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Notable and Obvious Ketene Substituent-Dependent Effect of Temperature on the Stereoselectivity in the Staudinger Reaction

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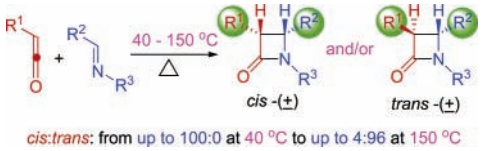

A notable and obvious ketene substituent-dependent effect of temperature on the stereoselectivity in the Staudinger reaction was observed. Most Staudinger reactions show concave Eyring plots characterized by two lines with an inversion point, following the principle of isoinversion. Their *cis*-selectivities decrease with increasing temperature. Reactions involving intramolecular p$-\pi$ and $\pi-\pi$ interactions between the ketene substituents and imine *C*-substituents reveal protruding, *S*-shaped or straight-line Eyring plots. Their *cis*-selectivities increase with increasing temperature in a certain temperature region because such interactions enhance the *cis*-selectivity. Staudinger reactions involving cyclic imines with different ketenes clearly indicate that the temperature-dependent stereoselectivity is caused by the different rate increases of the direct ring closure, which are affected by the p$-\pi$ and $\pi-\pi$ interactions between ketene substituents and imine *C*-substituents if they exist, and the isomerization of the zwitterionic intermediates generated from ketenes and imines during the change in the reaction temperature, not by the competition of the imine *exo* and *endo* attacks to the ketenes. Our results also indicate that nonlinear Eyring plots do not always reveal a change of the stereoselectivity-determining step. Thus, one should use them carefully to determine any changes in the stereoselectivity-determining step during the change in the reaction temperature.

Introduction

The Staudinger reaction (the [2+2] ketene−imine cycloaddition reaction) has been widely used to synthesize β-lactam (2-azetidinone) derivatives,[1] which are important intermediates in both synthetic and pharmaceutical fields, especially as important skeletons in antibacterial pharmaceuticals.[2−4] Generally the Staudinger reaction can produce *cis*-, *trans*-, or mixtures of *cis*- and *trans*-β-lactam derivatives. Thus, control of the cis/trans stereoselectivity is still one of the critical issues in this reaction[5] and presents challenging opportunities for investigation since the stereostructure of β-lactams is very significant to their biological activities. Much effort has been directed to the experimental[6] and theoretical[7] investigations into the stereoselectivity of the β-lactam formation in the Staudinger reaction

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over the past decades. After a series of investigations into the stereochemistry of Staudinger reactions involving cyclic imines and different ketenes,[8] we have recently proposed a model that successfully explains and predicts the relative stereoselectivity in the Staudinger reaction based on a kinetic analysis of the cis/trans ratios of reaction products.[9] We also investigated the factors which might affect the stereoselectivity in the Staudinger reaction.[10] We reasoned that temperature should be an important parameter affecting the stereoselectivity in the Staudinger reaction that might be used to tune the stereoselectivity. However, no detailed study on the influence of the temperature on the stereoselectivity in the Staudinger reaction has been reported to date. Thus, we conducted a series of investigations into the effect of the temperature on the stereoselectivity in the Staudinger reaction and found some interesting and important results. Herein, we present our experimental results.

Results and Discussion

The Staudinger reaction is a stepwise reaction involving nucleophilic attack of an imine to a ketene, giving rise to a zwitterionic intermediate, which undergoes a subsequent ring closure to produce the β-lactam product.[5] If this ring closure proceeds sufficiently fast, the final β-lactam product is cis; otherwise, the isomerization of the imine moiety in the zwitterionic intermediate occurs. The resultant sterically more favorable zwitterionic intermediate finally produces the *trans*-β-lactam product. The cis/trans stereoselectivity is a result of the competition between the direct ring closure and the isomerization of the zwitterionic intermediate.[9] This competition is mainly controlled by the electronic effect of the substituents on the ketene and the imine and the steric hindrance of the *N*-substituents of imines.[9] Solvents, additives, and the pathways of the ketene generation do not affect the stereoselectivity significantly.[10] The addition orders of the reagents affect the stereoselectivity in Staudinger reactions between acyl chlorides and imines because the reactions of acyl chlorides, imines, and tertiary amines could undergo three different pathways to produce β-lactams.[10] Herein, we investigate the effect of the temperature on the stereoselectivity in the Staudinger reaction involving different representative ketenes and imines over a broad temperature range from 40 to 150 °C to understand the effect completely.

On the basis of our previous work,[9,10] to observe obviously different cis/trans ratios of β-lactam products produced from different ketenes over a broad temperature range, we needed to select suitable imines for the different ketenes. For the ketenes with methyl, phenyl, chloro, and phenylthio substituents (the Moore ketenes[6f,h]), which favor *trans*-β-lactam products, the imine **2a** with *C*-*p*-nitrophenyl substituent was selected for favoring the formation of *cis*-β-lactams. For ketenes with phenoxy and phthalimido substituents (the Bose−Evans ketene[6a,c,d,11] and the Sheehan ketene[12]), the imine **2b** with *C*-*p*-methoxyphenyl substituent was selected for favoring the formation of *trans*-β-lactams. Staudinger reactions involving different representative ketenes and the corresponding matched imines were conducted over the temperature range from 40 to 150 °C. To compare the different effects of different ketene generations, the Staudinger reactions of imine **2a** with phenylthioketene generated both from phenylthioacetyl chloride (**1f**) and from *S*-phenyl 2-diazoethanethioate (**1g**) were also conducted. For each of the reactions, the ratios of *cis*- and *trans*-β-lactam products were determined directly via ^{1}H NMR spectra of the crude reaction mixtures.[13] The results are summarized in Table 1.

We have previously found that the Staudinger reaction between phthalimidoacetyl chloride and *N*-(4-nitrobenzylidene)-isopropylamine in the presence of triethylamine shows varying stereoselectivities at "80 °C" in different experimental runs.[9,10] After the investigation onto the effect of the temperature on the stereoselectivity in the Staudinger reaction, it was confirmed that these variations were caused by temperature deviations as it turned out that the stereoselectivity around 80 °C is particularly sensitive to the precise temperature. In previous experiments, we used a routine magnetic stirrer to control the reaction temperature in a small oil bath. However, after careful observation, we found that this method could cause a heavy disturbance (even more than ±10 °C) from the desired temperature. In our current experiments, we used a big water bath with a large

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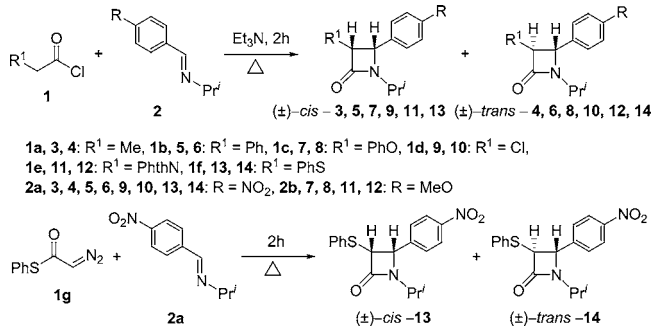
(13) The configurations of the β-lactam products can be easily determined by the coupling constants between the protons on C(3) and C(4) of the β-lactam ring. For *cis* β-lactam products, $J_{H(C3)-H(C4)}$ is 4−6 Hz; and for *trans* products, $J_{H(C3)-H(C4)}$ is about 2 Hz. The *cis*/*trans* ratios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

TABLE 1. Influence of Temperature on the Stereoselectivity in the Staudinger Reaction



		cis:*trans*[a]						
entry	reaction temp (°C)	**3**:**4** R^1 = Me R = NO_2	**5**:**6** R^1 = Ph R = NO_2	**7**:**8** R^1 = PhO R = MeO	**9**:**10** R^1 = Cl R = NO_2	**11**:**12** R^1 = PhthN R = MeO	**13**:**14**[b] R^1 = PhS R = NO_2	**13**:**14**[c] R^1 = PhS R = NO_2
1	150	42:58	66:34	59:41	45:55	4:96	75:25	77:23
2	140	42:58	67:33	63:37	46:54	8:92	84:16	80:20
3	130	42:58	68:32	68:32	47:53	15:85	85:15	81:19
4	110	42:58	71:29	75:25	71:29	51:49	90:10	84:16
5	100	42:58	74:26	84:16	77:23	65:35	88:12	80:20
6	90	49:51	79:21	91:9	83:17	70:30	87:13	79:21
7	80	60:40	85:15	96:4	89:11	72:28	80:20	77:23
8	70	68:32	86:14	98.5:1.5	92:8	76:24	80:20	76:24
9	60	77:23	87:13	99.5:0.5	95:5	80:20	75:25	70:30
10	50	88:12	87:13	100:0	98:2	84:16	75:25	
11	40	91:9	88:12	100:0	99:1	87:13	73:27	

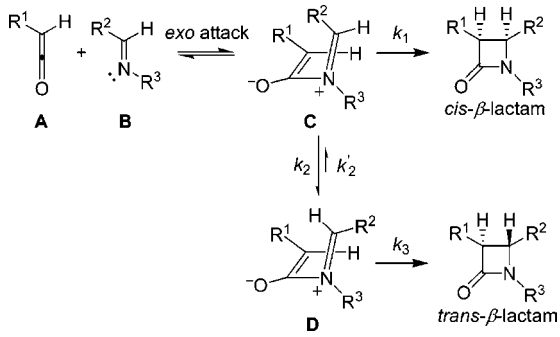
[a] Determined by ^{1}H NMR spectra of the crude reaction mixture and data given here are the average values derived from at least two independent experimental runs with less than 4% difference. [b] Data obtained from the reaction of **1f** and **2a**. [c] Data obtained from the reaction of **1g** and **2a**.

amount of water, covered with a thin layer of paraffin oil to avoid evaporation of water, and a thick asbestos coating outside the bath to control the temperature via a fine temperature controller. The temperature could be controlled within less than ±0.5 °C in the temperature region of 40−90 °C, and within less than ±2−3 °C in the temperature region of 100−150 °C, if paraffin oil was used instead of water.

The results indicate that most Staudinger reactions show less change in the stereoselectivity over the higher temperature range than that over the lower temperature range except for the Staudinger reaction involving phthalimidoketene. The phthalimidoketene-participating Staudinger reaction shows the most obvious effect of the temperature on the stereoselectivity and a more obvious change over the higher temperature range than that over the lower temperature range. Its stereoselectivity reverses from cis/trans 87:13 at 40 °C to 4:96 at 150 °C. For most reactions, the *cis*-selectivity decreases with increasing temperature. However, the stereoselectivity of the Staudinger reaction involving methylketene shows no change over the higher temperature range and that involving phenylthioketene increases with increasing temperature over the lower temperature range. The Staudinger reactions involving phenylthioketenes generated from both phenylthioacetyl chloride (**1f**) and *S*-phenyl 2-diazoethanethioate (**1g**) show similar temperature-dependent stereoselectivities. However, the phenylketene-participating Staudinger reaction shows no obvious change in either the lower or higher temperature regions. A notable and obvious ketene substituent-dependent effect of temperature on the stereoselectivity in the Staudinger reaction was observed.

In the Staudinger reactions between acyl chlorides and imines, ketenes are generated immediately after the addition of the acyl chloride into a solution of the imine and tertiary amine.[6j] To deal conveniently with the reaction process, the reactions can

SCHEME 1. Reaction Progress of the Staudinger Reaction



be simplified as shown in Scheme 1. According to the Curtin−Hammett principle,[14] the cis/trans ratio of products in our investigated Staudinger reactions (Scheme 1) should obey the following equation: $[\text{cis}]/[\text{trans}] = k_1/k_3 \times (k_3 + k_2')/k_2$ because the attack of the imine to the ketene is not related to the stereoselectivity (see ref 9, experiments and discussion in this article, vide post), k_1, k_3 are close to k_2, k_2' and $[\mathbf{D}]_o = [\text{cis}]_o = [\text{trans}]_o = 0$ in our cases. Because the intermediate **D** is more stable than **C** due to its less steric hindrance, the conversion from **D** to **C** should be very difficult. That is, $k_2' \rightarrow 0$ in the reaction, the equation could be simplified as $[\text{cis}]/[\text{trans}] = k_1/k_2$.

The stereoselectivity data in Table 1 have been plotted in Figures 1 and 2 against the reverse absolute temperature according to the Eyring formalism: $\ln([\text{cis}]/[\text{trans}]) = \ln(k_1/k_2) = -\Delta\Delta H^{\neq}/(RT) + \Delta\Delta S^{\neq}/R$. Obviously, the stereoselectivities depend largely on the reaction temperature and the ketene substituents. Reactions involving methyl, phenoxy, chloro,

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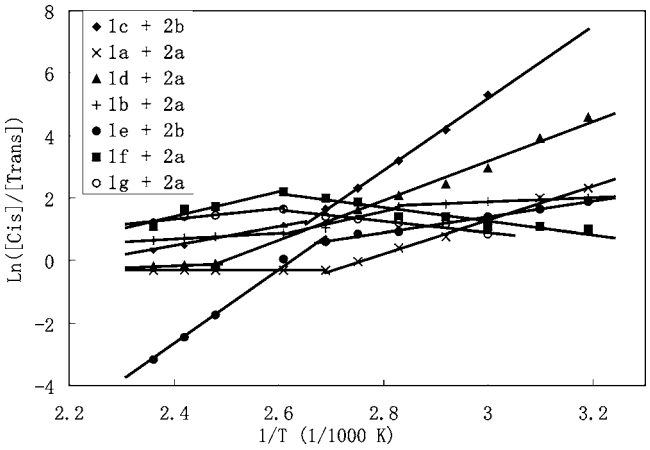

FIGURE 1. Eyring plots for the Staudinger reactions.

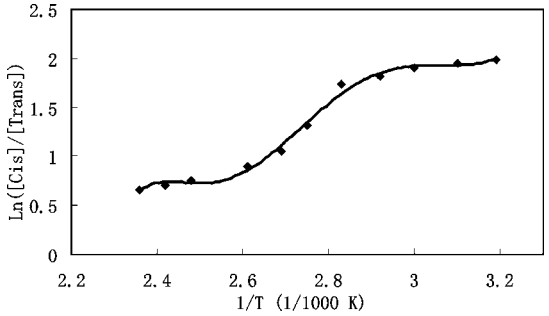

FIGURE 2. Eyring plot for the Staudinger reaction between phenylacetyl chloride **1b** and imine **2a**.

phthalimido, and phenylthio ketenes reveal similar temperature-dependent behaviors. Their Eyring plots characterized by two lines with a inversion point were observed. However, the reactions involving methyl, phenoxy, and chloro ketenes reveal concave Eyring plots, while the reactions involving phthalimido and phenylthio ketenes reveal protruding Eyring plots. The reactions involving phenylthioketene generated from both phenylthioacetyl chloride and *S*-phenyl 2-diazoethanethioate reveal similar temperature-dependent behavior. They show the highest *cis*-selectivity at their inversion points. This is very different from the reactions involving methyl, phenoxy, chloro, and phthalimido ketenes. For the reaction involving phenylketene, an *S*-shaped Eyring plot of the stereoselectivity with an obvious change in the temperature region (70 to 130 °C) was observed (Figure 2). The diverse Eyring plots were observed in the Staudinger reaction.

Why does the *cis*-selectivity in the phenylthioketene-participating Staudinger reaction increase slightly with increasing temperature in the lower temperature region? We assumed that a p$-\pi$ interaction between the larger sulfur atom in the ketene moiety and the phenyl ring of the 4-nitrophenyl group in the zwitterionic intermediate may play an additionally stabilizing role in the transition state which produces the *cis*-product (Figure 3a). To verify this assumption, we carried out the Staudinger reaction between phenylthioacetyl chloride (**1f**) and 4-methoxybenzylidene isopropylamine (**2b**) (Table 2, column 3). The results indicate that its *cis*-selectivity also increases with increasing temperature in the relatively higher temperature region. We could postulate that its *cis*-selectivity would decrease in the higher temperature region, but beyond our temperature range. This supports our assumption.

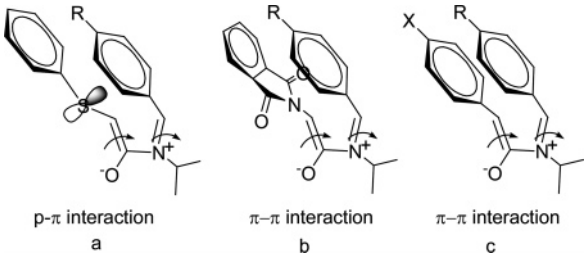

FIGURE 3. The p$-\pi$ and $\pi-\pi$ interactions between the ketene substituents and imine *C*-substituents in the transition states for the formation of *cis*-*β*-lactam products.

From Figures 1 and 2, it could be found that the Eyring plots involving phenylketene and phthalimidoketenes show less change in the stereoselectivity over the lower temperature region than that over the (relatively) higher temperature region. This seems to indicate that $\pi-\pi$ interaction between ketene substituents and imine *C*-substituents plays an important stabilizing role in the transition state which produces the *cis*-product (Figure 3b,c) like that in the photocycloaddition of alkenes to excited alkenes.[15] To investigate the generality, we conducted a series of Staudinger reactions involving different arylketenes and *C*-aryl imines (Table 2, columns 4−7). The stereoselectivity data in Table 2 have been plotted in Figure 4 against the reverse absolute temperature according to the Eyring formalism. Thus, we obtained some revealing Eyring plots. The Staudinger reactions between 4-methoxybenzylidene isopropylamine (**2b**) with phenylacetyl chloride (**1b**) and 4-methoxyphenylacetyl chloride (**1h**) show protruding Eyring plots with *cis*-selectivities increasing in the lower temperature region. They also show the highest *cis*-selectivity at their inversion points like that in the Staudinger reaction between phenylthioketene and imine **2a**. The increasing *cis*-selectivity should be attributed to the $\pi-\pi$ interaction between the aromatic ketene substituents and the imine *C*-substituent. However, the Staudinger reactions involving 4-nitrophenylketene generated from 4-nitrophenylacetyl chloride (**1i**) show no change in the stereoselectivity over the whole temperature region investigated (Table 2, columns 6 and 7). We rationalized that the higher temperature is favorable to the formation of the intermediate **D**, which gives rise to the *trans*-product. However, because of the existence of the intramolecular $\pi-\pi$ interactions between ketene and imine substituents, their direct ring closure rates increase at similar rates as their isomerization rates over the whole investigated temperature region. Another possibility is that the intramolecular $\pi-\pi$ interactions in their zwitterionic intermediates in these two reactions are very weak possibly because the intermolecular $\pi-\pi$ interactions between the 4-nitrophenyl group and aromatic solvents (such as toluene, xylene, or mesitylene) exists predominantly due to the electron-deficient nitro group. Thus, the electronic effect of the 4-nitrophenyl group plays a more important role in controlling the stereoselectivity over the whole temperature region. These results indicate that the p$-\pi$ and $\pi-\pi$ interactions between the ketene substituents and the imine *C*-substituents favor the formation of *cis*-products.

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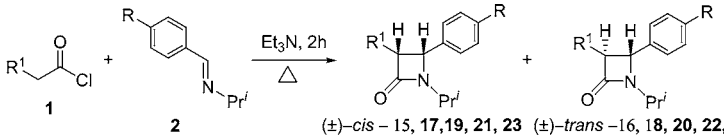
TABLE 2. Influence of Temperature on the Stereoselectivity in the Staudinger Reactions Involving Phenylthioketene and Different Arylketenes



1f, 15, 16: R^1 = PhS, **1h, 17, 18**: R^1 = 4-MeOC$_6$H$_4$, **1b, 19, 20**: R^1 = Ph, **1i, 21, 22, 23, 24**: R^1 = 4-O$_2$NC$_6$H$_4$, **2a, 23, 24**: R = NO_2, **2b, 15, 16, 17, 18,19, 20, 21, 22**: R = MeO

		cis:*trans*[a]				
entry	reaction temp (°C)	**15**:**16** R^1 = PhS R = MeO	**17**:**18** R^1 = 4-MeOPh R = MeO	**19**:**20** R^1 = Ph R = MeO	**21**:**22** R^1 = 4-NO_2Ph R = MeO	**23**:**24** R^1 = 4-NO_2Ph R = NO_2
1	150	23:77	22:78	11:89	4:96	15:85
2	140	20:80	29:71	13:87	3:97	13:87
3	130	18:82	33:67	16:84	4:96	14:86
4	110	11:89	51:49	27:73	3:97	14:86
5	100	10:90	64:36	30:70	3:97	14:86
6	90	10:90	61:39	27:73	3:97	14:86
7	80	9:91	53:47	24:76	3:97	15:85
8	70	9:91	50:50	21:79	3:97	13:87
9	60	9:91	47:53	17:83	3:97	13:87
10	50	9:91	41:59	14:86	3:97	13:87
11	40	9:91	36:64	10:90	3:97	13:87

[a] Determined by ^{1}H NMR spectra of the crude reaction mixture and data given here are the average values derived from two independent experimental runs with less than 3% difference.

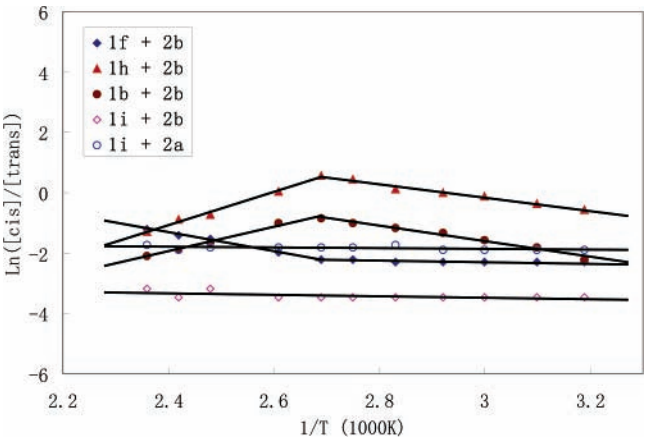


FIGURE 4. Eyring plots for the Staudinger reactions involving phenylthioketene and different arylketenes.

According to the principle of isoinversion,[16] the nonlinear Eyring plots are generally indicative of a change of the stereoselectivity-determining step during the change in the reaction temperature. The temperature at the point of inversion is called the inversion temperature, T_{inv}, of the system. The inversion temperature reveals two sets of parameters of activiation [$\Delta\Delta H^{\neq}_1$ and $\Delta\Delta S^{\neq}_1$ ($T > T_{inv}$), $\Delta\Delta H^{\neq}_2$ and $\Delta\Delta S^{\neq}_2$ ($T < T_{inv}$)], which were obtained from the slope and intercept of the linear plots for each of the systems. Table 3 presents the values for the parameters of activiation $\Delta\Delta H^{\neq}_1$ and $\Delta\Delta S^{\neq}_1$, $\Delta\Delta H^{\neq}_2$ and $\Delta\Delta S^{\neq}_2$, and the inversion temperature, T_{inv}. These large parameters of activiation are unprecedented, such as $\Delta\Delta H^{\neq}_2$ ranging from 1.9 to 98.7 kJ mol^{-1}, and $\Delta\Delta S^{\neq}_2$ ranging from 2.4 to 259.0 J mol^{-1} K^{-1}. Therefore, the stereoselectivity in the Staudinger reaction is strongly temperature dependent.

Moreover, an excellent linearity exists in the plot of $\delta\Delta\Delta H^{\neq}$ ($=\Delta\Delta H^{\neq}_1 - \Delta\Delta H^{\neq}_2$) against $\delta\Delta\Delta S^{\neq}$ ($=\Delta\Delta S^{\neq}_1 - \Delta\Delta S^{\neq}_2$) ($R^2 = 0.9995$) shown in Figure 5. The fitted line passes through the origin of the reaction coordinate. The linear correlation in the $\delta\Delta\Delta H^{\neq}/\delta\Delta\Delta S^{\neq}$ diagram was called the principle of isoinversion.[16] The slope of the straight line is the isoinversion temperature, $T_i = 374.2$ K (101.2 °C), which is a characteristic parameter of the dominance change of stereoselectivity in the Staudinger reactions.

The cis/trans selectivity of the Staudinger reaction is controlled by the competition between the direct ring closure and the isomerization of the zwitterionic intermediates.[9] On the basis of our current experimental results, it seems that the competition still controls the stereoselectivity over the whole temperature region and the rate increases of the direct ring closure and the isomerization are different over the different temperature regions.

Finally, there are two other possibilities for the temperature-dependent stereoselectivity to be investigated. One possibility is that sterically unstable *cis*-products could epimerize to the corresponding sterically more stable *trans*-products under our reaction conditions at higher temperatures as that reported at 230 °C.[6n] The second possibility is that the *endo* and *exo* nucleophilic attack of imine onto the ketene determines the stereoselectivities in the high-temperature region because the stereoselectivities in some Staudinger reactions depend slightly on the temperature over the high-temperature region, seeming to indicate that the stereoselectivity is just related to the structural feature of ketenes over the high-temperature region and affected by the isomerization of the imine moiety in the zwitterionic intermediates, and higher temperatures possibly provide enough energy for the nucleophilic attack to get across the higher energy barrier of the *endo*-attack (Scheme 2).

(16) (a) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Plath, M. W.; Runsink, J. *J. Am. Chem. Soc.* **1989**, *111*, 5367−5373. (b) For a review, see: Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515.

TABLE 3. Inversion Temperature, T_{inv}, and Parameters of Activation, $\Delta\Delta H^{\neq}_1$, $\Delta\Delta S^{\neq}_1$ ($T > T_{inv}$) and $\Delta\Delta H^{\neq}_2$, $\Delta\Delta S^{\neq}_2$ ($T < T_{inv}$) in the Staudinger Reaction

reaction	$\Delta\Delta H^{\neq}_1$, $\Delta\Delta H^{\neq}_2$ (kJ mol^{-1})	$\delta\Delta\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta\Delta S^{\neq}_1$, $\Delta S^{\neq}_2$ (J mol^{-1} K^{-1})	$\delta\Delta\Delta S^{\neq}$ (J mol^{-1} K^{-1})	T_{inv} (K) (°C)
1a + **2a**	0	44.8	−2.7	121.0	370.2
	−44.8		−123.7		97.2
1b + **2a**[a]	−8.0	23.7	−13.5	62.5	379.2
	−31.7		−76.0		106.2
1b + **2a**[b]	−31.7	−25.7	−76.0	−73.6	350.2
	−6.0		−2.4		77.2
1b + **2b**	−33.5	−55.2	−96.5	−148.1	372.2
	21.7		51.6		99.2
1c + **2b**	−24.8	71.3	−55.5	189.8	375.7
	−96.1		−245.3		102.7
1d + **2a**	−5.6	46.9	−14.7	116.6	402.2
	−52.5		−131.3		129.2
1e + **2b**	−20.8	77.9	−50.6	208.4	373.8
	−98.7		−259.0		100.8
1f + **2a**	18.0	51.5	64.7	133.3	386.3
	−33.5		−68.6		113.3
1g + **2a**	14.9	29.1	52.2	75.4	385.9
	−14.2		−23.2		112.9
1f + **2b**	25.8	23.9	51.0	64.5	371.4
	1.9		−13.5		98.4
1h + **2b**	−45.7	−64.4	−118.4	−173.1	371.4
	18.7		54.7		98.4

[a] This reaction has two inversion temperatures. The data are related to the first inversion temperature from the high temperature to the low temperature. [b] The data are related to the second inversion temperature from the high temperature to the low temperature.

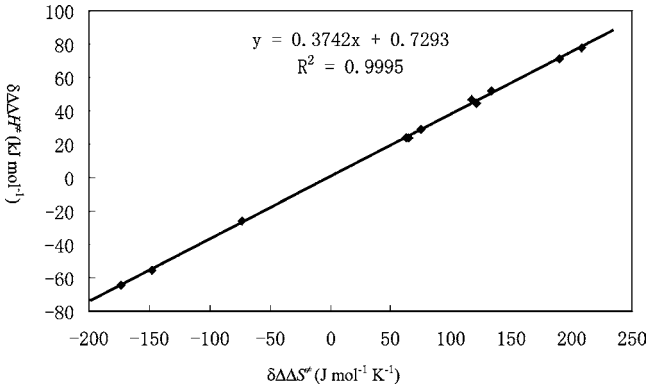
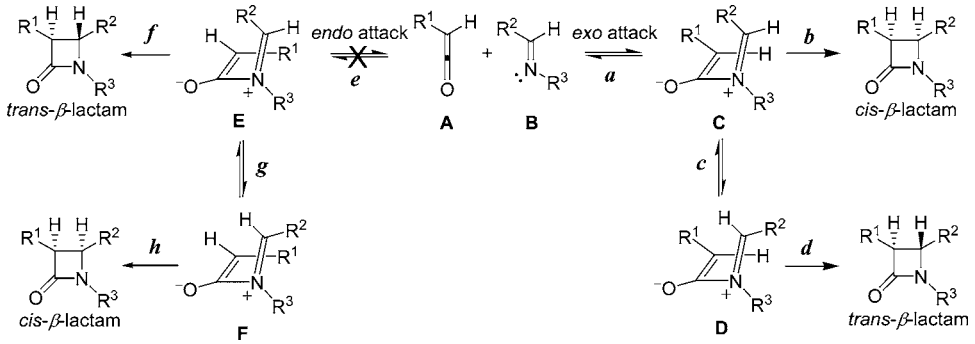


FIGURE 5. $\delta\Delta\Delta H^{\neq}/\delta\Delta\Delta S^{\neq}$ diagram (principle of isoinversion).

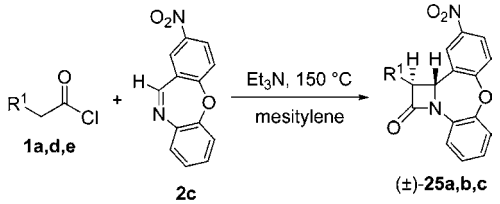
To explore the origin of the temperature-dependent stereoselectivity in the Staudinger reaction, first, we heated several representative *cis*-*β*-lactams (**3**, **5**, **7**, **9**, **11**, and **13**, respectively) in mesitylene at 150 °C for several hours. No epimerization was observed via ^{1}H NMR analysis. This clearly indicates that sterically unstable *cis*-products cannot be converted into sterically more stable *trans*-products within our experimental temperature region. Second, to distinguish whether the direction of the imine attack to the ketene is the major reason for the temperature-dependent stereoselectivity over the high-temperature region, we conducted the Staudinger reactions between different ketenes (including ketenes with small and more bulky substituents) and an excellent cyclic imine **2c** in mesitylene at 150 °C (Scheme 3). The cyclic imine is favorable to the direct ring closure because it possesses an electron-withdrawing group (NO_2), and is favorable to the attack to the *endo* side of ketenes because it possesses the least steric group (H) in the attacking side of the C═N bond. More importantly, it cannot isomerize during the ring closure due to its cyclic structure. The *trans*-products **25** were detected specifically by ^{1}H NMR spectra directly on the crude reaction mixtures for all of the reactions. The results indicate that the cyclic imine only attacks ketenes from their *exo*-side to give rise to zwitterionic intermediates, which undergo directly a conrotatory ring closure to produce *trans*-products specifically (Scheme 4). Our previous results of the reactions between phenylthioketene and arylketenes with cyclic imines conducted at 80 and 140 °C, respectively, also support the current results.[9] Now we can conclude that the origin of the temperature-dependent stereoselectivity in the Staudinger reaction is the different rate increases of the direct ring closure and the isomerization of the zwitterionic intermediates over the whole temperature regions investigated. Different zwitterionic intermediates show different characteristics in their rate increases of the direct ring closure and the isomerization at different temperatures. The isomerization rates of most zwitterionic intermediates increase faster than their direct ring closure rates with increasing reaction temperature, while the direct ring closure rates of zwitterionic intermediates with intramolecular p$-\pi$ and $\pi-\pi$ stacking interactions between ketene and imine substituents increases faster than their isomerization rate over a certain temperature region. Thus, the *cis*-selectivities of most Staudinger reactions decrease with increasing temperature. Only Staudinger reactions involving intramolecular p$-\pi$ and $\pi-\pi$ stacking interactions show increasing *cis*-selectivity along with the increase of temperature over a certain temperature region.

The current results indicate that it is the competition between the direct ring closure and the isomerization of the zwitterionic intermediates, and not the competition of the imine *exo* and *endo* attacks to the ketenes, that controls the stereoselectivity in the Staudinger reaction at any temperature. Our current results also reveal that the principle of isoinversion is indeed a characteristic parameter of the dominance change of the stereoselective steps in the Staudinger reaction. However, the nonlinear Eyring plots are not always indicative of a change of the stereoselectivity-determining steps during the change in the reaction temperature.

SCHEME 2. Possible Reaction Progress of the Staudinger Reaction

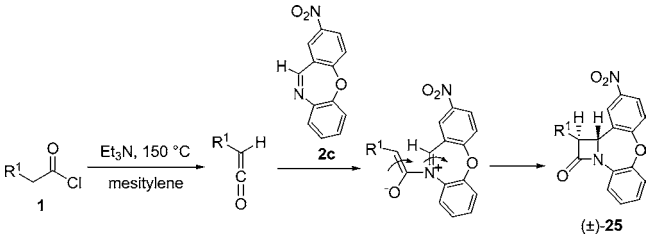


SCHEME 3. Staudinger Reactions between Acyl Chlorides and a Cyclic Imine



1a, 25a: R^1 = Me, **1d, 25b**: R^1 =Cl, **1e, 25c**: R^1 = PhthN

SCHEME 4. Reaction Progress of Acyl Chlorides and a Cyclic Imine in the Presence of Triethylamine



Conclusion

In summary, the effect of temperature on the stereoselectivity in the Staudinger reaction has been investigated systematically with representative ketenes and the corresponding matched imines. The results indicate that the effect of temperature on the stereoselectivity is obviously dependent on the ketene substituents over the temperature range of 40−150 °C. Staudinger reactions generally show concave Eyring plots characterized by two lines with a inversion point, following the isoinversion principle. Their *cis*-selectivities decrease with the increase in temperature. However, Staudinger reactions involving intramolecular p−π and π−π interactions between the ketene substituents and imine *C*-substituents reveal protruding, straight line, or *S*-shaped Eyring plots. Their *cis*-selectivities increase sometimes with increasing temperature over a certain temperature region. On the basis of the results of the Staudinger reactions involving a well-designed cyclic imine with different ketenes, the nonlinear Eyring plots clearly indicate that the temperature-dependent stereoselectivity is caused by the different rate increases of the direct ring closure and the isomerization of the zwitterionic intermediates during the change in the reaction temperature, and not by the competition of the imine *exo* and *endo* attacks to the ketenes. The results also indicate that the nonlinear Eyring plots do not reveal a change of the stereoselectivity-determining steps during the change in the reaction temperature for the Staudinger reaction. The current results illustrate the possibility that one can tune, or even invert the stereoselectivity of some Staudinger reactions by simply changing the reaction temperature. We hope that our results will prove useful in controlling the stereoselectivity of a certain given Staudinger reaction to prepare a β-lactam with the desired relative configuration by fine-tuning the reaction temperature.

It is important that our results also indicate that the nonlinear Eyring plots do not always reveal a change of the stereoselectivity-determining steps during the change in the reaction temperature. One should use the Eyring plot and the principle of isoinversion carefully to determine the change of the stereoselectivity-determining steps during the change in the reaction temperature.

Experimental Section

General Procedure for the Reactions of Acyl Chlorides 1 with Imines 2. A flame-dried round-bottom flask was charged with a solution of imine **2** (0.15 mmol) and triethylamine (20 mg, 0.195 mmol) in 1 mL of dry toluene (xylene or mesitylene). The flask was immersed in a water or oil bath that was preheated and finely controlled to the desired temperature. A solution of the desired acyl chloride **1** (0.195 mmol) in 0.5 mL of dry toluene (xylene or mesitylene) was then added through a syringe during 2 min. The resulting solution was stirred for another 2 h at the same temperature. To obtain the accurate cis/trans ratio at the desired temperature, the reaction mixture was washed with saturated sodium bicarbonate to remove unreacted acyl chloride and ketene to avoid the further Staudinger reaction that occurred when solvent was removed at higher temperatures for the reactions run at lower than 60 °C. After removal of the solvent, the residue was directly submitted to NMR analysis to determine the cis/trans ratio of the corresponding *cis*- and *trans*-β-lactam products. Column chromatograph of the crude mixture on silica gel afforded the corresponding *cis*- and *trans*-β-lactam products for unknown β-lactams.

General Procedure for the Reactions of *S*-Phenyl 2-Diazoethanethioate 1g with Imine 2a. A flame-dried round-bottom flask was charged with a solution of imine **2a** (28.8 mg, 0.15 mmol) in 1 mL of dry toluene (xylene or mesitylene). The flask was immersed in a water or oil bath that was preheated and finely controlled to the desired temperature. A solution of *S*-phenyl 2-diazoethanethioate **1g** (34.7 mg, 0.195 mmol) in 0.5 mL of dry toluene (xylene or mesitylene) was then added via a syringe. The resulting solution was stirred for another 2 h at the same temperature. After removal of the solvent, the residue was directly submitted to NMR analysis to determine the cis/trans ratio of the corresponding *cis*- and/or *trans*-β-lactam products.

General Procedure for the Reactions of Acyl Chlorides 1 with Cyclic Imine 2c. A flame-dried round-bottom flask was charged with a solution of cyclic imine **2c** (120 mg, 0.50 mmol) and triethylamine (65.7 mg, 0.65 mmol) in 3 mL of dry mesitylene. The flask was immersed in an oil bath that was preheated to 150 °C. A solution of the desired acyl chloride **1** (1.30 mmol) in 0.5 mL of dry mesitylene was then added through a syringe during 2

min. The resulting solution was stirred for another 2 h at 150 °C. The reaction mixture was washed with saturated sodium bicarbonate. After the mixture was dried with sodium sulfate and the solvent removed, the residue was directly submitted to NMR analysis to determine the cis/trans ratio of the corresponding *cis*- and/or *trans*-*β*-lactam products. No *cis*-*β*-lactam product was determined. Column chromatograph of the crude mixture on silica gel afforded the corresponding *trans*-*β*-lactam product.

(±)-*cis*-1-Isopropyl-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)azetidin-2-one (17): yellowish oil; yield 33%; R_f 0.15 (silica gel plate, petroleum ether:ethyl acetate 5:1, v/v); IR (KBr) ν (cm^{-1}) 1745.1 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.9 Hz, 3H), 3.69 (s, 3H), 3.71 (s, 3H), 3.86 (dd, J = 6.6, 6.9 Hz, 1H), 4.67 (d, J = 5.4 Hz, 1H), 4.94 (d, J = 5.4 Hz, 1H), 6.64 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.3, 21.3, 45.0, 55.0, 58.87, 58.88, 113.3, 113.4, 125.3, 128.2, 128.8, 129.7, 158.2, 159.0, 168.5; MS (EI) *m*/*z* (rel intensity, %) 325 (M^+, 5), 240 (22), 225 (10), 178 (35), 148 (100), 120 (26); HRMS calcd for $C_{20}H_{23}NO_3$ 325.1678, found 325.1668.

(±)-*trans*-1-Isopropyl-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)azetidin-2-one (18): yellowish oil; yield 29%; R_f 0.25 (silica gel plate, petroleum ether:ethyl acetate 5:1, v/v); IR (KBr) ν (cm^{-1}) 1744.7 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.9 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 3.85 (qq, J = 6.6, 6.9 Hz, 1H), 4.02 (d, J = 1.8 Hz, 1H), 4.39 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6, 21.3, 44.9, 55.22, 62.7, 63.5, 114.2, 127.5, 127.7, 128.4, 130.9, 158.9, 159.7, 168.6; MS (EI) *m*/*z* (rel intensity, %) 325 (M^+, 7), 296 (31), 240 (100), 225 (27), 178 (18), 148 (44), 121 (56); HRMS calcd for $C_{20}H_{23}NO_3$ 325.1678, found 325.1678.

(±)-*trans*-1-Isopropyl-4-(4-methoxyphenyl)-3-(4-nitrophenyl)-azetidin-2-one (22): yellowish oil; yield 58%; R_f 0.20 (silica gel plate, petroleum ether:ethyl acetate 5:1, v/v); IR (KBr) ν (cm^{-1}) 1769.2 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 6.9 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 3.76 (s, 3H), 3.78 (qq, J = 6.6, 6.9 Hz, 1H), 4.12 (d, J = 2.0 Hz, 1H), 4.40 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4, 21.2, 45.3, 55.3, 61.8, 63.3, 114.4, 124.0, 127.8, 128.1, 129.8, 142.7, 147.1, 160.1, 166.5; MS (EI) *m*/*z* (rel intensity, %) 340 (M^+, 9), 255 (100), 225 (9), 177 (30), 162 (72); HRMS calcd for $C_{19}H_{20}N_2O_4$ 340.1423, found 340.1426.

(±)-*trans*-2-Methyl-4-nitroazeto[1,2-*d*]dibenzo[*b*,*f*]oxazepin-1-one (25a): colorless crystals, mp 272.5−273.5 °C; yield 58%; R_f 0.20 (silica gel plate, petroleum ether:ethyl acetate 5:1, v/v); (KBr) ν (cm^{-1}) 1751.4 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (d, J = 7.5 Hz, 3H), 3.78 (dq, J = 2.7, 7.5 Hz, 1H), 5.29 (d, J = 2.7 Hz, 1H), 7.05 (dt, J = 1.5, 7.8 Hz, 1H), 7.14 (dt, J = 1.5, 7.8 Hz, 1H), 7.25 (dd, J = 2.1, 8.7 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 8.03 (dd, J = 1.5, 7.8 Hz, 1H), 8.16 (d, J = 2.4 Hz, 1H), 8.27 (ddd, J = 0.3, 2.7, 9.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0, 49.6, 58.8, 120.2, 121.4, 122.0, 122.9, 124.7, 125.89, 125.92, 129.4, 132.1, 142.9, 144.4, 162.7, 165.7; HRMS calcd for $C_{16}H_{12}N_2O_4$ 296.0797, found 296.0792.

(±)-*trans*-2-Chloro-4-nitroazeto[1,2-*d*]dibenzo[*b*,*f*]oxazepin-1-one (25b): colorless crystals, mp 270−271 °C; yield 69%; R_f 0.20 (silica gel plate, petroleum ether:ethyl acetate 5:1, v/v); (KBr) ν (cm^{-1}) 1769.2 (C═O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.95 (d, J = 1.8 Hz, 1H), 6.18 (d, J = 1.8 Hz, 1H), 7.15−7.22 (m, 2H), 7.14 (dt, J = 1.5, 7.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 8.32 (dd, J = 2.4, 9.0 Hz, 1H), 8.43 (ddd, J = 2.4 Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 57.8, 61.9, 119.4, 122.1, 122.8, 123.1, 125.7, 126.3, 126.6, 128.7, 129.7, 142.9, 144.4, 159.3, 162.0; MS (EI) *m*/*z* (rel intensity, %) 316 (M^+, 63), 281 (100), 240 (75), 235 (37), 206 (12), 194 (18), 166 (17); HRMS calcd for $C_{15}H_9ClN_2O_4$ 316.0251, found 316.0251.

(±)-*trans*-4-Nitro-2-phthalimidoazeto[1,2-*d*]dibenzo[*b*,*f*]oxazepin-1-one (25c): colorless crystals, mp 274−275 °C; yield 27%; R_f 0.25 (silica gel plate, petroleum ether:ethyl acetate 5:1, v/v); (KBr) ν (cm^{-1}) 1680.6, 1678.3 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, J = 3.0 Hz, 1H), 5.96 (d, J = 3.0 Hz, 1H), 7.12 (dt, J = 1.5, 7.8 Hz, 1H), 7.22 (dt, J = 1.5, 7.8 Hz, 1H), 7.29 (dd, J = 1.5, 9.0 Hz, 1H), 7.41 (dd, J = 3.0, 5.4 Hz, 2H), 7.98 (dd, J = 3.0, 5.4 Hz, 2H), 8.16 (dd, J = 1.5, 8.1 Hz, 1H), 8.30 (dd, J = 2.4, 9.0 Hz, 1H), 8.48 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 57.7, 58.7, 120.5, 121.6, 122.6, 123.0, 124.1, 125.4, 126.1, 126.3, 129.1, 130.3, 131.6, 134.9, 143.0, 144.6, 159.4, 162.6, 166.8; HRMS calcd for $C_{23}H_{13}N_3O_6$ 427.0804, found 427.0795.

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Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra of all unknown *β*-lactam products **17**, **18**, **22**, **25a**, **25b**, and **25c** and copies of the representative ^{1}H NMR spectra for determination of cis/trans ratios for each of Staudinger reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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