity in the electrocyclic ring-opening of substituted cyclobutenes.[1a] According to the theory, electron-donor substituents favor the outward rotation and electron-acceptor substituents prefer the inward rotation in ring-opening reactions of cyclobutenes. The stereoselectivity in the reactions is governed by the electronic control, not by the steric control.[1,2] The theory has been extended successfully to account for some aspects of the stereoselectivity in other electrocyclic reactions, such as the thermal ring-opening of the pentadienyl cation cyclization, the hexatriene-cyclohexadiene interconversion, and electrocyclic ring-opening of β-lactone enolates.[1c,3]

The Staudinger reaction (also called the Staudinger cycloaddition or the ketene-imine cycloaddition) is a versatile method to synthesize very important β-lactams, which are key structural elements in some antibiotics and synthetic intermediates as well.[4] The mechanism of the Staudinger reaction includes two major steps, an imine attacks a ketene to generate a zwitterionic intermediate and the ring closure of the zwitterionic intermediate,[4a] which is considered as a conrotatory electrocyclic ring-closure, similar to the reverse process of the electrocyclic ring-opening of substituted cyclobutenes. On the other hand, the theoretical study revealed that the ring closure step is the rate-determining step in the stepwise Staudinger reaction.[5] Thus, the torquoelectronic effect has also been employed to account for the stereoselectivity in Staudinger reactions.[6] The torquoelectronic effect rationalizes the stereoselectivity in the Staudinger reactions involving disubstituted ketenes. Hegedus and his coworker first explained their contrasteric outcome of the chromium carbene complex-derived alkoxy and dialkylaminoketene-imine reactions and that of the reported phenylfluoroketene-imine reactions with the torquoelectronic effect.[6b] Moore's[7] and our recent[6h] results from Staudinger reactions involving disubstituted ketenes with electron-acceptor groups also obey the torquoelectronic effect in the stereoselective control, indicating that the torquoelectronic effect controls the stereoselectivity in the disubstituted ketene participating in Staudinger reactions. However, there is an exception to the torquoselectivity. That is, the reactions of a cyclic ketene generated from tetrahydrofuran-2-carboxylic chloride and various aromatic imines gave rise to *anti*-torquoselective β-lactams as major products in some cases.[8] Our further investigation

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† Electronic supplementary information (ESI) available: Procedures for preparation of all ketene precursors (including diazo ketones, substituted acetyl chlorides and acetic acids), analytic data, ^{1}H and ^{13}C NMR spectral copies of diazo ketone precursors and known products, ^{1}H and ^{13}C NMR spectral copies of all unknown products, cif files of XRD analysis, and all calculation details. CCDC reference numbers 804599 & 804600. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00783h

confirmed that the torquoselectivity is not always applicable in the disubstituted ketene participating in Staudinger reactions, especially in the cases wherein the donor groups are less sterically crowding than the other ones in disubstituted ketenes and the imines possess strong electron-withdrawing substituents.[9]

Staudinger reactions of monosubstituted ketenes with electron-donor groups (EDGs) have been investigated thoroughly in both experiments[10,11] and the theoretical calculation,[12] in which the steric and torquoelectronic effects are consistent in the stereoselective control. Thus, torquoselectivity is applicable to the Staudinger reactions. However, the reactions involving monosubstituted ketenes with electron-acceptor groups (EAGs) have been seldom explored until now,[13,14] possibly because of difficult preparation of the ketene precursors and the tedious purification of the products due to low yields in most cases. Only a few examples involving the monosubstituted ketenes with EAGs have been studied in experiments with *trans*-β-lactams as products.[13,14] On the other hand, computational studies[15] only used formaldimine itself and did not explore the influence of the electron-acceptor substituents of ketenes on the stereoselectivity, possibly due to lack of enough experimental results. Additionally, they did not discuss the attacking direction of the imine to the ketenes with EAGs although the *endo*-attack was assumed previously to illustrate the stereoselectivity in previous documents.[12a] In the Staudinger reactions involving monosubstituted ketenes with EAGs, it can be considered probable that linear imines attack the ketenes from their *endo*-side and then the generated zwitterionic intermediates undergo a conrotatory ring closure in the EAG inward mode to give rise to *trans*-β-lactams as products according to the torquoselectivity. This provided a reasonable explanation for the formation of *trans*-β-lactams from the ketenes with EAGs and the explanation is in a good accordance with the recent experimental results.[13,14] However, on the basis of our recent proposal on the stereoselectivity in the Staudinger reaction,[11] imines should attack the ketenes from their less steric *exo*-side to generate the zwitterionic intermediates, which isomerize their imine moiety to less steric forms and then undergo a conrotatory ring closure to afford *trans*-β-lactams because the electron-acceptor groups are electron-withdrawing substituents and they should decrease the rate of the ring closure so that the isomerization occurs. The rationale is also logical. Thus, there are two different reasonable explanations on stereocontrol in the Staudinger reactions involving monosubstituted ketenes with EAGs. Importantly, in this class of Staudinger reactions, the steric and torquoelectronic effects would produce opposite impacts on the stereoselective control.

We have a curiosity to know which of the torquoselectivity and isomerization is the major factor to control the stereoselectivity in the Staudinger reaction involving the monosubstituted ketenes with EAGs to perfect our previous proposal because the proposal was suggested only on the basis of ketenes with EDGs. To get a thorough understanding on the stereoselectivity and to summarize a general rule for the stereoselectivity in various monosubstituted ketenes participating in Staudinger reactions, we studied the Staudinger reaction involving the monosubstituted ketenes with various electron-acceptor groups, especially π-acceptor groups, experimentally and theoretically because Staudinger reactions involving monosubstituted ketenes with σ-acceptor groups such as halogens have been studied previously in experiment[10a,k,l] and theory[15a,b] (Fig. 1). Herein, we present our results and hope to give a good understanding on the stereochemical control in Staudinger reactions.

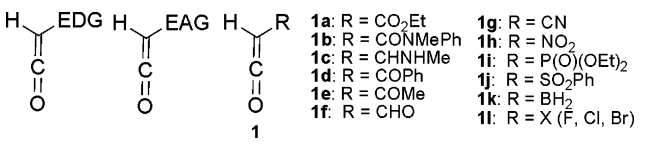
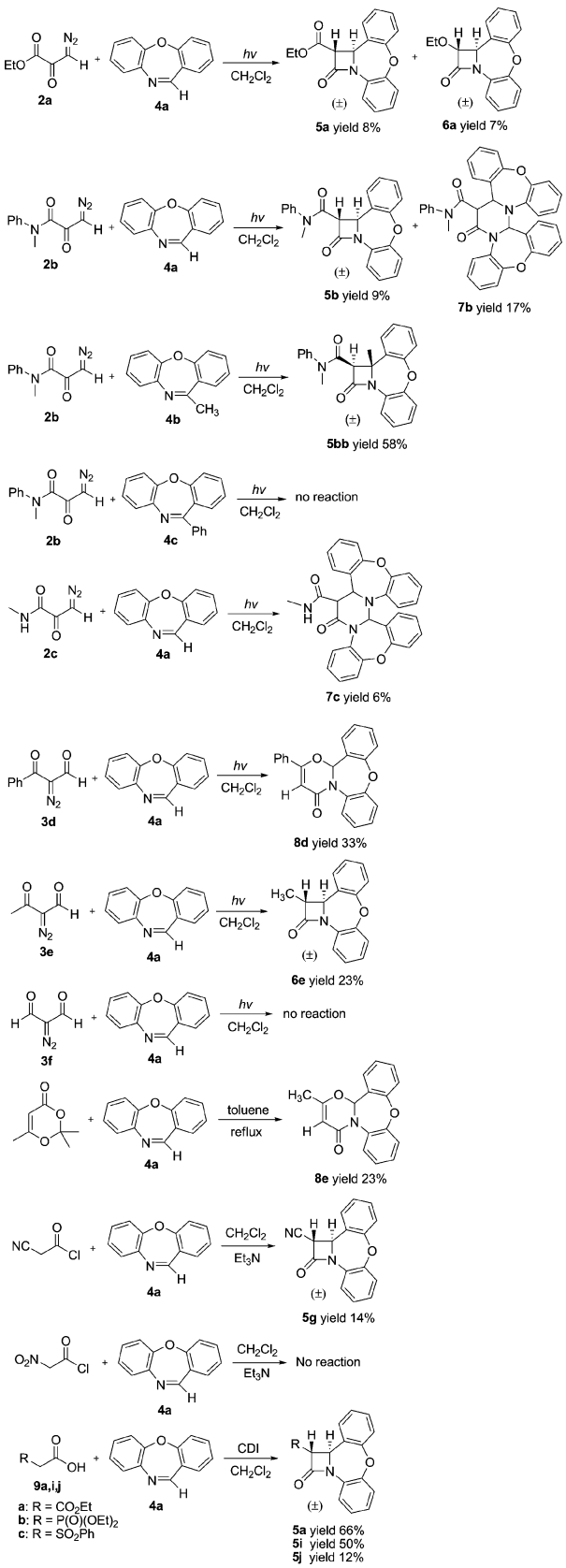


Fig. 1 Monosubstituted ketenes.

Results and discussion

To avoid the possible effect of a base or transition metal on the stereoselectivity in the Staudinger reaction, we hope to use a clear reaction system to study the original stereoselectivity. We first designed and synthesized two series of diazo ketone derivatives, 3-diazo-2-oxopropanoic acid derivatives **2a–c**[16–18] and 2-diazo-3-oxoalkanals **3d–f**,[19–21] as the precursors of ketenes with EAGs, according to reported methods. To identify the attacking direction of imines to the ketenes, we first explored the reaction of precursors **2** and **3** with cyclic imines **4**, in which we can conveniently verify the influence of the electron-acceptor substituents on the attacking direction of imines to the ketenes and the subsequent ring closure mode through the analysis of the product stereostructure. All reactions of precursors **2** and **3** with cyclic imines **4** were conducted in dried dichloromethane at 0 °C under UV photo-irradiation. The results are summarized in Scheme 1. Although the yields were generally low in all cases and some byproducts were generated in certain cases, the desired products were obtained in most cases with recovery of the imines. We attempted to use dropwise addition and to increase amount of diazo precursors to optimize the reaction conditions. However, no obvious difference was observed for the product yields. For the precursor ethyl 3-diazo-2-oxopropanate (**2a**), besides the desired ethyl *trans*-1,12b-dihydro-2*H*-azeto[1,2-*d*]dibenzo[*b*,*f*] [1,4]oxazepin-2-one-1-carboxylate (**5a**), a byproduct *trans*-1-ethoxy-1,12b-dihydro-2*H*-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxaze-pin-2-one (**6a**) was also obtained. The byproduct was generated from the reaction of the cyclic imine dibenzo[*b*,*f*][1,4]oxazepine (**4a**) and ethoxyketene. It was reported that acylketenes can lose a molecule of carbon monoxide to yield alkyketenes under UV photo-irradiation conditions.[22] Under the current reaction conditions, the precursor **2a** first generated ethoxycarbonylketene (**1a**), which, similarly, further gave rise to ethoxyketene by loss of carbon monoxide. The precursor 3-diazo-*N*-methyl-2-oxo-*N*-phenylpropanamide (**2b**) reacted with less steric cyclic imines **4a,b** smoothly, but did not with more steric cyclic imine 11-phenyldibenzo[*b*,*f*][1,4]oxazepine (**4c**), possibly due to the steric hindrance. It reacted with cyclic imine **4a** to afford the desired product *trans*-1,12b-dihydro-*N*-methyl-*N*-phenyl-2*H*-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-2-one-1-carboxamide (**5b**) and a byproduct 22,23-dihydro-*N*-methyl-*N*-phenyl-10a*H*,21*H*-tetrabenzo[*b*,*b*′,*f*,*f*′]pyrimido[1,2-*d*:3,4-*d*′]bis[1,4] oxazepin-21-one-22-carboxamide (**7b**), generated from ketene **1b** and two molecules of imine **4a**, similar reactions of which were observed previously.[10i] However, precursor **2b** and imine 11-methyldibenzo[*b*,*f*][1,4]oxazepine (**4b**) produced only the desired



Scheme 1 The Staudinger reactions involving monosubstituted ketenes with electron-acceptor substituents and cyclic imines.

product *trans*-1,12b-dihydro-12b,*N*-dimethyl-*N*-phenyl-2*H*-azeto-[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-2-one-1-carboxamide (**5bb**). Its stereostructure was identified by the single crystal XRD analysis (Fig. 2). The less steric precursor **2c** reacted with imine **4a** only to give rise to a byproduct 22,23-dihydro-*N*-methyl-10a*H*,21*H*-tetrabenzo[*b*,*b*′,*f*,*f*′]pyrimido[1,2-*d*:3,4-*d*′]bis-[1,4]oxazepin-21-one-22-carboxamide (**7c**) without the desired product.

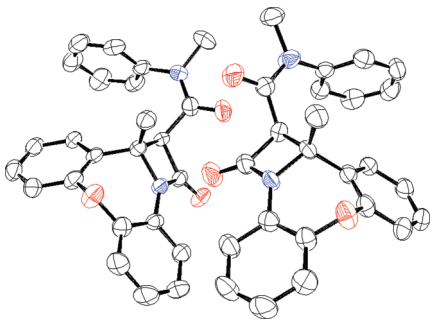


Fig. 2 The ORTEP drawing of the stereostructure of **5bb** (shown with 50% probability ellipsoids).

Although it has been well-documented that acylketenes favor to undergo [2+4] heteroatom Diels–Alder cycloaddition instead of [2+2] cycloaddition with imines,[23] to get a comprehensive investigation on the Staudinger reaction involving the monosubstituted ketenes with various EAGs experimentally, we still attempted the reaction of precursors **3d–f** with imine **4a**. As reported previously,[23] the [2+4] cycloadduct 2-phenyl-4*H*,14b*H*-dibenzo[*b*,*f*][1,3]oxazino[2,3-*d*]oxazepin-4-one (**8d**) was obtained as sole product for precursor **3d**. However, for precursor **3e**, *trans*-1-methyl-1,12b-dihydro-2*H*-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-2-one (**6e**) was obtained as a major product without the desired product. The byproduct was generated from the imine and methylketene, produced from acetylketene (**1e**) by loss of carbon monoxide as ethoxycarbonylketene (**1a**).[22] We also attempted to use 2,2,6-trimethyl-1,3-dioxin-4-one as the precursor of ketene **1e** to react with imine **4a** in refluxing toluene. As reported previously,[24] the [2+4] cycloadduct 2-methyl-4*H*,14b*H*-dibenzo[*b*,*f*][1,3]oxazino[2,3-*d*]oxazepin-4-one (**8e**) was obtained uniquely. It is also a pity that no reaction occurred for 2-diazomalonaldehyde (**3f**) with imine **4a** (Scheme 1).

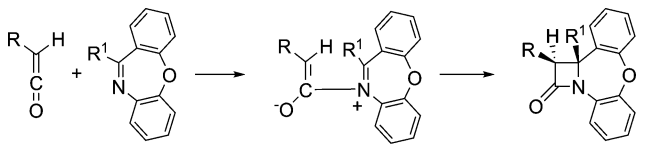
We prepared cyanoacetyl chloride and nitroacetyl chloride as precursors of cyanoketene (**1g**) and nitroketene (**1h**), respectively. The reaction of cyanoacetyl chloride and imine **4a** yielded the desired product *trans*-1-cyano-1,12b-dihydro-2*H*-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-2-one (**5g**) in the presence of triethylamine. However, for nitroacetyl chloride, no desired reaction occurred under similar conditions (Scheme 1).

Melman's group reported the direct synthesis of ethyl *trans*-azetidin-2-one-3-carboxylates from imines and ethyl hydrogen malonate in the presence of carbonyl diimidazole (CDI).[14] The same group previously elucidated that ethoxycarbonylketene is the key intermediate in the reactions.[25] They also extended their method to diethoxyphosphonoacetic acid and benzenesulfonoacetic acid to prepare the corresponding *trans*-β-lactams.[14] This provides another class of alternative ketene precursors for us. We used ethyl hydrogen malonate (**9a**), diethoxyphosphonoacetic

acid (**9b**), and benzenesulfonoacetic acid (**9c**) as the ketene precursors to react with cyclic imine **4a** in the presence of CDI to afford the desired products **5a,i,j**, respectively, in *trans*-configurations (Scheme 1). The results indicate that different reaction conditions (thermal and photo) do not affect the stereochemical outcome for ethoxycarbonylketene.

Although the experimental stereoselectivity in the Staudinger reaction of borylketene and imines is not clear, borylketene is not an accessible ketene in the Staudinger reaction.

On the basis of NMR and XRD analyses, all formed β-lactams from cyclic imines are in a *trans*-configuration, revealing that imines attack the ketenes from their *exo*-side, rather than the *endo*-side, even imine **4a** with the small substituent, hydrogen, on its imine moiety in the attacking side, to generate zwitterionic intermediates, which further undergo a conrotatory ring closure in the outward mode to give rise to the *trans*-β-lactam derivatives **5**. Because all cyclic imines **4** are in a *Z*-configuration, the β-lactam products **5** are in a *trans*-configuration. This implies that imines attack monosubstituted ketenes only from their *exo*-sides due to the steric hindrance whether they possess electron-donor or electron-acceptor substituents (Scheme 2).



Scheme 2 The stereochemical progress in the Staudinger reactions involving monosubstituted ketenes with electron-acceptor substituents and cyclic imines.

To figure out whether the torquoselectivity controls the stereoselectivity in the Staudinger reaction theoretically, we conducted a density functional theory (DFT) calculation investigation. We first studied the reaction of cyanoketene (**1g**) and cyclic imine **4a** as a model reaction. Structural optimization and single point energy were obtained at the B3LYP/6-31G(d) level[26,27] in the gas phase. The free energies in solution (Δ*G*) were computed by the CPCM method[28] in dichloromethane. The potential free energy surface of the reaction was obtained and is shown in Fig. 3.

The first step of the reaction is the generation of two possible zwitterionic intermediates (**INT-in-g** and **INT-out-g**) *via* the transition states (**TS1-in-g** and **TS1-out-g**), and the second step is the ring-closure to form the corresponding β-lactam products (***cis*-5g** and ***trans*-5g**) through the transition states (**TS2-in-g** and **TS2-out-g**), respectively. In the first step, the imine attack from the less hindered side (*exo*-side) of the ketene (the acceptor-out pathway, the formation of **INT-out-g**) is favored by 2.2 kcal mol^{-1} in terms of Gibbs free energy, compared with the attack at the hindered side (*endo*-side) (the acceptor-in pathway, the formation of **INT-in-g**). The generated zwitterionic intermediates, **INT-out-g** is 2.6 kcal mol^{-1} more stable than **INT-in-g**. Moreover, in the second step, the free energy of the acceptor-in transition state for the ring-closure step (*via* **TS2-in-g**) is 3.1 kcal mol^{-1} higher than that of the acceptor-out transition state (*via* **TS2-out-g**). This is consistent with the results reported by Sordo *et al.*[15b] Finally, for products, *trans*-product ***trans*-5g** (generated from **TS2-out-g**) is more stable 2.8 kcal mol^{-1} than *cis*-product ***cis*-5g** (generated from **TS2-in-g**). The results indicate that it is favorable to produce *trans*-product ***trans*-5g** from both the thermodynamic and dynamic viewpoints in the reaction.

To further investigate the effect of the cyano group on inward and outward rotations, the Natural Bond Orbital (NBO) analysis on **TS2-g** was also conducted. The result assigns a σ localized bond between C3 and C4, and the donating ability of $\sigma^{*}_{3,4}$ takes place mainly through two-electron interactions with the π* orbital between C5 and N6, as well with the π* orbital between C2 and O7, while the electron acceptor ability of $\sigma^{*}{}^{*}_{3,4}$ takes place mainly *via* donation from the $\pi_{5,6}$ bond and $\pi_{2,7}$ bond. Although the latter interactions are less efficient than the former, similar

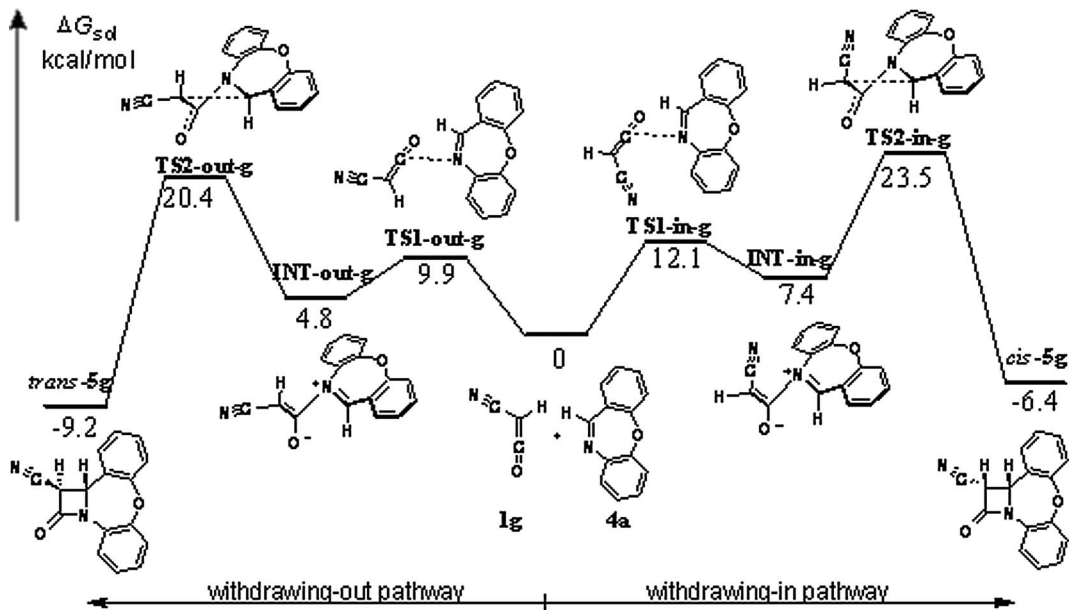


Fig. 3 The calculated energy surface for the reaction of ketene **1g** with imine **4a** at the B3LYP/6-31G(d) + ΔZPVE level of theory (Dichloromethane was used as solvent within the CPCM method).

to the reported result by Cossio *et al.* in the Staudinger reaction involving ketene and chloroketene,[12f] the total difference in $\Delta E(2)$ between **TS2-in-g** and **TS2-out-g** is mainly attributed to the latter interactions, especially, $\pi_{5,6} \rightarrow \sigma^{\neq *}_{3,4}$ (Fig. 4).

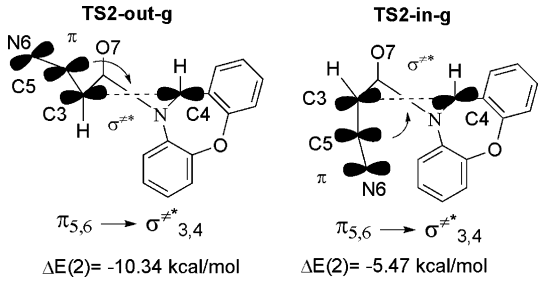


Fig. 4 Two-electron interactions in **TS2-g** structures.

The results from combined B3LYP and NBO studies are in good agreement with the experimental observation. The theoretically calculated results also reveal that the ring closure steps in both pathways are the rate-determining steps and the torquoelectronic effect of the cyano group does not reduce the energy of the transition state **TS2-in-g** to control the stereoselectivity in the reaction.

Sordo and coworkers previously investigated the influence of the torquoelectronic effect on the rotation mode of the ring closure in the reactions of formalimine and various monosubstituted ketenes at the RHF/6-31G* and MP2/6-31G*//6-31G* theory levels in gas-phase and solution phase.[15] They selected hydroxyl, halo, and methyl groups as ketene electron-donor groups and cyano, acyl (formyl and acetyl), and boryl groups as ketene electron-acceptor groups in their investigation.[15b] The results indicated that all electron-donor substituents presented a preference for the outward rotation in the ring closure in both gas and solution phases; the strong electron-acceptor substituent boryl presented a preference for the inward rotation in both gas and solution phases. However, for formyl and acetyl, the influence is somewhat complex. The formyl group inward ring closure was more favorable, 0.8–4.0 kcal mol^{-1} and 1.7 kcal mol^{-1}, than the outward one in gas and solution phases, respectively, while the acetyl group was favored 0.7 kcal mol^{-1} in the inward ring closure compared with the outward one in the gas phase for one of its two zwitterionic intermediate conformers; its other conformer favored the outward closure 0.4 kcal mol^{-1} compared to the inward closure in gas phase, and both of these conformers preferred the outward closure 1.3–1.6 kcal mol^{-1} in comparison with the inward closure in the solution phase.[7b] Although the previous studies indicated theoretically that the less strong electron-acceptor substituent formyl slightly favored the inward rotation in both phases,[15] the formylketene does not work in Staudinger reactions and borylketene cannot be prepared.

With development of computers and improvement of the software used in the calculations, the computed precision has been further improved recently. To understand the influence of other EAGs on the reactions, we further investigated theoretically the Staudinger reactions involving representative monosubstituted ketenes **1a,b,d–l** with various EAGs using a similar method. For ketenes **1a,b,d–f**, their optimized stable structures with different configurations were computed, respectively, and are shown in Fig. 5 and Table 1.

Table 1 Computed energies of optimized stable configurations of some ketenes

		$\Delta G^{\neq}$ (kcal mol^{-1})			
Entry	Ketene	s-*E*	s-*Z*		
1	**1a** (R═OEt)	0	0.41		
2	**1d** (R═Ph)	2.01	0		
3	**1e** (R═Me)	0	0.05		
4	**1f** (R═H)	0	0.53		
		s-*EE*	s-*ZE*	s-*EZ*	s-*ZZ*
5	**1b** (R═MeNPh)	0.88	5.41	0	3.01

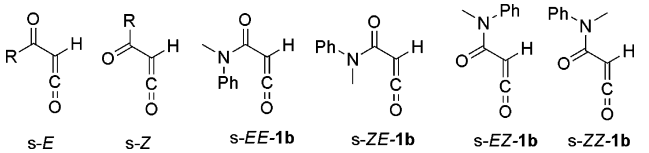
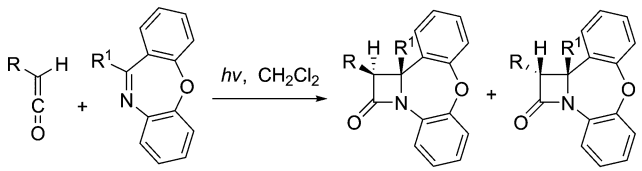


Fig. 5 Optimized stable configurations of some ketenes.

The results indicate that the s-*E* configurations are more stable 0.41, 0.05, and 0.53 kcal mol^{-1} than the s-*Z* configurations for ketenes **1a**, **1e**, and **1f**, respectively (Table 1, entries 1, 3 and 4). However, the s-*E* configuration is 2.01 kcal mol^{-1} higher than its s-*Z* configuration for ketene **1d** (Table 1, entry 2) because the phenyl group is not coplanar with the adjacent carbonyl group in its s-*E* configuration due to the steric hindrance with the ketene group to destroy the electron delocalization, leading to its energy to increase. Ketene **1b** possesses four different stable configurations because the C–N bond cannot rotate freely due to the p-π conjugation between the carbonyl group and the p-orbital in the nitrogen atom. Its s-*EZ* configuration is the most stable one and the s-*ZE* configuration locates in the highest energy level (Table 1, entry 5). Similarly, for ketene **1b**, the phenyl group is also not coplanar with the conjugative system in the amide with the phenyl group located in the s-*Z* configuration with the carbonyl group in the amide moiety, resulting in s-*ZE* and s-*ZZ* configurations in higher energy levels.

A calculational investigation on the Staudinger reaction of cyclic imines and representative ketenes with EAGs was conducted. For ketenes **1a,d–f**, their different stable configurations were considered. Similar results were obtained from different configurations of ketenes **1a,d–e** in each of the cases (Table 2, entries 1 *vs.* 2, entries 5 *vs.* 6, entries 7 *vs.* 8). However, comformers s-*E*-**1f** and s-*Z*-**1f** of ketene **1f** are favorable 0.1 kcal mol^{-1} (inward than outward) and 0.4 kcal mol^{-1} (outward than inward), respectively, in the solution phase (Table 2, entries 9 *vs.* 10). For ketene **1b**, only its most stable configuration was used in the calculation for its reactions with cyclic imines **4a,b**. The results are summarized in Table 2 and Table 23S (see Table 23S in the ESI†). For product **5bb**, its structural data are consistent with those obtained in XRD analysis (see Table 24S for details in the ESI†), further confirming that the calculated results are accurate. In a comparison between the free energies in the gas and solution phases, it is interesting to note that the differences of the activating energies in the two transition sates (**TS2-out** and **TS2-in**) in the ring closure decrease from the gas phase to solution for relatively strong

Table 2 Calculated transition state energies ($\Delta G^{\neq}$) for the reactions of ketenes **1** with imines **4** (in kcal mol^{-1})



1 **4** *trans*-(±)-**5** *cis*-(±)-**5**

Entry	Ketene	Imine	$\Delta G^{\neq}$ (**TS2-out**)	$\Delta G^{\neq}$ (**TS2-in**)	$-\Delta\Delta G^{\neq}$ (**TS2out-in**)	Calcd. *trans*:*cis*	Exp. *trans*:*cis*
1	s-*E*-**1a**	**4a**	28.6	30.9	2.3	97 : 3	100 : 0
2	s-*Z*-**1a**	**4a**	28.0	29.7	1.7	95 : 5	
3	s-*EZ*-**1b**[a]	**4a**	30.5	33.1	2.6	99 : 1	100 : 0
4	s-*EZ*-**1b**[a]	**4b**	37.4	39.1	1.7	95 : 5	100 : 0
5	s-*E*-**1d**	**4a**	31.9	33.9	2.0	96 : 4	100 : 0
6	s-*Z*-**1d**	**4a**	29.5	30.8	1.3	90 : 10	
7	s-*E*-**1e**	**4a**	27.9	30.1	2.2	97 : 3	—
8	s-*Z*-**1e**	**4a**	28.7	29.8	1.1	86 : 14	
9	s-*E*-**1f**	**4a**	26.5	26.4	–0.1	45 : 55	—
10	s-*Z*-**1f**	**4a**	27.8	28.2	0.4	65 : 35	
11	**1g**	**4a**	20.4	23.5	3.1	99 : 1	100 : 0
12	**1h**	**4a**	18.6	21.4	2.8	99 : 1	100 : 0
13	**1i**	**4a**	32.3	34.0	1.7	95 : 5	100 : 0
14	**1j**	**4a**	26.9	28.8	1.9	96 : 4	100 : 0
15	**1k**	**4a**	34.8	28.9	–5.9	0 : 100	—

[a] The most stable configuration s-*EZ*-**1b** was employed.

electron-acceptor ketenes **1f,i,k**, whereas they increase for other electron-acceptor ketenes **1a–e,g,h,j** (For details, see Table 23S in the ESI†). However, all accessible ketenes with EAGs present a preference for the outward rotation in the ring closure in the solution phase except for ketene **1f**.

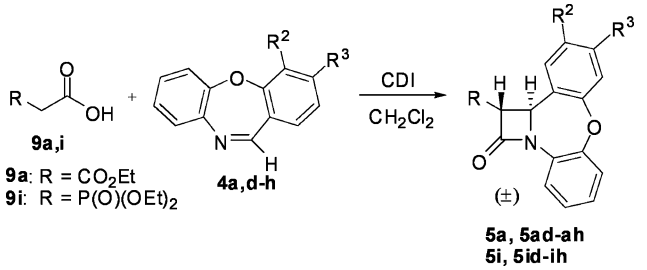
NBO studies also reveal that various EWGs investigated do not reduce energies of transition states **TS2-in** to control the stereoselectivity in the reactions (For details, see Table 25S in the ESI†). Additionally, dipole moments computed at the B3LYP/6-31G* level are larger for **TS2-out** than **TS2-in** (For details, see Table 26S in the ESI†).[12f] These differences in polarity promote higher $\Delta G_{\text{in-out}}$ differences in solution, also revealing that the reactions through **TS2-out** are dominant. Our results indicate, except for the unaccessible borylketene (**1k**) in the experiment, all other ketenes give similar results as the reaction of cyclic imine **4a** and cyanoketene (**1g**). That is, the energies of **TS2-in** are higher 1.1 to 3.1 kcal mol^{-1} than those of **TS2-out**, whereas, for ketene **1k**, the energy of **TS2-in-k** is 5.9 kcal mol^{-1} lower than that of **TS2-out-k**, indicating that, for the Staudinger reactions with practical monosubstituted ketenes with EAGs, imines attack ketenes more favourably at their *exo*-side (outward attack) than at their *endo*-side (inward attack) to generate zwitterionic intermediates. For the formed intermediates, all **INT-out** undergo a ring closure to give rise to *trans*-products *via* more stable transition states **TS2-out** rather than *cis*-products from the corresponding **INT-in** *via* **TS2-in**. The current results reveal that the substituents of the applicable monosubstituted ketenes with EAGs cannot control the stereoselectivity with the torquoelectronic effect in the Staudinger reaction.

Our theoretical calculated results are in great agreement with our experimental observation. It was reported that acyl Meldrum's acids can be utilitized as the precursors of acylketenes in the exclusive synthesis of *trans*-3-acyl-β-lactams.[13] The acyl Meldrum's acid derivatives reacted with cyclic imine methyl (*R*)-thiazolidinecarboxylate to afford *trans*-3-acyl-β-lactams derivatives.[13b] The experimental results also support our calculated results.

Because the influence of the imine substituents on the stereocontrol was observed in the disubstituted ketene participating in the Staudinger reaction and the influence is attributed to the change of the rate-determining step in the reactions through the experimental and theoretical studies,[9] to further confirm that the ring closure is the rate-determining step in the reaction experimentally and to explore whether the imine substituents affect the stereoselectivity in the Staudinger reaction involving monosubstituted ketenes with EAGs, we conducted a series of reactions between various cyclic imines **4a,d–h** with different electronic properties and both ethyl hydrogen malonate (**9a**) and diethoxyphosphonoacetic acid (**9i**) because these reactions produced the desired products in relatively high yields. The acids **9a** and **9i** were mentioned to generate the corresponding ketenes **1a,i** gradually in the presence of CDI to avoid the ketene dimerization.[25] The results are summarized in Table 3. The electronic effect of cyclic imines does not affect the stereoselectivity, but does on the yields of β-lactams in current cases. The cyclic imines with electron-withdrawing substituents generally gave rise to the desired products in higher yields than those with electron-donating substituents, revealing that the electron-deficient substituents are favorable to the ring closure to improve the yields because they can increase the rate of the ring closure according to our proposal.[11] This supports the idea that the ring closure is indeed the rate-determining step in the reaction experimentally.

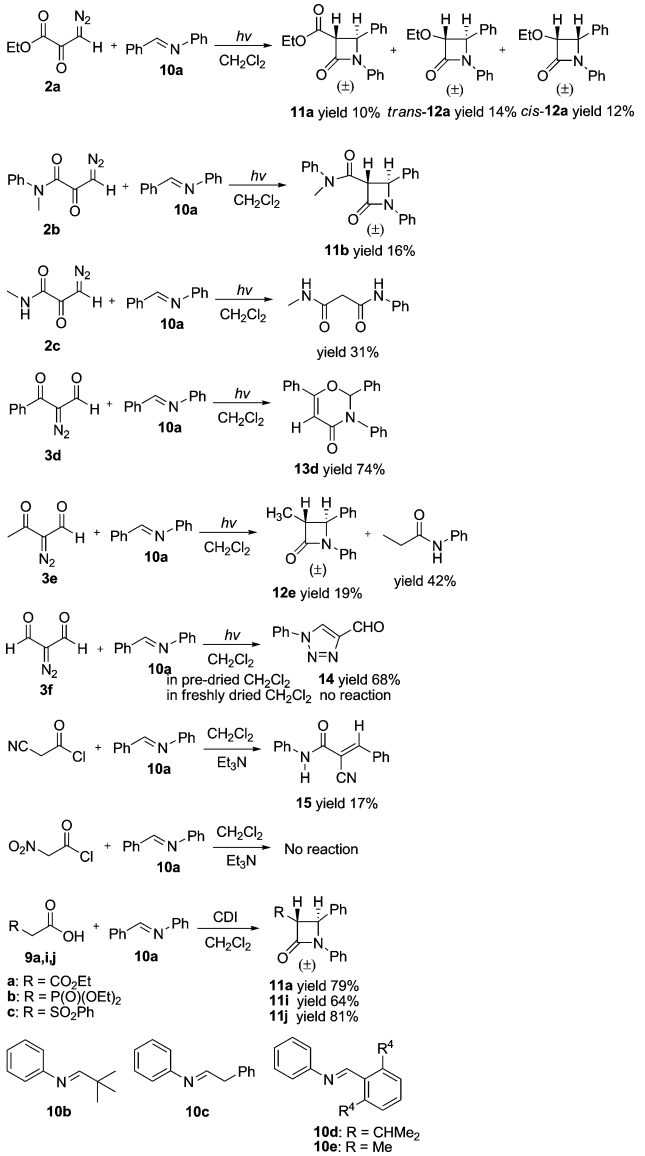
After figuring out the reaction process of cyclic imines and ketenes with EAGs, the stereoselectivity of which is controlled by steric hindrance instead of the torquoelectronic effect, to get a comprehensive understanding on the Staudinger reaction involving the monosubstituted ketenes with EAGs experimentally,

Table 3 Reactions of various cyclic imines **4a,d–h** with ethyl hydrogen malonate (**9a**) and diethoxyphosphonoacetic acid (**9i**)



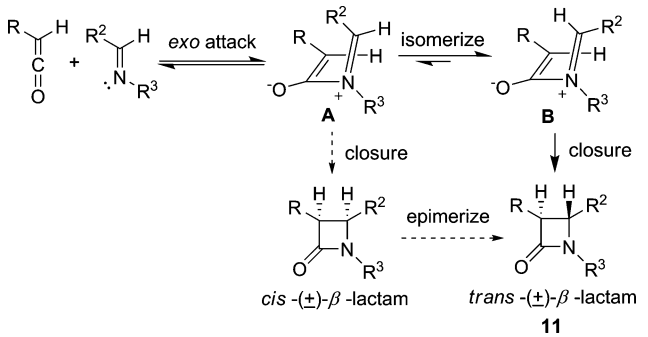
Entry	Imine **4**	R^2	R^3	Precursor **9**	Product **5**	Yield (%)
1	**4d**	H	NO_2	**9a**	**5ad**	94
2	**4e**	H	Cl	**9a**	**5ae**	80
3	**4a**	H	H	**9a**	**5a**	66
4	**4f**	H	Me	**9a**	**5af**	53
5	**4g**	Me	H	**9a**	**5ag**	61
6	**4h**	H	MeO	**9a**	**5ah**	37
7	**4d**	H	NO_2	**9i**	**5id**	95
8	**4e**	H	Cl	**9i**	**5ie**	64
9	**4a**	H	H	**9i**	**5i**	50
10	**4f**	H	Me	**9i**	**5if**	60
11	**4g**	Me	H	**9i**	**5ig**	42
12	**4h**	H	MeO	**9i**	**5ih**	42

we also conducted reactions of ketene precursors **2**, **3**, **9**, cyano and nitroacetyl chlorides with a linear imine benzylideneaniline (**10a**) to reveal the reaction process. The results are summarized in Scheme 3. As the reactions with cyclic imines, the desired products were obtained in most cases although the yields were generally low and some byproducts were generated in certain cases. For ethyl 3-diazo-2-oxopropanate (**2a**), besides the desired ethyl *trans*-1,4-diphenyl-azetidin-2-one-3-carboxylate (**11a**), both *trans*-3-ethoxyl-1,4-diphenyl-2-azetidinone (*trans*-**12a**) and *cis*-3-ethoxyl-1,4-diphenyl-2-azetidinone (*cis*-**12a**) were also obtained as byproducts. Similarly, the byproducts were produced from benzylideneaniline (**10a**) and ethoxyketene. The precursor **2b** generated only the desired product *trans*-*N*-methyl-1,4,*N*-triphenylazetidin-2-one-3-carboxamide (**11b**) in a low yield. However, the less steric precursor **2c** only gave rise to a byproduct *N*-methyl-*N′*-phenylpropanediamide without the desired product. Similarly to the cyclic imine, the [2+4] cycloadduct 2,3-dihydro-2,3,6-triphenyl-4*H*-1,3-oxazin-4-one (**13d**) was obtained as a major product in a good yield without the desired product in the reaction of precursor **3d** and imine **10a**. However, for the precursor **3e**, *trans*-3-methyl-1,4-diphenyl-2-azetidinone (**12e**) and *N*-phenylpropanamide were obtained instead of the desired product. 2-Diazomalonaldehyde (**3f**) yielded 1-phenyl-1*H*-1,2,3-triazole-4-carboxaldehyde (**14**)[20] in a moderate yield in pre-dried dichloromethane, and no reaction occurred in the freshly dried dichloromethane. It was reported in an early paper that the reaction of cyanoacetyl chloride and imine **10a** produced 3-cyano-1,4-diphenyl-2-azetidinone without identification of stereostructure and spectral analytical data.[29] However, in the same year, another group reported that the reaction yielded 2-cyano-*N*-phenylcinnamamide.[30] We re-conducted the reaction and found that cyanoacetyl chloride reacted with imine **10a** produced only 2-cyano-*N*-phenylcinnamamide (**15**), which was confirmed by single crystal XRD analysis. As with the reaction with the cyclic imine **4a**, the reaction of nitroacetyl chloride and imine **10a** did not occur (Scheme 3). However, it can react with aniline to produce 2-nitro-*N*-phenylacetamide.[31] To carefully study the effect of the ketene substituents on the stereoselectivity, we also repeated reactions of hydrogen malonate (**9a**), diethoxyphosphonoacetic acid (**9b**), and benzenesulfonoacetic acid (**9c**) with linear imine **10a** to afford the desired products **11a,i,j**, respectively, in *trans*-configurations in good yields as reported by Melman's group.[14] No *cis*-product was observed in careful analyses on the reaction mixtures (Scheme 3).



Scheme 3 The Staudinger reactions involving monosubstituted ketenes with electron-acceptor substituents and linear imines.

On the basis of ^{1}H NMR analyses, all formed β-lactams from the linear imine **10a** and the ketenes with EAGs are in a *trans*-configuration. Because linear imine **10a** is an *E*-configuration, the β-lactam products **11** from the ketenes with EAGs are in a *trans*-configuration, indicating that the zwitterionic intermediates generated from the imine attack at the *exo*-side of ketenes undergo an isomerization and then a conrotatory ring closure to give rise to the *trans*-β-lactam derivatives **11** (Scheme 4).

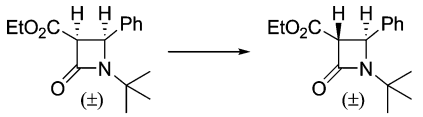


Scheme 4 The stereochemical progress in the Staudinger reactions involving monosubstituted ketenes with electron-acceptor substituents.

Although the utility of cyclic imines illustrates that the *trans*-products generated from the isomerization of the imine moiety in the zwitterionic intermediates for linear imines, we still hoped to verify the isomerization directly. *N*-*tert*-butyl group in imines can inhibit their isomerization in the Staudinger reactions.[11] We conducted reactions of *N*-benzylidene *tert*-butylamine with ethyl hydrogen malonate, diethoxyphosphonoacetic acid, and benzenesulfonoacetic acid, respectively, in the presence of CDI. However, unfortunately, no desired reaction occurred. The reaction of *N*-benzylidene benzylamine with these acids still did not work. The results indicate that the Melman's method was only limited to *N*-aryl imines. We had to design and synthesize two bulky aromatic imines, *N*-benzylidene 2,6-diisopropyl and 2,6-dimethyl-anilines, to inhibit the isomerization. However, neither of them can undergo the reactions with acids **9** in the presence of CDI, possibly due to steric hindrance in the imine attack to ketenes (Scheme 3). It is indeed a pity that the isomerization cannot be verified directly.

Additionally, β-lactam-3-carboxylic acid derivatives, β-lactam-3-phosphonates, and 3-benzenesulfonyl-β-lactam possess the structural feature of β-dicarbonyl compounds. They could epimerize under acidic and basic conditions. Thus, there is another possible pathway to generate *trans*-β-lactam-3-carboxylates for acyclic imines: Imines attack ketenes from their *exo*-sides to generate zwitterionic intermediates **A**, which undergo a conrotatory ring closure to give rise to *cis*-β-lactams. They further epimerize into *trans*-β-lactams under reaction conditions (Scheme 4). The attacking direction and the epimerization control the stereoselectivity. To make our results complete, we carried out studies on the epimerization. First, we prepared ethyl *cis*-1-*tert*-butyl-4-phenyl-azetidin-2-one-3-carboxylate (*cis*-**11m**), which should epimerize favourably due to steric hindrance in its *cis*-isomer, in a mixture of their *cis*/*trans*-isomers in a ratio of 30 : 70 according to the reported method.[32] The mixture of *cis*/*trans*-β-lactams was used to evaluate the epimerization of *cis*-β-lactams. Each of reactants (ethyl hydrogen malonate and CDI), the byproduct (imidazole), and their mixture were used in the epimerization experiments. The results are summarized in Table 4. Although epimerization occurred in each of cases, complete epimerization was not observed in any case during 3 h to 5 h (generally, the cycloaddition time for synthesis of β-lactams is 1 h, the whole reaction time is 2 h for the Melman's method). This implies that *trans*-β-lactams were not generated from the epimerization of *cis*-β-lactams because *trans*-β-lactams were obtained specifically on the basis of careful ^{1}H NMR analysis for the reaction mixture. If they were generated from the epimerization of their *cis*-isomers, some *cis*-isomers should be observed at least in the reaction mixture.

Table 4 Epimerization of ethyl *cis*-1-*tert*-butyl-4-phenyl-azetidin-2-one-3-carboxylate[a]



Entry	Epmierization conditions	Reaction time	*cis*:*trans*[b]
1	—		30 : 70
2	1 equiv. $EtO_2CCH_2CO_2H$	5 h	28 : 72
3	1 equiv. CDI	5 h	9 : 91
4	1 equiv. Imidazole	5 h	3 : 97
5	1 equiv. $EtO_2CCH_2CO_2H$ 1 equiv. CDI	5 h	2 : 98
6	2 equiv. Imidazole	3 h	13 : 87
7	2.3 equiv. $EtO_2CCH_2CO_2H$ 2.2 equiv. imidazole	3 h	14 : 86

[a] Conducted in dichloromethane in the concentration as that under the synthetic reaction conditions. [b] Determined with ^{1}H NMR.

The current investigation illustrates that, in the practical Staudinger reaction involving monosubstituted ketenes, either with electron-donor or acceptor substituents, imines attack ketenes from their *exo*-sides to generate zwitterionic intermediates. If ketenes do not possess a strong electron-donating substituent, their imine moiety undergoes an isomerization for linear imines. The degree of the isomerization is controlled by the electronic properties of the ketene and imine substituents and by the steric hindrance of the imine substituents, especially *N*-substituents.[11] The (isomerized) zwitterionic intermediates further undergo a conrotatory ring closure to afford the corresponding β-lactams. The imine attacking direction and the isomerization control the stereoselectivity. The electron-acceptor substituents, either σ- or π-acceptors, control the stereoselectivity in the reaction through decreasing the rate of the ring closure, resulting in the isomerization of the imine moiety in zwitterionic intermediates, not through the torquoelectronic effect in the ring closure. The current results provide a comprehensive understanding and further perfect our previous proposal on the stereoselectivity in the practical monosubstituted ketene-participating Staudinger reactions. The different behavior of the torquoelectronic effect in the Staudinger reaction is attributed to that the Staudinger reaction is multistep reaction, the ring closure step is not always rate-determining, and the conrotatory closure possesses certain nucleophilic character.

Conclusion

In summary, stereoselective control is one of the crucial issues in the Staudinger reaction and is still an unresolved problem in some cases, especially in the Staudinger reactions involving the monosubstituted ketenes with electron-acceptor substituents. After comparative analysis of the stereostructure of the products in the reactions involving ketenes with electron-acceptor substituents with cyclic and acyclic imines, DFT calculations, and evaluation on the epimerization of the product with a carboxylate, the results suggest that imines attack ketenes from their *exo*-sides to generate

zwitterionic intermediates, of which the imine moiety undergoes an isomerization for linear imines. The (isomerized) zwitterionic intermediates further undergo a conrotatory ring closure to afford the corresponding β-lactams. Namely, the imine attacking direction and the isomerization control the stereoselectivity. The torquoelectronic effect does not affect the stereoselectivity in the practical monosubstituted ketene-participating in Staudinger reactions although the unaccessible borylketene with a powerful acceptor group controls the stereoselectivity torquoelectronically in theory. After the current investigation, we perfect and expand our previous proposal on the stereoselectivity in the Staudinger reaction. That is, imines attack ketenes from their *exo*-sides to generate zwitterionic intermediates whatever the ketene subsituents are, electron-donor or acceptor groups. Their imine moiety could undergo an isomerization for the intermediates generated from the ketenes without strong electron-donor substituents. The (isomerized) zwitterionic intermediates further undergo a conrotatory ring closure to afford the corresponding β-lactams.

Experimental

General method

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 200 or a Varian Mercury 300 Plus spectrometer with TMS as an internal standard in $CDCl_3$ solution and the chemical shifts (δ) are reported in ppm. The IR spectra were taken on a Nicolet 5700 FT-IR spectrometer. HRMS data was carried out on an Agilent LC/MSD TOF mass spectrometer. TLC separations were performed on silica gel GF_{254} plates, and the plates were visualized with UV light. Linear imines **10**,[33] cyclic imines **4a,e–h**,[34] **4b,c**,[35] and **4d**;[36] cyanoacetyl chloride,[37] nitroacetyl chloride,[38,39] ethyl hydrogen malonate,[40] diethoxyphosphorylacetic acid,[41] and benzenesulfonylacetic acid[42] were prepared according to published procedures. Dichloromethane was refluxed with CaH_2 and freshly distilled prior to use. Toluene was refluxed with sodium and freshly distilled prior to use. All reactions were performed under a nitrogen atmosphere.

Recation of diazo precursors 2 or 3 and imines 4 or 10a under photo-irradiation (general procedure)

A solution of diazo precursor **2** or **3** (2 mmol) and imine **4** or **10** (1 mmol) in 3 mL of dry CH_2Cl_2 was stirred and irradiated by a high-pressure mercury lamp under a nitrogen atmosphere at 0 °C for 6–8 h. The solution was concentrated, and the residue was separated on a silica gel column with a mixture of ethyl acetate and petroleum ether (60–90 °C) (1 : 10 to 1 : 20, v/v) as an eluent to afford corresponding products.

Ethyl (±)-*trans*-1,12b-dihydro-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]-oxazepin-2-one-1-carboxylate (5a). Colorless crystals, yield 8%, m.p. 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.38 (t, J = 7.2 Hz, 3H, CH_3), 4.35 (q, J = 7.2 Hz, 2H, CH_2O), 4.50 (d, J = 3.0 Hz, 1H, CH), 5.96 (d, J = 3.0 Hz, 1H, CH), 7.01–7.97 (m, 8H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.2, 55.2, 57.7, 62.3, 120.1, 121.6, 121.7, 124.9, 125.26, 125.33, 125.9, 129.3, 129.5, 130.5, 144.0, 157.8, 158.2, 166.1. IR (KBr) ν/cm^{-1}: 1759 (C═O), 1729 (C═O). HRMS calcd for $C_{18}H_{15}NNaO_4$ ([M+Na]$^+$) m/z: 332.0893, found: 332.0904.

(±)-*trans*-1-Ethoxyl-1,12b-dihydro-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-2-one (6a). Colorless oil, yield 7%, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (t, J = 6.9 Hz, 3H, CH_3), 3.84 (dq, J = 9.0, 6.9 Hz, 1H in CH_2O), 3.97 (dq, J = 9.0, 6.9 Hz, 1H in CH_2O), 5.05 (d, J = 2.1 Hz, 1H, CH), 5.61 (d, J = 1.8 Hz, 1H, CH), 6.99–8.08 (m, 8H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 15.2, 60.5, 66.5, 84.5, 120.3, 121.6, 121.7, 124.8, 125.3, 126.0, 129.3, 129.7, 130.4, 144.1, 150.7, 158.6, 162.9. IR (KBr) ν/cm^{-1}: 1754 (C═O). HRMS calcd for $C_{17}H_{15}NNaO_3$ ([M+Na]$^+$) m/z: 304.0944, found: 304.0937.

(±)-*trans*-1,12b-Dihydro-*N*-methyl-*N*-phenylazeto[1,2-*d*]dibenzo[*b*,*f*][1,4] oxazepin-2-one-1-carboxamide (5b). Colorless crystals, yield 9%, m.p. 177–178 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.42 (s, 3H),4.43 (d, J = 2.8 Hz, 1H), 6.03(d, J = 2.8 Hz, 1H), 6.52–7.93 (m, 13H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 37.8, 55.7, 56.3, 120.0, 121.4, 121.7, 124.5, 124.9, 125.1, 125.4, 127.7, 128.6, 129.6, 129.7, 130.2, 142.7, 144.0, 158.3, 159.4, 165.0. IR (KBr) ν/cm^{-1}: 1755 (C═O), 1657 (C═O). HRMS calcd for $C_{23}H_{18}N_2NaO_3$ ([M+Na]$^+$) m/z: 393.1209, found: 393.1197.

22,23-Dihydro-*N*-methyl-*N*-phenyl-10a*H*,21*H*-tetrabenzo[*b*,*b*′,*f*,*f*′]pyrimido [1,2-*d*:3,4-*d*′]bis[1,4]oxazepin-21-one-22-carboxamide (7b). Colorless crystals, yield 17%, m.p. 256–257 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.03 (s, 3H, CH_3), 4.46 (d, J = 11.1 Hz, 1H, CH), 5.17 (d, J = 11.1 Hz, 1H, CH), 6.32 (s, 1H, CH), 6.79–7.48 (m, 21H, ArH), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 37.0, 51.9, 58.0, 77.3, 119.1, 120.7, 121.7, 121.9, 122.2, 122.4, 123.9, 124.8, 125.4, 126.0, 126.6, 127.3, 127.6, 127.8, 128.9, 129.3, 130.3, 130.3, 130.7, 132.3, 139.0, 142.9, 148.0, 153.8, 156.8, 158.1, 166.1, 167.7. IR (KBr) ν/cm^{-1}: 1653, 1676 (C═O). HRMS calcd for $C_{36}H_{28}N_3O_4$ ([M+H]$^+$) m/z: 566.2074, found: 566.2043.

(±)-*trans*-1,12b-Dihydro-12b,*N*-dimethyl-*N*-phenyl-azeto[1,2-*d*]dibenzo[*b*,*f*] [1,4]oxazepin-2-one-1-carboxamide (5bb). Colorless crystals, yield 58%, m.p. 200–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.06 (s, 3H, CH_3), 3.42 (s, 3H, NCH_3), 4.70 (s, 1H, CH), 5.31 (dd, J = 1.2, 7.8 Hz, 1H, ArH), 6.66–8.05 (m, 12H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.3, 37.9, 60.5, 64.5, 121.1, 121.3, 122.3, 124.6, 124.8, 124.9, 128.2, 128.5, 128.7, 129.7, 130.7, 134.6, 143.1, 143.3, 156.5, 160.2, 165.7. IR (KBr) ν/cm^{-1}: 1761, 1652 (C═O). HRMS calcd for $C_{24}H_{20}N_2NaO_3$ ([M+Na]$^+$) m/z: 407.1366, found: 407.1351.

22,23-Dihydro-*N*-methyl-10a*H*,21*H*-tetrabenzo[*b*,*b*′,*f*,*f*′]pyrimido[1,2-*d*:3,4-*d*′]bis[1,4]oxazepin-21-one-22-carboxamide (7c). Colorless crystals, yield 6%, m.p. 253–254 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.58 (d, J = 5.0 Hz, 3H, CH_3), 4.38 (d, J = 11.0 Hz, 1H, CH), 5.28 (d, J = 11.0 Hz, 1H, CH), 6.42 (s, 1H, CH), 6.61–7.60 (m, 17H, NH & ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.3, 54.2, 55.9, 78.2, 119.8, 120.5, 121.9, 122.1, 122.3, 122.5, 124.1, 125.0, 125.3, 125.9, 126.1, 127.5, 128.5, 128.6, 129.5, 130.2, 130.4, 131.6, 132.3, 139.1, 148.6, 153.2, 156.4, 157.9, 166.3, 166.8. IR (KBr) ν/cm^{-1}: 1645, 1681(C═O). HRMS calcd for $C_{30}H_{23}N_3NaO_4$ ([M+Na]$^+$) m/z: 512.1580, found: 512.1581.

2-Phenyldibenzo[*b*,*f*][1,3]oxazino[3,2-*d*][1,4]oxazepin-4(14b*H*)-one (8d). Colorless oil, yield 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.15 (s, 1H, CH), 6.80 (s, 1H, CH), 7.15–7.84 (m, 13H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 87.0, 97.8, 121.18, 121.21, 124.5, 124.7, 125.9, 126.4, 128.0, 128.1, 128.6, 128.9, 129.5, 131.1, 131.2, 131.7, 153.5, 156.8, 163.4, 163.6. IR (KBr) ν/cm^{-1}: 1676 (C═O). HRMS calcd for $C_{22}H_{16}NO_3$ ([M+H]$^+$) m/z: 342.1124, found: 342.1100.

(±)-*trans*-1,12b-Dihydro-1-methyl-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]-oxazepin-2-one (6e). Colorless oil, yield 23%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.57 (d, J = 7.4 Hz, 3H, CH_3), 3.67 (dq, J_1 = 7.4 Hz, J_2 = 2.8 Hz, 1H, CH), 5.26 (d, J = 2.6 Hz, 1H, CH), 6.93–8.02 (m, 8H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 12.9, 48.6, 59.3, 119.8, 121.40, 121.43, 124.0, 125.1, 125.8, 130.0, 130.5, 143.8, 158.1, 166.3. IR (KBr) ν/cm^{-1}: 1748 (C═O). HRMS calcd for $C_{16}H_{14}NO_2$ ([M+H]$^+$) m/z: 252.1019, found: 252.1007.

(±)-*trans*-3-Ethoxyl-1,4-diphenyl-2-azetidinone (*trans*-12a). Colorless crystals, yield 14%, m.p. 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.0 Hz, 3H, CH_3), 3.71 (dq, J = 9.3, 7.0 Hz, 1H in CH_2O), 3.81 (dq, J = 9.3, 7.0 Hz, 1H in CH_2O), 4.47 (d, J = 1.8 Hz, 1H, CH), 4.91 (d, J = 1.8 Hz, 1H, CH), 7.05–7.42 (m, 10H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 15.5, 63.8, 66.7, 90.1, 117.5, 124.3, 126.0, 128.7, 129.0, 129.2, 136.4, 137.1, 164.5. IR (KBr) ν/cm^{-1}: 1754 (C═O). HRMS calcd for $C_{17}H_{17}NNaO_2$ ([M+Na]$^+$) m/z: 290.1151, found: 290.1151.

(±)-*cis*-3-Ethoxyl-1,4-diphenyl-2-azetidinone (*cis*-12a). Colorless crystals, yield 12%, m.p. 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 6.9 Hz, 3H, CH_3), 3.16 (dq, J = 9.0, 6.9 Hz, 1H in CH_2O), 3.45 (dq, J = 9.0, 6.9 Hz, 1H in CH_2O), 4.93 (d, J = 4.8 Hz, 1H, CH), 5.20 (d, J = 4.5 Hz, 1H, CH), 7.03–7.40 (m, 10H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 15.5, 62.0, 66.4, 83.5, 117.4, 124.3, 128.0, 128.4, 128.5, 129.0, 133.4, 137.1, 164.4. IR (KBr) ν/cm^{-1}: 1745 (C═O). HRMS calcd for $C_{17}H_{18}NO_2$ ([M+H]$^+$) m/z: 268.1332, found: 268.1329.

(±)-*trans*-*N*-Methyl-1,4,*N*-triphenyl-azetidin-2-one-3-carboxamide (11b). Colorless crystals, yield 16%, m.p. 205–206 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.37 (s, 3H, CH_3), 3.89 (d, J = 2.4 Hz, 1H, CH), 5.51 (d, J = 2.4 Hz, 1H, CH), 7.22–7.33 (m, 15H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 37.8, 58.1, 62.4, 117.2, 124.1, 126.3, 127.4, 128.1, 128.7, 128.9, 129.0, 129.6, 136.6, 137.2, 142.3, 160.9, 165.1. IR (KBr) ν/cm^{-1}: 1758 (C═O), 1652 (C═O). HRMS calcd for $C_{23}H_{20}N_2NaO_2$ ([M+Na]$^+$) m/z: 379.1416, found: 379.1413.

Reaction of 2,2,6-trimethyl-1,3-dioxin-4-one and imine 4a. A mixture of 2,2,6-trimethyl-1,3-dioxin-4-one (142 mg, 1 mmol) and cyclic imine **4a** (195 mg, 1 mmol) was dissolved in 3 mL of dry toluene and refluxed for 2 h. After removal of the solvent, the residue was subjected to silica gel column chromatography (ethyl acetate and petroleum ether, 1 : 10 v/v) to afford the [4+2] product as a colorless oil 64 mg (23% yield). 2-Methyldibenzo[*b*,*f*][1,3]oxazino[3,2-*d*][1,4]oxazepin-4(14b*H*)-one (**8e**). Colorless oil, yield 23%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.09 (s, 3H, CH_3), 5.41 (s, 1H, CH), 6.54 (s, 1H, CH), 7.12–7.55 (m, 8H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.5, 86.6, 100.5, 121.0, 124.2, 124.6, 125.6, 128.0, 128.1, 128.6, 129.4, 131.1, 133.3, 153.6, 156.6, 162.7, 166.7. IR (KBr) ν/cm^{-1}: 1679 (C═O). HRMS calcd for $C_{17}H_{14}NO_3$ ([M+H]$^+$) m/z: 280.0968, found: 280.0975.

Reaction of Cyanoacetyl Chlorides and Imines 4a or 10a in the Presence of Triethylamine (General Procedure)

Et_3N (152 mg, 1.5 mmol) was added dropwise to a solution of cyanoacetyl chloride (104 mg, 1 mmol) and the appropriate imine **4a** or **10a** (1 mmol) in dry CH_2Cl_2 (3 mL) at –78 °C over 1 h. The reaction mixture was stirred for 6 h and was allowed to warm to room temperature. It was washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified on a silica gel column chromatography [elution with ethyl acetate and petroleum ether (60–90 °C) 1 : 6, v/v] to afford product.

(±)-*trans*-1-Cyano-1,12b-dihydro-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]-oxazepin-2-one (5g). Colorless crystals, yield 14%, m.p. 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.46 (d, J = 3.2 Hz, 1H, CH), 5.93 (d, J = 3.2 Hz, 1H, CH), 7.07–7.94 (m, 8H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 41.0, 56.6, 113.2, 120.1, 121.8, 122.1, 125.5, 125.7, 125.9, 127.8, 128.9, 131.4, 144.0, 153.2, 157.9. IR (KBr) ν/cm^{-1}: 1767 (C═O), 2248 (CN). HRMS calcd for $C_{16}H_{11}N_2O_2$ ([M+H]$^+$) m/z: 263.0815, found: 263.0829.

Reaction of acids 9 and imines 4 or 10a in the presence of CDI (general procedure)

Acid (1 mmol) and CDI (178 to 486 mg, 1.10 to 3.0 mmol) were dissolved in dichloromethane (2 mL) and the solution was stirred at RT for 1 h. To the stirring solution was added imine (1 mmol) in dichloromethane (1 mL). The resulting mixture was stirred for another 1 h. After removal of solvent, the residue was purified on a silica gel column with petroleum ether (60–90 °C) and ethyl acetate (30 : 1 to 20 : 1, v/v) as eluent to afford title compounds.

Diethyl (±)-*trans*-1,12b-dihydro-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]-oxazepin-2-one-1-phosphonate (5i). Colorless crystals, yield 50%, m.p.174–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41 (dt, J = 6.8, 7.2 Hz, 6H), 4.13 (dd, J = 3.0, 16.2 Hz, 1H), 4.31 (m, 4H), 5.85 (dd, J = 3.0, 8.4 Hz, 1H), 7.00–7.97 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.4, 16.5, 50.5, 52.4, 53.5, 62.9, 63.0, 63.2, 63.3, 120.0, 121.5, 121.6, 124.8, 125.2, 125.4, 126.0, 129.6, 130.5, 143.9, 157.9. IR (KBr) ν/cm^{-1}: 1746 (C═O). MS-ESI (m/z): 396 [M+Na]$^+$. HRMS calcd for $C_{19}H_{20}NNaO_5P$: 396.0971, found: 396.0972.

(±)-*trans*-1-Benzenesulfonyl-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one (5j). White solid, yield 12%, m.p.253–254 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.03 (d, J = 3 Hz, 1H), 6.09 (d, J = 3 Hz, 1H), 7.03–8.153 (m, 13H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 54.5, 73.2, 120.3, 121.7, 121.9, 125.4, 125.5, 125.6, 125.9, 127.9, 129.0, 129.6, 131.0, 134.9, 137.4, 144.1, 150.5, 154.3, 158.0. IR ν/cm^{-1}: 1771 (C═O). MS-ESI (m/z): 400 [M+Na]$^+$. HRMS calcd for $C_{21}H_{15}NNaO_4S$: 400.0614, found: 400.0622.

Ethyl (±)-*trans*-1,12b-dihydro-11-nitro-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-2-one-1-carboxylate (5ad). Colorless needle crystals, yield 94%, m.p. 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 4.57 (d, J = 3.0 Hz, 1H), 5.95 (d, J = 3.0 Hz, 1H), 7.06–8.31 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.1, 54.5, 58.1, 62.6, 120.2, 121.5, 122.0, 123.0, 125.3, 125.9,126.1, 128.8, 130.6, 142.9, 144.3, 157.1, 162.5, 165.4. IR (KBr) ν/cm^{-1}: 1767 (C═O), 1728 (C═O).

MS-ESI (*m*/*z*) 377 [M+Na]$^+$. HRMS calcd for $C_{18}H_{14}N_2NaO_6$ [M+Na]$^+$: 377.0744, found: 377.0754.

Ethyl (±)-*trans*-11-chloro-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-carboxylate (5ae). Colorless oil, yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3H), 4.20 (q, J = 7.2 Hz, 2H), 4.34 (d, J = 3.0 Hz, 1H), 5.72 (d, J = 3.0 Hz, 1H), 6.83–7.77 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.9, 54.4, 57.5, 62.0, 119.7, 121.2, 122.8, 124.6, 125.1, 125.8, 129.0, 129.9, 130.0, 130.6, 143.2, 156.2, 157.2, 165.5. IR (film) ν/cm^{-1}: 1770 (C═O), 1712 (C═O). MS-ESI (*m*/*z*): 366 [M+Na]$^+$. HRMS calcd for $C_{18}H_{14}ClNNaO_4$: 366.0503, found: 366.0509.

Ethyl (±)-*trans*-11-methyl-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-carboxylate (5af). Colorless oil, yield 53%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 4.23 (q, J = 7.2 Hz, 2H), 4.38 (d, J = 2.9 Hz, 1H), 5.81 (d, J = 2.9 Hz, 1H), 6.89–7.84 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.1, 20.8, 55.1, 57.5, 62.1, 119.9, 121.3, 121.4, 124.7, 125.0, 126.3, 128.7, 129.4, 130.7, 135.0, 144.1, 155.9, 157.7, 166.0. IR (film) ν/cm^{-1} 1773 (C═O), 1763 (C═O). MS-ESI (*m*/*z*): 346 [M+Na]$^+$. HRMS calcd for $C_{19}H_{17}NNaO_4$: 346.1049, found:346.1038.

Ethyl (±)-*trans*-10-methyl-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-carboxylate (5ag). Colorless oil, yield 61%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 4.32 (q, J = 7.2 Hz, 2H), 4.48 (d, J = 2.9 Hz, 1H), 5.87 (d, J = 2.9 Hz, 1H), 6.95–7.92 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.9, 20.8, 54.8, 57.4, 61.9, 119.7, 121.3, 121.9, 124.5, 124.9, 125.4, 125.5, 125.9, 129.3, 140.7, 143.8, 157.6, 157.7, 165.9. IR (film) ν/cm^{-1}: 1770 (C═O), 1761 (C═O). MS-ESI (*m*/*z*): 346 [M+Na]$^+$. HRMS calcd for $C_{19}H_{17}NNaO_4$: 346.1049, found: 346.1057.

Ethyl (±)-*trans*-11-methoxy-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-carboxylate (5ah). Colorless oil, yield 37%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.37 (t, J = 7.2 Hz 3H), 3.80 (s, 3H), 4.34 (q, J = 7.2 Hz, 2H), 4.44 (d, J = 3.0 Hz, 1H), 5.86 (d, J = 3.0 Hz, 1H), 6.72–7.96 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.2, 54.8, 55.6, 57.7, 62.2, 107.7, 110.6, 120.1, 121.4, 121.6, 124.8, 125.3, 126.4, 129.5, 143.9, 157.8, 158.9, 161.2, 166.2. IR (KBr) ν/cm^{-1}: 1770 (C═O), 1714 (C═O). MS-ESI (*m*/*z*): [M+Na]$^+$. HRMS calcd for $C_{19}H_{17}NNaO_5$: 362.0998, found: 362.0994.

Diethyl (±)-*trans*-1,12b-dihydro-11-nitro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-phosphonate (5id). Colorless crystals, yield 95%, m.p.150–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (dt, J = 7.2, 7.5 Hz, 6H), 4.17 (dd, J = 3.0, 16.2 Hz, 1H), 4.35 (m, 4H), 5.81 (dd, J = 3.0, 8.4 Hz, 1H), 7.11–8.31 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.36 16.44, 51.2, 53.01, 53.03, 53.2, 63.0, 63.1, 63.5, 63.6, 120.2, 121.4, 122.1, 122.9, 125.2, 125.8, 126.1, 128.8, 130.7, 142.9, 144.3, 156.9, 157.0, 162.1. IR ν/cm^{-1}: 1750 (C═O). MS-ESI (*m*/*z*): 419 [M+H]$^+$. HRMS calcd for $C_{19}H_{20}N_2O_7P$: 419.1002, found: 419.1010.

Diethyl (±)-*trans*-11-chloro-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-phosphonate (5ie). Colorless crystals, yield 64%, m.p.153–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (dt, J = 6.0, 6.9 Hz, 6H), 4.11 (dd, J = 3.0, 16.2 Hz, 1H), 4.33 (m, 4H), 5.80 (dd, J = 3.0, 8.4 Hz, 1H), 7.00–7.95 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.4, 16.5, 50.6, 52.6, 53.1, 62.94, 63.03, 63.3, 63.4, 120.0, 121.4, 123.1, 124.9, 125.4, 126.1, 129.3, 130.3, 130.5, 131.0, 131.1, 143.5, 156.2, 157.2, 157.3. IR (KBr) ν/cm^{-1}: 1755 (C═O). MS-ESI (*m*/*z*): 408 [M+H]$^+$. HRMS calcd for $C_{19}H_{20}NO_5PCl$: 408.0762, found: 408.0769.

Diethyl (±)-*trans*-11-methyl-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-phosphonate (5if). Colorless crystals, yield 60%, m.p.166–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (dt, J = 3.9, 6.9 Hz, 6H), 2.35 (s, 3H),4.12 (dd, J = 3.3, 16.2 Hz, 1H), 4.33 (m, 4H), 5.82 (dd, J = 3.3, 8.4 Hz, 1H), 7.00–7.96 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.4, 16.5, 20.8, 50.3, 52.3, 53.5, 62.86, 62.94, 63.1, 63.2, 119.9, 121.2, 121.4, 124.7, 125.0, 126.4, 128.9, 129.0, 129.6, 130.8, 135.1, 144.0, 155.7, 157.5, 157.6. IR (KBr) ν/cm^{-1}: 1752 (C═O). MS-ESI (*m*/*z*): 410 [M+Na]$^+$. HRMS calcd for $C_{20}H_{22}NNaO_5P$: 410.1127, found: 410.1144.

Diethyl (±)-*trans*-10-methyl-1,12b-dihydro-azeto[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-2-one-1-phosphonate (5ig). White solid, yield 42%, m.p.129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (dt, J = 6.9, 7.5 Hz, 6H), 2.35 (s, 3H), 4.10 (dd, J = 3.0, 16.2 Hz, 1H), 4.31 (m, 4H), 5.80 (dd, J = 3.0, 8.4 Hz, 1H), 6.98–7.95 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.4, 16.5, 21.0, 50.4, 52.4, 53.4, 62.8, 62.9, 63.1, 63.2, 118.3, 120.0, 121.5, 122.1, 124.7, 125.1, 125.6, 125.8, 126.4, 129.6, 141.0, 143.9, 157.7. IR (KBr) ν/cm^{-1}:1752 (C═O). MS-ESI (*m*/*z*): 410 [M+Na]$^+$. HRMS calcd for $C_{20}H_{22}NNaO_5P$: 410.1127, found: 410.1137.

Diethyl (±)-*trans*-11-methoxy-1,12b-dihydro-azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-2-one-1-phosphonate (5ih). Colorless crystals, yield 42%, m.p.94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (dt, J = 6.9, 7.2 Hz, 6H), 3.80 (s, 3H), 4.07 (dd, J = 3.3, 15.9 Hz, 1H), 4.31 (m, 4H), 5.76 (dd, J = 3.3, 8.4 Hz, 1H), 6.72–7.96 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.4, 16.5, 50.4, 52.4, 53.1, 55.5, 62.8, 62.9, 63.1, 63.2, 107.6, 110.6, 120.0, 121.5, 124.7, 125.2, 126.5, 129.5, 143.8, 157.7, 158.6, 161.2. IR (KBr) ν/cm^{-1}: 1744 (C═O). MS-ESI (*m*/*z*): 426 [M+Na]$^+$. HRMS calcd for $C_{20}H_{22}NNaO_6P$: 426.1076, found: 426.1063.

Preparation of ethyl 1-*tert*-butyl-4-phenyl-2-azetidinone-3-carboxylate (11m) *via* the $Rh_2(OAc)_4$ catalyzed intramolecular carbenoid C–H insertion reaction

Ethyl *cis*-1-*tert*-butyl-4-phenyl-azetidin-2-one-3-carboxylate (*cis*-**11m**) was obtained as a mixture of their *cis*/*trans*-isomers in a ratio of 30 : 70 according to the reported method.[32] A solution of *N*-benzyl-*N*-*tert*-butyl-2-diazo-3-ethoxy-3-oxopropanamide (0.512 g, 1.7 mmol) in dry toluene (5 mL) was added to a solution of $Rh_2(OAc)_4$ (2 mol%) in toluene (20 mL). The resulting mixture was stirred at 70 °C for 3 h until the diazo compound had been consumed. After removal of the solvent under reduced pressure, the residue was purified chromatographically on a silica gel column [elution with ethyl acetate and petroleum ether (30–60 °C) 1 : 10), v/v] to give rise to a mixture of *cis*- and *trans*-β-lactam as colorless crystals. 0.28 g (60% yield). *Cis*-11m: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84 (t, J = 7.2 Hz, 3H, CH_3), 1.31 (s, 9H, CMe_3), 3.76 (q, J = 7.2 Hz, 2H, CH_2), 4.21 (d, J = 6.3 Hz, 1H, CH), 4.91 (d, J = 6.3 Hz, 1H, CH), 7.27–7.40 (m, 5H, ArH). *trans*-**11m**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 9H, CMe_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3), 3.70 (d, J = 2.1 Hz, 1H, CH), 4.24 (dq, J = 2.1, 7.2 Hz, 2H, CH_2), 4.85 (d, J = 2.1 Hz, 1H, CH), 7.27–7.40 (m, 5H, ArH). The analytical data are identical to those reported previously.[6h]

General procedure for the determination of epimerization

To a solution of ethyl *cis*/*trans*-1-*tert*-butyl-4-phenyl-azetidin-2-one-3-carboxylate (30 : 70 *cis*:*trans*) (26 mg, 0.1 mmol) in dry CH_2Cl_2 (1.5 mL) was added additive indicated in Table 4 at room temperature. The resulting mixture was stirred for 3–5 h at room temperature and then was washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was subjected for ^{1}H NMR analysis in $CDCl_3$.

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