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Origin of the Relative Stereoselectivity of the β-Lactam Formation in the Staudinger Reaction

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Abstract: The relative (cis, trans) stereoselectivity of the β-lactam formation is one of the critical issues in the Staudinger reaction. Although many attempts have been made to explain and to predict the stereochemical outcomes, the origin of the stereoselectivity remains obscure. We are proposing a model that explains the relative stereoselectivity based on a kinetic analysis of the cis/trans ratios of reaction products. The results were derived from detailed Hammett analyses. Cyclic imines were employed to investigate the electronic effect of the ketene substituents, and it was found that the stereoselectivity could not be simply attributed to the torquoelectronic model. Based on our results, the origin of the relative stereoselectivity can be described as follows: (1) the stereoselectivity is generated as a result of the competition between the direct ring closure and the isomerization of the imine moiety in the zwitterionic intermediate; (2) the ring closure step is most likely an intramolecular nucleophilic addition of the enolate to the imine moiety, which is obviously affected by the electronic effect of the ketene and imine substituents; (3) electron-donating ketene substituents and electron-withdrawing imine substituents accelerate the direct ring closure, leading to a preference for *cis*-β-lactam formation, while electron-withdrawing ketene substituents and electron-donating imine substituents slow the direct ring closure, leading to a preference for *trans*-β-lactam formation; and (4) the electronic effect of the substituents on the isomerization is a minor factor in influencing the stereoselectivity.

Introduction

The Staudinger reaction (the [2 + 2] ketene−imine cycloaddition reaction) is regarded as one of the most fundamental and versatile methods for the synthesis of β-lactam (2-azetidinone) derivatives,[1] which are important in both pharmaceutical and synthetic chemistry.[2,3] Many experimental and theoretical investigations into the Staudinger reaction have been presented during the past decades,[4,5] and the most widely accepted reaction process is described as follows:[6] (1) the ketene−imine cycloaddition reaction is a stepwise reaction rather than a concerted one; (2) the reaction is initiated by the nucleophilic attack of an imine to a ketene, giving rise to a zwitterionic intermediate; (3) a conrotatory electrocyclic ring closure of the zwitterionic intermediate produces the final β-lactam product. The reaction of a monosubstituted ketene with an acyclic imine produces two new stereocenters (C3 and C4 in the β-lactam ring), so the product might be *cis*-, *trans*-, or a mixture of *cis*- and *trans*-β-lactam derivatives. Thus, the relative (cis, trans) stereoselectivity is considered as one of the critical issues in the Staudinger reaction.[6] However, the pathway for the formation of *cis*- and *trans*-β-lactams has not been well understood to date. Many possible stereochemical processes have been proposed in previous investigations[4d,4f−g,5b−c,5e,6] (Scheme 1), but each of them only focused on the Staudinger reaction involving a particular ketene or imine and failed to provide a universal explanation for the observed complicated stereochemical outcomes.

(1) For recent reviews on syntheses of β-lactam, see: (a) Van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503−7524. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235. (c) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631−7649.

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(3) For a review, see: *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993.

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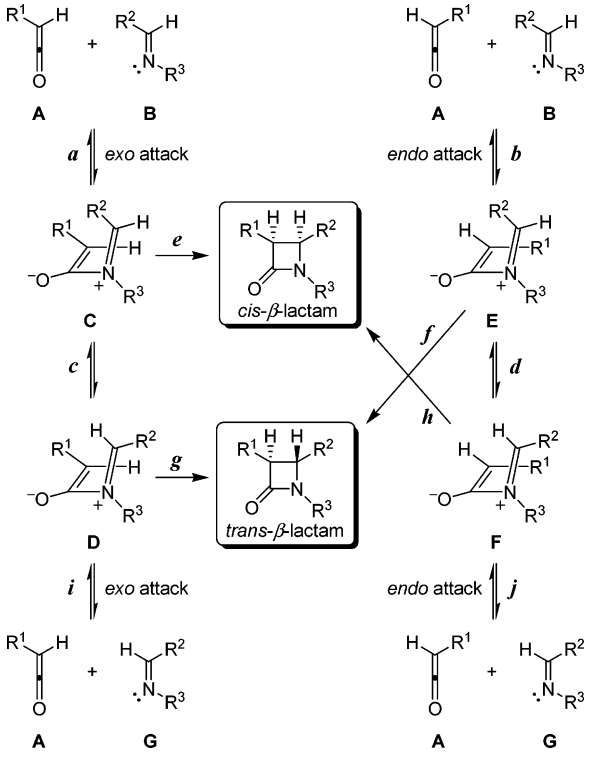
(6) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993; pp 295−368 and references therein.

10.1021/ja056711k CCC: $33.50

Scheme 1. Pathways for the Formation of *cis*- and *trans*-β-Lactams[a]



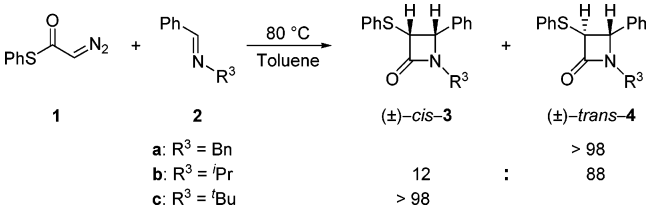
[a] Only one enantiomer is drawn.

Moreover, the nature of the relative stereoselectivity in the Staudinger reaction is still quite obscure. Hegedus and coworkers[4f] pointed out that the zwitterionic intermediate can isomerize and the stereochemistry is determined primarily by the structure of the imines and the character of the free or bound ketenes. Cossio et al. conducted computational investigations and concluded that the stereochemistry was decided by the configuration (*Z* or *E*) of the starting imines[5b] and the torquoelectronic effect of the ketene[5e] or imine substituents.[5c] Brady and Gu[4d] claimed that the stereochemistry was determined by the main resonance structure of the zwitterionic intermediates. Georg et al.[4g,6] suggested that the stereochemical results can be correlated well with the steric demands of the ketenes and classified the ketenes into three groups according to the size of their substituents. These investigators have suggested different models to predict the stereoselectivity, but their proposals are in conflict to some extent. The most pivotal problems regarding the relative stereoselectivity remain obscure: (1) How are the β-lactam products with different relative configurations generated; i.e., what is the most possible pathway for the formation of *cis*- and *trans*-β-lactams. And (2) why do different ketenes and imines lead to different stereochemical outcomes; especially, why do the reactions of different ketenes with the same imine generate distinct stereochemical results. Therefore, we reinvestigated the relative stereoselectivity of the Staudinger reaction. Herein, we present our experimental results to provide a comprehensive understanding of the origin of the relative stereoselectivity in the Staudinger reaction.

Results and Discussion

Selection of the Reaction Platform and the Discovery of a Good Probe. It is unequivocal that the nature of the substituents of ketenes and imines (R^1, R^2, and R^3, Scheme 1) is the crucial factor that determines the relative stereoselectivity of the Staudinger reaction. However, since the ketenes are usually generated in situ in the Staudinger reaction, many different experimental factors,[6] such as the temperature, the solvent,[7a] the base,[7b] the chloride anion,[4f,5e,7c] and the metal[4f,5f] could affect the stereochemical outcomes. These factors interfered with the elucidation of the origin of the stereoselectivity. Thus, to approach the "origin" ketene−imine reaction,[8] we wished to select a clean reaction system for the ketene generation as a platform to systematically investigate the substituent effects. Typically, there are mainly three ways to produce ketenes: (1) the elimination of acyl chlorides or related derivatives in the presence of a base,[4c,9] (2) the photolysis of metal−carbene complexes,[4f,10] and (3) the Wolff rearrangement of α-diazocarbonyl compounds.[11−14] Compared with methods (1) and (2), the use of α-diazocarbonyl compounds as precursors of ketenes has a distinct advantage: it is a clean reaction system without any additives (nucleophiles such as chloride anion and tertiary amine) that could affect the cis/trans ratio of the β-lactam products. We found that *S*-phenyl 2-diazoethanethioate (**1**) efficiently rearranged to phenylthioketene at 80 °C and gave β-lactam derivatives in good yields in the presence of imines. Thus, the reaction of **1** with imine was selected as an appropriate platform to investigate the origin of the stereoselectivity in the Staudinger reaction.

Scheme 2. Steric Effect of *N*-Substituent R^3 in the Staudinger Reaction



First, we conducted the reactions of **1** with imines **2a**−**c** at 80 °C in toluene, respectively. It was found that the *cis*-β-lactam product increased as the size of the *N*-substituent R^3 increased (Scheme 2), which is similar to the results of Moore et al.[4c] What is more important is that, a mixture of cis and trans products[15] was obtained from the reaction of **1** and **2b**. Because the cis/trans ratio of the β-lactam products carries the stereochemical information of the reaction, we hope to understand

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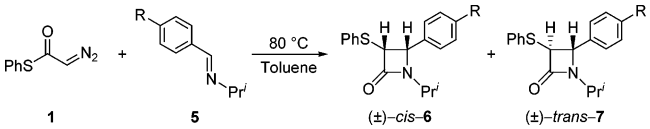
(11) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193−2256.
(12) For photoirradiation-induced Staudinger reaction, see: (a) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873−5883. (b) Linder, M. R.; Podlech, J. *Org. Lett.* **1999**, *1*, 869−871. (c) Linder, M. R.; Frey, W. U.; Podlech, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2566−2577.
(13) For microwave-assisted Staudinger reaction, see: Linder, M. R.; Podlech, J. *Org. Lett.* **2001**, *3*, 1849−1851.
(14) Liang, Y.; Jiao, L.; Zhang, S. W.; Xu, J. X. *J. Org. Chem.* **2005**, *70*, 334−337.

Table 1. Influence of the Electronic Effect of the C-Substituents of the Imines on the Stereoselectivity



1 5 (±)–*cis*–**6** (±)–*trans*–**7**

entry	imine	R	product	yield[a] (%)	cis/trans[b]
1	**5a**	MeO	**6a** + **7a**	87	4:96
2	**5b**	Me	**6b** + **7b**	80	7:93
3	**5c**	H	**6c** + **7c**	92	12:88
4	**5d**	Cl	**6d** + **7d**	75	17:83
5	**5e**	CF_3	**6e** + **7e**	81	42:58
6	**5f**	NO_2	**6f** + **7f**	79	73:27

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR of the crude products.

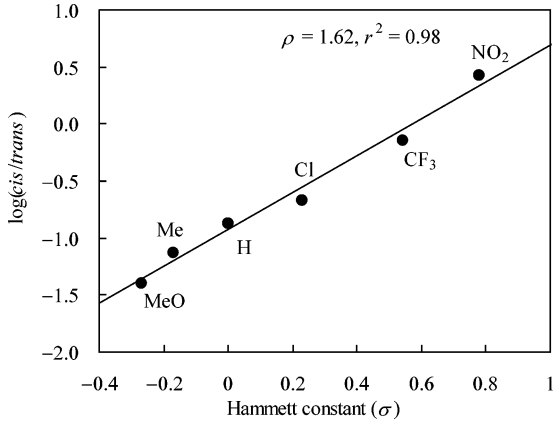


Figure 1. Hammett plot of the reactions between the ketene and imines with different *C*-substituents.

the origin of the stereoselectivity in the Staudinger reaction by systematically measuring a series of cis/trans ratios of the β-lactam products with different substituents. Thus, *N*-isopropyl imines are good probes for detecting the stereochemical information.

Electronic Effect of the Substituent R^2. A series of *N*-isopropyl imines **5a**−**f** with different *para*-substituents on the *C*-phenyl group were reacted with *S*-phenyl 2-diazoethanethioate (**1**) at 80 °C in toluene (Table 1). It was found that the electronic effect of the substituents plays an important role in the stereoselectivity, which obviously alters, even reverses, the stereochemical outcomes. For imine **5a** with a strong electron-donating group (*p*-MeO), the product is predominately trans (Table 1, entry 1), while, for imine **5f** with a strong electron-withdrawing substituent (*p*-NO_2), the product is mainly cis (Table 1, entry 6). It is notable that the cis/trans ratios of these reactions correlate well with the Hammett constants (σ) with a calculated ρ-value of +1.62 (Figure 1).[16]

To our best knowledge, the linear free energy relationship (LFER) of the relative stereoselectivity of the β-lactam formation in the Staudinger reaction has never been investigated. How to explain this intriguing result? According to Scheme 1, the simplest explanation was that the stereochemistry was determined by the configuration (*Z* or *E*) of the starting imines:[5b] (*E*) imines led preferentially to *cis*-β-lactams (pathway ***a*** → ***e***, Scheme 1) and (*Z*) imines gave predominantly the corresponding trans isomers (pathway ***i*** → ***g***, Scheme 1). In fact, all the starting imines **5** were determined to be exclusively *E* configuration based on ^{1}H NMR and 1D NOE experiments,[17] and most imines employed in the Staudinger reaction were confirmed to be *E* configuration.[18] Thus, we can conclude that the stereoselectivity, in most cases, cannot be explained by the configuration of the starting imines.

There are two other possibilities: (a) the stereochemistry is decided by the different initial approaches of the imine to the monosubstituted ketene[4d] (*cis*-β-lactam, pathway ***a*** → ***e***; *trans*-β-lactam, pathway ***b*** → ***f***, Scheme 1); and (b) the stereochemistry is decided by the competition between the direct ring closure (pathway ***e***) and the isomerization of the imine moiety in the zwitterionic intermediate (pathway ***c***). In this process, the approach of the imine to the ketene is opposite to R^1, and subsequent ring closure of the zwitterionic intermediate **C** leads to *cis*-β-lactam (pathway ***a*** → ***e***, Scheme 1), while the isomerization of the imine moiety in the zwitterionic intermediate **C** leads to the formation of *trans*-β-lactam[4f,6] (pathway ***a*** → ***c*** → ***g***, Scheme 1). For possibility (a), the observed variation of cis/trans ratios could be explained by the electronic effect of the imine substituent R^2 affecting the ratio of different approaches (pathway ***a*** vs pathway ***b***). For possibility (b), the experimental results could be explained by the electronic effect of the imine substituent R^2 affecting the competition between the direct ring closure (pathway ***e***) and the isomerization (pathway ***c***). To distinguish which one is reasonable, the best way is to replace imines **5** with a series of cyclic imines with different electronic substituents in the same reactions. Since cyclic imines cannot undergo the isomerization in the reaction,[4f,6,14] the possibilities (a) and (b) could be distinguished by the relative configuration of the bicyclic β-lactam products.

The reactions of **1** with cyclic imines, 2-substituted dibenzo[*b*,*f*][1,4]oxazepines **8**, were carried out under the same conditions (Scheme 3) as those of its reactions with imines **5**. The *trans*-β-lactam derivatives **9a**−**d** were exclusively formed in excellent yields. This indicates that the initial approach occurs exclusively at the nonsubstituted side of the ketene, and the electronic nature of the imine substituent R^2 does not affect the direction of the approach (Scheme 4).

Electronic Effect of the Substituent R^1. To understand the origin of the stereoselectivity in depth, a series of α-diazoarylethanones **10a**−**f** with different substituents were reacted with imine **5f** at 140 °C in xylenes[19] to afford a series of *cis*- and *trans*-β-lactams (Table 2). The results indicate that the electronic effect of the ketene substituents also plays an important role in the stereoselectivity. For the ketene with a strong electron-donating group (*p*-MeO), the product is mainly cis (Table 2, entry 1), while, for the ketene with a strong electron-withdrawing

(15) The configurations of the β-lactam products can be easily determined by the coupling constants between the protons on C(3) and C(4) of the β-lactam ring. For *cis*-β-lactam products, $J_{H(C3)-H(C4)}$ is 4−6 Hz, and for trans products, $J_{H(C3)-H(C4)}$ is about 2 Hz. The cis/trans ratios can be obtained by the integral of the corresponding protons in ^{1}H NMR spectra of crude reaction mixtures.

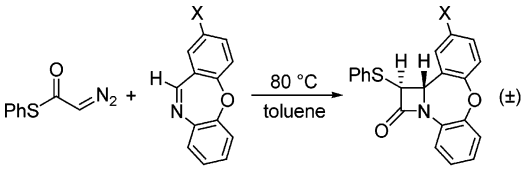
(16) The Hammett constants (σ) cited are all taken from: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(17) Another experiment involving the *N*-acetyl iminium was also conducted, which indicated that the isomerizations of the imine itself and *N*-acetyl iminium hardly occur under normal conditions. See Supporting Information for detailed discussion.

(18) It was reported that imines such as *C*-9-anthryl imines and *C*-2,6-disubstitutedphenyl imines partially exist in *Z* configuration; however, they are seldom used in the Staudinger reaction. See: Bjorgo, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B.; Jerina, D. M. *J. Chem. Soc, Perkin Trans. 2* **1974**, 1081−1084.

(19) The reactions of **10** with imines at 80 °C in toluene cannot proceed because compounds **10** cannot undergo the Wolff rearrangement at such a temperature.

Scheme 3. Reaction of **1** and Cyclic Imines **8** with Different Electronic Substituents

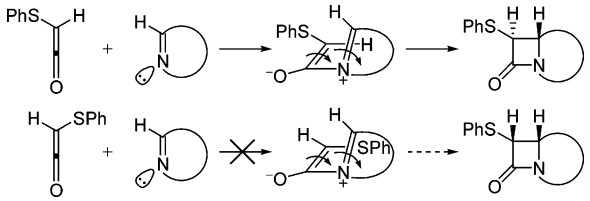


1 **8** **9** (sole diastereomer)

entry	substituent X	yield[a] (%)
1	**8a** X = Me	99
2	**8b** X = H	99
3	**8c** X = Cl	99
4	**8d** X = NO_2	98

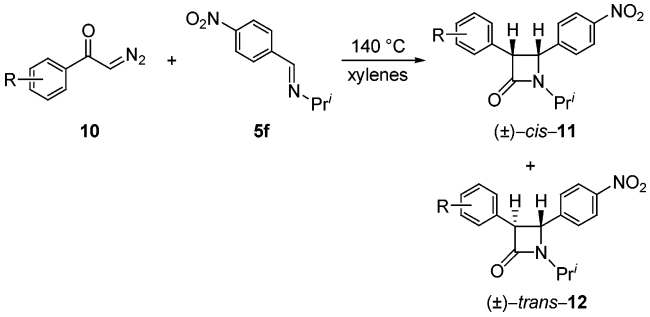
[a] Isolated yield after chromatography.

Scheme 4 [a]



[a] Only one enantiomer is drawn.

Table 2. Influence of the Electronic Effect of the Ketene Substituents on the Stereoselectivity



10 **5f**

entry	diazoketone	R	product	yield[a] (%)	cis/trans[b]
1	**10a**	*p*-MeO	**11a** + **12a**	93	66:34
2	**10b**	*p*-Me	**11b** + **12b**	68	55:45
3	**10c**	H	**11c** + **12c**	52	47:53
4	**10d**	*p*-Cl	**11d** + **12d**	65	40:60
5	**10e**	*m*-Cl	**11e** + **12e**	56	38:62
6	**10f**	*p*-NO_2	**11f** + **12f**	60	27:73

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR of the crude products.

substituent (*p*-NO_2), the product is mainly trans (Table 2, entry 6). The cis/trans ratios of the products also correlate well with the Hammett constants (σ) with a ρ-value of -0.63 (Figure 2). Since the temperature influences the reaction constant ρ, to get comparable data with the previous results obtained at 80 °C, the reactions were also conducted at 130 °C in xylenes,[20] and the cis/trans ratios of reactions at 80 °C were estimated according to the Eyring formula,[21] which have a good correlation with the Hammett constants (σ) with a ρ-value of -1.1 (Figure 2).

(20) The experimental results at 130 °C were given in the Supporting Information.

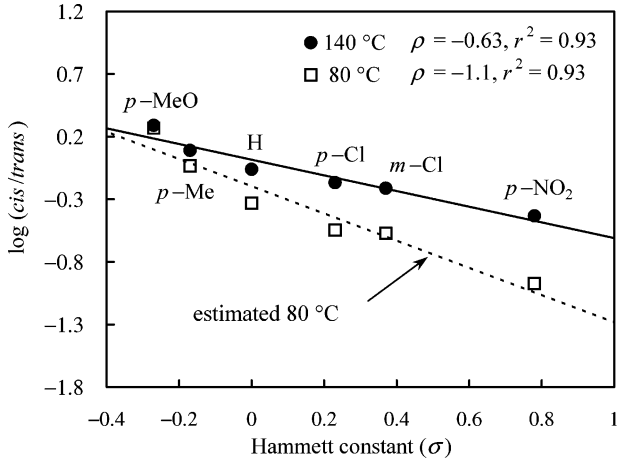


Figure 2. Hammett plot of the reactions between the imine and ketenes with different substituents.

The interesting fact that cis/trans ratio of the β-lactam products varied with the electronic nature of the ketene substituents was never reported before. First, it seemed that the above results could be simply explained by the torquoelectronic model: in the transition states for the conrotatory ring closure of the zwitterionic intermediates, the electron-donating groups (EDGs) in the ketene moiety favor occupying the outward position at C3 of the β-lactam ring, leading to the formation of *cis*-β-lactams (e.g., R^1 = *p*-MeOPh, Table 2, entry 1); while the electron-withdrawing groups (EWGs) in the ketene moiety favor occupying the inward position, leading to the formation of *trans*-β-lactams (e.g., R^1 = *p*-NO_2Ph, Table 2, entry 6). Second, the above results could also be explained by the competition between the direct ring closure and the isomerization (pathway ***e*** vs pathway ***c***, Scheme 1).

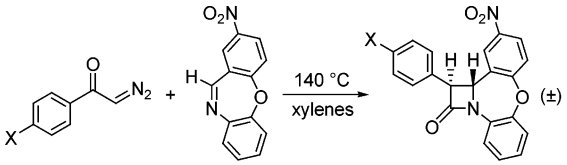
There have been several literatures concerning the torquoelectronic model in the Staudinger reaction, which discussed the inward/outward tendency of the ketene substituents:[5e,22] the *O*-alkyl, *N*-alkyl, halo, and alkyl groups on the ketene have a distinct preference of occupying the outward position in the transition state, while the boryl group[22a] on the ketene tends to occupy the inward position. It is not clear whether the phenyl groups with different electronic substituents have different preferences of occupimg inward/outward positions in the transition state to date.

To examine the above possibility, cyclic imine **8d** that has a similar structural feature to imine **5f** was selected to react with α-diazoarylethanones **10** (Scheme 5) under the same conditions. The reactions afforded the *trans*-β-lactam derivatives **13** exclusively, and the cis isomer was never observed by ^{1}H NMR of the crude products. This indicates that the substituted phenyl groups on the ketene, compared with the hydrogen atom, prefer to occupy the outward position. Thus, the results presented in Table 2 could not be simply explained by the torquoelectronic model, and they should relate to the competition between the direct ring closure and the isomerization.

(21) The detailed calculations were given in the Supporting Information. For reference, see: Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107−115.

(22) (a) Lpez, R.; Sordo, T. L.; Sordo, J. A.; González, J. *J. Org. Chem.* **1993**, *58*, 7036−7037. (b) Dumas, S.; Hegedus, L. S. *J. Org. Chem.* **1994**, *59*, 4967−4971. (c) Hegedus, L. S.; Moser, W. H. *J. Org. Chem.* **1994**, *59*, 7779−7784. (d) Alonso, E.; López-Ortiz, F.; del Pozo, C.; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333−6338. (e) Macías, A.; Alonso, E.; del Pozo, C.; Venturini, A.; González, J. *J. Org. Chem.* **2004**, *69*, 7004−7012.

Scheme 5. Reactions between Cyclic Imine **8d** and Phenylketenes with Different Electronic Substituents



10 **8d** **13** (sole diastereomer)

entry	substituent X	yield[a] (%)
1	**10a** X = MeO	95
2	**10b** X = Me	75
3	**10d** X = Cl	62
4	**10f** X = NO_2	60

[a] Isolated yield after chromatography.

Suggested Model for the Relative Stereoselectivity of the *β*-Lactam Formation. After systematic investigations into the electronic effect of both ketene and imine substituents, a model for the relative stereoselectivity of the *β*-lactam formation can be drawn: the initial *exo* attack of the imine **B** to the monosubstituted ketene **A** generates the intermediate **C**, and subsequent direct ring closure of **C** forms *cis*-*β*-lactam (pathway ***a*** → ***e***, Scheme 1); the isomerization of the imine moiety of **C** gives rise to the intermediate **D**, leading to the formation of *trans*-*β*-lactam (pathway ***a*** → ***c*** → ***g***, Scheme 1). The stereoselectivity in the Staudinger reaction should be attributed to the competition between these two pathways (also see Scheme 6, in which the k_a, k_d, k_1, k_2, k_2', and k_3 are the rate constants for each of the steps).

There are some points worth noting: (1) most of the starting acyclic imines employed in the Staudinger reaction exist in *E* configuration exclusively; (2) for the most frequently used monosubstituted ketenes, such as *O*, *N*, *S*-alkyl/aryl-, halo-, alkyl-, and arylketenes, the attack of the imine occurs exclusively at their *exo* side, and the ketene substituent R^1 always occupies the outward position in the ring closure transition state according to the torquoelectronic effect; (3) the imine moiety in the zwitterionic intermediate **C**, regardless of the imine substituents, has the possibility of the isomerization to form intermediate **D**;[23] (4) the stereoselectivity of the reaction is controlled by the competition between the direct ring closure and the isomerization;[24] and (5) the possibility of the **D** to **C** isomerization (k_2') cannot be excluded. However, from a geometric viewpoint, intermediate **D** is sterically more favorable than **C**, which facilitates the **C** to **D** isomerization (i.e., $k_2 > k_2'$). Thus, in our model, the **C** to **D** isomerization is assumed to be irreversible to facilitate the kinetic treatment.[25]

According to the suggested model (Scheme 6), the kinetic derivation of the relative stereoselectivity can be achieved:[26]

$$[\text{cis}] = k_1 \int [\text{C}]\, \mathrm{d}t \tag{1}$$

$$[\text{trans}] = k_3 \int [\text{D}]\, \mathrm{d}t = k_2 \int [\text{C}]\, \mathrm{d}t - [\text{D}] \tag{2}$$

$$\frac{[\text{cis}]}{[\text{trans}]} = \frac{k_1 \int [\text{C}]\, \mathrm{d}t}{k_2 \int [\text{C}]\, \mathrm{d}t - [\text{D}]} \tag{3}$$

Because the cyclization step is very fast, the concentration of the intermediate **D** is very low, i.e., [D] → 0. Thus, eq 3 could be simplified to eq 4.

$$\frac{[\text{cis}]}{[\text{trans}]} = \frac{k_1}{k_2} \tag{4}$$

In this way, a simple but significant conclusion is obtained: the product ratio (cis/trans) only depends on the rate constants of the direct ring closure (k_1) and the isomerization (k_2).

Relationship between the Structural Features and the Rate Constants. According to the Hammett equation, each independent rate constant can be correlated to the Hammett constant *σ* of the substituent (eqs 5 and 6).

$$\log k_{1,\text{Y}} = \rho_1 \sigma + \log k_{1,\text{H}} \tag{5}$$

$$\log k_{2,\text{Y}} = \rho_2 \sigma + \log k_{2,\text{H}} \tag{6}$$

$$\log \frac{k_{1,\text{Y}}}{k_{2,\text{Y}}} = \log k_{1,\text{Y}} - \log k_{2,\text{Y}} = (\rho_1 - \rho_2)\sigma + \log \frac{k_{1,\text{H}}}{k_{2,\text{H}}} = \rho \cdot \sigma + \log \frac{k_{1,\text{H}}}{k_{2,\text{H}}} \tag{7}$$

Since eq 4 shows that the cis/trans ratio is equal to k_1/k_2, eq 8 can be derived.

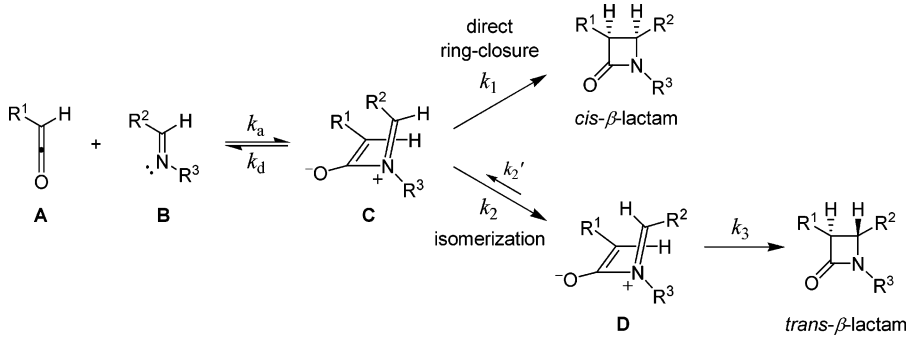
$$\log \frac{\text{cis}_\text{Y}}{\text{trans}_\text{Y}} = \log \frac{k_{1,\text{Y}}}{k_{2,\text{Y}}} = (\rho_1 - \rho_2)\sigma + \log \frac{k_{1,\text{H}}}{k_{2,\text{H}}} = \rho \cdot \sigma + \log \frac{\text{cis}_\text{H}}{\text{trans}_\text{H}} \tag{8}$$

Thus, a clear linear relationship between the logarithms of the determined cis/trans ratios and the Hammett constants of the electronic substituents in the ketene or imine moiety emerges, which is consistent with the experimental results (Figures 2 and 1). Reviewing the above Hammett analyses, we found that the slope (*ρ*) represented the difference between the reaction constants of the direct ring closure (ρ_1) and the isomerization (ρ_2), but ρ_1 and ρ_2 remained combined. Only if the signs of ρ_1 and ρ_2 are determined can we understand the relationship between k_1 (direct ring closure), k_2 (isomerization), and the electronic effect of the substituents.

Electronic Effect on the Rate Constant of the Direct Ring Closure k_1. It is reasonable to assume that the substituents R^2 and R^3 of the imine influence both the direct ring closure (k_1) and the isomerization (k_2), while the substituent R^1 of the ketene affects the direct ring closure but scarcely influences the isomerization of the imine moiety. Thus, it is easy to understannd the influence of the electronic effect of the ketene substituents R^1 on the direct ring closure. For the different

(23) In our opinion, the isomerization occurs during the direct ring closure step. See Supporting Information for detailed discussion.
(24) The exclusive *exo*-attack to form the zwitterionic intermediate **C** does not affect the cis/trans ratio of the products. If the exclusive *exo*-attack is the rate-determining step in the two-step Staudinger reaction, it will determine the rate of the product generation but not the cis/trans ratio.
(25) If the **C** to **D** isomerization is considered reversible, the precise derivation of the relationship between cis/trans ratio and the rate constants cannot be approached. Otherwise, no one has proved the applicability of the Curtin–Hammett rule in such a multistep and complex system as the Staudinger reaction.
(26) The detailed kinetic treatment is shown in the Supporting Information.

Scheme 6. Suggested Model for the Relative Stereoselectivity in the Staudinger Reaction[a]



[a] Only one enantiomer is drawn.

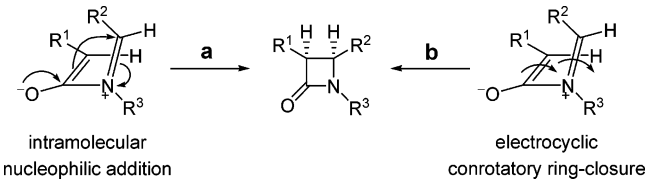


Figure 3. Two different interpretations of the ring closure step in the Staudinger reaction.

zwitterionic intermediates with the same imine moiety, the rate constants of isomerization (k_2) are almost the same; i.e., the reaction constant of the isomerization ρ_2 is about 0. Accordingly, the reaction constant ρ_1 of the direct ring closure is equal to the experimentally determined ρ ($\rho = \rho_1 - \rho_2 \approx \rho_1 = -1.1$ at 80 °C, Figure 2). The negative reaction constant ρ_1 indicates that the electron-donating group of the ketene can accelerate the direct ring closure (increase k_1), while the electron-withdrawing group can slow the direct ring closure (decrease k_1).

It is widely accepted that the ring closure step of the Staudinger reaction is an electrocyclic process.[6] The zwitterionic intermediate is regarded as a 4π-electron system, and its conrotatory ring closure is concluded according to the Woodward−Hoffmann rule. However, the observed electronic effect of the ketene substituent R^1 on the direct ring closure is difficult to explain if the ring closure step is considered as an electrocyclic process. Furthermore, our recent research on the photochemical Staudinger reactions showed that the zwitterionic intermediates cannot undergo the disrotatory ring closure under ultraviolet irradiation, which is quite different from that of substituted 1,3-butadienes.[14] This reveals the inapplicability of the Woodward−Hoffmann rule to the photoirradiation induced Staudinger reaction, suggesting that the ring closure step of the intermediates is far from a classic electrocyclic process. Meanwhile, Cossio et al.[5b] have pointed out that (a) the electronic structure of the transition state for the ring closure step of the zwitterionic intermediate differs from those responsible for classic conrotatory electrocyclic processes and (b) the ring closure step can be alternatively viewed as an intramolecular nucleophilic addition of the enolate to the imine moiety. Thus, we prefer to consider the ring closure step as an intramolecular nucleophilic addition of the enolate to the imine moiety (Figure 3, **a**), rather than an electrocyclic ring closure (Figure 3, **b**).

Reviewing the negative ρ_1 obtained from the Hammett analysis, it is clear that the electron-donating group of the ketene (R^1) can make the enolate more nucleophilic, increasing the rate constant of the direct ring closure k_1, while the electron-withdrawing group of the ketene (R^1) can decrease the nucleophilicity of the enolate, lowering the rate constant of the direct ring closure k_1. Similarly, it could be deduced that the rate constant k_1 could also be increased by the electron-withdrawing group of the imine (R^2 and R^3) due to the enhancement of the electrophilicity of the imine moiety (i.e., the reaction constant ρ_1 should be positive to σ_{R2} and σ_{R3}). Considering the electronic effect of the substituent R^2 of the imine on the stereoselectivity ($\rho = +1.62$ to σ_{R2}), though it can influence both the direct ring closure (k_1) and the isomerization (k_2), we can conclude that the electronic effect of R^2 mainly influences the direct ring closure. However, the influence of the electronic effect of R^2 on the isomerization remains unclear.

Probing the Electronic Effect on the Isomerization. The kinetics of the imine isomerization have been investigated in detail,[27] and it was reported that electron-withdrawing groups on the phenyl groups of aryl−aryl imines promote the isomerization. These isomerizations follow the Hammett equation, and the ρ-values are positive for substitution on both the nitrogen side and the carbon side. The positive ρ-values indicate that the low-electron density at the C=N bond facilitates the isomerization due to the low bond order. It is notable that the ρ-value is considerably higher for the substitution on the nitrogen side ($\rho = +1.85$) than that on the carbon side ($\rho = +0.41$).[27] We assume that the isomerization of the C=N bond in the zwitterionic intermediate would obey the similar rule to the imine itself. In the case of Figure 1, assuming that the reaction constant ρ_2 of the isomerization is about +0.4, we can deduce that the reaction constant ρ_1 of the direct ring closure is about +2.0 according to eq 7 ($\rho_1 = \rho + \rho_2$, Figure 4A). It is definite that the electronic effect of the substitution R^3 on the nitrogen side would influence both the direct ring closure (k_1) and the isomerization (k_2). We assumed that (1) the influence of the electronic effects of the substitution on the nitrogen side on the direct ring closure is at the same level as that on the carbon side (ρ_1' is also about +2.0) and (2) the influence of the electronic effect of the substitution at the nitrogen side on the isomerization is at the same level as that in the imine itself (ρ_2' is about +1.8). Thus, the combined influence of electronic effects on the stereoselectivity can be deduced: the ρ' would be about +0.2 ($\rho' = \rho_1' - \rho_2'$, Figure 4B).

To confirm our prediction, a series of substituted benzylideneanilines **14a**−**f** were reacted with *S*-phenyl 2-diazoethaneth-

(27) Wettermark, G. In *The Chemistry of the Carbon−Nitrogen Double Bond*; Patai, S., Ed.; Interscience: London, 1970; pp 565−596.

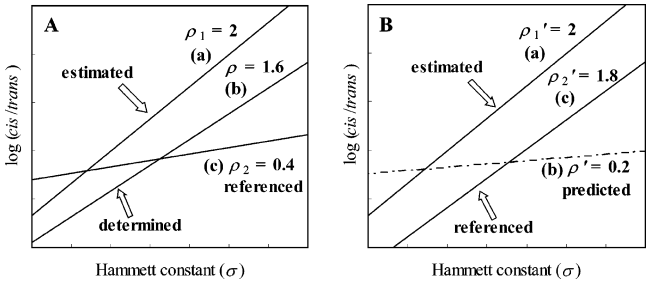
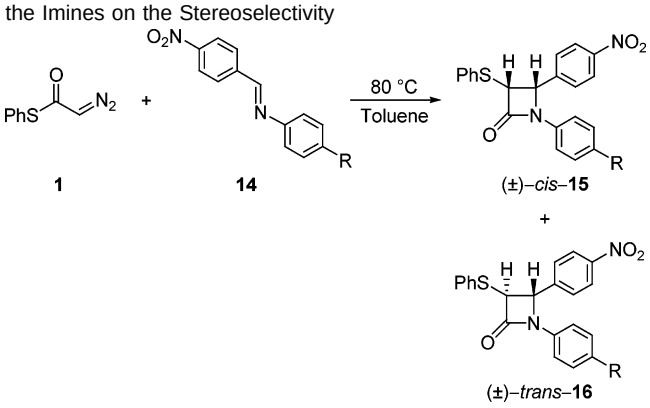


Figure 4. Electronic effects of the imine moiety on the direct ring closure (a) and on the isomerization (c). (A) Substitution on the carbon side (R^2). (B) Substitution on the nitrogen side (R^3).

Table 3. Influence of the Electronic Effect of the *N*-Substituents of the Imines on the Stereoselectivity



entry	imine	R	product	yield[a] (%)	cis/trans[b]
1	**14a**	MeO	**15a** + **16a**	75	27:73
2	**14b**	Me	**15b** + **16b**	76	33:67
3	**14c**	H	**15c** + **16c**	85	34:66
4	**14d**	Cl	**15d** + **16d**	72	35:65
5	**14e**	Ac	**15e** + **16e**	52	38:62
6	**14f**	NO_2	**15f** + **16f**	5[c]	48:52

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR of the crude products. [c] Yield determined by ^{1}H NMR of the reaction mixture.

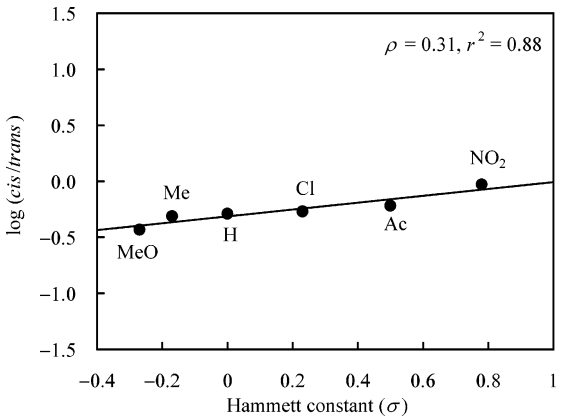


Figure 5. Hammett plot of the reactions between the ketene and imines with different *N*-substituents.

ioate (**1**) at 80 °C in toluene, respectively. It was found that the electronic effect of the substituents on the *N*-phenyl group affected the stereoselectivity (Table 3). The cis/trans ratios of the products correlate with the Hammett constants (σ) with a ρ-value of +0.31 (Figure 5), which is in good agreement with our prediction. This indicates that the influences of the electronic effects on the isomerization in the zwitterionic intermediates are at the same level as those in the imine itself, and our assumption is reasonable. The electron-withdrawing groups R^2 and R^3 in the imine could lower the electron density of the C=N bond, increasing the rate constant of the isomerization k_2 (i.e., ρ_2 is positive to σ_{R2} and σ_{R3}). Furthermore, the electronic effect of the R^3 group, compared with the R^2 group, exerts a more distinct influence on the isomerization.

Relationship between the Relative Stereoselectivity and the Structural Features. On the basis of the above results and discussion, a general view of the substituent effects on the rate constants of the direct ring closure (k_1) and isomerization (k_2) is presented (Figure 6).

The ring closure step of the Staudinger reaction is most likely to be an intramolecular nucleophilic addition of the enolate to the imine moiety. The relative stereochemistry is primarily determined by the rate of the direct ring closure. If the rate constant k_1 is much larger than k_2, the β-lactam product is predominantly cis; on the contrary, if k_1 is much smaller than k_2, the product is mainly trans. A mixture of cis and trans products would be obtained if k_1 is close to k_2. The electronic effect of substituent R^1 only influences k_1, and the electronic effects of substituents R^2 and R^3 mainly influence k_1. Thus, to predict the relative stereochemical outcomes of the Staudinger reaction, much attention should be paid to the rate of the direct ring closure.

An Overview of the Staudinger Reaction

Rationale of the Experiential Rule. The problem of why the reactions of different ketenes with the same imine generate distinctively different stereochemical outcomes is difficult to explain before the origin of the stereoselectivity is disclosed. For example, the most widely employed imine, *N*-benzylideneaniline, reacted with methoxyketene to afford *cis*-β-lactam predominately, while it reacted with methylketene or chloroketene to give *trans*-β-lactam exclusively.[28] According to the torquoelectronic model, all these ketene substituents, methoxy, methyl, and chloro, prefer to occupy the outward position.[22a] The above three reactions should have given similar stereochemical outcomes. On the other hand, according to other viewpoints,[4f,6] if attention was only paid to the isomerization of the imine moiety, the above three reactions should also have given similar stereochemical outcomes due to the same ability of the isomerization. The contradiction between the predictions based on the above models and the experimental results indicated that these interpretations were incomplete. However, once the rate of the direct ring closure was taken into consideration, this problem became clear. Furthermore, the influence of the electronic effect of the ketene substituents on the direct ring closure (k_1) can be semiquantitatively compared using eq 4. Two sets of experiments were designed and performed to semiquantitatively measure the relative rate constants of the direct ring closure (Table 4).

When R^1 = PhS, the relative rate constant of the direct ring closure is defined to 1 as a reference, and other relative rate constants are calculated and listed in Table 4. We can divide the ketene substituents R^1 into three groups on the basis of their relative rate constants (Figure 7): (1) $k_{1,rel} > 100$ (e.g., R^1 = PhO, $k_{1,rel} = 176$), (2) $1 < k_{1,rel} < 100$ (e.g., R^1 = PhthN, $k_{1,rel} = 6$), and (3) $k_{1,rel} < 1$ (e.g., R^1 = Ph, $k_{1,rel} = 0.17$). The above

(28) Bose, A. K.; Chiang, Y. H.; Manhas, M. S. *Tetrahedron Lett.* **1972**, *13*, 4091−4094.

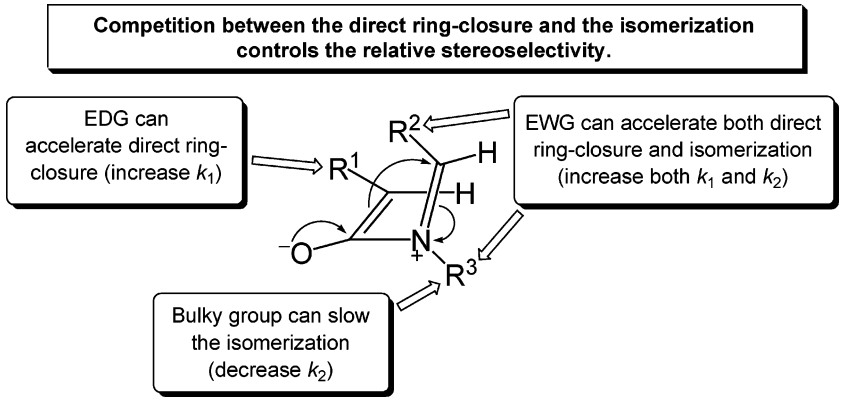
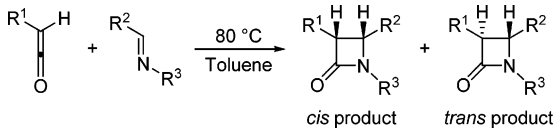


Figure 6. Influence of the structural features on the relative stereoselectivity in the Staudinger reaction.

Table 4. Influence of Different Ketene Substituents on the Stereoselectivity in the Staudinger Reaction



entry	R^1	R^2	R^3		cis/trans[a]	$k_{1,rel}$ (R^1)[h]
1	PhO[b]	*p*-MeOPh	*i*-Pr	**17a:17b**	88:12[f]	176
2	PhthN[b]	*p*-MeOPh	*i*-Pr	**18a:18b**	19:81[f]	6
3	PhS[c]	*p*-MeOPh	*i*-Pr	**6a:7a**	4:96	1
4	PhS[c]	*p*-NO_2Ph	*i*-Pr	**6f:7f**	73:27	1
5	Me[d]	*p*-NO_2Ph	*i*-Pr	**19a:19b**	35:65[g]	0.20
6	Ph[e]	*p*-NO_2Ph	*i*-Pr	**11c:12c**	32:68	0.17

[a] Cis:trans ratios obtained at the same temperature (80 °C). [b] Reaction performed by adding a solution of acyl chloride to a solution of an imine and Et_3N in toluene at 80 °C. [c] Taken from Table 1. [d] Reactions performed by adding a solution of diazoacetone to a solution of the imine in toluene at 100 and 110 °C, respectively, and then the mixtures were stirred for 12 h at the corresponding temperatures. [e] Taken from Figure 2. [f] Determined by ^{1}H NMR of the crude reaction mixture. [g] Derived from the data obtained at 100 and 110 °C by using the Eyring equation. [h] Calculated according to the equation: $k_{1,rel}(R^1) = k_1(R^1)/k_1(PhS) = [k_1(R^1)/k_2(R^1)]/[k_1(PhS)/k_2(PhS)] = [cis/trans(R^1)]/[cis/trans(PhS)]$.

classification rationalizes the previous experiential classification by Georg et al.:[6] (1) "Bose−Evans ketenes", possessing strong electron-donating substituents R^1 (such as *O*-alkyl, *O*-aryl, and *N*-alkylaryl), have a distinct preference for *cis*-*β*-lactam formation due to the large rate constant of the direct ring closure ($k_{1,rel} > 100$); (2) "Sheehan ketenes" produce complex stereochemical outcomes due to the moderate rate constant of the direct ring closure ($1 < k_{1,rel} < 100$); and (3) "Moore ketenes" possessing very weak electron-donating substituents R^1 (such as *S*-alkyl, *S*-aryl, alkyl, and aryl) have a strong preference for *trans*-*β*-lactam formation due to the small rate constant of the direct ring closure ($k_{1,rel} < 1$).

Another example also proved that the direct ring closure rate is the critical point in the stereoselectivity. It is generally considered that the use of *N*-*tert*-butyl imines can inhibit the isomerization of the imine moiety, leading to *cis*-*β*-lactam products. This is suitable for explaining the stereochemical outcome of the reaction of **1** with **2c** (Scheme 2). However, when another electron-withdrawing group (−CO_2Et) was attached to the ketene moiety, the stereoselectivity dramatically changed.[29] Product **21b** generated from the isomerized zwitterionic intermediate was obtained predominantly (Scheme 7). The difference was caused by a significant decrease of the rate of the direct ring closure.

Do Microwave and Photoirradiation Influence the Relative Stereoselectivity of the Staudinger Reaction? In recent years, microwave- and photoirradiation-induced Staudinger reactions, with α-diazoketones (derived from α-amino acids) as ketene precursors, have been reported.[12−14] These reactions exclusively produced *trans*-*β*-lactams, which was considered uncommon and explained that microwave and photoirradiation could efficiently promote the isomerization of the imine itself or the imine moiety of the zwitterionic intermediates. However, according to our model, the trans selectivity of the above microwave- and photoirradiation-induced Staudinger reaction can be well explained by the electronic nature of the ketene substituents. In the above cases, the R^1 groups of the ketenes are all protected aminoalkyls, which are more electron-poor than the alkyl group, leading to weaker nucleophilicity of the enolates in the zwitterionic intermediates. The rate constant of the direct ring closure (k_1) is quite small when R^1 is alkyl (Figure 7). So it can be concluded that the rate constant k_1 would be much smaller when R^1 is a protected aminoalkyl. Thus, we prefer to consider that the low direct ring closure rate k_1, rather than the microwave or photoirradiation, is the real reason for the exclusive formation of the trans products, even when more hindered *N*-*tert*-butyl imines were used.[12c,14]

To verify our opinion, we conducted the microwave- and photoirradiation-induced reactions of **1** with **2c**, respectively. Cis product **3c** was exclusively generated under both conditions, which is in great accordance with the result of the common thermal reaction (Scheme 8). This indicates that the microwave and photoirradiation cannot obviously change the stereoselectivity of the Staudinger reaction.

To further investigate the influence of the photoirradiation on the stereoselectivity, the reactions of **1** with **5a**−**f** were also conducted under the ultraviolet irradiation to compare with the results of the thermal reactions. Interestingly, the results are similar to those in the common thermal reactions (Table 5), except for **5f**. The results show that, in the common photochemical Staudinger reaction (under a medium-pressure or high-pressure mercury lamp), the influence of the photoirradiation is limited, and the stereoselectivity is predominately controlled by structural features of ketenes and imines, not reaction conditions.

(29) For more examples and discussion, see: Jiao, L.; Zhang, Q. F.; Liang, Y.; Zhang, S. W.; Xu, J. X. *J. Org. Chem.* **2006**, *71*, 815−818.

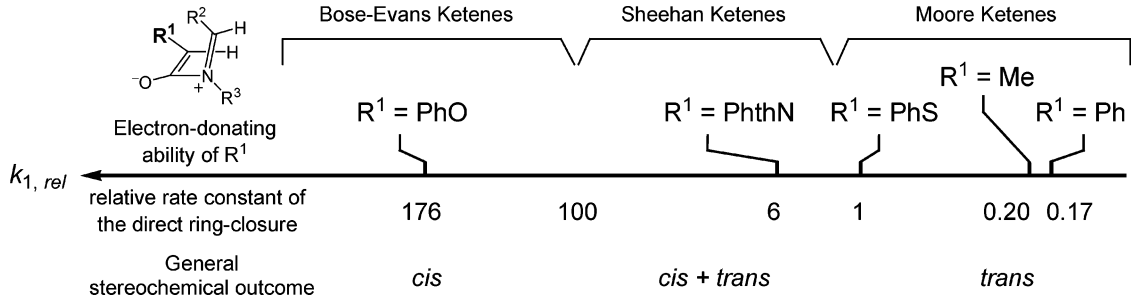
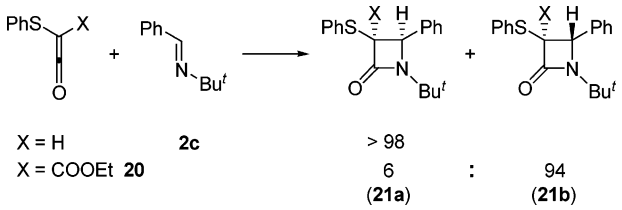


Figure 7. Relationship between the ketene classification and the relative rate constant.

Scheme 7. Effect of the Direct Ring Closure Rate on the Stereoselectivity in the Staudinger Reaction



Scheme 8. Comparison of the Microwave, Photoirradiation, and Common Thermal Reactions of **1** with **2c**

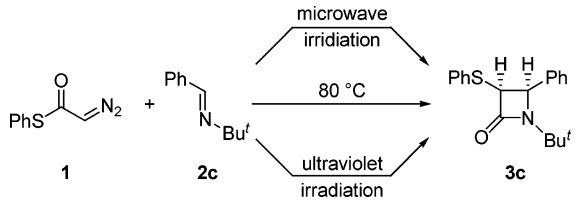


Table 5. Comparison of the Stereoselectivity under Thermal and Photoirradiation Conditions

	cis/trans					
conditions	**6a:7a**	**6b:7b**	**6c:7c**	**6d:7d**	**6e:7e**	**6f:7f**
Δ	1:24	1:13	1:7.3	1:4.9	1:1.4	1:0.37
hν[a]	1:36	1:11	1:6.7	1:5.0	1:2.6	1:5.4

[a] Performed under high-pressure mercury lamp in CH_2Cl_2 at −20 °C.[14]

Conclusion

In summary, we have proposed a model for the relative stereoselectivity in the Staudinger reaction and clearly pointed out the kinetic origin of the cis/trans ratio of β-lactam products. The cyclic imines were employed to investigate the electronic effect of the ketene substituents, and it was found that the stereoselectivity could not be simply attributed to the torquoelectronic model. Moreover, the Hammett analysis to the relative stereoselectivity of the Staudinger reaction was systematically conducted for the first time. The results indicate that it is reasonable to consider the ring closure step as an intramolecular nucleophilic addition process rather than an electrocyclic process. The electronic effect of the substituent is the key factor in the stereoselectivity: the electron-donating ketene substituents and the electron-withdrawing imine substituents accelerate the direct ring closure (increase k_1), leading to a preference for *cis*-β-lactam formation, while the electron-withdrawing ketene substituents and the electron-donating imine substituents lower the direct ring closure (decrease k_1), leading to a preference for *trans*-β-lactam formation. The electronic effect of the substituents on the isomerization is a minor factor in the stereoselectivity. Through semiquantitatively measuring the relative rate constants of the direct ring closure, we successfully rationalized the previous experiential rule. In addition, the comparison of the microwave- and photoirradiation-induced Staudinger reactions with the common thermal ones was also conducted, indicating that the nature of the substituents, rather than reaction conditions, predominately controlled the stereoselectivity.

On the basis of our results, the origin of the relative stereoselectivity of the Staudinger reaction is summarized as follows: (1) the relative stereoselectivity is generated as a result of the competition of the direct ring closure (k_1) and the isomerization of the imine moiety (k_2) in the zwitterionic intermediates, and the k_1/k_2 ratio generally determines the cis/trans ratio of the β-lactam products; and (2) the electronic effect is a key factor in the stereoselectivity, and the influence of the electronic effect on the direct ring closure is more distinct than that on the isomerization of the imine moiety. Thus, much attention should be paid to the influence of the substituent effects on the direct ring closure (k_1) to predict the relative stereoselectivity in the Staudinger reaction.

Experimental Section

General Procedure for the Reactions of *S*-Phenyl 2-Diazoethanethioate (1) with Imines 2, 5, 8, and 14. A flame-dried round-bottom flask was charged with a solution of imine (1 mmol) in 10 mL of dry toluene. The flask was immersed in an oil bath and heated to 80 °C. A solution of diazoethanethioate **1** (1.3 mmol) in 5 mL of dry toluene was then added through a dropping funnel during a period of 30 min. After the addition, the resulting solution was stirred for another 1 h at 80 °C. After removal of the solvent, the residue was directly submitted to NMR analysis to determine the cis/trans ratio. Column chromatography of the crude mixture on silica gel afforded the corresponding *cis*- and *trans*-β-lactam products.

General Procedure for the Reactions of α-Diazoacetophenones 10 with Imine 5f and 8d. A flame-dried round-bottom flask was charged with a solution of imine **5f** or **8d** (1 mmol) in 10 mL of dry xylenes. The flask was immersed in an oil bath and heated to the desired temperature (130 or 140 °C as mentioned). A solution of **10** (1.3 mmol) in 5 mL of dry xylenes was then added through a dropping funnel during a period of 30 min. After the addition, the resulting solution was stirred for another 12 h at the desired temperature. After removal of the solvent, the residue was purified by flash chromatography to remove highly polar impurities. The product mixture was then submitted to NMR or HPLC analysis to determine the cis/trans ratio. Column chromatography of the crude mixture on silica gel afforded the corresponding *cis*- and *trans*-β-lactam products.

General Procedure for the Reactions of Acyl Chlorides with Imines. A flame-dried round-bottom flask was charged with a solution of imine (1 mmol) and triethylamine (1.3 mmol) in 10 mL of dry toluene. The flask was immersed in an oil bath and heated to 80 °C. A solution of the desired acyl chloride (1.3 mmol) in 5 mL of dry toluene was then added through a dropping funnel during 30 min. The resulting

solution was stirred for another 2 h at 80 °C. The reaction mixture was diluted with chloroform, washed successively with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was directly submitted to NMR analysis to determine the cis/trans ratio. Column chromatography of the crude mixture on silica gel afforded the corresponding *cis*- and *trans*-β-lactam products.

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Supporting Information Available: Additional experiments and discussion, detailed kinetic treatment, experimental details, representative spectra for determining the cis/trans ratios, and spectroscopic data and ^{1}H NMR spectra of all β-lactam products. This material is available free of charge via the Internet at http://pubs.acs.org.

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